Clinical Practice Guideline for Dementia 2017

Publication of the English Version of "Clinical Practice Guideline for Dementia 2017"

The first "Treatment Guideline for Dementia" was released in 2002. This was followed by publication of the "Treatment Guideline for Dementia 2010" using the Clinical Question (CQ) format in 2010. In 2014, revision of the "Treatment Guideline for Dementia 2010" was decided. Around this time, preparation of the English version of the "Clinical Practice Guideline for Chronic Headache 2013" was in progress, aiming to be published in 2015. Furthermore, the XXIII World Congress of Neurology was scheduled to be held in Kyoto in September 2017. These events prompted a plan to publish the English version of the revised treatment guideline for dementia.

In August 2017, the "Clinical Practice Guideline for Dementia 2017" in Japanese language was published. However, the English version was not ready in time for the XXIII World Congress of Neurology. Nevertheless, discussions were continued toward publication of the English version as originally planned.

After the publication of the "Clinical Practice Guideline for Dementia 2017" (Japanese version), some questions and opinions were received. The Committee addressed these issues and made some revisions, and at the same time simplified the contents to some extent to prepare the text for the English version of the Guideline.

The policies of developing clinical practice guidelines are gradually evolving, and the current guideline is expected to be revised in the future. For the development of future guideline, some issues in the "Clinical Practice Guideline for Dementia 2017" have to be addressed. These will be discussed in the next revision. With anticipation to develop further improved and more refined clinical practice guideline for dementia in the future, we embarked on preparing the English version of "Clinical Practice Guideline for Dementia 2017".

Kenji Nakajima
Chairman
Dementia Clinical Practice Guideline Development Committee
Japanese Society of Neurology

Preface:
Clinical Practice Guideline for Dementia 2017, Japanese version

July 2017

The first "Treatment Guideline for Dementia" was published in 2002. Then in 2010, six academic societies; namely, the Japanese Society of Neurology, Japanese Society of Neurological Therapeutics, Japanese Society of Psychiatry and Neurology, Japan Society for Dementia Research, Japan Geriatrics Society and Japanese Psychogeriatric Society, jointly developed the "Treatment Guideline for Dementia 2010" using the Clinical Question (CQ) format. Thereafter, with the addition of some new knowledge, the "Treatment Guideline for Dementia 2010, Compact Edition" was published in 2012. Subsequent to this publication, revision of the guideline was discussed at the Japanese Society of Neurology Guideline Executive Committee, and revision of the guideline was decided in 2014.

[Target Readers of this Guideline]

Along with the 2002 and 2010 guidelines, the current guideline was prepared assuming that the readers are general doctors in principle. However, the preparation work was done with the intention that this guideline will also be read by people other than doctors.

[Flow of Guideline Revision]

In 2014, after revision of the guideline was decided, chairman of the committee was elected and the office of guideline preparation was placed in the chairman's affiliated facility. In the same manner as the previous guideline, the revision task was to be undertaken jointly by the six dementia-related societies mentioned above. Another five societies were invited to participate or collaborate. Committee members, research collaborators, and evaluation/coordination committee members were elected from the six societies. The method for the revision work was discussed and decided at the committee, and it was decided that each committee member would provide feedback to his/her academic society as the work progressed. Moreover, although the previous guidelines were called "treatment guidelines", the contents also included diagnosis. Like the previous guidelines, the revised guideline is not limited to treatment but covers the entire clinical practice from diagnosis to treatment of dementia. Therefore, the revised guideline was developed as a "clinical practice guideline"

The Japanese Society of Neurology Guideline Executive Committee considered that although the current revision was in principle to be implemented according to the Minds Handbook for Clinical Practice Guideline Development 2014, the system was still not fully developed in Japan. As a policy to respond appropriately to the actual situation, it was decided that the specific methods for guideline development should be decided through discussions at the Dementia Clinical Practice Guideline Development Committee.

Based on the above guideline development policy, the guideline: (1) used the CQ format; (2) confirmed the sources of funding for guideline preparation and managed the conflict of interest (COI) of committee members; (3) conducted literature search using a uniform method; (4) discussed and decided evidence level and strength of recommendation based on the GRADE system recommended by Minds 2014; (5) listened to opinions from patient groups; (6) for CQs in which "recommendation" statement was difficult to compose because the strength of recommendation could not be decided, an "Answer" statement was prepared; (7) the draft guideline was reviewed by the evaluation/coordination committee and external committees, and (8) the draft guideline was opened to the public, and comments were invited. Thereafter, the "Clinical Practice Guideline for Dementia" was finalized.

[Funding Sources and Conflict of Interest (COI)]

Funds necessary for preparation of this guideline were borne by the Japanese Society of Neurology. The funds provided payment of expenses such as meeting room charges for committee meetings and transportation expenses for attending the committee, but did not provide remuneration for committee members and research collaborators for drafting manuscripts and participation in meetings.

This guideline was prepared based on appropriate COI management according to the "Regulations related to preparation of Japanese Society of Neurology clinical practice guideline", "Guide to preparation of Japanese Society of Neurology clinical practice guideline" and "Rules for establishment and operation of Japanese Society of Neurology conflict of interest committee".

Every year, the chairman, vice chairman, committee members, research collaborators, and evaluation/coordination committee members declared COI to the Chairman of Board of Directors of the Japanese Society of Neurology. Declaration was based on the following criteria: board member renumeration, etc. (1 million yen or more); stocks, etc. (1 million yen or more, or 5% or more of the total stocks); patent royalty (1 million yen or more); lecture fees, etc. (500,000 yen or more); manuscript fee, etc. (500,000 yen or more); contract research fee, joint research fees, etc. (2 million yen or more, 1 million yen or more for the 2015 declaration); scholarship (incentive) donation, etc. (2 million yen or more, 1 million yen or more for the 2015 declaration); endowed chair; provision of travel and gifts (50,000 yen or more).

Enterprises that declared COI are as follows:

Ajinomoto Co., Inc.; Astellas Pharma Inc.; AstraZeneca Co., Ltd.; Igaku-Shoin, Ltd.; Iset Co.; Eisai Co., Ltd.; MSD K.K.; Otsuka Pharmaceutical Co., Ltd.; Ono Pharmaceutical Co., Ltd.; Kyowa Hakko Kirin Co., Ltd.; GlaxoSmithKline K.K.; Kowa Pharmaceutical Co., Ltd.; Social and Medical Corporation Kowakai Sapporo Shirakabadai Hospital; Medical Corporation Seijinkai; Daiichi Sankyo Co., Ltd.; Sumitomo Dainippon Pharma Co., Ltd.; Takeda Pharmaceutical Co., Ltd.; Chugai Pharmaceutical Co., Ltd.; Nippon Boehringer Ingelheim Co., Ltd.; Nippon Medi-Physics Co., Ltd.; Novartis Pharma K.K.; Bayer Yakuhin Ltd.; Pfizer Japan, Inc.; Mochida Pharmaceutical Co., Ltd.; Morimoto Pharma Co., Ltd.; Janssen Pharmaceutical K.K.

[Process of Guideline Revision, Determination of Level of Evidence and Recommended Grade]

The first committee meeting was held in September 2014, and guideline development work began. First, we invited an instructor from Minds to confirm the Minds policy for guideline development. We also invited external committee members to participate, and decided the committee composition, guideline development policy, schedule, and items, and also decided work sharing. The scope was discussed. The scope of this guideline was decided to cover from diagnosis to treatment and long-term care for dementia. CQs would be prepared taking into consideration that the guideline is a reference material for doctors to decide the best methods of clinical care. Comments would be written as general items according to the scope. CQs were to be formulated with reference to PICO (P: patients, problem, population; I: interventions; C: comparisons, controls, comparators; O: outcomes).

Thereafter, the Guideline Executive Committee decided that this guideline is expected to be written concisely with contents that support routine clinical care. To address this point, it was necessary to consider the user-friendliness of guidelines; i.e., users can easily access the content they want to read from the table of contents. Initially, the plan was to limit CQs to important clinical issues, while general clinical and epidemiological features are described under the preface of each section. However, the general features also would have to be presented in a way such that readers can easily find what they want to read. Eventually, the plan was changed: all the contents are presented based on CQs. This format is similar to that used in the previous version. For this reason, items concerning specific clinical issues are mixed with items describing general clinical and epidemiological features, all under CQs (without the initially planned preface). Despite the adoption of this format in the present guideline, which is also partially due to consideration of continuity with the previous version, continuous efforts have to be made to find the optimal format for use in the next revision.

We determined key words (KW) for the CQs and requested Professor Shinichi Abe at the Academic Information Center, the Jikei University School of Medicine to perform search of literature. Since literature search for the previous guideline was conducted until 2008, the search period for this guideline was in principle from 2009. Therefore, literature search from 2009 until April 2015 was conducted during May to July 2015. From the reference list obtained from the search, the references were evaluated using evaluation sheets, not only by subcommittee members and research collaborators, but also by collaborators recommended by each committee member. The level of evidence for each outcome and the body of evidence were evaluated. For CQs that did not have sufficient references from this search process, the key words were changed as necessary, and literature search was repeated. Furthermore, additional manual search was conducted when it was deemed necessary by the committee.

Regarding systematic reviews, the system for conducting quantitative systematic reviews including meta-analysis is not yet adequately established. Therefore, following the policy of the Japanese Society of Neurology Guideline Executive Committee, quantitative systematic review was a non-binding target, and would be conducted if feasible based on the judgment of each committee member, while the main work was to conduct systematic literature search followed by qualitative systematic review, as was done in previous guideline development. All the collaborators of this work will be acknowledged with gratitude at the end of this message.

The level of evidence was evaluated not for individual reference, but by each outcome for studies grouped by study design, such as randomized controlled trial and observational study. The body of evidence was evaluated for risk of bias, indirectness,

inconsistency, imprecision, and publication bias. In the next revision, the methods of conducting systematic review including quantitative systematic review will be thoroughly examined before the work begins. Next, the responsible area for each committee member and research coordinator was decided. Texts for CQs, recommendation statements, and comments and evidence were drafted, and the draft was discussed and decided by all members of the committee.

Table 1. Recommendation grade and level of confidence.

Recommendation grade:
1 (Strong): Recommend to "perform" or "not to perform"
2 (Weak): Propose to "perform" or "not to perform"
Strength of body of evidence:
A: Strong
B: Moderate
C: Weak
D: Very weak

The manuscript thus prepared was reviewed by the evaluation/coordination committee. In addition, external committee members and persons related to patient organizations were invited to review the manuscript, and this guideline development committee also participated to listen to their opinions.

Public comments were invited during August 1–21, 2016. The comments received were reviewed and corrections were made. There were opinions pointing out the need for including more recent references, especially reports from Japan, after April 2015, which exceeded the period of literature search set for this guideline. This was discussed at the guideline development committee and additional manual search as needed was adopted. Since the public comments also included a request to conduct another round of public comment invitation, public comments were again invited during November 16–30, 2016.

[Contents and Items in this Guideline]

This guideline also places importance on continuity, and the contents almost conform to the previous "Treatment Guideline for Dementia 2010". The guideline covers general items including definition, epidemiology, symptoms, assessment scales, diagnosis, examinations, non-pharmacological treatments and pharmacotherapy, interventions for delirium and coexisting diseases, risk factors, prevention, mild cognitive impairment, severity and interventions by severity, long-term care, social resources, community liaison, ethics, and legal issues. In addition, for diseases of dementia by etiology, which are dealt with in the section of "Specific Diseases", Alzheimer's disease dementia, Lewy body disease, frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain dementia, senile dementia of the neurofibrillary tangle type, vascular dementia, prion disease, and medical diseases are included.

For PSP, CBD, and Huntington's disease, although management of motor symptoms is important, including these discussions will further expand the volume of the guideline. Therefore, it was decided to limit discussions to cognitive impairment only, which is in line with the previous guideline. Incidentally, a guideline for these diseases has been planned, which includes motor symptoms and all other disorders except cognitive impairment. The guideline was in the process of development as of November 2016.

Although molecular pathological classification shows that FTLD includes PSP and CBD, clinical differentiation of these diseases is possible based on clinical symptoms and other tests. Furthermore, since FTLD, PSP, and CBD are specified separately as designated intractable disease in Japan, these three diseases are handled as related diseases and described in separate chapters in this clinical practice guideline. For differential use of terms between FTLD and frontotemporal dementia (FTD), and between CBD and corticobasal syndrome (CBS), please refer to the descriptions in the corresponding chapters.

On the other hand, since a separate guideline for prion disease has been developed (Clinical Practice Guideline for Prion Disease 2014), prion disease is described briefly in this guideline while citing the Clinical Practice Guideline for Prion Disease 2014.

In an evaluation questionnaire after publication of the previous guideline, there was opinion that medical diseases caused by vitamin deficiency should also be included. In this guideline, therefore, vitamin deficiency, hypothyroidism, neurosyphilis, hepatic encephalopathy, and idiopathic normal pressure hydrocephalus (iNPH) are described. In the next revision, while reviewing the target diseases to be included in the guideline, it seems necessary to discuss whether the above diseases/items should be included.

[Names of therapeutic drugs and terms]

In principle, the terms used in the previous "Treatment Guideline for Dementia 2010" are adopted in this guideline.

<Names of therapeutic drugs>

Drug that are approved for dementia treatment in Japan and those that are used clinically even though they are not covered by health insurance for dementia treatment in Japan are written in katakana. Drugs that are used only overseas but not used in Japan are written in English.

<"Cognitive impairment" and "behavioral and psychological symptoms of dementia (BPSD)">

"Core symptom" of dementia is described as "cognitive impairment". The term "peripheral symptoms" is not used, and is replaced by "behavioral and psychological symptoms of dementia (BPSD)". A combination of cognitive impairment an BPSD is described as "dementia symptoms".

<Description of severity>

Regarding the severity of dementia, the terms "severe" and "high level" are used almost synonymously for the advanced stage. "Severe" was used in the Treatment Guideline for Dementia 2002 and 2010. Following these previous guidelines, "severe" is used in this guideline.

<Classification related to time of onset: "juvenile dementia">

Depending on the time of onset, terms such as "juvenile dementia", "pre-senile dementia", "senile dementia", "early-onset dementia", and "late-onset dementia" are used. There is opinion that use of the term "juvenile dementia" may not be desirable, because the same term may denote different age groups [Japan Society for Dementia Research (Ed.): Textbook of Dementia, 2008]. However, the term "early-onset dementia" is used in administrative documents such as "Measures for early-onset dementia" (2009) (Ministry of Health, Labor and Welfare), as well as the Orange Plan and the New Orange Plan. In response to these developments, a patient aged under 65 years with dementia is referred to as "early-onset dementia" in this guideline (see "Chapter 5: Various Systems and Social Resources for Supporting Persons with Dementia and Their Families; C. Early-onset Dementia").

<"Alzheimer's disease" and "Alzheimer's disease dementia"

The term "Alzheimer's disease" may refer to the pathological state of the disease or may be used to describe the clinical syndrome when dementia symptoms due to "Alzheimer's disease" have become evident. According to the National Institute on Aging and Alzheimer's Association (2011), "Alzheimer's disease" is defined as a term encompassing the underlying pathophysiological processes, and "Alzheimer's disease" is distinguished from "Alzheimer's disease dementia" which describes the state of dementia caused by "Alzheimer's disease". In Japan, "Alzheimer's disease dementia" has been used from the past as a term to describe the state of dementia considered to be caused by "Alzheimer's disease". Therefore, in this guideline, the term "Alzheimer disease dementia" is used for dementia that is considered to have occurred based on the pathological background of "Alzheimer's disease". However, this guideline does not differentiate between "Alzheimer disease dementia" (diagnosed from clinical features) and "Alzheimer disease dementia caused by Alzheimer's disease" (evidence that dementia is caused by Alzheimer's disease has been confirmed), because this differentiation has little utility in clinical practice.

<Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)>

In DSM-5 published by the American Psychiatric Association in 2013, the term "neurocognitive disorder" was introduced. This term includes "delirium" and "major and mild neurocognitive disorder". The Japanese translations for "major and mild neurocognitive disorder" are "dementia (DSM-5)" and "mild cognitive impairment (DSM-5)", respectively.

<"Mild cognitive impairment" and "MCI">

In this guideline, "mild cognitive impairment" and "MCI" are described as "mild cognitive impairment (MCI)".

<Others>

Terms including "senile dementia of the neurofibrillary tangle type (SD-NFT)", "tangle-predominant senile dementia/ NFT-predominant form of senile dementia", "tangle only dementia", and "primary age-related tauopathy (PART)" are used uniformly in the guideline.

[Using this clinical practice guideline in clinical care for dementia]

This guideline provides reference materials to support the clinical practice and care for dementia with the purpose to improve clinical practice for dementia, and does not intend to constrain clinical practice for dementia in the clinical setting. With future developments and changes in medical care and research, as well as diversification of persons with dementia and the environment surrounding these persons, guidelines are expected to change over time. This guideline does not restrict the decision of clinicians over treatment, neither does it stipulate medical treatment in response to changes in the clinical setting. Sometimes the recommendations in this guideline may not apply. There are cases where the physician in charge may perform treatments that deviate from the descriptions in this guideline, and cases where the deviation may be appropriate. In actual clinical practice, it is important to formulate an individualized treatment plan that responds to the dementia of each patient, without being restricted by the contents of this guideline. In addition, the contents described in this guideline do not serve as grounds for medical lawsuits.

[Promotion of utilization of the guideline, future plans including the next revision, and evaluation]

In order to promote the utilization of this guideline, the guideline is scheduled to be introduced and publicized by posting on the websites of the academic societies that participated in guideline development, presented at scientific conferences and other meetings of the academic societies, and published in scientific journals.

For the convenience of readers, a compact edition has been published both for the Treatment Guideline for Dementia 2002 and 2010 editions. For this guideline also, publication of a compact version will be considered. Furthermore, the Japanese Society of Neurology has published the English version of other clinical practice guideline, and we hope that the possibility of publishing the English version of the Clinical Practice Guideline for Dementia will be discussed at the guideline development committee.

In the case that addition or correction is necessary due to new knowledge obtained after publication of this guideline, additional or revised CQ will be prepared as a supplement and posted on the society website. In addition, the Japanese Society of Neurology has a policy of revising clinical practice guidelines every five years. This guideline development committee will also consider the next revision and composition of the next guideline development committee, and the results will be submitted to the Japanese Society of Neurology Guideline Executive Committee for deliberation.

The previous two guidelines for the treatment of dementia were evaluated by an evaluation committee set up at the Japanese Society of Neurology. It is anticipated that the current Clinical Practice Guideline for Dementia 2017 will also be evaluated by an evaluation committee.

[Acknowledgment to committee members and research collaborators]

Revision and development of the present guideline were undertaken with the collaboration of six dementia-related associations. I would like to express my gratitude to all members of the committee and the research collaborators for their participation in the committee and for their great efforts despite their busy schedules. This guideline was developed with the support of many colleagues such as evaluation/coordinating committee members, external committee members, and collaborators. I would like to thank them all for their collaboration. I would also like to thank Ms. Noriko Ono and Ms. Yoriko Matsushita from the Tokyo Branch of the Alzheimer's Association Japan for their opinions in preparing the guideline. Furthermore, I would like to express my sincere appreciation to those who have provided many valuable comments in the invitation of public comments. I would also like to thank staff members of Minds for their advice.

Kenji Nakajima
Chairman
Dementia Clinical Practice Guideline Development Committee
Japanese Society of Neurology

LIST OF AUTHORS

Editing Supervisors:

Japanese Society of Neurology

Japanese Society of Neurological Therapeutics, Japanese Society of Psychiatry and Neurology, Japan Society for Dementia Research, Japan Geriatrics Society, Japanese Psychogeriatric Society

Editors:

Dementia Clinical Practice Guideline Development Committee

Participating societies: Japanese Society of Neurology, Japanese Society of Neurological Therapeutics, Japanese Society of Psychiatry and Neurology, Japan Society for Dementia Research, Japan Geriatrics Society, Japanese Psychogeriatric Society

Chairman

Kenji Nakajima: Matsue Medical Center

Vice-chairman

Hidekazu Tomimoto: Department of Neurology, Mie University

Committee members

Ikuko Aeba: Department of Neurology, Higashinagoya National Hospital
Masahiro Akishita: Geriatric Medicine, University of Tokyo Hospital
Shuichi Awata: Tokyo Metropolitan Institute of Gerontology
Setsu Iijima: National Rehabilitation Center for Persons with Disabilities
Takeshi Ikeuchi: Department of Molecular Genetics, Brain Research Institute, Niigata University
Manabu Ikeda: Department of Psychiatry, Osaka University Graduate School of Medicine
Masafumi Ihara: Division of Cerebrovascular Medicine and Neurology, National Cerebral and Cardiovascular Center
Hiroaki Kazui: Department of Psychiatry, Osaka University Graduate School of Medicine
Nobuo Sanjo: Department of Neurology and Neurological Science, Tokyo Medical and Dental University
Mikio Shoji: Department of Neurology, Hirosaki University Graduate school of Medicine
Kyoko Suzuki: Department of Clinical Neuroscience, Yamagata University Graduate School of Medical Science
Makio Takahashi: Department of Neurology, Osaka Red Cross Hospital
Akira Tamaoka: Graduate School of Comprehensive Human Sciences, University of Tsukuba
Seishi Terada: Department of Neuropsychiatry, Okayama University
Aki Nakanishi: Department of Neurology, Osaka City Kosaiin Hospital
Haruo Hanyu: Geriatric Medicine, Tokyo Medical University
Hideo Hara: Division of Neurology, Saga University
Katsuyoshi Mizukami: Faculty of Health and Sport Sciences, University of Tsukuba
Yukihiko Washimi: Department of Brain Function Examination, National Center for Geriatrics and Gerontology
Hirohisa Watanabe: Brain and Mind Research Center, Nagoya University
Kenji Wada: Division of Neurology, Tottori University

Research Collaborators

Haruhiko Akiyama: Dementia Research Project, Tokyo Metropolitan Institute of Medical Science
Tadashi Adachi: Division of Neurology, Tottori University
Atsushi Iwata: Department of Neurology, University of Tokyo
Tomomi Ogihara: Department of Psychiatry, Shinshu University
Naoto Kamimura: Department of Neuropsychiatry, Kochi University
Takayoshi Shimohata: Department of Neurology, Brain Research Institute, Niigata University
Kazuko Hasegawa: Department of Neurology, Sagamihara National Hospital
Osamo Yokoto: Kinoko Espoir Hospital

Evaluation/Coordination Committee Members

Takashi Asada: Center for Brain Integration Research, Tokyo Medical and Dental University
Naoji Amano: Okaya City Hospital
Hiroyuki Arai: Institute of Development, Aging and Cancer, Tohoko University
Fukashi Udaka: Sumitomo Hospital
Kochi Okamoto: Geriatrics Research Institute
Shun Shimohama: Department of Neurology, Sapporo Medical University
Masatoshi Takeda: Aino University
Akira Honma: Otafuku Monowasure Clinic
Masahito Yamada: Department of Neurology and Neurobiology of Aging, Kanazawa University
(Late)Dr. Hideo Mori: Department of Neurology, Juntendo University Koshigaya Hospital

External Committee Member

Masayo Kojima: Department of Medical Education, Nagoya City University

Collaborators

Yusuke Yakushiji: Division of Neurology, Saga University
Makoto Eriguchi: Division of Neurology, Saga University
Masafumi Kosugi: Division of Neurology, Saga University
Jun Tanaka: Division of Neurology, Saga University
Kohie Suzuyama: Department of Neurology, Saga University
Yasuo Harigaya: Japanese Red Cross Maebashi Hospital
Etsuro Matsubara: Department of Neurology, Oita University
Noriyuki Kimura: Department of Neurology, Oita University
Takeshi Kawarabayashi: Department of Neurology, Hirosaki University
Masaki Ikeda: Department of Neurology, Guma University
Kokoro Ozaki: Department of Neurology and Neurological Science, Tokyo Medical and Dental University
Maya Higuma: Department of Neurology and Neurological Science, Tokyo Medical and Dental University
Yoko Ito: Department of Neurology and Neurological Science, Tokyo Medical and Dental University
Fumiko Furukawa: Department of Neurology and Neurological Science, Tokyo Medical and Dental University
Takefumi Sato: Department of Neurology and Neurological Science, Tokyo Medical and Dental University
Ryo Tagawa: Tagawa Kusunoki Clinic
Yumi Kameyama: Geriatric Medicine, University of Tokyo Hospital
Michihito Masuda: Department of Neurology, Nagoya University
Kazunori Imai: Department of Neurology, Nagoya University

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Chapter 1

Overview of Dementia: Epidemiology, Definitions, Terms

CQ 1-1

What are the diagnostic criteria for dementia?

Answer

Representative diagnostic criteria for dementia include the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) published by the World Health Organization, the diagnostic criteria proposed by the National Institute on Aging–Alzheimer's Association Workgroup (NIA-AA), and Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) published by the American Psychiatric Association.

Comments and evidence

In ICD-10 (1993), dementia is described as "a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement". Detailed diagnostic criteria are provided in ICD-10 [1].

In the diagnostic criteria of dementia proposed by the NIA-AA (2011), impaired ability to acquire or remember new information, impaired executive function, impaired visuospatial abilities, and impaired language functions are treated equally, and the diagnostic criteria include behavioral impairment and subtypes of dementia other than Alzheimer's disease dementia [2].

DSM-5 (2013) introduced a new term, "neurocognitive disorders", and replaces the term "dementia" with "major neurocognitive disorder". DSM-5 details six cognitive domains that may be affected in neurocognitive disorders. A diagnosis of major neurocognitive disorder (dementia) requires evidence of significant decline in one or more of the following cognitive domains: complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition, and that the cognitive deficits interfere with independence in activities of daily living [3]. DSM-5 provides new information sources for these criteria.

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Search formula

PubMed search: July 3, 2015 (Friday), August 8, 2015 (Friday)

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CQ 1-2

What other terms are related to dementia?

Answer

The DSM-5 introduces the new terms of major neurocognitive disorder (replacing dementia) and mild neurocognitive disorder (replacing mild cognitive impairment or MCI). Other terms include subjective cognitive impairment (SCI) and subjective cognitive decline (SCD).

Comments and evidence

The National Institute on Aging–Alzheimer's Association (NIA-AA) workgroup classifies Alzheimer's disease into three disease stages based on the pathophysiological process of Alzheimer's disease: preclinical Alzheimer's disease [1], mild cognitive impairment (MCI) due to Alzheimer's disease [2], and dementia due to Alzheimer's disease (Alzheimer's disease dementia) [3]. In addition, the preclinical stage is divided into stage 1 (asymptomatic amyloidosis), stage 2 (amyloidosis + neurodegeneration), and stage 3 (amyloidosis + neurodegeneration + subtle cognitive decline).

In DSM-5 (2013), the new term "neurocognitive disorders" was introduced. Neurocognitive disorders are classified into delirium, major neurocognitive disorder, and mild neurocognitive disorder. DSM-5 details the diagnostic criteria for these three types [4].

Vascular cognitive impairment (VCI) is a concept that comprehensively encompasses a range of cognitive deficits from mild cognitive impairment caused by cerebrovascular disorder to vascular dementia (VaD) [5]. Vascular cognitive disorder (VCD) has been proposed as a diagnostic category that includes VCI, post-stroke dementia, genetic VaD [cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), Binswanger disease, and Alzheimer's disease with VaD [6]. (See CQ14-1).

Multiple definitions have been proposed for mild cognitive impairment, and the concept has undergone changes. Apart from the diagnostic criteria proposed by Peterson et al. [7] in 2004, diagnostic criteria have been provided in DSM-5, NIA-AA and ICD-10 [8], all of which differ to some extent (see CQ4B-5). In addition to mild cognitive impairment, other conditions such as age-associated memory impairment (AAMI), aging-associated cognitive decline (AACD), mild cognitive disorder (MCD), mild neurocognitive decline (MNCD), and cognitive impairment no dementia (CIND) have been included in the concept of prodromal stage of dementia[9].

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CQ 1-3

What are the causes of dementia and how are they classified?

Answer

Dementia is caused by a variety of diseases and conditions. In DSM-5, the etiological subtypes of major neurocognitive disorder (dementia) comprise Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance/drug use, HIV infection, prion disease, Parkinson's disease, Huntington's disease, other medical conditions, multiple etiologies, and unspecified.

Comments and evidence

Many diseases and conditions may cause dementia or dementia-like symptoms [1].

ICD-10 classifies dementia into Alzheimer's disease dementia, vascular dementia, dementia in other diseases classified elsewhere, and unspecified dementia [2].

In the neurocognitive disorder category of DSM-5, the etiological subtypes of major neurocognitive disorder (dementia) and minor neurocognitive disorder (mild cognitive impairment) are listed as follows: Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance/drug use, HIV infection, prion disease, Parkinson's disease, Huntington's disease, other medical conditions, multiple etiologies, and unspecified [3].

Among these causative diseases and conditions, some neurosurgical diseases such as normal pressure hydrocephalus and chronic subdural hematoma, as well as some medical diseases such as hypothyroidism and vitamin B_{12} deficiency are being treated under the concept of treatable dementia, and early diagnosis and appropriate treatments and interventions are desirable.

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PubMed search: July 3, 2015 (Friday)

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CQ 1-4

What pathological conditions should be differentiated from dementia?

Answer

Pathological conditions that should be differentiated from dementia, especially Alzheimer's disease dementia, include normal cognitive decline accompanying aging (physiological amnesia), delirium, depression, other learning disabilities, and mental retardation.

Comments and evidence

DSM-5 lists pathological conditions that should be differentiated from dementia as follows: normal cognitive decline accompanying aging, delirium, depression, other learning disabilities, and mental retardation [1]. Important points for differentiation of Alzheimer's disease dementia from the above disorders are summarized below.

1. Physiological amnesia accompanying aging

In general, physiological amnesia is differentiated from dementia by partial forgetfulness of past experience, with no or slow progression, preserved self-recognition of the disability, preserved orientation to time, and little disturbance in activities of daily living.

2. Delirium

Delirium is an acute psychiatric symptom accompanied by impaired consciousness, causing difficulties to focus and maintain attention. Common triggering factors include physical illnesses, environmental changes, and effects of drug. The symptoms fluctuate, which differ from symptom persistence in dementia, but delirium and dementia are often found concomitantly.

3. Depression

Pseudodementia due to depression or a depressive state may cause psychomotor retardation and difficulties in concentration, as well as memory decline and impaired judgement. Patients complain of reduced memorizing ability, which may be mistaken as dementia. Unlike Alzheimer's disease dementia, memory and executive dysfunctions usually do not persist in pseudodementia, and patients often over-estimate their functional impairment (while dementia patients underestimate their functional impairment, reflecting decreased awareness of disease). Response to antidepressants is another point of differentiation.

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CQ 1-5

What is the prevalence of dementia in Japan?

Answer

In the first half of the 2010s, the prevalence of dementia in older people aged 65 years and above in Japan was estimated to be approximately 15%. A

Comments and evidence

During the period from the 1980s to the 2000s, the prevalence of dementia in older people aged 65 years and above in Japan was reported to be 3.8-11%, and the prevalence of dementia has shown a tendency of increase [1]. A survey on the prevalence of dementia in 8 municipalities nationwide estimated that there were 4.26 million older people with dementia in 2012, and the prevalence was reported to be about 15% [2, 3]. Based on a longitudinal survey conducted in Hisayama Town, Fukuoka Prefecture, the future prevalence of dementia was estimated and reported. Assuming that the prevalence of dementia in each age group remains constant after 2012, the number of people with dementia in 2025 is estimated to be 6.75 million [95% confidence interval (CI); 5.41 million to 8.44 million]. When assuming that the frequency of diabetes increases by 20% in the future, the number of people with dementia in 2025 is estimated to be 7.3 million (95% CI: 5.7 million to 9.36 million) [4].

The number of people with dementia in the world is estimated to be 46.8 million in 2015, and predicted to increase at a pace of doubling every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050. Furthermore, the increase in low- to middle-income countries is predicted to be markedly higher compared to high-income countries [5]. On the other hand, a study in the UK has reported decrease in prevalence of dementia [6], while studies in the Netherlands, Germany, Sweden and US have reported decreases in incidence of dementia [7-10].

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Search formula: search period

PubMed search: May 28, 2015 (Thursday), October 19, 2015 (Thursday)

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Ichushi search: May 28, 2015 (Thursday)

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CQ 1-6

Are there changes in prevalence depending on subtype of dementia?

Answer

Dementia shows a tendency of increase in Japan, and Alzheimer's disease dementia is increasing compared to vascular dementia. B

Comments and evidence

According to a nationwide survey conducted in the first half of the 2010s, the frequency of Alzheimer's disease dementia was the highest at 67.6%, followed by vascular dementia at 19.5%, and dementia with Lewy bodies /dementia with Parkinson's disease at 4.3% [1]. In the 1980s, vascular dementia was more prevalent than Alzheimer's disease dementia in Japan, but Alzheimer's disease dementia has shown a trend of increase since the latter half of the 1990s, especially in older people aged 80 years and above [2-5]

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Ichushi search: May 28, 2015 (Thursday)
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CQ 1-7

Is the disease duration of dementia getting longer?

Answer

Studies have reported a possibility that the survival period of people with dementia may be prolonged. However, there is no report showing that the death rate of people with dementia is clearly lower compared to the general population.

C

Comments and evidence

In the United States, the hazard ratio (HR) for death in people with dementia aged 70 years and above compared to those without dementia was 2.53 in 1993 and 3.11 in 2002, with no significant change during the 9-year period (p = 0.09) [1]. In a study conducted in Stockholm, Sweden, the mortality rate of people with dementia decreased by 29% over the 14-year period from 1988 to 2002, but the HR compared to non-dementia subjects was 2.42 in 1988 and 2.47 in 2002, with no significant change during the 14 years [2]. In these reports, while the incidence of dementia has declined, prevalence has not changed, suggesting that the duration of dementia may be prolonged [1, 2]. In a study using medical insurance claim data in Germany, the death rate of people with dementia increased by 1% in men (p = 0.75) and 11% in women (P < 0.001) over a 3-year period from 2004 to 2007 [3].

When the mean loss of life expectancy (%) (survival period from dementia onset to the mean age of death divided by the mean life expectancy of the general population at the age of dementia onset) was analyzed by period, many reports show that loss of life expectancy in people with dementia decreases after mid-1990s when compared to that from the 1980s to early 1990s [4].

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CQ 1-8

What is the pathological background of dementia?

Answer

Various underlying pathologies are associated with dementia, such as degenerative disease, cerebrovascular disorder, infection, inflammation, and tumor, and the clinical picture is strongly influenced by the lesion distribution. The frequency of degenerative diseases is high, and in the majority of these cases, abnormal protein accumulation is the core feature of the pathology.

Comments and evidence

Alzheimer's disease is characterized by the formation of large numbers of senile plaques [amyloid β (Aβ) plaque formation] and neurofibrillary tangles (fibrous aggregates of tau protein). Both senile plaques and neurofibrillary tangles also appear in older people without dementia, but they are particularly abundant in Alzheimer's disease. It remains unclear how the formation of senile plaques and neurofibrillary tangles leads to neuronal degeneration and loss. The main lesion of dementia with Lewy bodies is abnormal accumulation of α-synuclein in neurons. In Parkinson's disease, Lewy lesions are confined to the brain stem, whereas in dementia with Lewy bodies, Lewy lesions spread to the cerebrum. Alzheimer's lesions are observed in many patients with dementia with Lewy bodies [1].

Fronto-temporal lobar degeneration (FTLD) is broadly divided into a disease group showing tau accumulation and a group showing TDP-43 accumulation, while there are rare cases of fused in sarcoma (FUS) protein accumulation [2]. Although there is not always a good correlation between clinical features and pathological diagnosis, many cases of semantic dementia and cases with coexisting motor neuron disease are associated with TDP-43 accumulation. In Japan, familial FTLD is often caused by tau gene mutations.

Argyrophilic grain dementia showing granular accumulation of tau inside neurites, and primary age-related tauopathy (PART) showing abundant neurofibrillary tangles (similar to Alzheimer's disease) localized to the hippocampal limbic system but no significant Aβ accumulation are increasingly common in older people aged 80-90 years and above [3]. Hippocampal sclerosis is a general term for disease conditions showing severe neuronal loss and gliosis in hippocampal CA1 and subiculum, with diverse underlying diseases.

Vascular dementia is frequently caused by ischemic brain lesions, and the culprit vascular lesions are broadly classified into those caused by macrovascular atherosclerosis and those caused by microvascular lesions. Microvascular lesions cause multiple lacunar infarcts and white matter lesions, and are strongly associated with dementia [4]. Amyloid angiopathy also causes dementia, and in this case is often accompanied by Alzheimer's lesions. The coexistence of Alzheimer's lesion and vascular lesion is not simply comorbidity, but is thought to influence each other in pathological mechanisms (see CQ14-4).

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Chapter 2

Syndrome, Rating Scales, Tests, Diagnosis

Objective

To understand the symptoms and rating scales of dementia, to conduct the necessary tests, and to diagnose dementia accurately.

Symptoms

The dementia syndrome comprises impairment of cognitive functions including memory, language, and visuospatial cognition, together with associated behavioral and psychological symptoms of dementia (BPSD). Multiple cognitive functions are impaired, reflecting the sites of functional decline in various disorders. The basis of BPSD is cognitive impairment, and arise as a result of influences by physical factors, environmental factors, and psychological factors. Various rating scales have been devised to prevent overlooking symptoms and to monitor changes over time.

History taking

Taking history from the patient, family members, and caregivers is important. By taking history from the patient, cognitive functions such as memory, language, and thinking; the degree of disease awareness; and psychological symptoms can be estimated. Ask family members about specific symptoms and their changes over time. Ask about the patient's life history including handedness, educational history, and occupation, which will be useful to estimate the patient's capabilities before disease onset and to explore the mechanisms of BPSD.

CQ 2-1

What kinds of cognitive function impairment are found in dementia?

Answer

Multiple cognitive functions are impaired in dementia, reflecting the sites of functional decline in various disorders. The main cognitive function impairments include general attention impairment, amnesia, aphasia, visuospatial impairment, apraxia, and executive function impairment.

Comments and evidence

As a part of the neurological examination, neuropsychological evaluations for the cognitive functions shown below can be used to capture the characteristic cognitive impairment of each disease [1].

1. General attention impairment

General attention is a function that forms the basis of perceiving and selecting stimulation in the surrounding and acting appropriately in response to the stimulation. In dementia, the retention, selectivity, and allocation of attention are often impaired from a relatively early stage, regardless of the etiological subtype, subsequently affecting various individual cognitive functions. If general attention is impaired, the amount of information that can be processed at one time is reduced, making it difficult to understand, memorize, and react to relatively complex matters.

2. Executive function impairment

Executive function refers to the functions of planning and executing a task with a purpose, and carrying on with the task while continuously feeding back the result. Impairment of executive function is a typical symptom of frontotemporal lobar degeneration (FTLD), but may also be present in other types of dementia. Executive function is related to all the complex actions, and its impairment may become noticeable when work and housework are not carried out in a usual manner.

3. Memory impairment

Memory is a function by which new experience is preserved, and that experience is reproduced in consciousness or action [2]. Memory includes the process of memorizing the experience, retaining (storing) it for a certain period, and then retrieving (recalling) the experience. Memory is classified according to the contents to be memorized and the period of retention as follows.

a. Classification by content

Declarative memory refers to the memory that can be consciously recalled and expressed verbally. Non-declarative memory is the memory that cannot be expressed explicitly; an example is procedural memory. Declarative memory is subdivided into episodic memory and semantic memory.

Episodic memory is the memory of events including the context of when and where, and impairment of episodic memory is called amnesia. Amnesia is observed in many types of dementia, and is a particularly common manifestation in the early stage of Alzheimer's disease. Episodic memory deficit is further divided into retrograde amnesia which is failure to recall events before the onset of disease, and anterograde amnesia which is failure to recall events after the onset of disease.

Semantic memory is equivalent to knowledge including meaning of objects and names. In semantic dementia, the patient initially cannot recall the names of objects, gradually cannot understand when being told the names of objects, and eventually cannot understand even though when being shown the actual objects.

Non-declarative memory includes procedural memory of skills such as riding a bicycle. Since non-declarative memory is preserved even in an amnestic patient, it may be useful for maintaining activities of daily living.

b. Classification by length of retention

Based on the length of time a stimulus is retained, memory can be divided into immediate (short-term) memory, recent memory, and remote memory. Immediate memory is a function related to general attention, while recent and remote memory are episodic memory. Immediate memory is a function that stores a stimulus for a few seconds and reproduces it immediately,

and can be tested, for example, by forward digit span. To assess the presence or absence of amnesia, it is necessary to test the episodic memory by asking the patient to memorize a stimulus and then to recall after other tasks have been completed.

c. Other types of memory

Working memory is a function that uses immediate memory to hold information and utilizes it to perform cognitive task. The task of sequentially subtracting 7 from 100 corresponds to this memory. Prospective memory is the function of remembering a planned action and executing it at an appropriate time and situation.

4. Aphasia

Aphasia refers to the state of impairment at the language level while basic functions such as articulation and hearing are preserved. Primary progressive aphasia is a subtype in which aphasia presents as the first symptom, and remains a foreground symptom as dementia advances (see CQ2-6). Aphasia coexists commonly with dementia.

5. Visuospatial impairment

Visuospatial impairment is commonly found in Alzheimer's disease and dementia with Lewy bodies (DLB), which are mainly related to posterior cerebral functions. Constructional apraxia can be detected by the inability to copy drawings and imitate hand postures. In dementia with Lewy bodies, illusion and vivid visual hallucination are found. Posterior cortical atrophy (PCA) is an atypical dementia with visuospatial impairment as the dominant symptom, and is commonly caused by Alzheimer's disease.

6. Apraxia

Apraxia refers to the failure to perform habitual movements or using tools, which cannot be explained by impaired motor ability or object recognition. Limb-kinetic apraxia mainly refers to a state of clumsy upper limb movement, and may be seen in corticobasal degeneration. Ideomotor apraxia (inability of gestures and habitual movements), ideational apraxia (inability of using tools), and dressing apraxia (inability of getting dressed) may occur in various subtypes of dementia. However, apraxia is often complicated by visuospatial impairment and extrapyramidal symptoms, manifesting complicated clinical presentations.

7. Social cognition impairment

Impairment of social cognition is the failure to recognize emotions and situations, and to act accordingly.

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CQ 2-2

What are the behavioral and psychological symptoms of dementia (BPSD)?

Answer

The basis of BPSD is cognitive impairment of dementia, and BPSD arise as a result of influences by physical factors, environmental factors, and psychological factors [1,2]. They consist of behavioral symptoms such as agitation, aggression, and disinhibition, and psychological symptoms including anxiety, depression, hallucination, and delusion.

Comments and evidence

Based on the classification of BPSD in Alzheimer's disease reported by the European Alzheimer Disease Consortium [1, 2], this section outlines the BPSD of Alzheimer's disease and other subtypes of dementia.

1. Symptoms related to hyperactivity

These symptoms include agitation, irritability, disinhibition, and abnormal behaviors. When patients become aware of their forgetfulness and start feeling anxious and frustrated, they get upset by even trivial matters leading to irritability. And, when fueled by inappropriate responses from people around them, they may develop into aggression and agitation such as using abusive language and violence. Behavioral symptoms include wandering and aggressive behaviors, which are related to various underlying cognitive impairments, and necessitate individual management.

2. Psychosis-like symptoms

These symptoms include hallucination, delusion, and nocturnal abnormal behaviors. Delusion is a false belief that cannot be corrected, and is caused by psychological factors with amnesia and misperception in the background. Delusion of theft and persecutory delusion are well known in Alzheimer's disease, while jealousy delusion and phantom boarder delusion are well known in DLB. Visual hallucination and REM sleep behavior disorder are considered to be one of the core symptoms of DLB.

3. Symptoms related to affective symptoms

Anxiety and a depressive state are often observed in the early stage of Alzheimer's disease. For DLB, more than one half of the patients show a depressive state during the course of disease, and these symptoms are included as supportive features in the diagnostic criteria of DLB. In addition, a depressive state is the first symptom of DLB in a considerable number of patients.

4. Symptoms related to apathy

Apathy refers to reduced spontaneity and motivation. Apathetic symptoms may manifest in the affective domain such as lack of emotions, in the behavioral domain such as inactivity, and in the cognitive domain such as lack of interest toward the surrounding. Unlike depression, apathy is characterized by a lack of feeling of sorrow and self-accusation. Apathy is seen at a high frequency in frontotemporal lobar degeneration, while it is the most common BPSD symptom in Alzheimer's disease, and is also found in more than one-half the patients with DLB.

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CQ 2-3

What are the useful scales for assessing cognitive impairment in dementia?

Answer

As a useful scale for evaluating cognitive impairment in dementia, the Mini Mental State Examination (MMSE) is widely used internationally in clinical setting and in research. It is desirable to add necessary tests according to the subject evaluated, the purpose and the environment, and interpret the results taking into account the background and condition of each patient. C

Comments and evidence

MMSE is widely used internationally in the clinical setting and in research as a screening for cognitive impairment. The maximum MMSE score is 30 points; 29 points for tests including language function and 1 point for copying a drawing. In general, a score of 23 points or below indicates a suspicion of dementia. The sensitivity is low in mild patients, in patients with high premorbid ability, and in patients with visuospatial impairment as the main symptom [1]. Even in mild dementia, the score will be low when the patient has language impairment. In Japan, the Revised Hasegawa's Dementia Scale (HDS-R) is also commonly used and has a high correlation with MMSE. There are no tasks that can be performed nonverbally in HDS-R. In general, a score of 20 or below indicates a suspicion of dementia.

For mild dementia and mild cognitive impairment (MCI), the Montreal Cognitive Assessment-Japanese version (MoCA-J) and the Japanese version of Addenbrooke's Cognitive Examination-Revised (ACE-R) are used (See CQ4B-4). Moreover, adding neuropsychological tests such as trail making test and logical memory task to MMSE increases the rate of diagnosing mild dementia [2]. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (Japanese version) (ADAS-Jcog) is an examination centered on memory and visuospatial recognition, and is used to evaluate the changes of Alzheimer's disease symptoms.

If more detailed examinations are required to assess various cognitive functions, select the appropriate tests. Severe Impairment Battery (SIB) [3, 4] and Severe Cognitive Impairment Rating Scale (SCIRS) [5, 6] are assessments for patients with severe dementia.

It is essential to evaluate cognitive dysfunction not only based on the cutoff values of various tests alone, but also to consider the patient's premorbid ability as well as the physical and mental states at the time of testing. Estimating the cognitive and behavioral changes from premorbid state is important.

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CQ 2-4

What are the useful rating scales for behavioral and psychological symptoms of dementia (BPSD), activities of daily living (ADL), and global severity?

Answer

The Neuropsychiatric Inventory (NPI) is a rating scale for BPSD, and Physical Self-Maintenance Scale (PSMS) is a rating scale for ADL . The Clinical Dementia Rating (CDR) is widely used to evaluate global severity, and the Japanese version is available. C

Comments and evidence

BPSD, ADL, and global severity are evaluated based on the behaviors of a person with dementia in various situations as observed by other persons. Since the methods of observing behavior may be affected by the observer's skill and condition, an appropriate rating method should be selected considering the patient's environment including the caregivers.

1. Evaluation of BPSD

BPSD are evaluated based on a semi-structured interview with the caregiver who closely observes the behaviors of the person with dementia. The NPI evaluates the presence or absence, frequency, and severity of 10 domains of psychiatric symptoms (delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, dysphoria, apathy, disinhibition, irritability, and aberrant motor behavior). Recently, a 12-domain version with the addition of two domains; nighttime behavior disturbance and appetite/eating abnormalities, is commonly used. This tool is widely used internationally and is also commercially available in Japan. A questionnaire version (NPI-Q) and a nursing home version (NPI-NH) are available. The Behavioral Pathology in Alzheimer 's Disease (Behave-AD) has 25 items and is scored on a 4-point severity scale. The Cohen-Mansfield Agitation Inventory (CMAI) is a scale that systematically evaluates the frequency of 29 agitated behaviors rated on a 7-point scale.

2. Evaluation of ADL

Patients with dementia have disability in daily living, and the core disability is deterioration of ADL. The Physical Self-Maintenance Scale (PSMS) consists of 6 basic ADL items (toilet, feeding, dressing, grooming, physical ambulation, and bathing), and Instrumental ADL Scale (IADL) consists of 8 ADL items using instruments (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility of own medications, and ability to handle finance), both of which are rated by the caregiver. These scales are widely used internationally, and Japanese versions of both scales are also available [1].

3. Evaluation of global severity

The Clinical Dementia Rating (CDR) is widely used internationally. It is an evaluation method based on a semistructured interview with the patient's caregiver regarding six domains of cognitive and functional performance: memory, orientation, judgment and problem solving, community affairs, home and hobbies performance, and personal care. The patient's impairment of each item is scored, and the global score is classified into five stages: 0; normal, 0.5: very mild dementia, 1: mild dementia, 2: moderate dementia, 3: severe dementia. Attention is required when there is insufficient information from the caregiver or when the rater's training is insufficient, because inter-rater agreement may not be adequate. Based on CDR, a method that considers a simple cognitive function test for the patient, a method that uses the total score of the 6 items, and a revised shortened version have been proposed [2]. Rating scales that were developed in Japan, including the Nishimura Mental Scale as well as the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) that examines changes between two time points [3], are also used.

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CQ 2-5

How is quality of life (QOL) evaluated in persons with dementia?

Answer

There are various viewpoints regarding the methods of QOL evaluation in people with dementia. Although there is no standard method, an appropriate one can be selected and used through considering the severity and environment of the person with dementia. C

Comment and evidence

QOL is a concept that integrates physical and mental functions, ability of performing activities of daily living, and social activities. The evaluation method varies depending on how the concept is perceived. QOL evaluation methods are broadly divided into self-rating and rating by others (proxy-rating), and a combination of the two. Self-rating becomes more difficult as dementia progresses, and proxy rating has limitations including observer bias [1].

SF-36 and EQ-5D are widely used internationally as self-rating methods for overall health-related QOL, but they are difficult to score for persons with advanced dementia and therefore have low validity in persons with dementia [2]. In English-speaking countries, there are more than 15 QOL rating methods specialized for dementia [3], but the definition and focus of QOL differ depending on the rating method, and there is no standard.

Quality of Life in Alzheimer's Disease (QoL-AD) [4], a simple rating method that combines self-rating and caregiver-rating, is suitable for Alzheimer's disease dementia up to moderate severity, and is widely used in clinical research [5].

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CQ 2-6

How is primary progressive aphasia (PPA) classified and evaluated?

Answer

Primary progressive aphasia (PPA) can be divided into (1) non-fluent/agrammatic type, (2) semantic type, and (3) logopenic type. Clinical classification is based on assessment of language and semantic memory as well as lesion distribution. C

Comments and evidence

PPA refers to a group of degenerative dementia that manifests aphasia as the onset symptom, and aphasia remains the foreground symptom as disease progresses. PPA is divided into 3 types according to the characteristics of aphasia. The 3 types show characteristic distribution of site of atrophy on MRI and site of decreased blood flow/metabolism on SPECT/PET [1].

For clinical diagnosis, examine the patient for speech production features (motor speech, sound errors, and word-finding pauses), single-word and syntax comprehension, functions of confrontation naming and repetition, and reading/writing. The non-fluent/agrammatic type is characterized by inconsistent speech sound errors called apraxia of speech as well as agrammatism in speech/comprehension, but some patients manifest only one of these features. A variant of this type is primary progressive apraxia of speech manifesting only apraxia of speech without aphasia, which has similar site of atrophy as non-fluent/agrammatic type PPA with prominent apraxia of speech [2]. In the semantic type, impaired single-word comprehension and confrontation naming are the core symptoms, which progress to impairment of semantic memory such as object knowledge. Speech fluency and repetition are spared. As disease progresses, semantic memory is impaired, and the patient becomes unable to understand even when being shown an object. The logopenic type manifests impaired single-word retrieval in spontaneous speech and naming. While single word comprehension and repetition are spared, repetition of sentences and phrases is impaired and phonetic errors are prominent.

The Western Aphasia Battery (WAB) and Standard Language Test of Aphasia (SLTA) are used for semi-quantitative evaluation of language. However, it has been reported that using a picture description task can reveal the distinct speech characteristics [3]. Using the current diagnostic criteria, approximately one-third of the cases cannot be classified into any of the clinical types, while some cases are classified into two types. Reconsidering the classification may be required [4].

Since PPA is a clinical syndrome, it has heterogeneous neuropathologic causes. Regarding agreement of PPA classification with pathological diagnosis, 77% of patients with non-fluent/agrammatic variant PPA had frontotemporal lobar degeneration (FTLD) (tau; 51%, TDP-43; 26%), and 21% of them had Alzheimer's disease. Moreover, 88% of the patients with semantic variant PPA had FTLD (tau; 15%, TDP-43; 73%), and 12% of them had Alzheimer's disease. Finally, 56% of the patients with logopenic variant PPA had Alzheimer's disease and 36% of them had FTLD (tau; 11%, TDP-43; 24%) [5, 6]. Roughly speaking, the semantic variant is strongly related to FTLD-TDP, while about a half of the non-fluent/agrammatic variant is related to FTLD-tau and about a half of the logopenic variant is related to Alzheimer's disease.

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CQ 2-7

How is dementia diagnosed and differentiated?

Answer

For clinical diagnosis of dementia, history taking as well as physical and neurological examinations are important. During this step, efforts should be made to comprehensively understand whether dementia is present, and if so, the symptoms and severity of dementia. Then conduct cognitive function tests, structural brain imaging (CT or MRI), functional brain imaging, as well as blood and cerebrospinal fluid tests to diagnose the type of dementia. In this process, efforts should be made not to overlook treatable dementia, and to rule out delirium, depression, and drug-induced cognitive impairment.

Comments and evidence

Dementia can be summarized as "a state of continuous impairment of multiple acquired cognitive and mental functions, not due to disturbance of consciousness, to the extent that daily living and social life are affected". Diagnosis of dementia requires two steps. First, determine whether the patient has dementia by comprehensively confirm whether the functions of daily living are disabled due to acquired and chronic cognitive impairment [1]. In this process, perform history taking and cognitive function tests. Definitions of and diagnostic criteria for dementia are provided by the International Statistical Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10) [2], the Diagnosis and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) [3], and the criteria of the National Institute on Aging–Alzheimer's Association workgroup (NIA-AA) [4]. Even when the conditions of a case do not meet the criteria for dementia, it may be classified into the category of mild cognitive impairment if there is cognitive impairment present in the background.

The next step is to determine the underlying disease of dementia. In this process, perform various examinations as necessary, such as physical findings, neurological examinations, imaging examinations, and blood and cerebrospinal fluid tests. In order not to overlook treatable dementia, it is desirable to perform structural imaging by head CT or MRI when dementia is diagnosed [5-7]. Blood counts, hematology and blood biochemistry, as well as measurements of thyroid hormone, electrolytes, fasting blood glucose, vitamin B_{12}, and folic acid are recommended. Cerebrospinal fluid test is recommended for patients with atypical types and other conditions that are difficult to differentiate [5-7]. In view of the diverse differential diagnoses for juvenile dementia, consider referring the patient to a specialist [1].

Refer to the dementia diagnosis flowchart (2017) modified from the previous version published in Treatment Guideline for Dementia 2010.

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CQ 2-8

How are imaging examinations carried out in dementia?

Structural imaging (CT or MRI) is used to exclude treatable dementia. On MRI, the brain atrophy pattern in brain regions, and the presence and distribution of signal changes are useful for differential diagnosis of dementia. Functional imaging techniques such as cerebral blood flow single-photon emission computerized tomography (SPECT), dopamine transporter scintigraphy, and MIBG myocardial scintigraphy are also useful for differential diagnosis of dementia.

B

Comment and evidence

It is desirable to perform structural imaging test (CT or MRI) to exclude dementia treatable by neurosurgery, such as chronic subdural hematoma, brain tumor, and normal pressure hydrocephalus [1]. In addition, MRI is superior for discriminating brain atrophy patterns, which is useful for differential diagnosis [2]. Evaluation of signal changes on MRI is useful for differential diagnosis of cerebrovascular diseases, leukoencephalopathy, encephalitis, demyelinating diseases, and others [2].

The basic MRI sequences are T1-weighted image, T2-weighted image, and FLAIR image. When a brain tumor, inflammatory lesion, or infectious lesion is suspected, perform contrast enhanced imaging to look for contrast enhancement [3]. Diffusion-weighted images are superior for detecting acute cerebral vascular lesions and lesions with high signal intensity in the cerebral cortex or striatum/thalamus in Creutzfeldt-Jakob disease. T2*-weighted imaging and susceptibility-weighted imaging (SWI) are excellent for detecting micro-hemorrhages in amyloid angiopathy.

Cerebral blood flow SPECT is useful for differential diagnosis of dementia due to lesions with low blood flow. Cerebral blood flow SPECT uses nuclides such as ^{123}I-IMP and ^{99m}Tc-ECD. Cerebral blood flow SPECT images can be interpreted visually or analyzed using statistical methods [such as 3D-stereotactic surface projection (3D-SSP) and easy Z-score imaging system (eZIS)]. Alzheimer's disease dementia is characterized by decreased blood flow in the posterior cingulate gyrus, anterior wedge, and parietal association area [3]. FDG-PET detects decreased glucose metabolism and is more sensitive than cerebral blood flow SPECT, but this examination is not covered by medical insurance in Japan [4]. In dementia with Lewy bodies, disturbance of cardiac sympathetic nerve causes a decrease in MIBG uptake on MIBG scintigraphy [5]. Dopamine transporter scintigraphy using ^{123}I-FP-CIT is considered to reflect the density of dopamine transporter in the striatum. This test is approved for health insurance coverage in Japan for differentiating between dementia with Lewy bodies and Alzheimer's disease dementia, and is increasingly being used clinically.

For molecular imaging, techniques for visualizing amyloid β (Aβ) and tau have been established [6]. ^{11}C-PIB, ^{18}F-Florbetapir, ^{18}F-Flutemetamol, and ^{18}F-Florbetaben have been developed as ligands targeting Aβ [7]. Refer to CQ6-6 for the clinical significance of amyloid PET testing. ^{11}C-PBB3 and ^{18}F-T807 have been developed as ligands for visualizing tau. These techniques are mainly used for research purposes, and currently they are not covered by health insurance in Japan.

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CQ 2-9

What are the useful blood and cerebrospinal fluid tests for the diagnosis of dementia?

Answer

Blood tests are done to identify dementia associated with medical diseases. No useful blood tests for identifying degenerative dementia have been established. Cerebrospinal fluid examination is used to exclude infections, tumors, and inflammatory disorders in the central nervous system. Decreased amyloid β42 (Aβ42) and elevated phosphorylated tau in cerebrospinal fluid have been reported in Alzheimer's disease dementia. B

Comment and evidence

Blood tests are recommended to diagnose dementia and detect cognitive decline associated with medical diseases. Blood counts, hematology and blood biochemistry, and measurements of thyroid hormone, electrolytes, fasting blood glucose, vitamin B_{12}, and folic acid are recommended. Serological tests for syphilis and human immunodeficiency virus (HIV) are performed when such diagnoses are suspected based on medical history [1].

Cerebrospinal fluid examination is performed in atypical cases and other cases in which dementia subtype is difficult to diagnose [2]. General examination and cytology are used to exclude infections, tumors (malignant lymphoma and metastatic tumors), and inflammatory diseases in the central nervous system.

Alzheimer's disease dementia manifests decrease in amyloid β42 (Aβ42) peptide and increases in total tau and phosphorylated tau proteins. The decrease in Aβ42 in cerebrospinal fluid is thought to reflect the accumulation of Aβ in the brain and correlates with the results of amyloid positron emission tomography (PET) [3]. These biomarkers have been incorporated into various diagnostic criteria for Alzheimer's disease dementia [International Working Group (IWG)-2 criteria [4] and National Institute on Aging–Alzheimer's Association workgroup (NIA-AA) diagnostic criteria [5]]. As a supplementary diagnostic test for dementia, phosphorylated tau measurement is covered by health insurance in Japan. However, Aβ42 measurement is not covered by insurance. Mild cognitive impairment that converts to Alzheimer's disease dementia has been reported to show decrease in Aβ42 and increases in total tau and phosphorylated tau [1, 2].

According to a meta-analysis, α-synuclein in cerebrospinal fluid is lower in dementia with Lewy bodies compared to Alzheimer's disease dementia, but this biomarker has not been applied to clinical use [6]. Biomarkers for frontotemporal lobar degeneration are also in the stage of development and none have been applied to clinical use. Measurement of total tau in cerebrospinal fluid as a supplementary diagnostic test for Creutzfeldt-Jakob disease is covered by health insurance in Japan.

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CQ 2-10

Which physical and neurological findings require attention when diagnosing dementia?

Answer

Physical and neurological examinations are performed in the process of diagnosing dementia. Findings from physical examination may lead to a diagnosis of treatable dementia associated with medical disorders. Findings obtained from neurological examinations are useful in the diagnosis of different types of degenerative dementia.

Comment and evidence

Physical and neurological examinations are performed as the first step in the diagnosis of dementia [1].

Physical examinations include (1) hair, skin; (2) palpebral conjunctiva, pupil; (3) oral mucosa, pharynx, tongue; (4) neck: lymph nodes, thyroid gland, auscultation of vascular murmur; (5) pulse and blood pressure; (6) chest; (7) abdomen; (8) extremities: skin, joints, check for edema [1]. Cervical vascular murmur and pulse irregularity suggest the presence of cerebrovascular lesions. Pay attention to the presence or absence of otolaryngologic disorders accompanied by hearing impairment. Alopecia, thyroid swelling, and non-pitting edema in the lower extremities are found in hypothyroidism. Erythema nodosum, oral aphtha, and genital ulcer are findings of *neuro-Behçet's disease*. Asterixis is observed in hepatic encephalopathy.

Neurological examinations include investigations of the (1) level of consciousness; (2) cognitive function tests; (3) cranial nerves, (4) motor system of extremities; (5) deep tendon reflex and pathological reflex; (6) involuntary movement; (7) sensory system; (8) posture/gait; and (9) autonomic nervous system [2, 3].

The presence or absence of impaired consciousness is required to differentiate dementia from delirium. The presence of semi-blindness (hemianopsia) may suggest cerebrovascular lesions in the brain. If observation of the fundus using an ophthalmoscope reveals optic disc edema, the presence of intracranial lesion causing increased intracranial pressure should be suspected. Finding of weakened light reflex but preserved convergence reflex (Argyll Robertson pupil) is a symptom of suspected neurosyphilis. Impairment of vertical eye movement is seen at high frequency in progressive supranuclear palsy. Restricted eye movement and diplopia are observed in Wernicke encephalopathy. Limb-kinetic apraxia and ideomotor apraxia are characteristics of corticobasal degeneration. Tongue atrophy and fasciculation are observed in dementia associated with motor neuron disorder. Chorea is observed in Huntington's disease and dentatorubral-pallidoluysian atrophy (DRPLA). Resting tremor is found in dementia with Lewy bodies and Parkinson's disease. Myoclonus is manifested in Creutzfeldt-Jakob disease, corticobasal degeneration, Alzheimer's disease dementia, and others. Frontal lobe signs such as grasp reflex and suck reflex are observed in patients with frontotemporal lobar degeneration. Sensory disturbances in distal extremities occur in patients with peripheral neuropathy due to vitamin B_{12} deficiency. Deep sensory impairment is observed in tabes dorsalis due to neurosyphilis and subacute combined degeneration of the spinal cord. Shuffling gait and freezing gait are characteristics of dementia with Lewy bodies. Shuffling wide-based gait is seen in normal pressure hydrocephalus. Autonomic dysfunction such as orthostatic hypotension, dysuria, and constipation are observed in dementia with Lewy bodies [4].

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CQ 2-11

What are the drugs that affect the diagnosis of dementia?

Recommendations

It is necessary to keep in mind the possibility that drug-induced effects may underlie the decline in cognitive function. Therefore, confirm the medications taken by the patients. Drug-induced cognitive impairment is more likely to occur when the patients are of advanced age, have hepatic or renal dysfunction, or are taking multi-drug combination. Apart from causing delirium, drugs may induce cognitive impairment with a latent or subacute course. Anticholinergics and benzodiazepines are risk factors of cognitive impairment and dementia. 1B

Comment and evidence

Drug-induced cognitive impairment has the following characteristics [1-2]: (1) decreased attention is prominent; (2) drug-induced cognitive impairment changes over time; (3) patient may manifest symptoms resembling delirium; (4) cognitive impairment improves by discontinuing drug use; and (5) cognitive function deteriorates by drug overdose. Drug-induced cognitive impairment occurs more commonly in patients with advanced age, hepatic or renal dysfunction, or are taking multi-drug combination.

Among patients who show cognitive impairment, 2-12% is estimated to be associated with drugs [1]. It should also be kept in mind that some drugs cause delirium. One report shows that delirium is related to drugs in 11-30% of hospitalized older patients [1].

Some drug classes tend to induce cognitive impairment. Among psychotropic drugs, phenothiazine antipsychotics with anticholinergic effects, benzodiazepines that are anxiolytics, and tricyclic antidepressants more readily induce cognitive impairment. Anti-parkinsonian drugs, opioid analgesics, NSAIDs and corticosteroids are drugs with a potential to induce cognitive impairment. Attention should also be paid to the following drugs: drugs for the cardiovascular system including some anti-hypertensive drugs, anti-arrhythmic drugs, digitalis, and diuretics; antibacterial and antiviral drugs; antitumor drugs; drugs for overactive bladder and drugs for asthma with anticholinergic effects; and drugs for the digestive system with anti-histamine effect.

Anticholinergic drugs used in older persons have been reported to increase the risk of cognitive decline and development of dementia [3]. Cognitive impairment caused by anti-cholinergic drugs includes reduced memory, impaired attention, and delirium, and is particularly common in older persons [4].

Cognitive impairment caused by long-term use of benzodiazepines includes impaired spatial perception, impaired verbal memory, and attention deficits. A meta-analysis reports that taking oral benzodiazepines is a risk of dementia [5].

The Beers criteria clearly define appropriate drug prescriptions, created for the purpose of correcting inappropriate multi-drug combinations and avoiding overdosage in older patients [6]. In addition, the "Guidelines for Medical Therapy and its Safety in the Elderly 2015" was published by the Japan Geriatrics Society [7]. Refer to this reference when prescribing for older patients. In addition, it is possible to browse the package inserts of pharmaceuticals from the website of the Pharmaceuticals and Medical Devices Agency (https://www.pmda.go.jp/) and search for adverse events of individual drugs [8].

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CQ 2-12

Are there useful genetic tests for the diagnosis of dementia?

Answer

For hereditary dementia with Mendelian mode of inheritance, the causative genes have been identified, and a definitive diagnosis can be established by identifying the gene mutation. Genetic diagnosis in principle requires patient's consent and should not be coerced. Provide genetic counseling as necessary. APOE polymorphism is a genetic factor of Alzheimer's disease dementia. and the frequency of carrier of the *APOE* ε4 allele is significantly higher in individuals with Alzheimer's disease dementia. Use of *APOE* polymorphism as a supplementary diagnostic test for Alzheimer's disease dementia is not recommended.

Comment and evidence

The causative genes of familial dementia that show Mendelian inheritance pattern have been identified. A diagnosis is established when a pathological mutation in the causative gene is identified. Mutations in *APP*, *PSEN1*, and *PSEN2* are known to cause familial Alzheimer's disease, and more than 100 cases have been reported in Japan [1]. Familial Alzheimer's disease associated with genetic mutations often develops in the 40s and 50s [1, 2]. The genetic causes of familial Lewy body dementia include *SNCA* missense mutation and duplication mutation. Several genes responsible for frontotemporal lobar degeneration (FTLD) have been reported [3]. In Japan, hereditary FTLD is associated frequently with *MAPT* mutations, and rarely with *GRN* mutations [1].

APOE is a susceptibility gene for Alzheimer's disease dementia, and polymorphisms of this gene influence the susceptibility of an individual to the disease [4]. The frequency of ε4 allele of *APOE* is high in Alzheimer's disease dementia. According to an analysis of a larger number of Japanese patients, *APOE* ε4 allele is positive in approximately one-half of the patients with Alzheimer's disease dementia. Testing the *APOE* polymorphism as a supplementary diagnostic test for Alzheimer's disease dementia is not recommended [5]. Genome-wide association studies in a large-scale sample of Alzheimer's disease dementia identifies 19 significant susceptibility genes, but the odds ratios are not high [6].

Genetic diagnosis in principle requires patient's consent and should not be coerced [7]. Consideration should be given to the patient's psychological burden of being diagnosed with a hereditary disease through genetic diagnosis, and the impact on the patient's family. Consider to provide opportunities for genetic counseling as needed.

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Chapter 3

Treatment

A | Overview of Treatment

CQ 3A-1

How should interventions and support be given following a diagnosis of dementia?

Answer

To improve the quality of life (QOL) of people with dementia and their families, it is necessary to provide post-diagnostic support from the early stage after dementia is diagnosed, which involves giving advice on ways to live with dementia, guidance to connect to social resources, and help with making future plans. Different countries adopt various approaches of post-diagnostic support, including education on dementia and participation in peer support groups such as dementia café, with some countries even considering to prepare written informed decision and future care plan according to each person's wishes. Careful discussions are required to find the approaches of post-diagnostic interventions and support which are appropriate to Japan.

Comment and evidence

Until now, medical care for dementia has focused on early diagnosis and treatment initiation. However, it has been pointed out that these approaches alone are not sufficient to mitigate the psychological impact on the patients and their families or their fear of a future without hope. The current view is that to help persons affected by dementia prepare their future with confidence, post-diagnostic support is necessary from the early stage following the diagnosis, by providing useful advice on living with dementia and information on social resources, and helping them plan the future. Such approaches have already been started in some countries [1].

Regarding the future approaches of post-diagnostic intervention and support in Japan, careful discussions from various perspectives are needed, taking into consideration the unique cultural characteristics and actual circumstances in Japan.

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CQ 3A-2

How should pharmacotherapy, non-pharmacologic interventions and care be provided during treatment of dementia?

Answer

Use a combination of pharmacotherapy and non-pharmacologic interventions to treat dementia with the goal to improve cognitive function and quality of life (QOL). For behavioral and psychological symptoms of dementia (BPSD), in principle, non-pharmacologic interventions should take priority over pharmacotherapy. When using psychotropic drugs, continuously monitor for adverse events and whether medication is necessary.

Comment and evidence

In the treatment of dementia, the target symptoms include cognitive impairment, which is called the core symptom, as well as BPSD including delusion and irritability. Treat these symptoms by a combination of pharmacotherapy and non-pharmacologic interventions. When BPSD are observed, investigate whether there are physical diseases causing these symptoms and whether care is appropriate; and for treatment, give priority to non-pharmacologic interventions over pharmacotherapy [1, 2].

1. Treatment for cognitive impairment

For Alzheimer's disease dementia, cholinesterase inhibitors and NMDA receptor antagonist are recommended. Cholinesterase inhibitors are recommended for dementia with Lewy bodies. After medication is started, evaluate cognitive function regularly by psychological tests such as the Mini-Mental State Examination.

2. Treatment for BPSD

For BPSD, evaluate changes in physical conditions that may have caused the symptoms, and whether care and environment are appropriate [1]. For environmental modification, consider using long-term care insurance services such as day service. Non-pharmacologic interventions mitigate BPSD [3]. Care for patients with dementia, whether at home or in an institution, should be based on person-centered care that respects the will and hope of individual patients [4]. Giving guidance to caregivers regarding appropriate care delays admission to institution [5]. Occupational therapy using sensory stimulation is reported to improve BPSD [6].

After starting psychotropic drugs, continuously evaluate efficacy and adverse effects. If the demerits outweigh the benefits, consider dose reduction or discontinuation of the drug, while paying attention to the possibility of relapse of psychiatric symptoms following drug withdrawal [1].

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1) Kales HC, Gitlin LN, Lyketsos CG, et al. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. J Am Geriatr Soc. 2014; 62(4): 762-769.
2) Gauthier S, Cummings J, Ballard C, et al. Management of behavioral problems in Alzheimer's disease. Int Psychogeriatr. 2010; 22(3): 346-372.
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5) Olazaran J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord. 2010; 30(2): 161-178.
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■ Search formula

PubMed search: July 7, 2015 (Tuesday)

#1 (("Dementia/drug therapy" [Majr] OR (dementia [TI] AND ("drug therapy" [TI] OR chemotherapy [TI] OR pharmacotherapy [TI] OR "pharmacological therapy" [TI]))) OR ("Cognition Disorders/drug therapy" [Majr] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND ("drug therapy" [TI] OR chemotherapy [TI] OR pharmacotherapy [TI] OR "pharmacological therapy" [TI]))) OR ("Memory Disorders/drug therapy" [Majr] OR (memory disorder* [TI] AND ("drug therapy" [TI] OR chemotherapy [TI] OR pharmacotherapy [TI] OR

"pharmacological therapy" [TI])))) OR (("Dementia/rehabilitation" [Majr] OR (dementia [TI] AND rehabilitation [TI]))OR("Cognition Disorders/rehabilitation" [Majr]OR((cognition disorder* [TI]OR cognitive disorder* [TI]) AND rehabilitation [TI])) OR ("Memory Disorders/rehabilitation" [Majr] OR (memory disorder* [TI] AND rehabilitation [TI])))) OR (("Dementia/therapy" [Majr] AND "Rehabilitation" [Mesh]) OR ("Cognition Disorders/therapy" [Majr] AND "Rehabilitation" [Mesh]) OR ("Memory Disorders/therapy" [Majr] AND "Rehabilitation" [Mesh])) OR (("Dementia/nursing" [Majr] OR (dementia [TI] AND nursing [TI])) OR ("Cognition Disorders/nursing" [Majr] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND nursing [TI])) OR ("Memory Disorders/nursing" [Majr] OR (memory disorder* [TI] AND nursing [TI])) OR (("Dementia/diet therapy" [Majr] OR (dementia[TI] AND "diet therapy" [TI])) OR ("Cognition Disorders/diet therapy" [Majr] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND "diet therapy" [TI])) OR ("Memory Disorders/diet therapy" [Majr] OR (memory disorder* [TI] AND "diet therapy"[TI])))) OR (("Dementia/surgery" [Majr] OR (dementia[TI] AND (surg* [TI] OR operation* [TI])))) OR ("Cognition Disorders/surgery" [Majr] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND (surg*[TI] OR operation* [TI])))) OR ("Memory Disorders/surgery" [Majr] OR (memory disorder* [TI] AND (surg* [TI] OR operation* [TI])))) OR (("Dementia/radiotherapy" [Majr] OR (dementia [TI] AND radiotherapy [TI])) OR ("Cognition Disorders/radiotherapy" [Majr] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND radiotherapy [TI])) OR ("Memory Disorders/radiotherapy" [Majr] OR (memory disorder* [TI] AND radiotherapy [TI])))) OR (((("Dementia/therapy" [Majr] AND "Psychotherapy" [Mesh]) OR (dementia [TI] AND psychotherapy [TI])) OR ("Cognition Disorders/therapy" [Majr] AND "Psychotherapy" [Mesh]) OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND psychotherapy [TI]) OR ("Memory Disorders/therapy" [Majr] AND "Psychotherapy" [Mesh]) OR (memory disorder* [TI] AND psychotherapy [TI])) OR ((("Dementia/therapy" [Majr] AND "Social Support" [Mesh]) OR (dementia [TI] AND social support* [TI])) OR ("Cognition Disorders/therapy" [Majr] AND "Social Support" [Mesh]) OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND social support* [TI]) OR ("Memory Disorders/therapy" [Majr] AND "Social Support" [Mesh]) OR (memory disorder* [TI] AND social support* [TI])) OR (("Dementia/therapy" [Majr] AND "Patient Care" [Mesh]) OR (dementia [TI] AND "patient care" [TI])) OR ("Cognition Disorders/therapy" [Majr] AND "Patient Care" [Mesh]) OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND "patient care" [TI]) OR ("Memory Disorders/therapy" [Majr] AND "Patient Care" [Mesh]) OR (memory disorder* [TI] AND "patient care" [TI]) OR (("Dementia/therapy"[Majr] AND "Quality of Life" [Mesh]) OR (dementia [TI] AND quality of life* [TI])) OR ("Cognition Disorders/therapy" [Majr] AND "Quality of Life" [Mesh]) OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND quality of life* [TI]) OR ("Memory Disorders/therapy" [Majr] AND "Quality of Life" [Mesh]) OR (memory disorder* [TI] AND quality of life* [TI]) OR (("Dementia/therapy" [Majr] AND "Informed Consent" [Mesh]) OR (dementia [TI] AND "informed consent" [TI]) OR ("Cognition Disorders/therapy" [Majr] AND "Informed Consent" [Mesh]) OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND "informed consent" [TI]) OR ("Memory Disorders/therapy" [Majr] AND "Informed Consent" [Mesh]) OR (memory disorder* [TI] AND "informed consent" [TI]) OR (("nonpharmacological therapy" OR "non pharmacological therapy") AND ("Dementia/therapy" [Majr] OR dementia [TI] OR "Cognition Disorders/therapy" [Majr] OR cognition disorder* [TI] OR cognitive disorder* [TI] OR "Memory Disorders/therapy" [Majr] OR memory disorder* [TI]))

Ichushi search: July 7, 2015 (Tuesday)
#1 (Dementia/MTH OR Dementia/TI OR Cognitive impairment/MTH OR Cognitive impairment/TI OR Cognitive function impairment/TI OR Memory disorder/MTH OR Memory Disorder/TI) AND ((SH = Pharmacotherapy, Rehabilitation, Nursing, Surgical therapy, Transplantation, Dietary therapy, Psychiatric therapy, Radiotherapy) OR Pharmacotherapy/MTH OR Pharmacological action/MTH OR Pharmacotherapy/TI OR Pharmacotherapy/TI OR Medication/TI OR Rehabilitation/MTH OR Rehabilitation/TI OR Nursing/MTH OR Nursing/TI OR Surgery/MTH OR Surgical operation/TI OR Surgery/TI OR Transplantation/TI OR Dietary therapy/MTH OR Dietary therapy/TI OR Therapeutic diet/TI OR Psychiatric therapy/TH OR Psychiatric therapy/TI OR Radiotherapy/MTH OR Radiological treatment/TI OR Radiotherapy/TI OR Social support/MTH OR Social support/TI OR Patient management/MTH OR Patient management/TI OR Patient care/TI OR Informed consent/TH OR "Informed Consent"/TI OR QOL/TH OR QOL/TI OR "Quality of Life"/TI)

CQ 3A-3

What are the principles and precautions of pharmacotherapy in older people with dementia?

Answer

Older people with dementia tend to develop adverse events during pharmacotherapy. (1) Consider starting with a low dose, such as one-half to one-quarter of the dose used in young adults, depending on the type of drug to be prescribed. (2) Evaluate drug efficacy after a short period of treatment. (3) Simplify the method of drug taking. (4) Avoid taking multiple drugs as far as possible, while paying attention to adverse events specific to older people. Periodically evaluate the type of drug, the dosage, and the necessity of long-term prescription. (5) Confirm adherence to drug-taking with family members, caregivers, pharmacists, and others.

Comments and evidence

Many older people are affected by multiple diseases and the symptoms tend to be atypical. In addition, they show large individual differences in symptoms and response to drugs. For these reasons, they tend to use multiple drugs in combination for prolonged periods. The frequencies of adverse events are also high in older people; 15% of those aged 75 years or above have adverse events [1].

In view of the physiological deterioration of liver and renal functions in older people, consider starting with a low dose, such as one-half to one-quarter of the dose used in young adults, depending on the type of drug used.

Evaluate efficacy after a short period of treatment.

Simplify the method of drug taking.

Avoid using multiple drugs.

Confirm adherence to drug-taking with both the patient and also the caregiver.

■ References

1) Toba K, Akishita M, Mizuno Y, et al. Adverse drug reaction in the elderly. Japanese Journal of Geriatrics (Nippon Ronen Igakkai Zasshi) 1999; 36(3): 181-185. (In Japanese)

■ Search formula

PubMed search: July 7, 2015 (Tuesday)

#1 ("Dementia/drug therapy" [Majr] OR (dementia [TI] AND ("drug therapy" OR chemotherapy)) OR "Cognition Disorders/drug therapy" [Majr] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND ("drug therapy" OR chemotherapy)) OR "Memory Disorders/drug therapy" [Majr] OR(memory disorder* [TI] AND ("drug therapy" OR chemotherapy))) AND "Aged, 80 and over" [Mesh]

Ichushi search: July 6, 2015 (Monday)

#1 (Dementia/MTH OR Dementia/TI OR Cognitive impairment/MTH OR Cognitive impairment/TI OR Cognitive function impairment/TI OR Memory disorder/MTH OR Memory disorder/TI) AND (CK = Elderly (80~)) AND ((SH = Pharmacotherapy) OR Pharmacotherapy/MTH OR Pharmacological effect/MTH OR Drug treatment/TI OR Pharmacotherapy /TI OR Therapeutic drug/TI)

CQ 3A-4

What are the adverse events of psychotropic drugs [such as falls, declined activity of daily living (ADL), cognitive impairment, and aspiration pneumonia]?

Answer

Adverse events of antipsychotic drugs include over-sedation, hypotension, falls, dysphagia, constipation, and neuroleptic malignant syndrome. Antipsychotic drugs are also associated with increased risk of death. Pay special attention to impaired glucose tolerance when using olanzapine and quetiapine. Selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) may cause nausea, loose stools, and serotonin syndrome. Benzodiazepine anxiolytics and hypnotic drugs may cause falls, aspiration, somnolence, and respiratory depression. A

Comments and evidence

Older people with dementia are prescribed drugs under the situations of impaired walking function and judgement ability together with increased susceptibility to developing adverse events. Adverse events of antipsychotics include over-sedation, falls, fracture, dysphagia, constipation, urinary tract infection, cerebrovascular disease, cardiovascular event, venous thrombosis, edema, gait disturbance, neuroleptic malignant syndrome, and increased risk of death [1].

Olanzapine and quetiapine are contraindicated in patients with diabetes and those with a history of diabetes. Risperidone and aripiprazole should be administered with caution in patients with diabetes or a history of diabetes, and patients with risk factors of diabetes including a family history of diabetes, hyperglycemia, and obesity. For olanzapine, quetiapine, and aripiprazole, warning has been issued regarding the need to monitor blood glucose and explain to patients what to do when adverse effects occur.

The antidepressant SSRI and SNRI may cause gastrointestinal symptoms such as nausea and loose stools, and serotonin syndrome (including tremor, sweating, tachycardia, anxiety, and agitation). Among anxiolytics and hypnotic drugs, benzodiazepines is the main drug class that may cause weakness, falls, aspiration, dysphagia, somnolence, and respiratory depression, etc.

■ Reference

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■ Search formula

PubMed search: July 7, 2015 (Tuesday)

#1 ("Dementia/drug therapy" [Mesh] OR (dementia [TI] AND ("drug therapy" OR chemotherapy)) OR "Cognition Disorders/drug therapy" [Mesh] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND ("drug therapy" OR chemotherapy)) OR "Memory Disorders/drug therapy" [Mesh] OR (memory disorder* [TI] AND ("drug therapy" OR chemotherapy))) AND ("Psychotropic Drugs/adverse effects" [Mesh] OR ((psychotropic drug* [TI] OR psychotropic agent* [TI]) AND (side effect* [TI] OR adverse effect* [TI] OR adverse reaction* [TI])) OR "Psychopharmacology/adverse effects" [Mesh] OR (psychopharmacology [TI] AND (side effect* [TI] OR adverse effect* [TI] OR adverse reaction* [TI])) OR ((antipsychotic agent* [TI] OR antipsychotic drug* [TI]) AND (side effects* [TI] OR adverse effect* [TI] OR adverse reaction* [TI])))

Ichushi search: July 6, 2015 (Monday)

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CQ 3A-5

What are the treatment procedures when using pharmacotherapy for dementia?

Answer

Before starting pharmacotherapy for dementia patients, consider carefully whether such therapy is necessary. If pharmacotherapy is required, confirm adherence to drug taking and the indications of the drug, give sufficient explanations to patients and caregivers, and then start treatment. B

Comments and evidence

Since older people already have other physical illnesses, they may be using a combination of multiple drugs. Before starting pharmacotherapy for dementia, consider carefully the necessity of the therapy, and initiate treatment if the treatment is judged to be necessary.

Before initiating pharmacotherapy, explain the general benefits and risks of pharmacotherapy using language that is easy to understand even for the patient with dementia, and give due consideration also to respect the will of the patient. Despite these explanations, if the patient's intention cannot be confirmed, or if the patient lacks the ability to make a judgment, explain to family members or other proxies and obtain consent.

People with dementia have difficulties managing medication from a relatively early stage of the disease due to cognitive impairment. Accidents such as unintentional overdose may occur due to the inability to manage medication. When prescribing medications for patients with dementia, it is necessary to simplify the method of drug taking such as minimizing the number of drug-taking, to facilitate visual medication management by dispensing drugs together in one package or using a pill box, and to modify the environment so that it can be shared between the patient and caregiver. Depending on the severity of dementia, the caregiver may need to fully manage the medication. It is desirable to start pharmacotherapy after making the above preparations and confirming that the environment allows maintenance of good adherence.

Behavioral and psychological symptoms of dementia (BPSD) can appear at any stage of dementia. Parallel to pharmacotherapy for cognitive impairment, start treatment (non-pharmacological interventions or pharmacotherapy) for BPSD any time when the need arises. Also provide concomitant treatments for neurological symptoms associated with the primary disease, coexisting conditions specific to older people (including delirium, dysphagia, falls/fractures, pneumonia, urinary disorder, and constipation), and physical complications (including hypertension, diabetes, and dyslipidemia).

Regardless of the drugs used, pay close attention to adverse events. When adverse events are observed, consider changing or discontinuing the drug promptly.

■ Further reading

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2) Japan Geriatrics Society, Japan Agency for Medical Research and Development / Study Group on Safety of Medical Treatment in the Elderly (Ed.) Guidelines for Medical Treatment and its Safety in the Elderly 2015. Tokyo; Medical Tribune; 2015. (In Japanese)

■ Search formula

PubMed search: July 4, 2015 (Saturday), July 18, 2015 (Saturday)

#1 "Dementia/drug therapy" [Majr] OR (dementia[TI] AND ("drug therapy" OR chemotherapy)) OR "Cognition Disorders/drug therapy" [Majr] OR ((cognition disorder* [TI] OR cognitive disorder* [TI]) AND("drug therapy" OR chemotherapy)) OR "Memory Disorders/drug therapy" [Majr] OR (memory disorder* [TI] AND ("drug therapy" OR chemotherapy))

Ichushi search: July 4, 2015 (Saturday)

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CQ 3A-6

What are the adverse events due to cholinesterase inhibitors and NMDA receptor antagonists, and what should be done in case of these events?

Recommendation

The common adverse events of cholinesterase inhibitors are gastrointestinal symptoms including nausea/vomiting and diarrhea.

The common side effects of NMDA receptor antagonists include somnolence, dizziness, constipation, and headache.

In principle, these adverse events are managed by dose reduction or discontinuation of the responsible drug.

1B

Comments and evidence

Regarding serious adverse events of medications used to treat Alzheimer's disease dementia, cholinesterase inhibitors have been reported to cause adverse effects of the cardiovascular system such as syncope, bradycardia, and QT prolongation [1]. The NMDA receptor antagonist memantine has been reported to cause serious adverse events including syncope and psychiatric symptoms [2].

Cholinesterase inhibitors are associated with high frequencies of adverse events of the gastrointestinal system such as diarrhea, nausea/vomiting, and headache [3]. Gastrointestinal symptoms are more likely to appear when administration is initiated or when the dose is increased, and the incidence increases as the dose becomes higher. The rates of syncope [1, 4], fracture [1, 4], accidental injury [4], bradycardia [1], pacemaker implantation [1] have been shown to be higher under administration of cholinesterase inhibitors compared to controls [3]. Rivastigmine patch is a transdermal formulation that achieves relatively stable blood level. While the frequency of gastrointestinal symptoms associated with the patch formulation is lower than that of the oral formulation [5], skin reaction may occur at the site of application.

Although dizziness, somnolence, headache, and constipation have been reported to be relatively frequent adverse effects of memantine [2], one meta-analysis finds no significant difference compared with placebo [6].

Since the frequencies of occurrence of common adverse events differ depending on the disease, attention is required.

There is little evidence on how to manage adverse effects. Domperidone may be effective for gastrointestinal symptoms [7]. A moisturizer may be used to prevent inflammation at the site of application of the rivastigmine patch. If inflammation persists, consider using topical steroids [8].

In all cases, including those mentioned above, if adverse events are serious, consider reducing the dose or discontinuing the causative drug.

There is little evidence on the treatment of acute intoxication due to overdose or mistaken administration. Since acute intoxication may sometimes lead to death, caution is required.

References

1) Howes LG. Cardiovascular effects of drugs used to treat Alzheimer's disease. Drug Saf. 2014; 37(6): 391-395.
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7) Kano O, Urita Y, Ito H, et al. Domperidone effective in preventing rivastigmine-related gastrointestinal disturbances in patients with Alzheimer's disease. Neuropsychiatr Dis Treat. 2013; 9: 1411-1415.
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Search formula

PubMed search: July 4, 2015 (Saturday)

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Ichushi search: July 4, 2015 (Saturday)

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CQ 3A-7-1

What are the non-pharmacological therapies for dementia?

Answer

Non-pharmacological interventions for persons with dementia include cognitive function training, cognitive stimulation, exercise therapy, reminiscence, music therapy, and activities of daily living (ADL) training. C

Comment and evidence

Among the treatments for dementia, all the therapies other than pharmacotherapy are grouped together as non-pharmacological therapies. Non-pharmacological therapies aim to improve not only cognitive impairment but also behavioral and psychological symptoms of dementia (BPSD) as well as functions of daily living. Non-pharmacological therapies for dementia are broadly divided into interventions for patients with dementia and interventions for the caregivers. In practice, however, the two kinds of interventions are conducted in combination.

It should be noted that non-pharmacological therapies are intended not only for mitigating psychiatric symptoms and behavioral disorders but also for other benefits. For example, methods such as music therapy and reminiscence therapy are highly significant as means to engage dementia patients in active communication and involve them in daily living. Therefore, the validity and importance of these therapies cannot be judged solely based on whether mental symptoms are improved. In the clinical setting, it is necessary to consider intervention methods also for the purpose of maintaining the patients' quality of life (QOL) and their motivation in daily living.

Caregivers also should receive care. Appropriate interventions for caregivers are effective to preventive burnout. Structured psychological education for caregivers (a combination of learning knowledge, communication skills, behavior management, cognitive behavioral therapy, etc.) has been shown to reduce caregiver burnout and depression [1].

■ Reference

1) Jensen M, Agbata IN, Canavan M, et al. Effectiveness of educational interventions for informal caregivers of individuals with dementia residing in the community: systematic review and meta-analysis of randomised controlled trials. Int J Geriatr Psychiatry. 2015; 30 (2):130-143.

■ Further reading

1) Olazaran J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord. 2010; 30(2): 161-178.
2) Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. Am J Psychiatry. 2012; 169(9): 946-953.

■ Search formula

PubMed search: July 4, 2015 (Saturday), August 3, 2015 (Sunday)

#1 ("Dementia/therapy" [Majr] OR (dementia [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI])) OR "Cognition Disorders/therapy" [Majr] OR ("cognition disorder*" [TI] AND (therapy [TI] OR therapeutic[TI] OR treatment [TI])) OR "Memory Disorders/therapy" [Majr] OR (memory disorder* [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI]))) NOT ("Dementia/drug therapy" [Mesh] OR (dementia [TI] AND ("drug therapy" OR chemotherapy)) OR "Cognition Disorders/drug therapy" [Mesh] OR ("cognition disorder*" [TI] AND ("drug therapy" OR chemotherapy)) OR "Memory Disorders/drug therapy" [Mesh] OR (memory disorder* [TI] AND ("drug therapy" OR chemotherapy))) OR ("Dementia/therapy" [Mesh] OR (dementia [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI])) OR "Cognition Disorders/therapy" [Mesh] OR ("cognition disorder*" [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI])) OR "Memory Disorders/therapy" [Mesh] OR (memory disorder* [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI]))) AND (neuropsychiatric symptom* OR behavioral symptom* OR behavioural symptom* OR psychological symptom*) OR "neuropsychiatric symptoms of dementia" OR "behavioral and psychological symptoms of dementia"

Ichushi search: July 4, 2015 (Saturday)

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CQ 3A-7-2

What are the symptoms that respond to non-pharmacological therapies for dementia?

Recommendation

Non-pharmacological therapies and exercise therapy that exert effects on cognitive function, such as cognitive stimulation, are effective in improving cognitive impairment in dementia. Exercise therapy may be effective in improving activities of daily living (ADL), and music therapy may be effective to treat behavioral and psychological symptoms of dementia (BPSD). 2C

Comments and evidence

Non-pharmacological therapies that are effective for cognitive impairment in Alzheimer's disease dementia include cognitive stimulation [1, 2]. A meta-analysis shows that interventions using cognitive stimulation improves the Mini Mental State Examination score by 1.74 points (95% confidence interval 1.13 to 2.36) and ADAS-cog by 2.27 points (95% confidence interval 0.99 to 3.55) compared to the no intervention group, and the effect remains evident during the follow-up period of 1 to 3 months [3]. Multi-component interventions have also been shown to improve ADL, quality of life (QOL), as well as behavior and mood [1]. When cognitive stimulation is used, participants' self-evaluation for QOL and well-being improves [1]. However, little evidence is available for other non-pharmacological interventions including transcutaneous electrical stimulation therapies (transcranial, peripheral), exercise therapy, music therapy, reminiscence therapy, ADL training, massage, recreational therapy, light therapy, multisensory stimulation therapy, supportive psychotherapy, validation therapy, acupuncture, transcranial magnetic stimulation, and muscle relaxation. Future reports with high-quality evidence are awaited. In the actual clinical setting, it is important to select an intervention method that matches the individuality of the patient.

Providing multi-component interventions including psychological education for caregivers delays institutionalization of home-care patients, reduces BPSD, and improves caregiver outcomes.

■ References

1) Olazaran J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord. 2010; 30(2): 161-178.
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■ Search formula

PubMed search: July 4, 2015 (Saturday), August 3, 2015 (Sunday)

#1 ("Dementia/therapy" [Majr] OR (dementia [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI])) OR "Cognition Disorders/therapy" [Majr] OR ("cognition disorder*" [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI])) OR "Memory Disorders/therapy" [Majr] OR (memory disorder* [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI]))) NOT ("Dementia/drug therapy" [Mesh] OR (dementia [TI] AND ("drug therapy" OR chemotherapy)) OR "Cognition Disorders/drug therapy" [Mesh] OR ("cognition disorder*" [TI] AND ("drug therapy" OR chemotherapy)) OR "Memory Disorders/drug therapy" [Mesh] OR (memory disorder* [TI] AND ("drug therapy" OR chemotherapy))) OR ("Dementia/therapy" [Mesh] OR (dementia [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI])) OR "Cognition Disorders/therapy" [Mesh] OR ("cognition disorder*" [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI])) OR "Memory Disorders/therapy" [Mesh] OR (memory disorder* [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI])) AND (neuropsychiatric symptom* OR behavioral symptom* OR behavioural symptom* OR psychological symptom*) OR "neuropsychiatric symptoms of dementia" OR "behavioral and psychological symptoms of dementia"

Ichushi search: July 4, 2015 (Saturday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI OR Memory disorder/TI OR Memory disorder/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment) OR Treatment/TH OR Treatment /TI OR Therapy/TI) NOT ((SH = Pharmacotherapy) OR Pharmacotherapy/TH OR Drug treatment/TI OR Pharmacotherapy/TI OR Therapeutic drug/TI)

B | Treatment for behavioral and psychological symptoms of dementia (BPSD)

CQ 3B-1

What are the effective non-pharmacological therapies and pharmacotherapy for anxiety?

Recommendation

Anxiety is an important symptom that can cause or induce other behavioral and psychological symptoms of dementia (BPSD). The fundamental approach is to interact with the patient by speaking in a reassuring tone with a caring attitude. As non-pharmacological therapies for anxiety, music therapy and cognitive behavioral therapy may be effective, and they should be considered. If these treatments are not adequately effective, consider prescribing risperidone, olanzapine or quetiapine. 2C

Comments and evidence

Anxiety is an important symptom that can cause or induce other BPSD. First, the fundamental approach is to interact with the patient in a reassuring voice and attitude. Music therapy has been confirmed to be effective as a non-pharmacological therapy for anxiety [1]. Music therapy is desirably provided directly by music therapists, and is especially recommended for people with moderate to severe dementia. Cognitive behavioral therapy has been shown to be effective for persons with mild to moderate dementia [2].

If the above interventions do not provide adequate effect, consider pharmacotherapy.

A double-blind RCT comparing risperidone with haloperidol confirms the superiority of risperidone for anxiety symptoms [3]. Olanzapine has also been shown to be a safe and effective drug compared with placebo as control in a double-blind RCT for the treatment of anxiety in patients with Alzheimer's disease dementia [4]. In an open-label study comparing quetiapine and haloperidol, quetiapine improves anxiety and is well tolerated whereas haloperidol is not effective [5]. Since these atypical antipsychotics are used off-label, it is necessary to give adequate explanations to the patients and families, and to pay attention to adverse events while using the drugs. In addition, even if a drug is effective, it should not be used casually; keep in mind to reduce the risk of adverse effects by adjusting the dose or withdrawing the drug when symptoms have improved.

Benzodiazepines have been used to mitigate mild anxiety symptoms, but there is no clear evidence. When using this drug, pay attention to adverse events such as sedation, disorientation, delirium, confusion, disinhibition, ataxia, falls, fracture, and drug dependence at usual doses.

■ References

References 3-5 on pharmacotherapy are the same as the references in the previous version of the guideline.

1) Raglio A, Bellelli G, Mazzola P, et al. Music, music therapy and dementia: a review of literature and the recommendations of the Italian Psychogeriatric Association. Maturitas. 2012; 72(4): 305-310.
2) Stanley MA, Calleo J, Bush AL, et al. The Peaceful Mind Program: a pilot test of a CBT-based intervention for anxious patients with dementia. Am J Geriatr Psychiatry. 2013; 21(7): 696-708.
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5) Savaskan E, Schnitzler C, Schroder C, et al. Treatment of behavioural, cognitive and circadian rest-activity cycle disturbances in Alzheimer's disease haloperidol vs. quetiapine. Int J Neuropsychopharmacol. 2006; 9(5): 507-516.

■ Search formula

Non-pharmacological therapy
PubMed search: October 2, 2015 (Friday)

#1 (“Dementia/therapy” [Majr] OR dementia [TI] OR “Alzheimer disease” [TI] OR “Alzheimer’s disease” [TI] OR “vascular dementia” [TI] OR “Lewy Body” [TI] OR “frontotemporal dementia” [TI] OR “frontotemporal lobar degeneration” [TI]) AND (“nonpharmacological therapy” OR “non pharmacological therapy” OR “nonpharmacologic therapy” OR “non pharmacologic therapy” OR “nonpharmacological treatment” OR “non pharmacological treatment” OR “nonpharmacologic treatment” OR “non pharmacologic treatment” OR nonpharmacological intervention* OR non pharmacological intervention* OR nonpharmacologic intervention* OR non pharmacologic intervention* OR “nonpharmacological management” OR “non pharmacological management” OR “nonpharmacologic management” OR “non pharmacologic management” OR “validation therapy” OR “reality orientation” OR “reminiscence therapy” OR “music therapy” OR “light therapy” OR “tactile therapy” OR “aromatherapy” OR “occupational therapy” OR “exercise therapy” OR “exercise training” OR “exercise program” OR “physical exercise” OR “cognitive training” OR “rehabilitation” OR “stimulation therapy” OR “psychological therapy” OR (caregiver* AND (“psycho-education” OR intervention)) OR “dementia care service” OR “adult day service” OR “dementia day service” OR “Rehabilitation” [Mesh] OR “Phototherapy” [Mesh] OR “Exercise” [Mesh] OR “rehabilitation” [Mesh] OR “Psychotherapy” [Mesh] OR (“Caregivers” [Mesh] AND (“psycho-education” OR intervention)) OR “Touch” [Mesh] OR “Day Care” [Mesh]) AND (“Anxiety” [Mesh] OR anxiety [TI] OR indifference* [TI] OR “Aggression” [Mesh] OR aggression [TI] OR “Psychomotor Agitation” [Mesh] OR agitation [TI] OR “Irritable Mood” [Mesh] OR irritability [TI] OR “Delusions” [Mesh] OR delusion* [TI] OR “Hallucinations” [Mesh] OR hallucination* [TI] OR “Depression” [Mesh] OR depression [TI] OR dysphoria [TI] OR “Wandering Behavior” [Mesh] OR wandering [TI] OR “Inhibition (Psychology)” [Mesh] OR disinhibition* [TI] OR (“Sexual Behavior” [Mesh] AND inappropriate [TI]) OR “inappropriate sexual behaviour” [TI] OR “inappropriate sexual behavior” [TI] OR restlessness [TI] OR(“Motor Activity” [Mesh]AND aberrant [TI]) OR “aberrant motor behaviour” [TI] OR “aberrant motor behavior” [TI] OR “Sleep Disorders” [Mesh] OR “nighttime insomnia” [TI] OR “sleep disturbance” [TI] OR “daytime napping” [TI] OR “daytime sleepiness” [TI] OR “Apathy” [Mesh] OR apathy [TI] OR “Delirium” [Mesh] OR delirium [TI] OR ((anxiety OR indifference OR aggression OR agitation OR irritability OR delusion* OR hallucination* OR depression OR dysphoria OR wandering OR disinhibition* OR “inappropriate sexual behaviour” OR “inappropriate sexual behavior” OR restlessness OR “aberrant motor behaviour” OR “aberrant motor behavior” OR “nighttime insomnia” OR “sleep disturbance” OR “daytime napping” OR “daytime sleepiness” OR apathy OR delirium) AND (in process [SB] OR publisher [SB])))

Ichushi search: October 2, 2015 (Friday)
#1 (Dementia/TH OR Dementia/TI OR Alzheimer/TI OR Alzheimer/TI OR frontotemporal lobar degeneration/TI OR “frontotemporal lobar degeneration”/TI) AND ((SH = Surgical therapy, transplantation, dietary therapy, radiotherapy, nursing, rehabilitation) OR Non-pharmacotherapy/TI OR Non-pharmacological treatment/TI OR validation therapy/TH OR validation therapy/TI OR “validation therapy”/TI OR Reality orientation/TH OR “Reality orientation”/TI OR Reminiscence/TH OR Reminiscence/TI OR “reminiscence therapy”/TI OR Music therapy/TH OR Music therapy/TI OR “music therapy”/TI OR Light therapy/TH OR Light therapy/TI OR “light therapy”/TI OR Aromatherapy/TH OR Aromatherapy/TI OR “aromatherapy”/TI OR Occupational therapy/TH OR Occupational therapy/ TI OR “occupational therapy”/TI OR Exercise therapy/TH OR Exercise therapy/TI OR “exercise therapy”/TI OR Exercise training/TH OR Exercise training/TI OR “exercise training”/TI OR Physical exercise/TH OR Physical exercise/TI OR “physical exercise”/TI OR “exercise program”/TI OR Cognitive training/TH OR Cognitive training/TI OR “cognitive training”/TI OR Rehabilitation/TH OR Rehabilitation/TI OR “rehabilitation”/TI OR Stimulation therapy/TI OR “stimulation therapy”/TI OR Psychological therapy/TH OR Psychological therapy/TI OR “psychological therapy”/TI OR ((Caregiver/TH OR Caregiver/TI) AND (Education/TI OR Intervention/TI)) OR (caregiver/TI) AND (“psycho-education”/TI OR intervention/TI)) OR Nursing care service/TH OR Nursing care service/TI OR “dementia care service”/TI OR Day care/TH OR Day care/TI OR “adult day service”/TI OR “dementia day service”/TI OR Therapeutic touch/TH OR “tactile therapy”/TI OR Tactile care/TI) AND (Anxiety/TH OR Anxiety/TI OR Indifference/TI OR Aggression/TH OR Aggression/TI OR Psychomotor agitation/TH OR Irritable mood/TH OR Hallucination/TH OR Hallucination/TI OR Delusion/TH OR Delusion/TI OR Depression/TH or Depression/TI or Depression/TI OR Violence/TH or Violence/TI OR Wandering/TH or Wandering/TI OR Restlessness/TI OR (Psychomotor agitation/TH AND Restlessness) OR Inappropriate sexual behavior/TI OR Sexual perversion/TH OR ((Deviation OR Abnormality) AND Sexual behavior/TH) OR Sleep disorder/TH or Sleep disorder/TI OR Sleeping disturbance/TI OR Dyssomnia/TI OR Insomnia/TI OR Sleepiness/TI OR Apathy/TH or Apathy/TI OR Delirium/TH or Delirium/TI)

Pharmacotherapy
PubMed search: June 23, 2015 (Tuesday)
#1 (Dementia [Mesh] AND (“drug therapy” [subheading] OR “Drug therapy” [Mesh])) OR (“Dementia/therapy” [Mesh] AND (“Antipsychotic Agents” [Mesh] OR “Benzodiazepines” [Mesh] OR “Serotonin Uptake Inhibitors” [Mesh] OR “Antidepressive Agents” [Mesh] OR “Anticonvulsants” [Mesh] OR “Anticonvulsants” [PA] OR “Yi-Gan San” [Supplementary Concept] OR “Herbal Medicine” [Mesh] OR “Medicine, Kampo” [Mesh] OR “ramelteon” [Supplementary Concept] OR “suvorexant” [Supplementary Concept])) OR ((dementia OR “alzheimer disease” OR “alzheimer’s disease” OR “frontotemporal lobar degeneration”) AND (pharmacological OR drug OR medicine OR antipsychotics OR benzodiazepine OR “selective serotonin reuptake inhibitors” OR “serotonin-norepinephrine reuptake inhibitors” OR antidepressant* OR “mood stabilizer” OR anticonvulsant* OR Yokukansan OR “Japanese herbal” OR “traditional herbal” OR kampo OR ramelteon OR suvorexant OR “orexin receptor antagonist” OR “melatonin receptor agonist”))

Ichushi search: June 23, 2015 (Tuesday)
#1 (Dementia/TH OR Dementia/TI) AND ((SH = Pharmacotherapy) OR Pharmacotherapy/TH OR Drug treatment/TI OR Pharmacotherapy/TI OR Therapeutic drug/TI OR Kampo medicine/TH OR Antipsychotics/TH) AND (Anxiety/TH OR Anxiety/TI OR Indifference/TI)

CQ 3B-2

What are the effective non-pharmacological therapies and pharmacotherapy for agitation?

Recommendation

Treat agitation based on person-centered care; consider the reasons and causes for the symptoms and try to resolve them. It is also effective for the caregivers to learn appropriate conversation skills with persons with dementia and to practice the skills. Other non-pharmacological interventions such as group activities, music therapy, tactile care, and massage have been shown to be effective. For pharmacotherapy, atypical antipsychotics such as risperidone and aripiprazole have been shown to be effective. Consider also to use *Yokukansan* (liver-inhibiting powder), tiapride, carbamazepine, sertraline, escitalopram, and trazodone. 2C

Comments and evidence

In a systematic review that examines the effectiveness of 33 non-pharmacological interventions for agitation, educating caregivers about personal-centered care and training them to acquire appropriate communication skills with persons with dementia improve agitation [1]. Other non-pharmacological therapies including group activities, music therapy conducted by experts based on a program, tactile care, and massage have been shown to be effective.

If non-pharmacological therapies do not provide adequate effect, consider pharmacotherapy. Note that all the drugs described below are used off-label, and should be used with caution after explaining adequately to the patients and families and paying attention to adverse events during use. In addition, even when a drug is effective, it should not be used casually, and efforts should be made to decrease the risk of adverse effects by reducing the dose or withdrawing the drug when symptoms have improved.

In a systematic review that summarizes 18 studies on atypical antipsychotics compared with placebo for agitation and aggression in Alzheimer's disease dementia, low-dose risperidone is most promising and aripiprazole can be expected to be as effective as risperidone, while the effect of olanzapine is variable, and quetiapine is not effective [2].

A systematic review on antidepressants finds little research and insufficient evidence, but the effectiveness of sertraline, escitalopram, and trazodone has been reported [3]. Carbamazepine can also be expected to be effective [2]. A multicenter study in Japan has reported the effectiveness of *Yokukansan* [4]. Tiapride is also reported to be effective for agitation and aggression [5]. Use of tiapride may be considered because it is covered by health insurance in Japan for aggressive behavior and hyperphrenia associated with the sequelae of cerebral infarction.

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2) Ballard C, Corbett A. Agitation and aggression in people with Alzheimer's disease. Curr Opin Psychiatry. 2013; 26(3): 252-259.
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5) Allain H, Dautzenberg PH, Maurer K, et al. Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment. Psychopharmacology (Berl). 2000; 148(4): 361-366.

■ Search formula

Non-pharmacological therapies

PubMed search: October 2, 2015 (Friday)

#1 ("Dementia/therapy" [Majr] OR dementia [TI] OR "Alzheimer disease" [TI] OR "Alzheimer's disease" [TI] OR "vascular dementia" [TI] OR "Lewy Body" [TI] OR "frontotemporal dementia" [TI] OR "frontotemporal lobar degeneration" [TI]) AND ("nonpharmacological therapy" OR "non pharmacological therapy" OR "nonpharmacologic therapy" OR "non pharmacologic therapy" OR "nonpharmacological treatment" OR "non pharmacological treatment" OR "nonpharmacologic treatment" OR "non pharmacologic treatment" OR nonpharmacological intervention* OR non pharmacological intervention* OR nonpharmacologic intervention* OR non pharmacologic intervention* OR "nonpharmacological management" OR "non pharmacological management" OR "nonpharmacologic management" OR "non pharmacologic management" OR "validation therapy" OR "reality orientation" OR "reminiscence therapy" OR "music therapy" OR "light therapy" OR "tactile therapy" OR

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Ichushi search: October 2, 2015 (Friday)
#1 (Dementia/TH OR Dementia/TI OR Alzheimer/TI OR frontotemporal lobar degeneration/TI OR "frontotemporal lobar degeneration"/TI) AND((SH = Surgical therapy, transplantation, dietary therapy, radiotherapy, nursing, rehabilitation) OR 非Pharmacotherapy/TI OR Non-pharmacological treatment/TI OR validation therapy/TH OR validation therapy/TI OR "validation therapy"/TI OR Reality Orientation/TH OR "Reality Orientation"/TI OR reminiscence/TH OR reminiscence/TI OR "reminiscence therapy"/TI OR Music therapy/TH OR Music therapy/TI OR "music therapy"/TI OR Light therapy/TH OR Light therapy/TI OR "light therapy"/TI OR Aromatherapy/TH OR Aromatherapy/TI OR "aromatherapy"/TI OR Occupational therapy/TH OR Occupational therapy/ TI OR "occupational therapy"/TI OR Exercise therapy/TH OR Exercise therapy/TI OR "exercise therapy"/TI OR Exercise training/TH OR Exercise training/TI OR "exercise training"/TI OR Physical exercise/TH OR Physical exercise/TI OR "physical exercise"/TI OR "exercise program"/TI OR Cognitive training/TH OR Cognitive training/TI OR "cognitive training"/TI OR Rehabilitation/TH OR Rehabilitation/TI OR "rehabilitation"/TI OR Stimulation therapy/TI OR "stimulation therapy"/TI OR Psychological therapy/TH OR Psychological therapy/TI OR "psychological therapy"/TI OR ((Caregiver /TH OR Caregiver/TI) AND (Education/TI OR Intervention/TI)) OR (caregiver/TI) AND ("psycho-education"/TI OR intervention/TI)) OR Nursing care service/TH OR Nursing care service/TI OR "dementia care service"/TI OR day care/TH OR day care/TI OR "adult day service"/TI OR "dementia day service"/TI OR Therapeutic touch/TH OR "tactile therapy"/TI OR Tactile care/TI) AND(Anxiety/TH OR Anxiety/TI OR Indifference/TI OR Aggression/TH OR Aggression/TI OR Psychomotor agitation/TH OR Irritable mood/ TH OR Hallucination/TH OR Hallucination/TI OR Delusion/TH OR Delusion/TI OR Depression/TH or Depression/TI or Depression/TI OR Violence/TH or Violence/TI OR Wandering/TH or Wandering/TI OR Restlessness/TI OR (Psychomotor agitation/TH AND Restlessness)OR Inappropriate sexual behavior/TI OR Sexual perversion/TH OR ((Deviation OR Abnormality)AND Sexual behavior/TH) OR Sleep disorder/TH or Sleep disorder/TI OR Sleeping disturbance/TI OR Dyssomnia/TI OR Insomnia/TI OR Sleepiness/TI OR Apathy/TH or Apathy/TI OR Delirium/TH or Delirium/TI)

Pharmacotherapy
PubMed search: June 23, 2015 (Tuesday)
#1 Dementia [Mesh] AND ("drug therapy" [subheading] OR "Drug therapy" [Mesh]) OR ("Dementia/therapy" [Mesh] AND ("Antipsychotic Agents" [Mesh] OR "Benzodiazepines" [Mesh] OR "Serotonin Uptake Inhibitors" [Mesh] OR "Antidepressive Agents" [Mesh] OR "Anticonvulsants" [Mesh] OR "Anticonvulsants" [PA] OR "Yi-Gan San" [Supplementary Concept] OR "Herbal Medicine" [Mesh] OR "Medicine, Kampo" [Mesh] OR "ramelteon" [Supplementary Concept] OR "suvorexant" [Supplementary Concept])) OR (dementia OR "alzheimer disease" OR "alzheimer's disease" OR "frontotemporal lobar degeneration") AND (pharmacological OR drug OR medicine OR antipsychotics OR benzodiazepine OR "selective serotonin reuptake inhibitors" OR "serotonin-norepinephrine reuptake inhibitors" OR antidepressant* OR "mood stabilizer" OR anticonvulsant* OR Yokukansan OR "Japanese herbal" OR "traditional herbal" OR kampo OR ramelteon OR suvorexant OR "orexin receptor antagonist" OR "melatonin receptor agonist")

Ichushi search: June 22, 2015 (Monday)
#1 (Dementia/TH OR Dementia/TI) AND ((SH = Pharmacotherapy) OR Pharmacotherapy/TH OR Drug treatment/TI OR Pharmacotherapy/TI OR Therapeutic drug/ TI OR Kampo medicine/TH OR Antipsychotics/TH) AND (Aggression/TH OR Aggression/TI OR Psychomotor agitation/TH OR Irritable mood/ TH)

CQ 3B-3

What are the effective non-pharmacological therapies and pharmacotherapy for hallucinations and delusions?

Recommendation

For persons with dementia who manifest hallucinations and delusions, the first step is to reduce their anxiety through an approach of acceptance. In addition, when a specific person is the object of delusion, consider keeping a temporal and physical distance from that person. Also consider the possibility that the drugs being taken may cause hallucinations and delusions, and investigate this possibility. In patients with Alzheimer 's disease dementia, if symptoms do not improve by anti-dementia drugs and the above methods, consider using atypical antipsychotics such as risperidone, olanzapine, quetiapine, and aripiprazole. *Yokukansan* may also be considered. 2C

Comment and evidence

For hallucinations and delusions, it is important to listen to the patients' complaint first, and then give them a sense of security in a receptive and sympathetic manner without denial or affirmation. It is also important to give them a role and something to live for.

When a specific person in the family is the subject of delusion, it is useful to utilize care services to keep a time and physical distance between the patient and that person. If such intervention does not solve the problem, pharmacotherapy has to be considered. For delusions in Alzheimer 's disease dementia, try to administer anti-dementia drug. If the symptoms do not improve, consider using antipsychotic drugs. However, since these drugs are used off-label, it is necessary to explain carefully to the patients and families and pay attention to adverse events during use. In addition, even if a drug is effective, it should not be taken casually. Bear in mind the need to reduce the risk of adverse effects by adjusting the dose or withdrawing the drug when symptoms have improved.

Regarding the use of antipsychotic drugs in persons with dementia, effectiveness has been reported in a few studies with small numbers of cases, but no large-scale randomized controlled trial (RCT) has been reported [1-3]. When using antipsychotic drugs, atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole) are recommended.

For drugs other than antipsychotics, *Yokukansan* has been reported to be effective in a small number of cases [2].

Regarding pharmacotherapy for visual hallucinations in Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB), see CQ7-6.

■ References

1) Cipriani G, Danti S, Vedovello M, et al. Understanding delusion in dementia: a review. Geriatr Gerontol Int. 2014; 14(1): 32-39.
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3) Shinagawa S, Nakajima S, Plitman E, et al. Psychosis in frontotemporal dementia. J Alzheimers Dis. 2014; 42(2); 485-499.

■ Search formula

Non-pharmacological therapies

PubMed search: October 2, 2015 (Friday)

#1 ("Dementia/therapy" [Majr] OR dementia [TI] OR "Alzheimer disease" [TI] OR "Alzheimer's disease" [TI] OR "vascular dementia" [TI] OR "Lewy Body" [TI] OR "frontotemporal dementia" [TI] OR "frontotemporal lobar degeneration" [TI]) AND ("nonpharmacological therapy" OR "non pharmacological therapy" OR "nonpharmacologic therapy" OR "non pharmacologic therapy" OR "nonpharmacological treatment" OR "non pharmacological treatment" OR "nonpharmacologic treatment" OR "non pharmacologic treatment" OR nonpharmacological intervention* OR non pharmacological intervention* OR nonpharmacologic intervention* OR non pharmacologic intervention* OR "nonpharmacological management" OR "non pharmacological management" OR "nonpharmacologic management" OR "non pharmacologic management" OR "validation therapy" OR "reality orientation" OR "reminiscence therapy" OR "music therapy" OR "light therapy" OR "tactile therapy" OR "aromatherapy" OR "occupational therapy" OR "exercise therapy" OR "exercise training" OR "exercise program" OR "physical exercise" OR "cognitive training" OR "rehabilitation" OR "stimulation therapy" OR "psychological therapy" OR (caregiver* AND ("psycho-education" OR intervention)) OR "dementia care service" OR "adult day service" OR "dementia day service" OR "Rehabilitation" [Mesh] OR "Phototherapy" [Mesh] OR "Exercise" [Mesh] OR "rehabilitation" [Mesh] OR "Psychotherapy" [Mesh] OR ("Caregivers" [Mesh] AND ("psycho-education" OR intervention)) OR "Touch" [Mesh] OR "Day Care" [Mesh]) AND ("Anxiety" [Mesh] OR anxiety [TI] OR indifference* [TI] OR "Aggression" [Mesh] OR aggression [TI] OR "Psychomotor Agitation" [Mesh] OR agitation [TI] OR "Irritable Mood" [Mesh] OR irritability [TI] OR "Delusions" [Mesh] OR delusion* [TI] OR "Hallucinations" [Mesh] OR hallucination* [TI] OR "Depression" [Mesh] OR depression [TI] OR

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Pharmacotherapy
PubMed search: June 23, 2015 (Tuesday)
#1 (Dementia [Mesh] AND ("drug therapy" [subheading] OR "Drug therapy" [Mesh])) OR ("Dementia/therapy" [Mesh] AND ("Antipsychotic Agents" [Mesh] OR "Benzodiazepines" [Mesh] OR "Serotonin Uptake Inhibitors" [Mesh] OR "Antidepressive Agents" [Mesh] OR "Anticonvulsants" [Mesh] OR "Anticonvulsants" [PA] OR "Yi-Gan San" [Supplementary Concept] OR "Herbal Medicine" [Mesh]OR "Medicine, Kampo" [Mesh] OR "ramelteon" [Supplementary Concept] OR "suvorexant" [Supplementary Concept])) OR ((dementia OR "alzheimer disease" OR "alzheimer's disease" OR "frontotemporal lobar degeneration") AND (pharmacological OR drug OR medicine OR antipsychotics OR benzodiazepine OR "selective serotonin reuptake inhibitors" OR "serotonin-norepinephrine reuptake inhibitors" OR antidepressant* OR "mood stabilizer" OR anticonvulsant* OR Yokukansan OR "Japanese herbal" OR "traditional herbal" OR kampo OR ramelteon OR suvorexant OR "orexin receptor antagonist" OR "melatonin receptor agonist")) AND ("Delusions" [Mesh] OR delusion* OR "Hallucinations" [Mesh] OR hallucination*)

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CQ 3B-4

What are the effective non-pharmacological therapies and pharmacotherapy for depression?

Recommendation

For depressive symptoms, consider the situation of the person with dementia and communicate with a receptive attitude. Regarding non-pharmacological interventions, utilization of social support, reminiscence therapy, and music therapy are effective. In Japan, utilization of long-term care services is a realistic measure. If no improvement is observed after the above interventions have been given for a certain period of time, consider using antidepressants such as selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI). 2C

Comments and evidence

A systematic review clarifies that social support, classified as a non-pharmacological intervention, may improve depressive symptoms in people with dementia [1].

Two randomized controlled trials (RCTs) have demonstrated the effectiveness of music therapy. Both individual therapy [2] provided by music therapists and group music activity program [3] are effective, and both singing and music appreciation are also effective. A meta-analysis also shows that reminiscence therapy has a moderate improvement effect in reducing depressive symptoms in older people with dementia [4]. For exercise therapy, a meta-analysis concludes with moderate confidence that there is no effect on depression [5].

Regarding antidepressants, a systematic review of 10 RCTs and 3 meta-analyses finds that the effect of antidepressants for depression in dementia is inconclusive [6]. In addition, a meta-analysis of 6 RCTs on SSRI also does not support the effectiveness of SSRI for depression in dementia [7]. Furthermore, mirtazapine is not effective [8]. The observation periods in most of the above studies on non-pharmacological interventions are 5-12 weeks. Therefore, if symptoms do not improve after 12 weeks of non-pharmacological intervention, consider starting antidepressants. When selecting drug options, start with SSRI and SNRI that have few adverse effects.

References

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2) Raglio A, Oasi O, Gianotti M, et al. Effects of music therapy on psychological symptoms and heart rate variability in patients with dementia. A pilot study. Curr Aging Sci. 2010; 3(3): 242-246.
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6) Leong C. Antidepressants for depression in patients with dementia: a review of the literature. Consult Pharm. 2014; 29(4): 254-263.
7) Sepehry AA, Lee PE, Hsiung GY, et al. Effect of selective serotonin reuptake inhibitors in Alzheimer's disease with comorbid depression: a meta-analysis of depression and cognitive outcomes. Drugs Aging. 2012; 29(10): 793-806.
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Search formula

Non-pharmacological therapies

PubMed search: October 2, 2015 (Friday)

#1 ("Dementia/therapy" [Majr] OR dementia [TI] OR "Alzheimer disease" [TI] OR "Alzheimer's disease" [TI] OR "vascular dementia" [TI] OR "Lewy Body" [TI] OR "frontotemporal dementia" [TI] OR "frontotemporal lobar degeneration"[TI]) AND ("nonpharmacological therapy" OR "non pharmacological therapy" OR "nonpharmacologic therapy" OR "non pharmacologic therapy" OR "nonpharmacological treatment" OR "non pharmacological treatment" OR "nonpharmacologic treatment" OR "non pharmacologic treatment" OR nonpharmacological intervention* OR non pharmacological intervention* OR nonpharmacologic intervention* OR non pharmacologic intervention* OR "nonpharmacological management" OR "non pharmacological management" OR "nonpharmacologic management" OR "non pharmacologic management" OR

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CQ 3B-5

What are the effective non-pharmacological therapies and pharmacotherapy for wandering?

Recommendation

Consider the reason or cause of wandering from the viewpoint of the patient with dementia and take preventive measures. For a person with dementia who wanders frequently, make a plan to facilitate finding of the missing person. Regarding pharmacotherapy, risperidone may be considered, but the scientific evidence is insufficient. Tiapride may also be considered, because this drug is covered by health insurance in Japan for wandering associated with the sequelae of cerebral infarction. However, if the above interventions and treatments do not solve the issue, consider using nursing care services such as institutional care service. 2C

Comments and evidence

To address wandering in patients with dementia, non-pharmacological interventions are the first choice, and when they are not effective, pharmacotherapy is selected. Many of the drugs used for these behavioral symptoms are used off-label. Therefore, it is necessary to use with caution, giving sufficient explanations to the patients and families and paying attention to adverse events during use. In addition, even if the drug is effective, it should not be used casually. Keep in mind to decrease the risk of adverse effects by reducing the dose or withdrawing the drug when symptoms have improved.

Wandering

Various actions of a person with dementia can be recognized by others as signs of wandering. First, consider the nature, reason and cause of the actions from the viewpoint of the person with dementia, and take preventive measures. While wandering, the persons with dementia are often tense and confused. It is important to listen to them and make them feel reassured. For persons with dementia who frequently wander, it is important to take precautions even while they are calm. For example, dress them in easily recognizable clothes, write contact information on the clothes and shoes they wear, and use devices such as global positioning systems (GPS). Moreover, it is useful to obtain support from neighbors and to register in programs for wandering persons in municipalities that have such mechanisms. Although there is no study that evaluates the effectiveness of pharmacotherapy focusing on wandering in dementia patients, a randomized controlled trial (RCT) that compares the effects of risperidone on behavioral and psychological symptoms of dementia (BPSD) reports significant improvement for wandering [1]. Therefore, use of risperidone may be considered. Tiapride may also be used, as its indication for wandering associated with the sequelae of cerebral infarction is covered by health insurance in Japan. In the case of wandering associated with agitation, drugs for agitation may be considered (see CQ3B-2). In addition, improvement of sleep/wake pattern has been reported to reduce wandering [2]. Therefore, if the patient also has sleep disturbance, consider treatment for sleep disturbance (see CQ3B-6). If there is no improvement despite various treatments and interventions, consider utilizing institutional care services.

■ References

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■ Search formula

Non-pharmacological therapies

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CQ 3B-6

What are the effective non-pharmacological therapies and pharmacotherapy for sleep disturbance (excluding REM sleep behavior disorder)?

Recommendation

First, assess sleep disturbance accurately and conduct differential diagnosis. If there are physical symptoms (such as pain, urinary frequency, and itchiness), psychological or social stress, stimulant-containing products, and drugs that may contribute to sleep disturbance, mitigate those factors. In addition, encourage the patient to do sunbathing and physical activities during the day, and to attempt to improve the sleep environment. If possible, consider bright light therapy. For pharmacotherapy, use of trazodone or risperidone may be considered. However, benzodiazepines as sleep inducing agents are not recommended because of the risk of adverse events such as sedation and falls. 2C

Comment and evidence

In Alzheimer's disease dementia and dementia with Lewy bodies, complex sleep disturbances such as insomnia, hypersomnia, and sleep/wake rhythm disturbances may occur [1]. In addition, the patients tend to have various conditions such as sleep apnea syndrome, restless legs syndrome (RLS), periodic limb movement disorder, nocturnal leg cramp, and REM sleep behavior disorder. Therefore, it is important to assess sleep disturbance accurately and conduct differential diagnosis. Furthermore, sleep disturbance may become chronic due to diverse underlying factors including physical symptoms (such as pain, urinary frequency, and itchiness), exacerbation of psychiatric symptoms, increased psychological and social stress, and influence by stimulant-containing products (such as alcohol, caffeine, and nicotine) and drugs. Therefore, removal of these factors is also important.

In a systematic review of 38 pharmacological or non-pharmacological intervention studies targeting sleep disturbances in patients with mild to moderate Alzheimer's disease dementia, bright light therapy gives the best results and is effective in reducing nocturnal awakening and prolonging nighttime sleep [2]. In addition, multi-faceted interventions including daytime sunlight exposure, physical activity, exercise, restriction of daytime napping, structured bedtime routines (performing certain actions in a predetermined order before going to bed), improvement of sleep environment such as reducing noise and light at night are also effective in improving sleep disturbance. The use of pharmacotherapy is limited when considering safety. In particular, although sedative-hypnotic medications represented by benzodiazepines are widely used clinically, there are few data supporting their use. Conversely, they may cause sedation, daytime somnolence, falls, confusion, and amnesia, and should therefore be used with caution. Two randomized controlled trials (RCTs) have shown the effectiveness of risperidone, and this drug may be considered.

It has been reported that trazodone given to patients with Alzheimer's disease dementia at a dose of 50 mg per day for 2 weeks prolongs total sleeping time and improves sleep efficiency. Use of this drug may be considered [3].

Regardless of which drugs are being used, even if they prove to be effective, they should not be used casually. Always remember to reduce the risk of adverse effects by reducing the dose or withdrawing the drug when symptoms have improved.

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1) Mishima K (Ed.) Clinical Guidelines for Proper Use and Cessation of Hypnotics. Tokyo: Jibo; 2014. (In Japanese)
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Non-pharmacological therapies

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Pharmacotherapy
PubMed search: June 23, 2015 (Tuesday)
#1 (Dementia [Mesh] AND ("drug therapy" [subheading] OR "Drug therapy" [Mesh])) OR ("Dementia/therapy" [Mesh] AND ("Antipsychotic Agents" [Mesh] OR "Benzodiazepines" [Mesh] OR "Serotonin Uptake Inhibitors" [Mesh] OR "Antidepressive Agents" [Mesh] OR "Anticonvulsants"[Mesh] OR "Anticonvulsants" [PA] OR "Yi-Gan San" [Supplementary Concept] OR "Herbal Medicine" [Mesh] OR "Medicine, Kampo" [Mesh] OR "ramelteon" [Supplementary Concept] OR "suvorexant" [Supplementary Concept])) OR ((dementia OR "alzheimer disease" OR "alzheimer's disease" OR "frontotemporal lobar degeneration") AND (pharmacological OR drug OR medicine OR antipsychotics OR benzodiazepine OR "selective serotonin reuptake inhibitors" OR "serotonin-norepinephrine reuptake inhibitors" OR antidepressant* OR "mood stabilizer" OR anticonvulsant* OR Yokukansan OR "Japanese herbal" OR "traditional herbal" OR kampo OR ramelteon OR suvorexant OR "orexin receptor antagonist" OR "melatonin receptor agonist")) AND ("Sleep Disorders" [Mesh] OR "nighttime insomnia" OR "sleep disturbance" OR "daytime napping" OR "daytime sleepiness")

Ichushi search: June 23, 2015 (Tuesday)
#1 (Dementia/TH OR Dementia/TI AND ((SH = Pharmacotherapy) OR Pharmacotherapy/TH OR Drug treatment/TI OR Pharmacotherapy/TI OR Therapeutic drug/TI OR Kampo medicine/TH OR Antipsychotics/TH)) AND (Sleep disorder/TH or Sleep disorder/TI OR Sleep disturbance/TI OR Dyssomnia/TI OR Insomnia/TI OR Somnolence/TI)

CQ 3B-7

What are the effective non-pharmacological therapies and pharmacotherapy for apathy?

Recommendation

As a non-pharmacological intervention for apathy, therapeutic activities customized for individual patients with dementia are suggested to be effectiveness. In Japan, incorporating this approach as a program in dementia care service seems to be a realistic measure. For pharmacotherapy, cholinesterase inhibitor is the first choice if indicated for the disease. Memantine may be considered, but antidepressants and antiepileptic drugs have not been reported to be effective.

2C

Comments and evidence

Apathy is a state of reduced spontaneity, initiative, interest, concern, motivation, and emotion. Because these are not positive symptoms such as delusion and irritability, they tend to be misunderstood as posing less burden on nursing care. However, since patients may gradually stop executing actions that should be taken in daily life, or do not respond to communication from other persons, apathy is a symptom that requires treatment.

To verify the effects of non-pharmacological interventions for apathy, a systematic review of 56 studies suggests that therapeutic activities, particularly those planned to match the level and interest of the individual, can be expected to be beneficial [1]. Specifically, these activities involve participant-led interactive discussions, and activities such as solving puzzles, making salad, sorting beads, woodwork, and catching ball are conducted while an occupational therapist provides guidance to the family caregivers. In Japan, receiving this treatment as a program in dementia care service seems to be a realistic measure.

A systematic review that summarizes the effects of pharmacotherapy confirms the benefit of cholinesterase inhibitors for apathy, and recommends these drugs as first-line drug for patients with dementia if there is no contraindication [2]. Memantine may also be effective.

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Search formula

Non-pharmacological therapies

PubMed search: October 2, 2015 (Friday)

#1 ("Dementia/therapy" [Majr] OR dementia [TI] OR "Alzheimer disease" [TI] OR "Alzheimer's disease" [TI] OR "vascular dementia" [TI] OR "Lewy Body" [TI] OR "frontotemporal dementia" [TI] OR "frontotemporal lobar degeneration" [TI]) AND ("nonpharmacological therapy" OR "non pharmacological therapy" OR "nonpharmacologic therapy" OR "non pharmacologic therapy" OR "nonpharmacological treatment" OR "non pharmacological treatment" OR "nonpharmacologic treatment" OR "non pharmacologic treatment" OR nonpharmacological intervention* OR non pharmacological intervention* OR nonpharmacologic intervention* OR non pharmacologic intervention* OR "nonpharmacological management" OR "non pharmacological management" OR "nonpharmacologic management" OR "non pharmacologic management" OR "validation therapy" OR "reality orientation" OR "reminiscence therapy" OR "music therapy" OR "light therapy" OR "tactile therapy" OR "aromatherapy" OR "occupational therapy" OR "exercise therapy" OR "exercise training" OR "exercise program" OR "physical exercise" OR "cognitive training" OR "rehabilitation" OR "stimulation therapy" OR "psychological therapy" OR (caregiver* AND ("psycho-education" OR intervention)) OR "dementia care service" OR "adult day service" OR "dementia day service" OR "Rehabilitation" [Mesh] OR "Phototherapy" [Mesh] OR "Exercise" [Mesh] OR "rehabilitation" [sh] OR "Psychotherapy" [Mesh] OR ("Caregivers" [Mesh] AND ("psycho-education" OR intervention)) OR "Touch" [Mesh] OR "Day Care" [Mesh]) AND ("Anxiety" [Mesh] OR anxiety [TI] OR indifference* [TI] OR "Aggression" [Mesh] OR aggression [TI] OR "Psychomotor Agitation" [Mesh] OR agitation [TI] OR "Irritable Mood" [Mesh] OR irritability [TI] OR "Delusions" [Mesh] OR delusion* [TI] OR "Hallucinations" [Mesh] OR hallucination* [TI] OR "Depression" [Mesh] OR depression [TI] OR dysphoria [TI] OR "Wandering Behavior" [Mesh] OR wandering [TI] OR "Inhibition (Psychology)" [Mesh] OR disinhibition* [TI] OR ("Sexual Behavior" [Mesh] AND inappropriate [TI]) OR "inappropriate sexual behaviour" [TI] OR "inappropriate sexual behavior" [TI] OR restlessness [TI] OR ("Motor Activity" [Mesh] AND aberrant [TI])OR "aberrant motor behaviour" [TI] OR "aberrant motor behavior" [TI] OR "Sleep Disorders" [Mesh] OR "nighttime insomnia"[TI] OR "sleep disturbance" [TI] OR "daytime napping" [TI] OR "daytime sleepiness" [TI] OR "Apathy" [Mesh] OR apathy [TI] OR "Delirium" [Mesh] OR delirium [TI] OR ((anxiety OR indifference OR aggression OR agitation OR

irritability OR delusion* OR hallucination* OR depression OR dysphoria OR wandering OR disinhibition* OR "inappropriate sexual behaviour" OR "inappropriate sexual behavior" OR restlessness OR "aberrant motor behaviour" OR "aberrant motor behavior" OR "nighttime insomnia" OR "sleep disturbance" OR "daytime napping" OR "daytime sleepiness" OR apathy OR delirium) AND (in process [SB] OR publisher [SB])))

Ichushi search: October 2, 2015 (Friday)
#1 (Dementia/TH OR Dementia/TI OR Alzheimer/TI OR Alzheimer/TI OR Frontotemporal lobar degeneration/TI OR "frontotemporal lobar degeneration"/TI) AND ((SH = Surgical therapy, transplantation, dietary therapy, radiotherapy, nursing, rehabilitation) OR Non-pharmacotherapy/ TI OR Non-pharmacological treatment/TI OR Validation therapy/TH OR Validation therapy/TI OR "validation therapy"/TI OR Reality Orientation/TH OR "Reality Orientation"/TI OR Reminiscence/TH OR Reminiscence/TI OR "reminiscence therapy"/TI OR Music therapy/TH OR Music therapy/TI OR "music therapy"/TI OR Light therapy/TH OR Light therapy/TI OR "light therapy"/TI OR Aromatherapy/TH OR Aromatherapy/TI OR "aromatherapy"/TI OR Occupational therapy/TH OR Occupational therapy/ TI OR "occupational therapy"/TI OR Exercise therapy/TH OR Exercise therapy/TI OR "exercise therapy"/TI OR Exercise training/TH OR Exercise training/TI OR "exercise training"/TI OR Physical exercise/TH OR Physical exercise/TI OR "physical exercise"/TI OR "exercise program"/TI OR Cognitive training/TH OR Cognitive training/TI OR "cognitive training"/TI OR Rehabilitation/TH OR Rehabilitation/TI OR "rehabilitation"/TI OR Stimulation therapy/TI OR "stimulation therapy"/TI OR Psychological therapy/TH OR Psychological therapy/TI OR "psychological therapy"/TI OR ((Caregiver /TH OR Caregiver/TI) AND (Education/TI OR Intervention/TI)) OR (caregiver/TI AND ("psycho-education"/TI OR intervention/TI)) OR Nursing care service/TH OR Nursing care service/TI OR "dementia care service"/TI OR Day care/TH OR Day care/TI OR "adult day service"/TI OR "dementia day service"/TI OR Therapeutic touch/TH OR "tactile therapy"/TI OR Tactile care/TI) AND (Anxiety/TH OR Anxiety/TI OR Indifference/TI OR Aggression/TH OR Aggression/TI OR Psychomotor agitation/TH OR Irritable mood/ TH OR Hallucination/TH OR Hallucination/TI OR Delusion/TH OR Delusion/TI OR Depression/TH or Depression/TI or Depression/TI OR Violence/TH or Violence/TI OR Wandering/TH or Wandering/TI OR Restlessness/TI OR (Psychomotor agitation/TH AND Restlessness) OR Inappropriate sexual behavior/TI OR Sexual perversion/ TH OR ((Deviation OR Abnormality)AND Sexual behavior/TH) OR Sleep disorder/TH or Sleep disorder/TI OR Sleep disturbance/TI OR Dyssomnia/TI OR Insomnia/TI OR Somnolence/TI OR Apathy/TH or Apathy/TI OR Delirium/TH or Delirium/TI)

Pharmacotherapy
PubMed search: June 23, 2015 (Tuesday)
#1 (Dementia [Mesh] AND ("drug therapy" [subheading] OR "Drug therapy" [Mesh])) OR ("Dementia/therapy" [Mesh] AND ("Antipsychotic Agents" [Mesh] OR "Benzodiazepines" [Mesh] OR "Serotonin Uptake Inhibitors" [Mesh] OR "Antidepressive Agents" [Mesh] OR "Anticonvulsants" [Mesh] OR "Anticonvulsants" [PA] OR "Yi-Gan San" [Supplementary Concept] OR "Herbal Medicine" [Mesh] OR "Medicine, Kampo" [Mesh] OR "ramelteon" [Supplementary Concept] OR "suvorexant" [Supplementary Concept])) OR ((dementia OR "alzheimer disease" OR "alzheimer's disease" OR "frontotemporal lobar degeneration") AND (pharmacological OR drug OR medicine OR antipsychotics OR benzodiazepine OR "selective serotonin reuptake inhibitors" OR "serotonin-norepinephrine reuptake inhibitors" OR antidepressant* OR "mood stabilizer" OR anticonvulsant* OR Yokukansan OR "Japanese herbal" OR "traditional herbal" OR kampo OR ramelteon OR suvorexant OR "orexin receptor antagonist" OR "melatonin receptor agonist")) AND ("Apathy" [Mesh] OR apathy)

Ichushi search: June 23, 2015 (Tuesday)
#1 (Dementia/TH OR Dementia/TI) AND ((SH = Pharmacotherapy) OR Pharmacotherapy/TH OR Drug treatment/TI OR Pharmacotherapy/ TI OR Therapeutic drug/ TI OR Kampo medicine/TH OR Antipsychotics/TH) AND (Apathy/TH OR Apathy/TI)

C | Interventions for Coexisting Diseases

CQ 3C-1

How is delirium treated?

Recommendation

Always remember to prevent delirium. When delirium has emerged, treat or remove the direct causative or inducing factors. If symptoms do not respond to these interventions and treatments, consider treatment with atypical antipsychotics such as quetiapine, perospirone, risperidone, and olanzapine. Also consider hospitalization for the purposes of detailed investigations of the cause of delirium, smooth implementation of treatment, and ensuring safety of the patient. Clinical guidelines for delirium have been prepared by the Japanese Society of General Hospital Psychiatry, refer to the guidelines as needed. 2C

Comments and evidence

Since dementia is a risk factor for the development of delirium, it is necessary to be always vigilant for early detection and treatment of delirium. The background factors of delirium include the following: (1) predisposing factors (current or past history of organic brain disorder, old age); (2) precipitating factors (environmental factors such as hospitalization and noise; physical factors such as pain, dehydration, and malnutrition; sensory factors such as decreased vision and hearing; mental factors such as psychological stress and anxiety; sleep-related factors such as disrupted circadian rhythm; (3) direct factors that may induce delirium even as a single factor (stroke, electrolyte abnormality, infection, initiation or withdrawal of drug use) [1].

For treatment of delirium in dementia, refer to the clinical guidelines on delirium prepared by the Delirium Guideline Revision Group of Japanese Society of General Hospital Psychiatry [2]. First, always try to remove the precipitating factors. Also, treat the direct factor, if possible. If delirium does not improve after these treatments, consider atypical antipsychotics (quetiapine, perospirone, risperidone, and olanzapine). The former two are recommended from the viewpoint of short half-life. The latter two have the advantage of being a liquid formulation and an orally disintegrating tablet, respectively. Use haloperidol injection if intake of oral medication is difficult. Use the minimum required dose, and in principle administer in the evening. For treatment of delirium, also consider hospitalization for the purposes of detailed investigations of the cause, ensuring safety of the patient, smooth implementation of treatment, and provision of a calm environment.

In a multicenter randomized controlled trial (RCT) conducted in Japan, the frequency of delirium is reduced by taking ramelteon from the time of admission [3]. Therefore use of this drug may be considered. All of the drugs mentioned above are used off-label. When prescribing these drugs, it is necessary to explain in detail to the patients and families, and to be aware of adverse events.

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■ Search formula

PubMed search: June 23, 2015 (Tuesday)

#1 ((Dementia [Mesh] AND ("drug therapy" [subheading] OR "Drug therapy" [Mesh])) OR ("Dementia/therapy" [Mesh] AND ("Antipsychotic Agents" [Mesh] OR "Benzodiazepines" [Mesh] OR "Serotonin Uptake Inhibitors" [Mesh] OR "Antidepressive Agents" [Mesh] OR "Anticonvulsants" [Mesh] OR "Anticonvulsants" [PA] OR "Yi-Gan San" [Supplementary Concept] OR "Herbal Medicine" [Mesh] OR "Medicine, Kampo" [Mesh] OR "ramelteon" [Supplementary Concept] OR "suvorexant" [Supplementary Concept])) OR ((dementia OR "alzheimer disease" OR "alzheimer's disease" OR "frontotemporal lobar degeneration") AND (pharmacological OR drug OR medicine OR antipsychotics OR benzodiazepine OR "selective serotonin reuptake inhibitors" OR "serotonin-norepinephrine reuptake inhibitors" OR antidepressant* OR "mood stabilizer" OR anticonvulsant* OR Yokukansan OR "Japanese herbal" OR "traditional herbal" OR kampo OR ramelteon OR suvorexant OR "orexin receptor antagonist" OR "melatonin receptor agonist"))) AND ("Delirium" [Mesh]OR delirium)

Ichushi search: June 23, 2015 (Tuesday)

#1 (Dementia/TH OR Dementia/TI) AND ((SH = Pharmacotherapy)OR Pharmacotherapy/TH OR Drug treatment/TI OR Pharmacotherapy/TI OR Therapeutic drug/ TI OR Kampo medicine/TH OR Antipsychotics/TH) AND (Delirium/TH or Delirium/TI)

CQ 3C-2

How epilepsy including seizures should be treated in patients with dementia?

Recommendation

The former antiepileptic drugs may worsen cognitive function, and should be used with caution in older patients with dementia. Novel antiepileptic drugs are relatively well tolerated and effective if the drug titration is applied. 2C

Comments and evidence

In dementia patients, the risk of both generalized and partial seizures is six times higher than in the control group [1, 2]. Especially in Alzheimer's disease, the accumulation of amyloid β (Aβ) induces hyperexcitation of the cortical network in the hippocampus, resulting in cognitive impairment, and the hippocampus can be the focus of epileptic seizures at the same time [3, 4]. In patients with Alzheimer's disease, epilepsy with seizure focus in temporal lobe is common, and transient memory impairment tends to occur especially if cognitive decline occurs at a younger age [5]. In familial Alzheimer's disease, several cases with seizures and myoclonus have been reported [4]. Cheng et al. [6] compared the age-adjusted annual incidence of epilepsy between control and Alzheimer's disease, and reported that the risk of epilepsy is increased by 1.85 times in patients with Alzheimer's disease at 3.6 years after the onset of dementia [6].

Because epileptic seizures worsen the prognosis of patients with dementia due to the higher risk of falls, trauma, and death, appropriate treatment with anti-epileptic drugs is required. However, the semiology of seizures is often non-convulsive, subtle, and diverse, and often not recognized as seizures by the patient or the caregiver, which makes the diagnosis difficult. Therefore, once a diagnosis of epilepsy is confirmed and the risk of seizure recurrence is high, it is necessary to start antiepileptic drug with monotherapy in a small dose at first and then upwardly titrating slowly [7]. Since carbamazepine has many drug interactions and adverse effects including cardiac conduction disorder, hyponatremia, and over-sedation, it should be used with caution in older patients. Benzodiazepines, primidone, and phenobarbital are not recommended because they worsen cognitive function. Sodium valproate has little effect on cognitive function, and it is effective for convulsive seizures in older patients and for behavioral and psychological symptoms of dementia such as irritability, aggression and mood disorders.

New antiepileptic drugs (lamotrigine, levetiracetam, gabapentin, topiramate) are effective for seizures in older patients and cause few adverse events. Among them, lamotrigine and levetiracetam are effective for epilepsy in patients with amnestic mild cognitive impairment or early Alzheimer's disease [5]. In Japan, monotherapy of these drug is also indicated for the treatment of epilepsy. Rowan et al. [8] recommend lamotrigine and gabapentin as antiepileptic drugs for older people with dementia, because they have less adverse effects compared with carbamazepine. Levetiracetam has been shown to be effective and safe also in post-stroke epilepsy patients, and have less effect on cognitive function than carbamazepine [9].

In general, since older people often have lower serum albumin and liver and kidney dysfunctions, serum levels of antiepileptic drugs can be readily elevated. Therefore, monotherapy of antiepileptic drugs starting with a low dose is highly recommended. In addition, careful attention should be paid for drug interactions in older patients with dementia, because they are usually taking multiple drugs.

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Search formula

PubMed search: July 5, 2015 (Sunday)
#1 ("Dementia" [Mesh] OR dementia OR "Cognition Disorders" [Mesh] OR cognition disorder* OR cognitive disorder*) AND ("Seizures/therapy" [Mesh] OR (seizure* AND (therapy OR therapeutic OR treatment OR prophylaxis OR prevention)) OR ("Seizures" [Mesh] AND "Anticonvulsants/therapeutic use" [Mesh]) OR (anticonvulsant* AND (therapy OR therapeutic OR treatment OR prophylaxis OR prevention)))

Ichushi search: June 23, 2015 (Tuesday)
#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI) AND (Epilepsy/TH OR Epilepsy/TI OR Epilepsy/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment) OR Treatment/TH OR Treatment/TI OR Therapy/TI OR Preventive/TI OR Anti-convulsive agent/TH OR Anti-convulsive agent/TI OR Anti-epileptic drug/TI OR Anti-convulsive agent/TI OR Anti-epileptic drug/TI OR Anti-convulsive drug/TI OR Anti-epileptic agent/TI OR Anti-convulsive drug/TI OR Anti-epileptic agent/TI)

CQ 3C-3

What are the interventions for dysphagia (including prevention of aspiration pneumonia)?

Recommendation

To prevent the onset of aspiration pneumonia, angiotensin converting enzyme (ACE) inhibitor, amantadine, cilostazol (not covered by insurance), capsaicin, oral care, swallowing rehabilitation, chin down maneuver, maintaining sitting position for 1 hour after eating, and influenza and pneumococcal vaccination are effective.

There is no data showing the usefulness of percutaneous endoscopic gastrostomy (PEG) in preventing aspiration pneumonia or improving activities of daily living (ADL) and survival in patients with advanced stage dementia.

2D

Comments and evidence

In frontotemporal lobar degeneration and Alzheimer's disease dementia, abnormalities in eating behavior such as overeating occur due to functional impairment of the limbic system and frontal lobe, and are particularly marked in the former. Vascular dementia and dementia caused by parkinsonism often manifest impaired swallowing reflex, and aspiration pneumonia is often caused by occult aspiration at night. On the other hand, in Alzheimer's disease dementia, the swallowing reflex is preserved until the late stage of the disease, and is often maintained even in a bed confined state.

Activation of the dopamine–substance P system is important for the prevention of aspiration pneumonia. Sensory stimulation of the oral cavity through oral care increases substance P, increases the sensitivity of the cough reflex, and consequently improves the swallowing reflex [1, 2]. Administration of ACE inhibitors that suppress substance P degradation is also useful [3]. In addition, cilostazol [4] and amantadine with dopamine release effect [5] have been reported to be effective in the prevention of aspiration pneumonia. Furthermore, rivastigmine [6] and the Kampo herbal medicine "*banxia houpo tang*" [7] have been reported to improve swallowing function. Conversely, since cholinergic and dopaminergic systems act to maintain the swallowing function, drugs with anticholinergic action and dopamine antagonistic action increase the risk of aspiration pneumonia [8].

In the advanced stage of dementia, use of PEG does not show benefit regarding survival duration, improvement of quality of life (QOL), or reduction of aspiration pneumonia [9]. Systematic reviews that evaluate the effect of PEG in dementia patients with dysphagia have not found a survival-extending effect [10, 11].

References

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Search formula

PubMed search: July 15, 2015 (Wednesday)

#1 ("Dementia" [Mesh] OR dementia OR Alzheimer* OR "Cognition Disorders" [Mesh] OR cognition disorder* OR cognitive disorder*) AND ("Deglutition Disorders/therapy" [Mesh] OR ((deglutition disorder* OR swallowing disorder* OR dysphagia) AND (therapy OR therapeutic OR treatment OR prophylaxis OR prevention)) OR "Pneumonia, Aspiration/therapy" [Mesh] OR (aspiration pneumonia* AND (therapy OR therapeutic OR treatment OR prophylaxis OR prevention)))

Ichushi search: July 15, 2015 (Wednesday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI) AND (dysphagia/TH or dysphagia/TI OR Pneumonia-aspiration/TH or aspiration pneumonia/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment, rehabilitation, prevention) OR Treatment/TH OR Therapeutic use/TH OR Treatment/TI OR Therapy/TI OR Prevention/TI)

CQ 3C-4

What are the interventions for eating disorder and undernutrition?

Recommendation

In Alzheimer's disease, eating difficulties may be caused by changes in eating behavior, loss of appetite, dysphagia, and autonomic disturbance. It is important to take history of the changes in body weight and quantity of food eaten; implement nutritional assessment, prevention of aspiration, and review of medications; and examine the merits and demerits of oral intake and tube feeding. 2C

Comments and evidence

Many people with dementia are affected by eating disorders, weight loss, and undernutrition.

Among people with mild Alzheimer's disease, over 30% experience some changes in eating behavior, and 16% have loss of appetite [1]. Riviere et al. [2] studied 224 people with moderate Alzheimer's disease, and observed that 26% had eating behavior disorders such as "getting up while eating" and "eating by hand". In patients with severe dementia, 80% showed weight loss, dysphagia, eating refusal, reduced food intake, and dehydration [2].

To investigate why people with Alzheimer's disease lose appetite, Ismail et al. [3] observed reduced blood flow in various regions including the anterior cingulate gyrus on blood flow SPECT, and speculated that these changes were related to appetite loss.

The adverse effects of cholinesterase inhibitors used as a treatment for Alzheimer's disease include gastrointestinal symptoms, although the symptoms are generally transient. There is a report suggesting that long-term administration of these agents may prevent weight loss [4].

In 2014, Goldberg et al. [5] conducted a systematic review on the usefulness of percutaneous endoscopic gastrostomy (PEG) for severe dementia with dysphagia (publications from 1995 to 2012), and reported no evidence that PEG prolongs survival long-term [5].

According to a review by Affoo et al. [6], while evidence suggests a possibility that dysphagia and autonomic nervous system dysfunction may occur together in Alzheimer's disease, the relationship between the two has not been clarified.

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■ Search formula

PubMed search: June 8, 2015 (Monday)

#1 ("Dementia" [Mesh] OR dementia) AND ("Deglutition Disorders/therapy" [Mesh] OR (dysphagia AND (therapy OR therapeutic OR treatment))) AND ("percutaneous endoscopic gastrostomy" OR PEG OR ("Endoscopy" [Mesh] AND "Gastrostomy" [Mesh] AND "percutaneous") OR "Enteral Nutrition" [Mesh] OR "tube feeding")

Ichushi search: June 8, 2015 (Monday)

#1 (Dementia/TH or Dementia/TI) AND (Eating dysfunction/TH or Eating disorder/TI) AND (Gastrostomy construction/TH OR PEG/TI OR Gastrostomy/TH OR Gastrostomy/TI OR Enteral nutrition/TH or Tube feeding/TI)

CQ 3C-5

What are the interventions for sarcopenia and frailty?

Answer

Dementia tend to coexist with sarcopenia and frailty. Resistance training may be useful in improving sarcopenia and frailty associated with dementia. C

Comments and evidence

Sarcopenia is a common pathological condition seen in old age. Sarcopenia is defined as "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death" [1]. The causes of sarcopenia include aging, reduced activity, poor nutrition, and disease [1]. Frailty is the decline of various physiological functions with ageing, and is a risk factor that leads to undesirable outcomes such as falls, hospitalization, and death.

Sarcopenia and frailty tend to occur more frequently in older people with dementia than in older adults with normal cognitive function. In recent years, the relationship between frailty and cognitive impairment has attracted attention [2].

Persons with Alzheimer's disease in a nursing home who received the dual-task intervention of walking and conversation showed less decline in physical function compared with persons given either conversation or walking intervention alone [3]. When frail persons with Alzheimer's disease living at home participated in a home-based exercise program (aerobics, strength training, and balance exercise) guided by the caregiver for 12 weeks, their hand function and lower extremity strength significantly improved compared with the control group [4]. A three-month resistance training program designed specifically for older dementia persons significantly improved muscle strength and physical function compared with the control group [5]. A cohort study of frail older adults with dementia also found that 4 weeks of resistance exercise improved muscle strength and physical functions [6]. The above evidence shows that sarcopenia and frailty may be improved in people with dementia through exercise customized for each individual.

Although there is no interventional study of nutrition therapy focused on people with dementia, nutritional supplementation for sarcopenia generally improves muscle mass and muscle strength of older people [7]. Hence, together with exercise, nutritional supplementation is important.

References

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Search formula

PubMed search: June 8, 2015 (Monday)
#1 ("Dementia" [Mesh] OR dementia) AND ("Sarcopenia/therapy" [Mesh] OR(sarcopenia AND "Muscular Atrophy" [Mesh]) OR (sarcopenia AND (therapy OR therapeutic OR treatment)) OR (frailty AND (therapy OR therapeutic OR treatment)))

Ichushi search: June 8, 2015 (Monday)
#1 (Dementia/TH OR Dementia/TI) AND (sarcopenia/TI OR Sarcopenia/TH OR frailty/AL)

CQ 3C-6

What are the interventions and preventive measures for falls and fractures?

Answer

People with dementia have approximately 8 times higher risk for falls and approximately 3 times higher risk for fracture compared with people without dementia. To prevent falls, use multi-faceted interventions including treatment of underlying diseases, adjustment of drugs, exercise, walking and balance training, training wearing aids, environmental modification, and training to adjust to home environment. Also consider treatment for osteoporosis. B

Comment and evidence

In older people, fracture caused by falling is one of the main causes of confining to bed, and falls lower the ability of activities of daily living (ADL) and motivation, and also induce delirium.

People with dementia have approximately 8 times higher risk for falls and approximately 3 times higher risk for fractures compared with people without dementia [1]. Dementia patients with orthostatic hypotension have a higher frequency of falls compared to patients without orthostatic hypotension, with a hazard ratio of 2.13. For the incidence of falls, Parkinson's disease with dementia (PDD) was the highest, followed by dementia with Lewy bodies (DLB), vascular dementia, and Alzheimer's disease (AD). For PDD and DLB, the high incidence may be related to orthostatic hypotension and autonomic nervous system dysfunction [1].

A retrospective study conducted from 1988 to 2007 in the UK showed that the incidence of hip fracture was 17.4 per 1,000 people with dementia and 6.6 per 1,000 people without dementia, and the risk was 3.2 times higher in patients with dementia [2].

The guidelines for fall prevention prepared by the Orthopedic Surgery Committee of American Geriatric Society/ British Geriatric Society[3] recommends multifactorial interventions including minimization of medications, customized exercise program, treatment of vision impairment, management of orthostatic hypotension, management of arrhythmia, vitamin D supplementation, management of foot and footwear problems, modification of the home environment, and providing education and information. However, there is insufficient evidence for supporting any single or multifactorial intervention to reduce fall risk in older people with cognitive impairment. Subsequently, a meta-analysis of exercise interventions (7 randomized controlled trials) was conducted, and found that exercise interventions reduce falls in people with dementia (odds ratio, 0.68) [4].

Although people with dementia are prone to osteoporosis-derived fractures, they are often not treated with drugs for osteoporosis. Consider appropriate assessment, treatment and guidance for osteoporosis [5]. The risk of femoral neck fracture is increased in older patients with Alzheimer's disease who have vitamin K and vitamin D deficiency [6].

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Search formula

PubMed search: June 9, 2015 (Tuesday)
#1 ("Dementia" [Mesh] OR dementia) AND ("Accidental Falls/prevention and control" [Mesh] OR (accident* AND (falls OR fall) AND (prevention OR preventing)))

Ichushi search: June 9, 2015 (Tuesday)
#1 (Dementia/TH OR Dementia/TI) AND (Falls/TI OR Falls/TH) AND (Accident prevention/TH OR (SH = Prevention) OR Prevention/TI OR Prevention/TI)

CQ 3C-7

What are the interventions for pressure ulcers?

Answer

Currently, there is no clear evidence for the therapeutic or preventive effects of supplements, tube feeding, and parenteral nutrition for pressure ulcers, and there is a lack of high-level evidence for comprehensive management. For local treatment, refer to the "Evidence-based Guidelines for Local Treatment of Pressure Ulcers" published by the Japanese Society of Pressure Ulcers. 2C

Comment and evidence

Pressure ulcers are necrosis of ischemic cutaneous or subcutaneous tissues caused by blood circulation failure due to continuous pressure on localized skin area. Pressure sores are formed frequently in sites with bone protrusion and little subcutaneous fat tissue, and are strongly affected by ageing, undernutrition, motor paralysis, joint contracture, and urinary and fecal incontinence. Pressure ulcers tend to occur when activities of daily living (ADL) decrease accompanying progression of dementia.

Although it has been reported that an increase in number of pressure ulcers is related to higher risk of death in people with advanced dementia [1], there is currently no clear evidence for the therapeutic or preventive effects of supplements, tube feeding, and parenteral nutrition for pressure ulcers [2].

A meta-analysis has indicated that the presence of increasing pain is more useful than purulent exudate, heat, and redness for the diagnosis of pressure ulcer infection [3].

■ References

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■ Search formula

PubMed search: June 9, 2015 (Tuesday)
#1 ("Dementia" [Mesh] OR dementia) AND ("Pressure Ulcer" [Mesh] OR "bed sore" OR bedsore OR "decubitus position" OR "decubitus ulcer" OR "pressure sore" OR "pressure ulcer")

Ichushi search: June 9, 2015 (Tuesday)
#1 (Dementia/TH OR Dementia/TI) AND (Pressure ulcer/TI OR decubitus ulcer/TH)

CQ 3C-8

What are the approaches to treat acute physical illness?

Answer

In people with dementia, acute physical illness is difficult to detect because typical symptoms are frequently absent and the patients cannot complain. In Alzheimer's disease, as dementia becomes severe, the number of hospital admissions increases and mortality also increases. C

Comment and evidence

There is still no evidence for acute physical illness in people with dementia.

According to the 2014 data of the Fire and Disaster Management Agency of Japan [1], 61.6% (2.03 million) of the patients transported to emergency department were elderly, which doubled the percentage of 28.8% in 1993. Among these cases, cerebrovascular system, heart disease, and respiratory system accounted for 11% each. For people with dementia transported to emergency department, the major causes are pneumonia, stroke, fractures of lower limbs, bruise or sprain, ileus, and gastrointestinal bleeding [2, 3]. In addition, more than 70% of 107 cases of suffocation are secondary to neurological disorders including dementia, cerebral infarction, schizophrenia, and Parkinson's disease [4]. Therefore, neurological disorders including dementia can be considered to be risk factor of suffocation. People with Alzheimer's disease have more hospital admissions than the general elderly population, and people with severe Alzheimer's disease are hospitalized 2.3 times more than the general elderly population [5]. Moreover, people with dementia who require emergency admission have high death rate [6].

When a person with dementia is admitted to the hospital, make sure that the patient is placed in a room that is within watching distance from the nurses, and avoid rooms near the entrance and exit of the ward. Ensure safety by using measures such as a bed exit sensor and a protective cover to prevent needle removal. Provide care with consideration to monitor changes in patient's symptoms or conditions. People with dementia are prone to develop delirium due to anxiety and fear as a result of change in environment and physical distress. As a measure for delirium, provide care with special considerations for patients with dementia: ask family members to accompany the patient, have the same nurse in charge of the patient, explain the nurse call and location of the toilet in simple language, tell patient the status repeatedly, resolve pain / anxiety / insomnia, and do not restrain actions. Consider medication as necessary.

When dementia is advanced, detection of urinary tract infection is difficult because typical symptoms are frequently absent, and the patients cannot complain[7].

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Search formula

PubMed search: June 10, 2015 (Wednesday)
#1 ("Dementia" [Mesh] OR dementia) AND ("Pneumonia/therapy" [Mesh] OR (pneumonia AND (therapy OR therapeutic OR treatment)) OR "Acute Disease/therapy" [Mesh] OR "Emergency Medicine" [Mesh])

Ichushi search: June 10, 2015 (Wednesday)
#1 (Dementia/TH OR Dementia/TI) AND (Pneumonia/TH OR Pneumonia/TI OR Acute illness/TH OR Acute illness/TI OR Emergency medicine/TH)

CQ 3C-9

How should decisions be made regarding invasive examinations and treatments including dialysis and dental treatment?

Answer

When a person with dementia requires dialysis, refer to the "Proposal for the shared decision-making process regarding initiation and continuation of maintenance hemodialysis" published by the Japanese Society for Dialysis Therapy. Dental treatment and oral care are essential for people with dementia, and providing preventive and continuous oral hygiene management is recommended. D

Comments and evidence

As of the end of 2010, 9.9% of the total dialysis population had dementia (23,000 of 234,000 of all dialysis patients, excluding those unknown and undocumented). For dialysis patients aged 90 years or above, 25-35% also have dementia and require support [1]. As the number of people with dementia who require dialysis increase, there is also an increase in number of patients who stand up or become restless during dialysis, impeding safe execution of dialysis. There are limits to sedation and caregiver attendance.

The "Proposal for the shared decision-making process regarding initiation and continuation of maintenance hemodialysis" in Japan are recommendations on providing appropriate information to patients, giving support to patients when making their own decisions, and obtaining written informed consent [2]. Among the situations that require review of whether to suspend dialysis, "extracorporeal circulation cannot be performed safely without restrain and sedation using medications" and "oral intake not possible" and included, and these situations may arise in people with dementia.

As dementia emerges, self-cleaning behavior is impaired, and the state of oral hygiene worsens. People with dementia have more caries and periodontal diseases than healthy people [4]. Evidently oral care is important for the prevention of aspiration pneumonia. In the clinical setting, patients with dementia often discontinue dental treatment because they do not understand the meaning of the treatment. As a result, some patients require treatment under general anesthesia since the inflammation cannot be controlled. Before dementia deteriorates to the above states, providing continuous preventive oral hygiene management to people with dementia is recommended.

■ References

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■ Search formula

Trauma

PubMed search: June 10, 2015 (Wednesday)

#1 ("Dementia" [Mesh] OR dementia) AND ("Wounds and Injuries/therapy" [Mesh] OR ((fracture OR fractures OR trauma OR traumas) AND (therapy OR therapeutic OR treatment))

Ichushi search: June 10, 2015 (Wednesday)

#1 (Dementia/MTH OR Dementia/TI) AND (Wound and injury/MTH OR Fracture/TI OR Trauma/TI)

Invasive examinations

PubMed search: June 12, 2015 (Friday)

#1 ("Dementia/diagnosis" [Mesh] OR (dementia AND (diagnosis OR diagnostic))) AND ("Endoscopy" [Mesh] OR "Endoscopes" [Mesh] OR endoscopy OR endoscopic OR endoscope* OR "invasive examination")

Ichushi search: June 12, 2015 (Friday)
#1 (Dementia/TH OR Dementia/TI) AND (Endoscopy/TH OR ((Endoscope/TH OR Endoscope/AL) AND (Diagnosis OR Examination)) OR (Invasive examination/AL NOT (Non-invasive examination /AL OR Non-invasive examination/AL)))

Surgery or dialysis
PubMed search: June 12, 2015 (Friday)
#1 ("Dementia" [Mesh] OR dementia) AND ("surgical indication" OR operability OR "Renal Dialysis" [Mesh] OR dialysis OR hemodialysis OR dialyses OR hemodialyses) OR "Dementia/complications" [Mesh] AND ("Surgical Procedures, Operative" [Majr] OR "surgery" [Subheading]) AND "Risk" [Mesh]

Ichushi search: June 12, 2015 (Friday)
#1 (Dementia/TH OR Dementia/TI) AND (Surgical indication/AL OR ((Surgery/MTH OR(SH = Surgical therapy) OR hemodialysis/TH OR Dialysis/TI) AND Risk/TH))

CQ 3C-10

What are the interventions for edema?

Answer

In addition to interventions for immobility due to long-term bed confinement and undernutrition, provide treatments for underlying diseases as well as for concomitant diseases such as skin infections and pressure ulcers. Pay attention to the possibility of edema induced by drugs such as *Yokukansan* and antipsychotics, and consider discontinuation or dose reduction of the causative drugs as appropriate. C

Comments and evidence

Diseases that cause edema commonly seen in older people include: (1) causes of systemic edema; congestive heart failure, renal disease, hepatic disease, and hypothyroidism, and (2) causes of localized edema; cerebrovascular disroder, deep vein thrombosis, knee osteoarthritis, and malignant tumors. Edema becomes more common with ageing, due to variability of capillary pressure, changes in interstitial components and reduced tissue pressure, lowered plasma osmotic pressure due to decreased serum albumin, and increased capillary permeability.

In people with dementia, it is necessary to consider the possibility of edema induced by drugs including antipsychotic drugs [1] and *Yokukansan* [2], and to consider discontinuation or dose reduction of the causative drug as appropriate [2]. According to an observational study that examined the safety and efficacy of long-term use of *Yokukansan* in 163 patients who had been prescribed *Yokukansan* for more than 6 months, edema appeared in 10.8% of the patients and many recovered by discontinuing *Yokukansan* with no need for treatment [2].

Treatment of edema involves the treatment of underlying diseases identified by diagnosis of the cause as well as treatment of coexisting illnesses such as skin infections and pressure ulcers. Especially in older people, extreme salt restriction and water restriction to reduce edema may cause rapid intravascular dehydration, because of the low water and sodium retention ability in older people. When using diuretics, monitor body weight to ensure that fluid is removed gradually. In addition, since diuretics tend to disrupt electrolyte balance and cause hypotension, hypernatremia or hyponatremia, and hypokalemia, close monitoring of blood electrolyte levels and urinary electrolyte excretion is necessary.

■ References

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2) Okahara K, Ishida Y. Safety and efficacy evaluation of long-term treatment with a traditional Japanese medicine, Yokukansan, on behavioral and psychological symptoms of dementia. Dementia Japan. 2012; 26: 196-205. (In Japanese)

■ Search formula

PubMed search: June 12, 2015 (Friday)
#1 ("Dementia" [Mesh] OR dementia) AND ("Edema" [Mesh] OR edema)

Ichushi search: June 12, 2015 (Friday)
#1 (Dementia/TH OR Dementia/TI) AND (Edema/AL OR Edema/TH)

CQ 3C-11

What are the interventions for urinary disorder?

Answer

Many people with dementia have functional urinary incontinence and urge urinary incontinence. Behavioral therapy can be expected to be effective for urinary disorder, after ruling out underlying urological disorder. On the other hand, there is no sufficient evidence for pharmacotherapy in people with dementia. C

Comments and evidence

Carefully investigate the presence or absence of organic diseases causing urinary disorder, and rule out a diagnosis of such diseases. In people with dementia, functional urinary incontinence and urge urinary incontinence are common. Treat these conditions by referring to guidelines (https://minds.jcqhc.or.jp/) [1-3].

1. Behavioral therapy [4-6]

The following interventions are recommended: (1) toileting assistance: [1] toileting at fixed time, [2] toileting according to an established voiding pattern, and [3] reeducating toileting habit; (2) bladder training; and (3) pelvic floor muscle rehabilitation for stress urinary incontinence.

2. Pharmacotherapy for urinary disorder

For urge urinary incontinence in women, use anticholinergic drugs (propiverine and tolterodine). For prostatic hypertrophy in overflow urinary incontinence, use the sympathetic selective α1 inhibitors (tamsulosin and naftopidil). For neurogenic bladder, use cholinergic agonists (muscarinic receptor agonists; bethanechol). Attention should be paid to aggravation of constipation and cognitive decline caused by anticholinergic drugs [7], and orthostatic hypotension caused by α1 inhibitors.

For overactive bladder with major symptoms of urinary urgency, urge incontinence, and frequent urination, use selective muscarinic receptor antagonists (anticholinergic drugs) including fesoterodine, tolterodine, solifenacin, imidafenacin, and oxybutynin; and the β_3 receptor agonist mirabegron [3]. Oxybutynin is highly fat-soluble and crosses the blood-brain barrier, and the possibility of this drug of causing cognitive impairment has been suggested [8]. In addition, combined use of cholinesterase inhibitor and anti-cholinergic drug causes significant decline in activities of daily living compared with cholinesterase inhibitor monotherapy [9].

3. Other treatment methods [1]

The following interventions have been recommended: (1) modify the environment depending on cognitive function and physical function; (2) modify clothes; (3) use urinary catheter, suprapubic catheter, external urine receptacle, or urine absorbent product; (4) use of bladder support device has been proposed; and (5) if urinary incontinence is detected, wipe the genital area promptly to maintain cleanliness.

4. Drug-induced urinary disorder

Tricyclic antidepressants should be avoided as much as possible in male patients with urinary disorder [10]. Among the drugs for Parkinson's disease, levodopa is recommended, whereas trihexyphenidyl and biperiden may cause urinary disorder.

■ References

1) The Japanese Continence Society, Working Committee for Clinical Practice Guideline for Male Lower Urinary Tract Symptoms. Clinical Practice Guideline for Male Lower Urinary Tract Symptoms. Tokyo: Blackwell Publishing; 2008. (In Japanese)
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Search formula

PubMed search: June 12, 2015 (Friday), July 18, 2015 (Saturday)
#1 ("Dementia" [Mesh] OR dementia OR alzheimer* [TI]) AND ("Urinary Incontinence/therapy" [Mesh] OR "Urinary disorders/therapy" [Mesh] OR "Urinary Bladder Diseases/therapy" [Mesh] OR "Dysuria/therapy" [Mesh] OR (("urinary incontinence" OR urinary disorder* [TI] OR urinary incontinence* [TI] OR urinary bladder disease* [TI] OR bladder dysfunction* [TI] OR neurogenic bladder* [TI] OR dysuria [TI]) AND (therapy OR therapeutic OR treatment OR management OR care OR training OR intervention)))

Ichushi search: June 12, 2015 (Friday), July 18, 2015 (Saturday)
#1 (Dementia/TH OR Dementia/TI) AND (urinary disorder/TH OR urinary disorder/TI OR Urinary incontinence/TI OR Bladder disease/TH OR Bladder disease/TI OR Micturition pain/TH OR Micturition pain/TI OR Neurogenic bladder/TI OR Overactive bladder/TI)

CQ 3C-12

What are the interventions for constipation?

Answer

Constipation is a common disease among people with dementia, and may impair quality of life (QOL) and cause delirium. Differentiate constipation from organic diseases, and use laxatives when diet (high fiber foods) and exercise do not improve the constipation. C

Comments and evidence

Constipation impairs QOL of people with dementia, causes irritability, decreases appetite, and may even result in delirium. The rates of constipation by subtype of dementia are 43% in dementia with Parkinson's disease, 28% in Lewy body disease, and 26% in vascular dementia, and were all higher than the rate of 2% in controls; whereas the rate is 3% in Alzheimer's disease and not significantly different from controls [1].

Constipation becomes more common with aging, due to weakness of the pelvic floor muscles, autonomic disturbances, and abnormalities in the colon wall. Constipation is classified into functional (atonic, convulsive, rectal), organic, symptomatic (such as diabetes and cerebrovascular disorder), and drug-induced. Atonic constipation is the most common, and is classified as functional constipation. Organic constipation is caused by colon cancer or scarring. Medications associated with constipation include anticholinergic drugs, antidepressants, antipsychotic drugs, antiparkinsonian drugs, antihistamines, diuretics, and opioids [2]. Symptoms of nausea/vomiting, abdominal distension, and retention of feces and gas suggest ileus. Change in stool caliber, occult blood in stool, bloody stool, iron deficiency anemia, and weight loss are signs of suspected organic constipation [2].

After ruling out the above conditions, use non-pharmacological interventions such as lifestyle modification and diet therapy. Recommend patients to (1) eat a fiber-rich diet, (2) keep regular eating and defecation habits, and (3) do walking exercise. For convulsive constipation, it is important to remove stress. For atonic constipation, advice patients to drink sufficient water to prevent hard stool, and to take water-soluble vitamins such as vitamins B_1 and B_2, as well as to increase bifidobacteria in the bowel. If there is no improvement despite the above interventions, prescribe pharmacotherapy. Laxatives include osmotic laxatives (magnesium oxide), colonic stimulants (such as senna, sennoside, *Daio*, and sodium picosulfate), chloride channel activator (lubiprostone) that promotes water secretion in the intestinal tract, *Daikenchuto* suppository, and enemas. Select medications according to the number of defecations and the nature of the stool.

Although enema is widely used, the rates of complications such as perforation, hyperphosphatemia, and sepsis are particularly high in older patients, and should be used with caution [3].

References

1) Allan L, McKeith I, Ballard C, et al. The prevalence of autonomic symptoms in dementia and their association with physical activity, activities of daily living and quality of life. Dement Geriatr Cogn Disord. 2006; 22: 230-233.
2) Lindberg G, Hamid SS, Malfertheiner P, et al. World Gastroenterology Organisation global guideline: Constipation- a global perspective. J Clin Gastroenterol. 2011; 45(6): 483-487.
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Search formula

PubMed search: June 12, 2015 (Friday), July 18, 2015 (Saturday)
#1 ("Dementia" [Mesh] OR dementia OR alzheimer* [TI]) AND ("Constipation/therapy" [Mesh] OR "Colonic Diseases, Functional/therapy" [Mesh] OR ((constipation [TI] OR bowel dysfunction* [TI] OR colonic disease* [TI] OR neurogenic bowel*[TI]) AND (therapy OR therapeutic OR treatment OR management OR care OR training OR intervention)))

Ichushi search: June 12, 2015 (Friday), July 18, 2015 (Saturday)
#1 (Dementia/TH OR Dementia/TI) AND (Constipation/TH OR Constipation/TI OR Defecation disorder/TH OR Defecation disorder/TI OR Colonic disease-functional/ TH OR Functional colonic disease/TI OR Neurogenic bowel/TI OR irritable colon/TI)

CQ 3C-13

How should diabetes, hypertension and other lifestyle-related diseases be managed?

Recommendation

Individualized approach to diabetes control is recommended, with consideration of the severity of dementia and physical dysfunction, coexisting diseases, frailty, and other factors. Although there is little evidence regarding the effects of antihypertensive treatment for hypertensive patients with dementia, treatment that does not excessively reduce blood pressure should be considered. 2C

Comments and evidence

It has been pointed out that lifestyle-related diseases (or vascular risk factors) such as hypertension, diabetes, dyslipidemia, and obesity that coexist with dementia may potentially modify the progression of cognitive dysfunction. Proper treatment of vascular risk factors accompanying Alzheimer's disease dementia has been shown to mitigate the deterioration of Mini Mental State Examination (MMSE) score [1].

For glycemic control in older diabetic patients who have developed dementia, set the treatment target considering the activities of daily living (ADL), coexisting diseases, and risk of severe hypoglycemia. Hypoglycemia, falls and fractures increase when HbA1c is less than 7.0%; and cognitive decline, frailty, and geriatric syndrome increase gradually when HbA1c exceeds 8.0%. In older people with diabetes, setting HbA1c target for individual patient is recommended, taking into consideration not only the presence or absence and severity of dementia, but also the coexisting diseases, basic ADL (BADL) and instrumental ADL (IADL), frailty, and risk of severe hypoglycemia [2]. Current recommendation is HbA1c 7.0% to below 7.5% for older people with normal cognitive and physical functions, below 8.0% for mild to moderate dementia, and below 8.5% for moderate to severe dementia or severely impaired physical function. Furthermore, according to the proposal of the Joint Committee in Japan, lower limits of the targets have been set to avoid hypoglycemia in patients using drugs for which severe hypoglycemia is a concern (such as insulin, sulphonylureas, and glinides).

There is little evidence for the effect of antihypertensive agents in hypertensive patients with dementia. An observational study finds that antihypertensive therapy prevents the progression of mild cognitive impairment to Alzheimer's disease dementia [3]. Antihypertensive treatment should be considered [4]. However, although there are no descriptions for the recommended blood pressure targets for older people with frailty or dementia, care should be taken not to excessively lower blood pressure in older people with dementia receiving antihypertensive treatment [5].

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■ Search formula

PubMed search: July 3, 2015 (Friday)
#1 ("Dementia/prevention and control" [Majr] OR (dementia [TI] AND (prevent* OR control*)) OR "Cognition Disorders/prevention and control" [Majr] OR ((cognition disorder* [TI] OR "cognitive dysfunction" [TI]) AND (prevent* OR control*))) AND ("Diabetes Mellitus" [Mesh] OR "Hypertension" [Mesh] OR (("diabetes mellitus" [TI] OR hypertension [TI])) OR "Life Style" [Majr] OR lifestyle related disease* [TI] OR lifestyle disease* [TI])

Ichushi search: July 3, 2015 (Friday)
#1 (Dementia/MTH OR Dementia/TI OR Cognitive impairment/MTH OR Cognitive impairment/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiotherapy, rehabilitation, prevention)OR Pharmacotherapy/TH OR Pharmacological effect/TH OR Treatment/TI OR Therapy/TI OR Control/TI OR Prevention/TI) AND (Lifestyle related disease /TH OR Lifestyle related disease /TI OR Diabetes/TH OR Diabetes/ TI OR Hypertension/TH OR Hypertension/TI)

Chapter 4

Clinical Course and Treatment

A | Risk Factors and Protective Factors of Dementia

CQ 4A-1

What are the risk factors and protective factors of dementia?

Answer

Risk factors for dementia include ageing, genetic risk factors (*APP*, *PS1*, *PS2*, *APOEε4*), vascular risk factors (hypertension, diabetes, dyslipidemia), lifestyle-related factors (such as smoking), and related diseases (metabolic syndrome, sleep apnea syndrome, depression, and bipolar disorder). Protective factors include moderate exercise, dietary factors, leisure activities, social participation, mental activity, and cognitive training. Acquired elements include education history and head trauma.

Comments and evidence

Risk factors that can be modified to prevent dementia include (midlife) hypertension, diabetes, (midlife) obesity, dyslipidemia, smoking, low physical activity, and depression [1-3].

The effects of hypertension on dementia and cognitive impairment vary with age. Since midlife hypertension is a risk factor for dementia and cognitive impairment in older age, active treatment is recommended from the viewpoint of dementia prevention.

Diabetes is a risk factor for dementia (Alzheimer's disease dementia, vascular dementia, and mixed dementia); especially, glycemic control in midlife is necessary to prevent the onset of dementia.

Midlife dyslipidemia, especially hypercholesterolemia, has been shown to be a risk factor for Alzheimer's disease dementia, and strict control of dyslipidemia in midlife is desirable. In older people, report has indicated that higher serum cholesterol level is associated with a lower risk of developing Alzheimer's disease dementia. Therefore, statins have to be used with caution in older people.

An increasing number of reports suggest a relationship of metabolic syndrome with ageing-associated cognitive impairment, mild cognitive impairment, and vascular dementia, but the association with Alzheimer's disease dementia is not consistent. Many reports have shown that metabolic syndrome in midlife, in particular, is associated with cognitive impairment.

Smoking aggravates dementia [risk ratio (RR) 1.30], vascular dementia (RR 1.38), and Alzheimer's disease dementia (RR 1.40).

Many observational studies on exercise therapy have reported that regular physical activity prevents the onset of dementia and Alzheimer's disease dementia. Interventional trials on the effect of physical activity in older people report the protective effect of physical activity against cognitive impairment, and recommends active incorporation of exercise [4].

Several observational studies report that a past history of depression and bipolar disorder increases the risk of dementia onset in later life [5-7].

Leisure activities comprise intellectual, physical, and social elements. Many reports show that leisure activities have protective effects against the development of dementia and Alzheimer's disease dementia.

High-calorie diets containing mainly carbohydrates, low-protein diets, and low-fat diets tend to increase the risk of mild cognitive impairment and dementia. Moderate drinking has been reported to prevent dementia. Hyperhomocysteinemia has been reported to be a risk factor for Alzheimer's disease dementia and other types of dementia [1]. Sleep apnea syndrome and sleep-disordered breathing are known to be vascular risk factors associated with cognitive impairment.

A shorter education history is associated with increase in the risk of Alzheimer's disease dementia [2].

Head injury increases the odds ratio (OR) of a pathological diagnosis of Alzheimer's disease dementia in men (OR 1.47), but not in women (OR 1.18) [8].

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CQ 4A-2

Are hypertension control and antihypertensive drugs effective in dementia prevention?

Recommendation

Hypertension in midlife is a risk factor for dementia, and should be treated actively. However, large-scale studies have not clearly shown the preventive effect of antihypertensive therapy against onset of dementia and cognitive impairment.

2C

Comments and evidence

The effect of hypertension on dementia and cognitive impairment varies with age. In particular, hypertension in midlife is a risk factor for dementia in old age. Therefore, active treatment is recommended from the viewpoint of dementia prevention [1].

In a 12-year follow-up study of adults with no dementia at baseline, blood pressure at baseline had a greater effect on the speed of cognitive decline in subjects who were in midlife (aged under 65 years) at the start of the study compared with those who were in old age (aged 65 years or above). This finding suggests that blood pressure control in midlife has a pronounced effect on cognitive function [2].

The relationship between hypertension and dementia in old age is not consistent.

The dementia preventive effect of antihypertensive medications has been observed for dementia in general and for vascular dementia.

A Cochrane review reports a meta-analysis of large-scale double-blind interventional trials (SHEP, Syst-Eur, SCOPE, HYVET). The subjects of the analysis were older people (mean age 75 years) with hypertension. Blood pressure was adequately lower in the intervention group compared with the control group. However, with regard to the onset of dementia, the intervention group showed only a tendency of preventive effect [odds ratio (OR) 0.89, 95% confidence interval (CI) 0.74 to 1.07] [3].

A pooled meta-analysis of 8 large-scale clinical trials found that blood pressure lowering had no significant dementia prevention effect overall, but diuretics and calcium antagonists were effective [4].

In a pooled meta-analysis of 14 longitudinal studies on the relationship between antihypertensive therapy and onset of dementia or cognitive impairment in subjects without dementia at baseline, use of antihypertensive drugs had no significant preventive effect on the development of Alzheimer's disease dementia and cognitive impairment. However, there was a preventive effect on vascular dementia and dementia in general [5].

In a meta-analysis based on 19 randomized controlled trials (RCTs) and 11 observational studies on the prevention effects of antihypertensive drugs in patients with no history of stroke, the risk of developing dementia was significantly reduced by 9%. In a sub-analysis of the antihypertensive classes, angiotensin II receptor blocker (ARB) tended to be beneficial for cognitive function [6].

In another meta-analysis of 12 studies in older subjects without dementia or cerebrovascular disorders (4,076 subjects), hypertension significantly reduced episodic memory and global cognition [7].

In the Honolulu-Asia Aging Study, 2,197 male hypertensive patients (mean age 77 years) without dementia or cognitive impairment were followed. The risk of progression of cognitive decline was reduced in patients taking β-blockers as antihypertensive drug (incidence ratio 0.69, 95% CI 0.50 to 0.94) [8].

In the Hisayama study, the relative risk of developing vascular dementia increased linearly with increasing blood pressure from midlife to late life [9].

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PubMed search: June 13, 2015 (Saturday)

#1 (("Dementia/prevention and control" [Mesh]) OR (dementia AND prevent*) OR "Cognition Disorders/prevention and control" [Mesh] OR ("cognition disorder*" AND prevent*)) AND ("Antihypertensive Agents" [Mesh] OR "Antihypertensive Agents" [Pharmacological Action] OR antihypertensive agent*)

Ichushi search: June 13, 2015 (Saturday)

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CQ 4A-3

Is diabetes control effective in dementia prevention?

Recommendation

In many reports, including meta-analyses, diabetes is a risk factor for Alzheimer's disease dementia, vascular dementia, and mixed dementia. Especially, glycemic control in midlife is necessary for prevention of dementia onset. 2C

Comments and evidence

Many meta-analysis and systematic reviews of observational studies have reported that diabetes is a risk factor for dementia (Alzheimer's disease dementia, vascular dementia, and mixed dementia) [1-9]

A 9-year follow-up of older people aged 75 years and above, comprising 963 subjects with normal cognitive function and 302 subjects with mild cognitive impairments (120 with amnestic mild cognitive impairments, 182 without dementia but having other cognitive impairment), the rate of conversion to dementia was 2.87 times in the diabetes group and 4.96 times in the pre-diabetes group [1].

The mechanisms by which diabetes affects the pathology of Alzheimer's disease dementia presumably involve cell biological and molecular interactions of multiple factors including hyperinsulinemia and impaired insulin secretion [2]. It remains unclear whether endogenous or exogenous insulin adversely affects cognitive function.

According to the results of the Hisayama study, diabetes is a significant risk for the development of Alzheimer's disease dementia and vascular dementia. The risk of developing vascular dementia increased with increased level of glucose tolerance impairment, and the risk of developing Alzheimer's disease dementia increased significantly with increased severity of diabetes (hazard ratio 2.1) [3].

A report indicates that controlling diabetes together with hypertension and lipids can reduce vascular events, and improve cognitive decline related to vascular dementia [4].

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Search formula

PubMed search: June 13, 2015 (Saturday)

#1 (("Dementia" [Majr] OR dementia [TI] OR "Cognition Disorders" [Majr] OR "cognition disorder*" [TI]) AND ("Diabetes Mellitus" [Majr] OR "diabetes mellitus" [TI] OR "Insulin Resistance" [Majr] OR "Insulin" [Majr] OR insulin [TI])) OR (("Dementia/prevention and control" [Mesh] OR (dementia AND prevent*) OR "Cognition Disorders/prevention and control" [Mesh] OR ("cognition disorder*" AND prevent*)) AND ("Diabetes Mellitus/ therapy" [Mesh] OR ("diabetes mellitus" AND (therapy OR therapeutic OR treatment))))

Ichushi search: June 13, 2015 (Saturday)

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CQ 4A-4

Is treatment for dyslipidemia effective for dementia prevention?

Recommendation

Dyslipidemia in midlife is a risk factor for dementia, especially Alzheimer's disease dementia. Statins have been reported to reduce the risk of dementia, and lipid control in midlife is desirable. Since the effects of serum cholesterol level on dementia in older people remain uncertain, statins should be used with caution in older people. 2C

Comments and evidence

Research so far has shown that hypercholesterolemia is a risk for Alzheimer's disease dementia [1]. Therefore, many studies have been conducted to examine the effect of administration of statins, therapeutic drugs for dyslipidemia, in preventing development of dementia including Alzheimer's disease dementia. However, the results of these studies are not consistent. In general, randomized controlled trials (RCT) have not yielded effective results, and data indicating effectiveness are largely reported by observational studies.

In a Cochrane review that analyzed two RCTs in patients with dyslipidemia and risk of developing dementia (cardiovascular and cerebrovascular disorder, lifestyle-related diseases), administration of statins was not associated with the onset of dementia, changes in various neuropsychological tests, or occurrence of adverse events [2].

Regarding the prevention of further cognitive decline by statin administration in persons with Alzheimer's disease dementia (including suspected cases), a Cochrane review reported a meta-analysis of only three large-scale RCTs with 748 subjects. No significant preventive effect of disease progression was observed in any of the three batteries: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), Mini Mental State Examination (MMSE), and Clinician's Global Impression of Change (CGIC) [3].

In a systematic review of observational studies that examined the effects of statins other than improvement of dyslipidemia in the general population, the incidence of dementia among statin users was low in 13 meta-analysis [5].

In a meta-analysis based on 8 prospective observational studies, statins reduced the risk of dementia by 38% [relative risk (RR) 0.62, 95% confidence interval (CI) 0.4 to 0.81] [6].

In a meta-analysis based on 20 studies (16 observational studies, 3 case-control studies, 1 RCT), statins reduced the risk of developing dementia by 38% (RR 0.62, 95% CI 0.43 to 0.82). Even when the endpoint was limited to Alzheimer's disease dementia, the risk of developing dementia was reduced by 24% (RR 0.76, 95% CI 0.65 to 0.90) [7].

The effect of dyslipidemia on cognitive decline varies with age. Midlife dyslipidemia, especially hypercholesterolemia, has been shown to be a risk factor for Alzheimer's disease dementia, and strict control of lipid abnormalities in midlife is desirable. There are also reports that higher serum cholesterol level in older people is associated with lower risk of developing Alzheimer's disease dementia. Therefore, statins have to be used with caution in older people.

In one report, statin treatment for mild cognitive impairment reduced the hazard risk of developing Alzheimer's disease dementia by 67% [8].

In another report, statin administration to older people with vascular risk factors did not prevent cognitive decline or prevent dementia [9].

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Search formula

PubMed search: June 13, 2015 (Saturday)

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Ichushi search: June 13, 2015 (Saturday)

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CQ 4A-5

Does metabolic syndrome worsen dementia?

Recommendation

There are many reports indicating that metabolic syndrome and its factors (abnormal glucose tolerance, obesity, hypertension, and dyslipidemia) are associated with ageing-related cognitive decline, mild cognitive impairment, and vascular dementia. However, opinions on Alzheimer's disease dementia are divided. 2C

Comments and evidence

Many reports have shown that metabolic syndrome, especially in midlife, is associated with cognitive decline. Obesity in midlife is associated with an increase in risk of dementia [risk ratio (RR) 1.41], although the risk decreases at age 65 and above (RR 0.83) [1].

In one study of adults aged below 65 years, metabolic syndrome was associated with memory impairment, visuospatial impairment, and impaired executive function [2]. In a 25-year longitudinal study of 3,555 subjects, patients who fulfilled multiple items of metabolic syndrome had increased risk of dementia, particularly vascular dementia, but no increase in risk of Alzheimer's disease dementia [3].

According to a 3.5-year longitudinal study of 2,097 persons aged 65 to 84 years, among subjects with mild cognitive impairment, those who had coexisting metabolic syndrome had a significantly higher risk of developing dementia compared with those without metabolic syndrome [3].

When 837 persons with mild cognitive impairment were observed for 5 years, 352 (42.1%) converted to Alzheimer's disease dementia, and these patients had significantly more vascular risk factors than those who remained having mild cognitive impairment (2.33 vs 1.15, $p < 0.001$) [4]. In the group treated for all the vascular risk factors (hypertension, diabetes, and dyslipidemia) during the stage of mild cognitive impairment, the rate of conversion to Alzheimer's disease dementia was lower compared to the group not treated at all [4].

Persons with Alzheimer 's disease dementia who had no cerebrovascular disorders and were treated for hypertension, diabetes, and dyslipidemia have slower decline in cognitive function compared with persons without any risk factors [5].

Even in persons with metabolic syndrome, treating risk factors for arteriosclerosis may prevent cognitive decline [6].

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■ Search formula

PubMed search: June 13, 2015 (Saturday)

#1 (("Dementia" [Majr] OR dementia [TI] OR "Alzheimer's disease" [TI] OR "Alzheimer disease" [TI] OR "Cognition Disorders" [Majr] OR "cognition disorder*" [TI]) AND ("Metabolic Syndrome X" [Majr] OR "metabolic syndrome" [TI])) OR (("Dementia/prevention and control" [Mesh] OR ((dementia OR "Alzheimer's disease" OR "Alzheimer disease") AND prevent*) OR "Cognition Disorders/prevention and control" [Mesh]OR("cognition disorder*" AND prevent*)) AND ("Metabolic Syndrome X" [Mesh] OR "metabolic syndrome"))

Ichushi search: June 13, 2015 (Saturday)

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CQ 4A-6

Does smoking worsen dementia?

Recommendation

Smoking worsens all-cause dementia, vascular dementia, and Alzheimer's disease dementia. 1B

Comments and evidence

The results of 37 large-scale studies show that smoking worsens dementia [risk ratio (RR) 1.30], vascular dementia (RR 1.38), and Alzheimer's disease dementia (RR 1.40). The risk of Alzheimer's disease dementia is significantly higher in current smokers who are APOE ε4 non-carriers. People aged between 65 and 75 who smoke have an increased risk of all-cause dementia and Alzheimer's disease dementia compared with those who do not smoke [1-3].

Smoking 20 cigarettes a day increases the risk of all-cause dementia (RR 1.34) [1]. Persons who have ever smoked are at higher risk for all-cause dementia (RR 1.13) and vascular dementia (RR 1.25) than those who never smoke. On the other hand, those who smoked before but have quitted smoking do not have an increased risk for all-cause dementia [1].

In recent large-scale trials, smoking is often reported as a risk factor for all-cause dementia [1, 3].

The global smoking rate is 27.4%. The increase in risk of Alzheimer's disease dementia due to smoking has a RR of 1.59, and the population attributable risk (PAR) is 13.9%. Approximately 14% of Alzheimer's disease dementia worldwide is reported to be caused by smoking [3].

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■ Search formula

PubMed search: June 13, 2015 (Saturday)

#1 (("Dementia" [Majr] OR dementia [TI] OR "Alzheimer's disease" [TI] OR "Alzheimer disease" [TI] OR "Cognition Disorders" [Majr] OR "cognition disorder*" [TI]) AND ("Smoking" [Majr] OR smoking [TI])) OR (("Dementia/ prevention and control" [Mesh] OR ((dementia OR "Alzheimer's disease" OR "Alzheimer disease") AND prevent*) OR "Cognition Disorders/prevention and control" [Mesh] OR ("cognition disorder*" AND prevent*)) AND ("Smoking" [Mesh] OR "smoking"))

Ichushi search: June 13, 2015 (Saturday)

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CQ 4A-7

Is exercise effective in preventing dementia?

Recommendation

Many observational studies have reported that regular physical activity is associated with reduced incidence of all-cause dementia and Alzheimer's disease dementia. Interventional studies in older persons without dementia and older persons with mild cognitive impairment report that physical activity protects against cognitive decline. Active incorporation of exercise is recommended. 1B

Comments and evidence

Decreased walking speed and reduced grip strength in middle-aged to older persons are related to cognitive impairment [1]. Physical activity and habitual exercise during middle age to old age have been shown to be associated with reduced incidence of dementia and Alzheimer's disease dementia [2, 3].

A meta-analysis has reported that intervention of physical activity for older persons without dementia improves attention and judgment [4]. In a meta-analysis of 14 randomized controlled trials (RCT) that studied older people aged 65 years and above with mild cognitive impairment or Mini Mental State Examination (MMSE) scores of 24-28 points, exercise intervention significantly improved verbal fluency, but did not significantly improve executive function, memory or information processing [5]. In a RCT studying older Japanese persons with mild cognitive impairment, implementation of a combination of physical exercise and cognitive tasks that stimulate attention and memory (such as calculation and word chain), so-called "cognicise", improved logical memory and MMSE score as well as prevented the progression of hippocampal atrophy [6].

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■ Search formula

PubMed search: June 2, 2015 (Tuesday)
#1 (("Dementia/prevention and control" [Mesh] OR "Cognition Disorders/prevention and control" [Mesh] OR "Alzheimer Disease/therapy" [Majr] OR "Mild Cognitive Impairment/therapy" [Majr]) AND ("Exercise" [Majr] OR "Exercise therapy" [Majr])) OR (("Dementia/prevention and control" [Majr] OR "Cognition Disorders/prevention and control" [Majr]) AND ("Exercise" [Mesh] OR "Exercise therapy" [Mesh]))

Ichushi search: June 2, 2015 (Tuesday)
#1 (Dementia/TH OR Dementia/TI) AND (Preventive medicine/TH OR (SH = Prevention) OR Prevention/TI) AND (Physical exercise/TH OR Sports/TH OR Exercise therapy/TH)

CQ 4A-8

Are leisure activities, social participation, mental activities, cognitive training, and artistic activities such as music effective in preventing dementia and cognitive decline in older people?

Recommendation

The effect of cognitive training is not consistent. While some reports show that cognitive training is effective in preventing cognitive decline, other reports find no significant difference. Cognitive training and exercise reduce the risk of cognitive decline. For leisure activities, since the definitions are not clear, further analysis is needed in the future.

2C

Comments and evidence

Leisure activities include intellectual elements (such as games, chess, mahjong, and going to movies or theater), physical elements (such as sports, walking, and aerobics, etc.), and social elements (such as meeting friends, volunteer activities, and travelling). Many reports have shown that leisure activities are effective in preventing the onset of dementia and Alzheimer's disease dementia. Although observational studies [1, 2] report that leisure activities from middle age to old age reduce the risk of developing Alzheimer's disease dementia, the definition of leisure activity is not clear [3]. Therefore, further analysis is necessary.

While reports have indicated a possibility that cognitive training (see CQ3A-7-1) is effective in preventing functional decline with respect to memory [4, 5], other report shows no significant difference [6]. Some randomized controlled trials (RCT) report that cognitive training and exercise reduce the risk of cognitive impairment [7-9].

There are 12 reports on meditation therapy, including 6 RCTs. The results suggest that mediation may prevent cognitive decline [10].

The preventive effect of music therapy for cognitive decline is unknown, but a meta-analysis of RCTs in patients with dementia finds that rather than cognitive function, music therapy is effective in improving behavioral and psychological symptoms of dementia (BPSD) as well as anxiety [11].

There are only case reports and reports of small-scale study on the effect of art therapy [12,13].

References

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Search formula

PubMed search: June 15, 2015 (Monday)

#1 ("Dementia/prevention and control" [Mesh] OR (dementia AND prevent*) OR "Cognition Disorders/prevention and control" [Mesh] OR ("cognition disorder*" AND prevent*)) AND ("Leisure Activities" [Mesh] OR leisure activity* OR "Learning" [Mesh] OR "memory training" OR cognitive activity* OR "Neuronal Plasticity" [Mesh] OR "cognitive plasticity" OR (physical AND social component*) OR "Psychotherapy" [Mesh] OR "music therapy" OR "art therapy")

Ichushi search: June 15, 2015 (Monday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Leisure activities/TH OR Leisure activities/TI OR Leisure/TI OR Social participation/TH OR Social participation/TI OR Social participation/TI OR mental activities/AL OR Cognitive training/AL OR Perceptive art therapy/TH OR Art therapy/TI OR Music therapy/TI) AND (Prevention/TI OR Management/TI OR (SH = Prevention))

CQ 4A-9

Are there dietary factors associated with dementia?

Recommendation

There are many reports on dementia, diet and nutrition. High-calorie diets composed mainly of carbohydrates, low-protein diets and low-fat diets tend to increase the risk of mild cognitive impairment and dementia. No definitive results are available for individual nutrients. 2C

Comments and evidence

Many studies on dementia and dietary factors have been reported, most of which are observational studies. While these observational studies have accumulated a vast amount of knowledge about the relationship between diet, nutrition and cognitive function, no definitive conclusions have been reached on the specific foods, nutrients, or dietary patterns that increase the risk of developing dementia or prevent the development of dementia. Some randomized controlled trials (RCTs) have been performed, but they have not yielded any definitive results so far.

High-calorie diets composed of mainly carbohydrates may increase the risk of mild cognitive impairment and dementia. As a possible cause, diets with high blood glucose load may have adverse effects on glucose and insulin metabolism. On the other hand, low-protein diets and low-fat diets also tend to increase the risk of mild cognitive impairment and dementia [1].

According to reports of the Hisayama study on the relation between dietary patterns and risk of dementia, consumption of soybeans, soybean products, vegetables, seaweed, milk and dairy products reduces the risk of dementia, while consuming larger quantity of rice increases the risk of dementia [2, 3].

The Rotterdam study reports on the relation between antioxidants and dementia. Consumption of foods high in vitamin E slightly reduces the risk of dementia over the long term. On the other hand, vitamin C, beta-carotene, and flavonoids are not associated with the risk of dementia. Furthermore, consumption of fish and omega-3 fatty acid is also not related to the risk of dementia [4, 5].

Opinions are divided on caffeine, coffee, and tea. In general, the degree of cognitive decline tends to be lower in consumers of the above products. However, the level of consumption related to this effect remains unclear [6].

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6) Arab L, Khan F, Lam H. Epidemiologic evidence of a relationship between tea, coffee, or caffeine consumption and cognitive decline. Adv Nutr. 2013; 4(1): 115-122.

■ Search formula

PubMed search: June 15, 2015 (Monday)

#1 ("Dementia/etiology"[Mesh] OR "Dementia/epidemiology"[Mesh] OR (dementia AND (etiology* OR epidemiology*)) OR "Cognition Disorders/etiology" [Mesh] OR "Cognition Disorders/epidemiology" [Mesh] OR ("cognition disorder*" AND (etiology* OR epidemiology*))) AND ("Food and Beverages" [Mesh] OR food OR beverage*) AND ("Risk" [Mesh] OR risk)

Ichushi search: June 15, 2015 (Monday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Foods and drinks/TH OR Foods/TI OR Drinks/TI OR Diet/TH OR Diet/TI) AND (Risk/TH OR Risk/TI OR Risk/TI)

CQ 4A-10

Is moderate drinking effective in preventing cognitive decline and dementia?

Recommendation

A report has shown that moderate drinking of alcoholic drinks has preventive effect on dementia. Caution should be exercised in interpreting this finding, because the definition of "moderate drinking" differs depending on race and on individuals. This should not be recommended to persons who cannot drink. 2C

Comments and evidence

Alcohol is inherently neurotoxic, and heavy drinking causes atrophy of the brain. On the other hand, moderate drinking has been reported to prevent dementia. In particular, appropriate consumption of red wine has been reported to prevent cognitive decline.

According to observational studies in persons with a healthy lifestyle, low to moderate alcohol consumption reduces the odds ratio of cognitive decline or dementia [1], but heavy alcohol consumption increases the risk of conversion from mild cognitive impairment to dementia [2]. While red wine has a preventive effect against cognitive decline, other alcoholic beverages such as beer, white wine, fortified wine (wine with high alcohol content), spirits (such as gin and vodka) have no such effect, suggesting that ingredients other than alcohol in red wine may have a preventive effect [3]. In addition, a case-control study has found that habitual drinking in older people protects against the development of vascular dementia (odds ratio 0.48) [4].

Note that the relationship between drinking and cognitive function has not been proven by randomized controlled trial (RCT) due to ethical restrictions.

References

1) Elwood P, Galante J, Pickering J, et al. Healthy lifestyles reduce the incidence of chronic diseases and dementia: evidence from the Caerphilly cohort study. PLoS One. 2013; 8(12): e81877.
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Search formula

PubMed search: June 15, 2015 (Monday)
#1 ("Dementia/prevention and control" [Mesh] OR (dementia AND prevent*) OR "Cognition Disorders/prevention and control" [Mesh] OR ("cognition disorder*" AND prevent*)) AND ("Alcohol Drinking" [Mesh] OR alcohol drinking* OR "Alcoholic Beverages" [Mesh] OR alcoholic beverage*)

Ichushi search: June 15, 2015 (Monday)
#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Alcoholic beverage/TH OR Alcohol/TI OR Drinking/TH OR Drinking/TI)

CQ 4A-11

Does sleep apnea syndrome worsen cognitive function?

Recommendation

Sleep apnea syndrome, while being a vascular risk factor, is also associated with cognitive impairment. Continuous positive airway pressure therapy improves cognitive impairment. 2C

Comments and evidence

Many observational studies have shown that sleep apnea syndrome and sleep-disordered breathing are vascular risk factors, and at the same time are associated with cognitive decline. In addition, although continuous positive airway pressure therapy, which is used as a treatment for sleep apnea syndrome, is expected to contribute to the improvement of cognitive function, there remain many unclear aspects about the relationship between severity and therapeutic effect.

A report from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study has shown that the presence of sleep apnea syndrome accelerates the development of mild cognitive impairment and Alzheimer's disease dementia, and that treatment with continuous positive airway pressure delays the progression of dementia [1].

A meta-review of reports suggesting that sleep apnea syndrome affects cognitive function indicates that sleep apnea is related to deficits in attention, long-term visual and verbal memory, visuospatial cognitive function, and executive function, but does not affect language ability and psychomotor function [2, 3]. In older women, reports have shown that shortened sleep time, hypoxia during sleep, and sleep apnea increase the risk of cognitive decline [4, 5].

Several observational studies [1, 2] and randomized controlled trials (RCT) [6, 7] have reported that continuous positive airway pressure therapy improves the decline of cognitive functions associated with sleep apnea.

■ References

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■ Search formula

PubMed search: June 17, 2015 (Wednesday)
#1 ("Dementia" [Mesh] OR dementia OR "Cognition Disorders" [Mesh] OR cognition disorder*) AND ("Sleep Apnea Syndromes" [Mesh] OR "sleep apnea syndrome")

Ichushi search: June 17, 2015 (Wednesday)
#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (sleep apnea syndrome/TH OR sleep apnea syndrome/TI)

CQ 4A-12

Are depression and bipolar disorder risk factors for dementia?

Recommendation

Multiple observational studies have reported that a history of depression 1B or bipolar disorder 2C is associated with increased risk of developing dementia.

Comments and evidence

Many studies have reported that a history of depression is associated with increased risk of developing dementia in older age [1, 2]. Although the possibility that depression symptoms *per se* may be the initial symptoms of dementia has been noted, the relationship between early-onset depression and development of dementia in old age, as well as the relationship between the number of episodes of depressive symptoms and the risk of dementia have been reported [3], supporting the notion that depressive symptoms are a risk factor for dementia.

While many studies focus on Alzheimer's disease dementia, there are reports indicating that a history of depression is also a risk factor for vascular dementia (VaD).

A few reports have shown that a history of bipolar disorder increases the development of dementia, but there is opinion that a bias may be present since patients with bipolar disorder are in an environment that facilitates a diagnosis of dementia compared to control patients [1]. Although observational studies have reported that the rate of developing dementia decreases with continuous treatment with antidepressants for depression and lithium for bipolar disorder [4, 5], there is no clear evidence from interventional study that these treatments reduce the development of dementia.

References

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Search formula

PubMed search: June 3, 2015 (Wednesday)
#1 ("Dementia/etiology" [Mesh] AND ("Mood Disorders/complications" [Mesh] OR "Depression/complications" [Mesh]) AND "Risk Factors" [Mesh]) OR ("Dementia/epidemiology" [Majr] AND ("Mental Disorders/epidemiology" [Majr] OR "Mood Disorders/epidemiology" [Majr]) AND "Age Factors" [Mesh] AND "Epidemiologic Methods" [Mesh] AND risk [TI]) OR (risk [TI] AND dementia [TI] AND (depression OR "bipolar disorder"))

Ichushi search: June 3, 2015 (Wednesday)
#1 (Dementia/TH OR Dementia/TI) AND (Depression OR Depression OR bipolar disorder) AND (Risk factor OR Risk)

B | Mild Cognitive Impairment

CQ 4B-1

What are the prevalence and incidence of mild cognitive impairment (MCI)?

Answer

Although the data vary from study to study, the prevalence of MCI is estimated to be 15-25% in older people aged 65 years and above, and the incidence is estimated to be 20-50 per 1,000 people per year.

Comments and evidence

1. Prevalence [1-4)]

The original diagnostic criteria for MCI was published by Petersen et al.[1)]. Since then, various criteria for diagnosis of mild cognitive impairment have been used in epidemiological studies, which greatly affect the prevalence and incidence obtained from these studies. Since a large amount of epidemiological data focuses on amnestic mild cognitive impairment, which is a subtype of mild cognitive impairment restricted to memory impairment, this situation also causes some confusion. Moreover, the prevalence would differ depending on whether subject recruitment of an epidemiological study is community-based or population-based. The range of the results obtained also differs depending on the magnitude (how high or how low) and the range of the subjects' ages.

If one only views the data without considering the above factors, the statistics would yield a prevalence of approximately 15-25% in most studies. When limited to amnestic mild cognitive impairment, prevalence with a range from 2.4% to 28.3% in those aged 65 and above has been reported.

2. Incidence [4, 5)]

Since the age of the cohort participating in survey varies from study to study, the incidence ranges from 20 to 50 per 1,000 person per year. When limited to amnestic mild cognitive impairment, the incidence has been reported to be 9.9-40.6 per 1,000 persons per year.

The prevalence is higher in recent reports.

■ References

1) Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999; 56(3): 303-308.
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■ Search formula

PubMed search: June 5, 2015 (Friday)
#1 ("Mild Cognitive Impairment/epidemiology" [Mesh] OR "Mild Cognitive Impairment" AND "Cognition Disorders/epidemiology" [Mesh]) AND "Morbidity" [Mesh]

Ichushi search: June 5, 2015 (Friday)
#1 (mild cognitive impairment/TH OR mild cognitive impairment/TI) AND (prevalence OR incidence OR incidence)

CQ 4B-2

What is the conversion rate from mild cognitive impairment (MCI) to dementia, and the reversion rate from MCI to cognitive normal?

Answer

The conversion rate from mild cognitive impairment to dementia is estimated to be approximately 5-15% per year. The reversion rate is estimated to be approximately 16-41% per year.

Comments and evidence

The data for conversion from mild cognitive impairment to dementia varies from study to study. In addition, it should be noted that the results differ depending on whether the study involves follow-up by medical specialists or is community-based. Naturally, the conversion rate would be high if follow-up is done by specialists. Conversion occurs at a rate of approximately 5-15% per year. By type of dementia, the rate of conversion diagnosed by specialists is 8.1% for Alzheimer's disease dementia and 1.9% for vascular dementia. In community-based studies, the conversion rates for the two types are 6.8% and 1.6%, respectively, with higher rate for Alzheimer's disease dementia.

On the other hand, the reversion rates from mild cognitive impairment to a cognitive normal state range widely from 16 to 41% per year.

■ Further reading

1) Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand. 2009; 119(4): 252-265.
2) Roberts R, Knopman DS. Classification and epidemiology of MCI. Clin Geriatr Med. 2013; 29(4): 753-772.

■ Search formula

PubMed search: June 5, 2015 (Friday), August 14, 2015 (Friday)

#1 ((“Mild Cognitive Impairment” [Mesh] OR (“Mild Cognitive Impairment” AND “Cognition Disorders” [Mesh])) AND “Dementia” [Mesh] AND(“conversion rate” OR “conversion rates” OR “reversion rate” OR “reversion rates” OR ((convert [TI] OR conversion [TI] OR reversion [TI] OR revert [TI]) AND (rate [TI] OR rates [TI])))) OR ((“Mild Cognitive Impairment/epidemiology” [Majr] OR (“Mild Cognitive Impairment” [TI] AND “Cognition Disorders/epidemiology” [Majr])) AND “Dementia/epidemiology” [Mesh] AND (“Incidence” [Mesh] OR “Prevalence” [Mesh]))

Ichushi search: June 5, 2015 (Friday)

#1 (mild cognitive impairment/TH OR mild cognitive impairment/TI) AND (Dementia/TH OR Dementia/TI) AND (Convert OR Conversion OR Revert OR Reversion)

CQ 4B-3

What are the useful biomarkers for predicting conversion of mild cognitive impairment (MCI) to dementia?

Answer

Abnormal cerebrospinal fluid levels of Aβ42, phosphorylated tau, and total tau; presence of APOE gene ε4 polymorphism; and abnormal findings on amyloid PET and ^{18}FDG-PET have been considered to be useful biomarkers for predicting conversion from mild cognitive impairment (MCI) to dementia. B

Comments and evidence

Most studies on risk factors for conversion of mild cognitive impairment to dementia focus on Alzheimer's disease. The clinical state of MCI due to Alzheimer's disease coincides with the pathological stage of completion of Aβ and phosphorylated tau accumulation in the brain. Persons showing an Alzheimer's disease pattern in biomarker study tend to convert to dementia.

1. Humoral markers

a. Cerebrospinal fluid [1)]

In a meta-analysis that analyzed 10 studies, cerebrospinal fluid biomarkers predicted conversion from MCI to dementia with the following performance: abnormal Aβ42 level with 79% sensitivity and 72% specificity, abnormal total tau level with 72% sensitivity and 70% specificity, abnormal phosphorylated tau with 84% sensitivity and 93% specificity, and abnormal ratio of Aβ42/phosphorylated tau with 85% sensitivity and 79% specificity.

b. Genes [2)]

A meta-analysis of 8 studies found that carriers of APOE ε4 polymorphism tended to convert from MCI to dementia, with a relative risk of 2.09.

c. Blood

Reports of research on various blood biomarkers including proteins and microRNA have been published, but none of the biomarkers showed consistent performance that is reproducible in multiple studies.

2. Imaging biomarkers

a. MRI

Cohort studies have reported that the volumes of hippocampus, amygdala, and entorhinal cortex at the start of study were reduced in the group showing conversion compared to the group that did not convert. Moreover, higher atrophy rates of hippocampus, entorhinal cortex, and temporal cortex depicted on serial images taken over time were associated with higher rate of conversion. However, no conclusion has been reached as to the site and size of atrophy, and the rate of atrophy that best predicts conversion [3-7)].

b. FDG-PET [8)]

In a meta-analysis analyzing 14 studies, ^{18}FDG-PET predicted conversion with 76% sensitivity and 82% specificity.

c. Amyloid PET [9)]

In a meta-analysis that analyzed 11 studies using ^{11}C-labelled Pittsburgh Compound-B (^{11}C-PIB)-PET, this method predicted conversion of MCI to dementia with 96% sensitivity and 58% specificity. There is no meta-analysis of studies using ^{18}F ligand preparations.

d. SPECT [10)]

Although SPECT is a frequently used examination in Japan, this method is not widely used globally. In a meta-analysis of 8 studies, this test predicts conversion with 83.8% sensitivity and 70.4% specificity.

References

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2) Fei M, Jianhua W. Apolipoprotein ε4-allele as a significant risk factor for conversion from mild cognitive impairment to Alzheimer's disease: a meta-analysis of prospective studies. J Mol Neurosci. 2013: 50(2): 257-263.
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Search formula

PubMed search: June 27, 2016 (Monday)

#1 ("Mild Cognitive Impairment" [Mesh] OR Mild Cognitive Impairment* [TIAB]) AND (convert [TIAB] OR conversion [TIAB] OR reversion [TIAB] OR revert [TIAB]) AND ("Biomarkers" [Mesh] OR biomarker* [TIAB] OR marker* [TIAB] OR predict* [TIAB] OR marked* [TIAB])

Ichushi search: June 27, 2016 (Monday)

#1 (mild cognitive impairment/TH OR mild cognitive impairment/TI) AND (Convert OR Conversion OR Revert OR Reversion) AND (Biomarker/TH OR Marker)

CQ 4B-4

What rating scales are recommended when mild cognitive impairment (MCI) is suspected?

Answer

The Mini Mental State Examination (MMSE) is not adequate to detect mild cognitive impairment (MCI). Therefore, the Montreal Cognitive Assessment-Japanese version (MoCA-J) is recommended. Instead of MMSE alone, adding slightly complex memory tasks such as sentence memorization facilitates the diagnosis of amnestic mild cognitive impairment.

C

Comments and evidence

The MoCA-J is more challenging than MMSE because the memory task requires recall of five words and the scale also includes tests of frontal lobe function., and is therefore suitable for the diagnosis of MCI. When the cutoff score for MoCA was set at 25/26 out of 30, MCI is diagnosed with 95% sensitivity and 50% specificity for the English version, and 93% sensitivity and 87% specificity for the Japanese version [1, 2]

Addenbrooke's Cognitive Examination-Revised (ACE-R) is an MMSE test with the addition of other elements including anterograde/retrograde memory, naming words, and visuospatial cognitive function. When the cut-off score is 88/100, ACE-R differentiates MC1 with better sensitivity and specificity than MMSE [3].

Amnestic MC1 can be detected more easily by adding detailed memory tests such as Wechsler Memory Scale-Revised (WMS-R) and Rey Auditory Verbal Learning Test (RAVLT). Although the clock drawing test is widely used, this test has been reported to be unsuitable for the discrimination of MCI because of low sensitivity (58.2%) and specificity (57.3%) [4].

Regarding evaluation based on questionnaires and interviews with caregivers, reports have indicated the effectiveness of questionnaires on instrumental activities of daily living and total score of Clinical Dementia Rating (CDR) for diagnosing MCI [5, 6]. Some studies use CDR 0.5 as a test for MCI, for convenience. Cognitive Function Instrument (CFI), which asks the patient and the family about changes in cognitive activities compared to one year ago, has been reported to be useful for the evaluation of functional abilities before onset of Alzheimer's disease dementia [7].

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CQ 4B-5

How is mild cognitive impairment (MCI) diagnosed?

Answer

Mild cognitive impairment (MCI) is originally a concept centered on memory impairment. MCI is classified into amnestic MCI and non-amnestic MCI by the presence or absence of memory impairment. Furthermore, it is divided into single-domain or multiple-domain depending on whether the impairment involves a single cognitive function domain or multiple domains. Similar concept is also found in Clinical Dementia Rating (CDR) 0.5; mild neurocognitive disorder in Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5); and mild cognitive disorder (MCD) in International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10).

Comments and evidence

Petersen established the concept that the state of mild cognitive impairment may represent the prodrome stage of dementia [1]. The diagnostic criteria for MCI were defined in 1995 [2]. Since then, some additions and corrections have been made based on research and books, but the fundamental concept remains unchanged. As subtypes of mild cognitive impairment, amnestic mild cognitive impairment is defined as predominantly memory impairment, and non-amnestic mild cognitive impairment is defined as impairment of other functions including execution, attention, language, and visuospatial cognition [3]. It should be noted that MCI is a diagnosis based on symptoms, and the pathological background is diverse.

1. Criteria of Petersen [2, 4, 5]

Mild cognitive impairment is a concept centered on memory impairment, and refers to a state (not dementia) in a person who complains of memory loss and who has low scores in memory tests adjusted for age and years of education. The detailed criteria are as follows.

- Cognitive function has declined compared to before, which is reported by the patient and corroborated by informant and experienced clinical doctor.
- Has impairment in at least one of the following cognitive function domains: memory, execution, attention, language, and visuospatial cognition.
- Is independent in activities of daily living. May require more time than before, or become inefficient, or make mistakes.
- Not dementia.

2. Diagnostic criteria of DSM-5 [6]

In DSM-5, dementia is renamed major neurocognitive disorder, and mild cognitive impairment is termed mild neurocognitive disorder. The diagnostic criteria for mild neurocognitive disorder in DSM-5 include mild decline in one or more cognitive domains that can be confirmed from cognitive function tests and a reliable informant, but the impairment does not interfere with daily life. These criteria are not much different from other diagnostic criteria. On the other hand, regarding the results of neuropsychological test battery, the decline in cognitive function is described as -1 to -2SD. This range differs slightly from the NIA-AA criteria, which will be described later.

3. Diagnostic criteria of ICD-10 [7]

In ICD-10, mild cognitive disorder (MCD) is adopted as a concept equivalent to mild cognitive impairment.

4. Clinical Dementia Rating (CDR) 0.5 [8]

The CDR evaluates memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care; each scored on a 5-grade scale of 0, 0.5, 1, 2, and 3. The overall score is determined after weighting. An overall score of 0.5 corresponds to mild cognitive impairment.

5. Diagnostic criteria of National Institute on Aging–Alzheimer's Association workgroup (NIA-AA) [9, 10]

In addition to clinical diagnostic criteria, biomarker criteria are provided in the NIA-AA criteria. The degree of cognitive decline based on the neuropsychological test battery is described as -1 to -1.5 SD compared with age- and education-matched peers, which is slightly different from that described in DSM-5.

6. Criteria of International Working Group-2 [11)]

In the diagnostic criteria for Alzheimer's disease published in 2014, an attempt was made to change the conventional division of "preclinical Alzheimer's disease", "prodromal Alzheimer's disease", and "Alzheimer's disease dementia" into two groups: "preclinical Alzheimer's disease" and "Alzheimer's disease". In other words, the concept is not to distinguish between mild cognitive impairment and dementia based on the pathological background of Alzheimer's disease, but to diagnosis Alzheimer's disease when clinical symptoms are present, including amnesia alone.

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■ Search formula

PubMed search: June 5, 2015 (Friday), August 26, 2015 (Wednesday)
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diagnosis" [Majr] AND "diagnostic criteria" [TI]) OR ("clinical dementia rating" AND "Dementia/psychology" [Majr] AND "Psychiatric Status Rating Scales" [Majr]))

Ichushi search: June 5, 2015 (Friday)
#1 (mild cognitive impairment/MTH OR mild cognitive impairment/TI) AND (SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis)

CQ 4B-6

Are there methods to prevent progression from mild cognitive impairment (MCI) to dementia?

Recommendation

Control of hypertension, diabetes, dyslipidemia and other risk factors, as well as continued practice of moderate exercise are recommended. There is no sufficient evidence that anti-dementia drugs should be used for the purpose of preventing progression to dementia in persons with mild cognitive impairment. 2C

Comments and evidence

Methods for preventing progression from mild cognitive impairment to dementia include pharmacotherapy, non-pharmacological therapies, and interventions for risk factors.

For pharmacotherapy, the effect of cholinesterase inhibitors in improving cognitive function has been confirmed in patients with mild cognitive impairment, but the effect of preventing progression from mild cognitive impairment to dementia remains unclear [1-3]. Estrogen therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), extract from leaves of ginkgo tree (*Ginkgo biloba*), and vitamin E have been studied, but the effect of preventing progression from mild cognitive impairment to dementia has not been confirmed for any of these treatments.

Non-pharmacological therapies including moderate physical activity, aerobic exercise, Mediterranean diet, cocoa, and smoking cessation have been suggested to be effective, but most studies were conducted in a small number of subjects and hence do not provide sufficient evidence [4-6]. Several studies suggest that cognitive rehabilitation or cognitive training is effective in maintaining and improving cognitive function, but further intervention studies are needed to standardize intervention and assessment methods [7-10] (see CQ4A).

Studies have clarified that a history of hypertension, diabetes, dyslipidemia (hypercholesterolemia) or cerebrovascular disorders is a risk factor that promotes progression from mild cognitive impairment to dementia, not only for vascular dementia but also for Alzheimer's disease dementia [11]. Although there is still insufficient evidence that controlling these risk factors can prevent progression to dementia, appropriate control is recommended for patients with these risk factors (see CQ4A).

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Search formula

PubMed search: July 17, 2015 (Friday), August 26, 2015 (Wednesday)

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Ichushi search: July 17, 2015 (Friday)

#1 (Mild cognitive impairment/TH OR Mild cognitive impairment/TI OR MCI/TI) AND ((SH = Therapeutic use, Treatment, Drug treatment, Surgical treatment, Transplantation, Dietary treatment, Psychiatric treatment, Radiologic treatment, Rehabilitation, Prevention) OR Treatment/TH OR Treatment/TI OR Therapy/TI OR Rehabilitation/TI OR Training/TI OR Training/TI OR Program/TI) AND (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI) AND ((SH = Prevention) OR Prevention/TH OR Prevention/TI)

CQ 4B-7

What kinds of guidance and support are available for people with mild cognitive impairment (MCI)?

Answer

It is necessary to provide proper information about mild cognitive impairment to the patients as well as caregivers in order to promote correct understanding of the disease.

Provide support to enable the patients to continue living independently for as long as possible by introducing assistive devices utilizing information technology (IT), practicing the use of calendars and notebooks, and modifying the living environment. C

Comments and evidence

Unlike those with dementia, persons at the stage of mild cognitive impairment (MCI) are independent in basic activities of daily living (ADL). Therefore, daily care and support for these persons are not necessary. However, in situations such as heart failure where self-care is required, MCI may worsen the prognosis.

The memory support system (MSS) that trains patients to enter schedules and events in calendars and notebooks can be expected to improve ADL and self-efficacy of patients with MCI and reduce the burden on caregivers [1]. Acquiring a habit of using calendars and notebooks would also be helpful in the future when mild cognitive impairment has progressed to dementia.

Risk factors for lifestyle-related diseases such as hypertension, diabetes, and dyslipidemia can become risk factors that promote progression from mild cognitive impairment to dementia. Therefore, it is necessary to provide guidance on lifestyle modification and medication management.

It is necessary to first of all help the patient and family understand correctly that mild cognitive impairment is an unstable condition that may progress to dementia or may return to normal cognition, and then provide guidance to prepare for progression to dementia in the future.

See also CQ3A-1.

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PubMed search: July 18, 2015 (Saturday), July 23, 2015 (Thursday)

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Ichushi search: July 17, 2015 (Friday)

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C | Disease Severity and Interventions According to Severity

CQ 4C-1

What kind of guidance and support can be given to persons with mild to moderate dementia?

Answer

Case management (care management) has been reported to be effective in reducing admission to care facilities and costs of care in the short term. Education on dementia and peer support are effective in improving the patients' depressive state and quality of life (QOL). C

Comments and evidence

Case management is carried out by professionals such as nurses and social workers, and involves a variety of activities including coordination of care and formulation of a care plan according to the needs of the persons with dementia living in the community. According to a review of 13 randomized controlled trials (RCTs), case management is effective in reducing admission to care facilities and long-term care costs in the short term, but the long-term effect is uncertain [1].

Social support groups for people with dementia provide a venue for education related to dementia, mutual assistance, peer support, and information exchange. They are effective in improving the patients' depression state, QOL, and self-esteem [2].

A multi-disciplinary educational program for persons with early-stage dementia and their families should contain a core component of medical knowledge about the symptoms and progression of dementia [3].

Many cognitive training or cognitive rehabilitation programs are conducted for the purpose of improving cognitive function centered on memory. Cognitive rehabilitation has been suggested to improve ADL in patients with mild Alzheimer's disease dementia [4]. Cognitive training provides training of specific tasks targeting cognitive functions, while cognitive rehabilitation introduces compensatory approaches to meet patients' needs.

Many research articles have suggested the effectiveness of non-pharmacological therapies such as reminiscence therapy, validation therapy, music therapy, exercise, aromatherapy [5], and light therapy [6]. However, there are issues in these reports concerning the quality of evidence. Therefore these therapies cannot be actively recommended.

Assistive devices using computer and robotic assistance for ADL and entertainment activities are being evaluated in clinical trials, and future development can be expected. A system that prompts bathing and other activities at specific time is effective for persons with mild dementia [7]. In a study of persons with moderate Alzheimer's disease dementia, presenting pictorial step-by-step instructions of work procedures on a computer allowed the patients to make coffee and snacks by themselves [8]. In addition, the patients were able to enjoy music by choosing from music options by themselves [8].

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Search formula

PubMed search: July 17, 2015 (Friday), August 26, 2015 (Wednesday)

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Ichushi search: July 17, 2015 (Friday)

#1 (Dementia/TH OR Dementia/TI) AND (Mild/TI OR Moderate/TI OR severity/TH) AND (Patient care management/TH OR Health education/TH OR Home care support service/TH OR Social support/TH OR Mental support/TH) AND (Support/TI OR Guidance/TI OR Education/TI OR Support/TI OR Support/TI OR Guidance/TI OR Instruction/TI OR Service/TI)

CQ 4C-2

What kind of guidance and support can be given to caregivers of persons with mild to moderate dementia?

Answer

Educational support for caregivers of persons with dementia is effective in lessening their care burden and depressive state. Telephone counseling and Internet educational programs are also effective. C

Comments and evidence

Caregivers of persons with dementia often report feeling the care burden and depressive symptoms. According to a meta-analysis of studies that provide educational interventions for caregivers of persons with dementia, a moderate beneficial effect on care burden and a small beneficial effect on the depressive state were observed, but the effects of improving quality of life (QOL) and reducing admission to care facilities were not clear [1].

A meta-analysis on counseling using telephone found a significant effect in improving the caregivers' depressive state [2].

There is also a study suggesting the effectiveness of caregiver education via the Internet [3], and this method may be further developed by the widespread use of the Internet.

An Italian study was conducted using reduction of caregiver burden and avoidance of admission of persons with dementia to care facilities as markers of effectiveness of an intervention program for caregivers. In this study, case management, visits by nurses, and introduction of technological devices were effective in reducing care burden and avoiding admission to care facilities [4].

A meta-analysis of 78 studies on caregiver interventions showed significant improvements in caregivers' feeling of care burden, depression, subjective well-being, satisfaction, and ability/knowledge, as well as care receivers' symptoms. The intervention effect for caregivers of persons with dementia was less than that for other groups of caregivers. Psychoeducational or psychotherapeutic interventions showed the most consistent short-term effects [5].

See also CQ3A-1.

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Search formula

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#1 ((("Dementia" [Majr] OR dementia [TI] OR alzheimer* [TI]) AND ("early stage" [TI] OR mild [TI] OR moderate [TI])) AND ("Caregivers" [Mesh] OR "Family" [Mesh] OR caregiver* [TI] OR family* [TI]) AND ("Patient Care" [Mesh] OR "Health Education" [Mesh] OR education [TI] OR support* [TI] OR guidance [TI] OR instruction [TI] OR service* [TI])) OR ((dementia OR alzheimer*) AND ("early stage" OR mild OR moderate) AND (caregiver* OR family) AND (education OR support* OR guidance OR instruction OR service*))

Ichushi search: July 17, 2015 (Friday)

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CQ 4C-3

What kind of guidance and support can be given to persons with severe dementia?

Answer

For persons with severe dementia, it is desirable to help them receive medical and long-term care continuously without changing their living environment or lifestyle as far as possible. C

Comments and evidence

Persons with severe dementia have increased frequencies of physical symptoms including loss of appetite, sleep disturbance, urinary disorders such as incontinence, defecation disorders such as constipation, and gait disturbance. There are also more emergency admissions for infections, cerebrovascular disorders, and undernutrition. A study has found when these patients require emergency admission, admission to a special ward cared by a team comprising doctor, nurse, physiotherapist, social worker, and counselor, and then having the same team in charge of home care after discharge resulted in significantly less behavioral disturbance, use of fewer antipsychotic drugs, and less caregiver stress compared to admission to a general ward [1]. It is desirable to coordinate the system to enable patients to receive continuous medical and long-term care, so that they can receive medical care in a familiar environment without changing their lifestyle.

For persons with severe dementia, admission to care facilities is an important consideration. A report has shown that while appropriate home care management can delay admission to care facilities, it is ultimately impossible to avoid facility admission for persons with severe dementia [2]. In addition, it is also known that the cost of nursing care increases as the severity of dementia increases [3]. Compared to mild and moderate cases, the difference between the costs of institutional care and the costs of home care is small.

There is no research with high-level evidence on the treatment of pneumonia and nutritional disorders in persons with severe dementia. For management of dysphagia, hand feeding of small portions by a caregiver (comfort feeding by hand) with mouth care is preferable to tube feeding [4].

In a survey of a nursing home in the United States, patients with severe dementia were given quinolone and cephalosporin antibiotics without adequate evidence, resulting in extensive colonization of multidrug-resistant bacteria. Comfort is the goal of care for many patients with advanced dementia, and more sensible use of antibacterial drugs is desirable [5, 6].

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Search formula

PubMed search: July 17, 2015 (Friday)
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CQ 4C-4

What kind of guidance and support can be given to caregivers of persons with severe dementia?

Answer

Providing support to caregivers can help maintain the quality of life (QOL) of the caregivers and reduce their psychological burden. Support given by a multidisciplinary team is recommended to enable patients with dementia to receive continuous medical and long-term care. C

Comments and evidence

A family booklet about comfort care for persons with severe dementia may be useful [1]. The contents of the booklet consist of symptoms, decision-making, and treatments accompanying progression of Alzheimer's disease dementia, and the booklet is perceived as acceptable and useful by bereaved families of persons with dementia in Canada, Holland and Italy.

Support through telephone is also effective. Sixteen telephone conversations in six months from therapists who provided educational instructions to caregivers systematically improved caregivers' depressive symptoms and reactions to care recipients' behaviors [2].

Since caring for persons with severe dementia imposes heavy burden on caregivers 24 hours a day, 365 days a year, the use of respite care is recommended. However, there are few high-quality studies on respite care, and the benefits and adverse effects have not been clarified so far [3].

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Search formula

PubMed search: July 17, 2015 (Friday)

#1 (("Dementia" [Majr] OR dementia [TI] OR alzheimer* [TI]) AND (advanced [TI] OR severe [TI])) AND ("Caregivers" [Mesh] OR "Family" [Mesh] OR caregiver* [TI] OR family* [TI]) AND ("Patient Care" [Mesh] OR "Health Education" [Mesh] OR education [TI] OR support* [TI] OR guidance [TI] OR instruction [TI] OR service* [TI] OR management* [TI]) OR ((dementia OR alzheimer*) AND (advanced OR severe) AND (caregiver* OR family) AND (education OR support* OR guidance OR instruction OR service* OR management*))

Ichushi search: July 17, 2015 (Friday)

#1 (Dementia/TH OR Dementia/TI) AND Severity/TI AND (Caregiver/TH OR Caregiver/TI OR Care personnel/TI OR Family/TH OR Family/TI) AND (Patient care management/TH OR Health education/TH OR Home care support service/TH OR Social support/TH OR Mental support/TH OR Support/TI OR Guidance/TI OR Education/TI OR Support/TI OR Support/TI OR Guidance/TI OR Instruction/TI OR Service/TI)

CQ 4C-5

How should end-of-life care be given to persons with dementia?

Answer

In the terminal stage of persons with advanced dementia, providing medical care and general care with an emphasis on alleviating the person's pain is desirable. C

Comments and evidence

The survival prognosis for persons with advanced dementia is extremely poor. A survey conducted at nursing homes in the United States on 323 persons (median age 86.0 years) with Global Deterioration Scale (GDS) stage 7 dementia found a 24.7% probability of death within 6 months and a median survival duration of 478 days, which was equivalent to the life expectancy of metastatic breast cancer and stage IV congestive heart failure [1].

No method has been established to predict the survival prognosis of persons with dementia [2]. Medicare in the United States requires Functional Assessment Staging (FAST) stage 7c as a requirement for initiation of palliative care, but this is not a reliable predictor of death after 6 months [2].

Persons with advanced dementia may experience pain, breathing difficulty, and anorexia, as in patients with terminal stage cancer, but control of these conditions is extremely inadequate in persons with dementia [3]. In the terminal stage of persons with advanced dementia, care based on advance care planning (ACP) [4] aiming at comfort of the person rather than prolonging life is desirable, but the introduction of ACP is not easy in clinical practice [5]. According to observational studies, tube feeding is not recommended because the benefits are unclear. Report suggests the effectiveness of palliative care or hospice care [4]. Appropriate assessment and management of pain as well as effective management of behavioral problems can improve the quality of life (QOL) of persons with severe dementia [6].

Persons with advanced dementia often have difficulties with self-determination and confirmation of intent. As an alternative, decision has to be based on presumed intent, proxy intent, or prior intent. Based on the opinions of the family, speculate the patient's intent as far as possible and respect it. As a tool that supports the decision-making process through discussions between the parties concerned, the Japan Geriatrics Society has published the "Guidelines for the decision-making process in medical and long-term care for the elderly: focusing on the initiation of artificial hydration and nutrition" [7].

The family plays an important role in end-of-life care. At the same time, since the family is under great mental and physical stress, support for the family is important. In addition, after the person with dementia has died, grief care for the family is necessary.

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PubMed search: July 17, 2015 (Friday)

#1 (("Dementia" [Mesh] OR dementia [TI] OR alzheimer* [TI]) AND (advanced [TI] OR severe [TI]) AND ("Terminal Care" [Mesh] OR "Advance Care Planning" [Mesh] OR "Palliative Care" [Mesh] OR "terminal care" [TI] OR hospice [TI] OR "palliative care" [TI] OR "end of life" [TI] OR bereavement* [TI])) OR ((dementia OR alzheimer*) AND (advanced OR severe) AND ("terminal care" OR hospice OR "palliative care" OR "end of life" OR bereavement*))

Ichushi search: July 18, 2015 (Saturday)

#1 (Dementia/TH OR Dementia/TI) AND (Severe/TI OR Advanced dementia/AL OR End-stage dementia/AL) AND (Terminal care/TH OR Terminal care/TI OR Advance care plan/TH OR Advance care plan/TI OR Palliative care/TH OR Palliative care/TI OR Hospice/TH OR Hospice/TI OR Bereavement/TH OR Bereavement/TI)

Chapter 5

Various Systems and Social Resources for Supporting Persons with Dementia and Their Families

A | Various Systems and Social Resources for Supporting Medical and Long-term Care for Persons with Dementia

CQ 5A-1

What are the functions and roles of the medical center for dementia?

Answer

The Medical Center for Dementia is required to provide two key functions: specialized medical functions (specialized medical consultation, differential diagnosis of dementia and initial response, and emergent responses for behavioral/psychological symptoms of dementia and physical comorbidities) and community liaison hub functions (establishment and operation of the Local Liaison Council for Dementia Care, and organizing workshops). In each prefecture, the Medical Center for Dementia is expected to design the hub function, deployment, and method of liaison, which match the characteristics of local communities, and to manage the quality of the activities.

Comments and evidence

The objective of the Medical Center for Dementia is "to build a functional system for people with dementia, which can provide comprehensive health care services in the community ranging from prevention of disease progression to support for community living. Specifically, the Medical Center for Dementia supports differential diagnosis for dementia-related diseases and initial response; emergent responses for acute treatments of behavioral/psychological symptoms, and physical comorbidities; and specialized medical consultations, while also conducts training for community health and nursing care personnel". Currently, there are three types of Medical Center for Dementia: "core type", "regional type", and "liaison type".

The functions required of the Medical Center for Dementia include (1) specialized medical services (1. differential diagnosis of dementia and initial response, 2. emergent response for behavioral/psychological symptoms and physical comorbidities, 3. specialized medical consultations) and (2) community liaison hub functions (1. establishment and operation of Local Liaison Council for Dementia Care, 2. organizing workshops).

Specialized medical consultations take place in a medical consultation room staffed with psychiatric social worker, public health nurse, and other personnel. In response to telephone or face-to-face consultations from persons with dementia, their families or related organizations, the staff of the medical consultation room makes medical appointments or arranges for referral to medical institutions [1]. Following the diagnosis, staff of the medical consultation room provides information to the persons with dementia and their families, liaises and coordinates with relevant organizations, and supports them in using the services they need [1]. The medical consultation room plays an important role in improving the functions of the Medical Center for Dementia [2]. To support differential diagnosis and initial response, the medical consultation room is staffed with specialized doctors and equipped with testing facilities. The staff also provides information to persons with dementia and their families after the diagnosis, and liaises with primary care physicians to secure continuous medical care. To support emergent response for behavioral/psychological symptoms and physical comorbidities, the medical consultation room responds to emergent cases by coordinating with hospitals with general or psychiatric beds, as well as with psychiatric and general emergency systems.

The Local Liaison Council for Dementia Care is a council formed and operated by local health and medical professionals, the Community General Support Center, long-term care insurance personnel, and experts related to dementia medical care. The aim is to promote the establishment of a community-based dementia support system. Workshops are organized for training local professionals as well as families and community residents. Training of medical specialists and specialized staff knowledgeable in a wide range of activities stipulated by the Medical Center for Dementia is an important responsibility of the core-type Medical Center for Dementia [3]. In addition, organization of regular training programs including case studies with active participation by primary care physicians and certified dementia support doctors will contribute to maintain a high level of dementia medical care in the region [4].

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Search formula

PubMed search: July 14, 2015 (Tuesday)
#1 ("Dementia/therapy" [Majr] OR (dementia [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI])) OR "Cognition Disorders/therapy" [Majr] OR (cognition disorder* [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI]))) AND ("Health Services for the Aged" [Mesh] OR "Community Health Services" [Mesh] OR "Community Health Centers" [Mesh])

Ichushi search: July 14, 2015 (Tuesday)
#1 Medical Center for Dementia/TH OR Medical Center for Dementia/TI

CQ 5A-2

What are the roles of certified dementia support doctors?

Answer

The roles of certified dementia support doctors (dementia support doctor hereinafter) are: (1) to support primary care doctors and care professionals involved in medical and long-term care for people with dementia; (2) to facilitate multidisciplinary liaison mainly at the Community General Support Center; and (3) to train primary care doctors aiming to improve dementia managing skills and to educate residents of the community. Dementia support doctors are expected to promote collaboration between different medical disciplines and between medical care and long-term care in the community. C

Comments and evidence

Accompanying aging of the population, the number of people with dementia has increased rapidly, and dementia is now considered a common disease. Under such circumstances, there is an urgent need to establish a support system for older people from the early stage of dementia with the participation of primary care doctors, and to educate doctors and care staff. By the end of 2015, a total of 5,085 dementia support doctors were certified. The roles of dementia support doctors are as follows: (1) to support primary care doctors and care professionals involved in medical and long-term care for persons with dementia; (2) to facilitate multidisciplinary liaison mainly at the Community General Support Center; and (3) to serve as lecturers in training of primary care doctors aiming to improve dementia managing skills and to educate residents of the community [1]. Compared with general primary care doctors, dementia support doctors possess superior capabilities in differential diagnosis of dementia, management of behavioral and psychological symptoms of dementia (BPSD) in outpatient setting, and community liaison and long-term care [2]. In a survey of dementia support doctors, 84% are engaged in liaison and 64% in training and educational activities [3].

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PubMed search: June 17, 2015 (Wednesday)
#1 ("Dementia" [Majr] OR dementia [TI] OR "Cognition Disorders" [Majr] OR "cognition disorder*" [TI]) AND "Japan" [Mesh] AND (doctor OR doctors)

Ichushi search: June 17, 2015 (Wednesday)
#1 Dementia support doctor/AL

CQ 5A-3

What are the roles of long-term care insurance system for persons with dementia and their caregivers?

Answer

The long-term care insurance is the foundation that supports the living of people with dementia and their families. The long-term care insurance provides diverse services including consultation support services mainly at the Community General Support Center; home-visit services such as home help service, home-visit bathing, and home-visit nursing; and facility services such as day care and day rehabilitation service; as well as community-based services such as group home for older people with dementia and small-scale multifunctional in-home care. A

Comments and evidence

1. Outline of long-term care insurance system

a. Basic design of the system

Based on the Long-term Care Insurance Act enacted in 1997, the long-term care insurance system was started in 2000 as the fifth social insurance system. The insured persons are those aged 40 years and above (65 years and above: primary insured persons, 40-64 years: secondary insured persons), and the insurer is a municipality. The insured persons can receive insurance benefits (use of services) if they are judged as requiring long-term care or requiring support, after going through a screening/evaluation process of "whether or not they are in a state of needing long-term care". The screening/evaluation process is called "certification of long-term care need". The process consists of (1) application submitted by the insured person to the insurer; (2) investigation of physical condition (primary screening by computer); (3) report written by the family doctor from the medical viewpoint [secondary screening, considering also (2)]. There are seven levels of certification, ranging from mild to severe: "support needed" levels 1-2 to "care needed" levels 1-5. Those certified as "support needed" can use the preventive care services, and those certified as "care needed" can utilize the care services.

b. Long-term care insurance services

Over 20 services are provided by the long-term care insurance, and they are broadly classified as follows: (1) home services, (2) facility services, and (3) community-based services that utilize multiple home services in a package [1]. (1) Home services and (3) community-based services, with some exceptions, are provided based on a monthly service utilization plan (care plan). The care plan is basically prepared by a care support specialist (care manager). In principle, the plan is prepared by combining services within the monthly payment limit (use limit) which is determined depending on the level of care needed. Although the usefulness of all these services has not been verified, disappearance or reduction of behavioral and psychological symptoms was observed by using day care for dementia, which is a facility service for dementia [2].

2. System reform in 2015 and fee revision [3]

The long-term care insurance system is operated based on a project plan developed by the insurer every three years, and insurance premiums and care fees (unit price for service) are revised every three years. In addition, if necessary, the system will be reformed accompanying revision of the Act. In fiscal year 2015, the system was reformed in response to the Act for Securing Comprehensive Medical and Long-term Care (Tax and Social Security Integrated Reform), and the fees were also revised following the usual 3-year schedule.

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Search formula

PubMed search: June 17, 2015 (Wednesday)
#1 ("Dementia" [Majr] OR dementia [TI] OR "Cognition Disorders" [Majr] OR cognition disorder* [TI]) AND ("Insurance, Long-Term Care" [Mesh] OR "long-term care insurance" [TI])

Ichushi search: June 17, 2015 (Wednesday)
#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Long-term care insurance/TH OR Long-term care insurance/TI)

CQ 5A-4

What are the functions and roles of Community General Support Center?

Answer

The Community General Support Center was established in 2006. The contents of operation for dementia are not necessarily clearly defined so far, but the Center has played an important role as the core facility to provide support for persons with dementia in the following work areas: (1) general consultation/support, (2) protection of patients' rights, (3) comprehensive and continuous case management support, and (4) preventive benefits and preventive care management. In the future, its importance will increase as a core organization for the community-based comprehensive care system.

A

Comments and evidence

With the revision of the Long-term Care Insurance Act in 2006, Community General Support Center was established in each municipality as a base for promoting comprehensive community care. The center is mandated as a facility that "aims to comprehensively support the improvement of health care and promotion of welfare by providing assistance necessary for maintaining physical and mental health and stabilizing lives of residents living in the community". Specifically, a team consisting of three professionals: social worker, chief care manager, and public health nurse or nurse with experience in community care, is responsible for the following work areas: (1) general consultation/support, (2) protection of patients' rights, (3) comprehensive and continuous case management support, and (4) preventive benefits and preventive care management. However, some problems have been identified [1], which include 1) issue of support for households without family care capability, 2) issue related to daily life support with the rapid increase in households of single persons without relatives, 3) issue related to certification of long-term care need for dementia, and 4) issue of medical collaboration in community care for dementia [2-5]. As indicated in another section, the installation of an initial-phase intensive support team for dementia in the Community General Support Center is expected to be one solution to these issues.

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PubMed search: June 17, 2015 (Wednesday)
#1 ("Dementia" [Majr] OR dementia [TI] OR "Cognition Disorders" [Majr] OR cognition disorder* [TI]) AND ("Comprehensive Health Care" [Mesh] OR "integrated care") AND ("Community Health Centers" [Mesh] OR "community based")

Ichushi search: June 17, 2015 (Wednesday), July 7, 2015 (Tuesday)
#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Community general care center/AL OR Community General Support Center/TH OR Community General Support Center/TI OR Community general center/AL OR (Community/TI AND Comprehensive/TI AND Center/TI))

CQ 5A-5

What are the functions and roles of the initial-phase intensive support team for dementia?

Answer

Medical and general care for dementia in the future is expected to base on early and proactive response aiming to prevent crisis, and to be equipped with functions for early support and support to avoid crisis. The initial-phase intensive support team for dementia is a promising mechanism to fulfill these functions. An expert team visits persons with dementia and provides comprehensive support at an early stage to enable them to continue living in the community. The model project started in 2012, and activities in all municipalities were scheduled to begin by the end of 2017. C

Comments and evidence

The mission of the initial-phase intensive support team for dementia is to visit persons with dementia and provide comprehensive support at the earliest possible stage to enable them to continue living in the community. "Initial" in this case does not necessarily denote the initial stage of the disease, but means "first touch". Furthermore, "intensive" refers to visiting the persons with dementia and their families, providing assessment and family support comprehensively and intensively (for approximately 6 months), and after providing support for independent living, referring them back to their usual medical and general care team. Persons who should be targeted are those who have not received medical services or long-term care services, or who have stopped receiving these services. Some examples of such cases are those (1) who have not received a clinical diagnosis of dementia-related disease; (2) who are not receiving continuous medical services; (3) who are not connected to long-term care insurance services, (4) who were diagnosed with dementia but have stopped receiving long-term care services, or those who despite receiving medical and long-term care services are struggling to cope with behavior and psychological symptoms of dementia (BPSD).

Model projects were conducted at 14 locations nationwide in 2013 [1], and at 41 locations nationwide in 2014 [2]. The results showed that persons targeted for visit and support were identified centrally through the Community General Support Centers, but details of the route of identification showed that consultations from the families and the patients accounted for 50%, indicating that the persons concerned requested consultation. In addition, 85-90% of the patients continued to live at home after receiving intervention from the team, showing that the team did not respond to difficult cases simply by hospitalization and admission to care facilities. Furthermore, improvement in the care burden scale has been reported [2, 3]. From 2015, the initial-phase intensive support team was scheduled to start operation in all the municipalities in which this initiative was feasible as a community support project. By the end of 2017, the team was scheduled to start in all municipalities nationwide. Results of a study show that the initial-phase intensive support team for dementia is useful in enabling persons with dementia to continue living at home, and can be expected to be an attempt that improves the overall community care [4]. However, since this project has just been started, further verification is needed in the future.

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Search formula

PubMed search: June 17, 2015 (Wednesday)
#1 ("Dementia" [Majr] OR dementia [TI] OR "Cognition Disorders" [Majr] OR cognition disorder* [TI]) AND "Patient Care Team" [Mesh] AND "Intensive Care" [Mesh]

Ichushi search: June 17, 2015 (Wednesday)
#1 Dementia initial-phase intensive support team/AL OR ((Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND Initial-phase intensive/AL AND (Support team/TI OR Team care/TH OR Team care/TI))

B | Advocacy for People with Dementia

CQ 5B-1

Is it possible to evaluate the abilities of judgment and decision-making in persons with dementia?

Answer

When obtaining consent for performing a medical action or considering the use of the adult guardianship system, doctors need to determine the mental capacity (abilities of judgement and decision-making) of a person with dementia. The mental capacity has a three-layer structure: (1) functional ability, (2) capacity, and (3) competence. Doctors are able to determine the mental capacity of an individual with dementia by assessing the cognitive function (functional ability) associated with a specified legal action and assessing the underlying clinical state (capacity).

Comments and evidence

Mental capacity is the ability to effectively express an intention and understand the result of one's actions (abilities of judgment and decision-making). Capacity to act refers to a legal status or legal qualification that a person can execute an effective legal act alone. In routine medical care for persons with dementia, it is necessary to evaluate the mental capacity of these individuals when obtaining consent for a medical action or when considering the use of the adult guardianship system.

1. Structure of assessment of mental capacity

The structure of assessing mental capacity has three levels: (1) functional ability, (2) capacity, and (3) competence.

Functional ability is the mental function required at each stage of the psychological process leading to decision-making, and is a phenomenon that can be measured as a continuous variable, as for cognitive function. Capacity is the clinical state judged by a doctor, and is a categorical phenomenon related to whether a person can make meaningful decision under the circumstances in which the person is placed. For example, a medical diagnosis of severe dementia state belongs to this category. Competence is a legal status which is judged by a legal personnel, especially a judge, and is a categorical phenomenon judged by the dichotomy of "yes" or "no" regarding whether a person possesses the ability required to execute a legal act alone.

2. Practical judgment of mental capacity

The conventional judgment of mental capacity used for determining capacity for criminal responsibility consists of the following procedures: (1) confirm the psychiatric diagnosis (biological factor), (2) determine whether or not the psychiatric disorder is severe enough to impede legal action (psychological factor), and (3) make a legal judgment based on the above. On the other hand, Igarashi [1] advocates that since not all the persons diagnosed with dementia lack mental capacity and ability to act, the following procedures are more appropriate in the era of normalization: (1) assess functional ability related to a specific legal action; (2) next, evaluate capacity as an underlying factor; and (3) entrust the judgment of competence to a judge.

There are various approaches to the assessment of the functional ability of a person with dementia: (1) an approach that focuses on cognitive function, (2) an approach that focuses on the ability to execute a specific action, and (3) an approach based on observation of daily actions [2]. The approach focusing on cognitive function employs Mini Mental State Examination (MMSE), but there is insufficient evidence regarding the relationship with mental capacity [3]. For the approach focusing on the ability to execute a specific action (related to consent to treatment), Applebaum et al. [4] advocated a concept consisting of four steps: (1) understand the information related to decision making (understanding), (2) rationally process the information obtained (rational thinking), (3) recognize the situation in which decision is made and the result of decision-making (recognition), and (4) express the result of decision-making to others (statement of choice). Based on this concept, they developed a scale for measuring the ability to consent to treatment [5]. In addition, Marson et al. [6] have developed the "Financial Capacity Instrument".

3. Issues related to informed consent and medical consent for persons with dementia

Individuals who receive medical care have the right to make decisions about receiving the medical care. A doctor must obtain the patient's consent before performing the medical action, and as a premise, the doctor should give an explanation necessary for obtaining the consent. In other words, medical actions must be performed based on informed consent.

From this perspective, a person who has been diagnosed with dementia is entitled to receive explanations including the diagnosis (name of disease), symptoms, predicted clinical course, treatments, and systems and services available. In addition, as a premise of such explanations, the patient has the right of self-determination about receiving (or rejecting) the medical action.

If a person with dementia lacks the ability to consent to medical care, the health care personnel customarily obtains consent from the family or relatives, and then conducts the medical practice. However, if there are no family members or relatives who can cooperate with consent to medical care, medical decision for a person with dementia who lacks the ability to consent to medical care becomes a difficult problem. In Japan, there is currently no legislation on medical consent for adults who lack the ability to consent.

In Japan, from the legal side, the Japan Federation of Bar Associations has published "Outline of the act on proxy medical consent for persons lacking medical consent ability" (2011), and the Legal-Support Adult Guardianship Center has published the "Interim report on consent to medical action" (2009). From the medical side, the Japan Geriatrics Society has issued a "Position Statement" on "End-of-life medical and general care for the elderly" (2012). From the administration side, the "Guidelines on the decision-making process of medical care at the end of life" (2015) has been published. In addition, the method of (written) advance healthcare directive is increasingly being used to decide in advance the contents of medical care that one wishes to receive (or not to receive).

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#1 ("Dementia/diagnosis" [Mesh] OR dementia [TI] OR "Cognition Disorders/diagnosis" [Mesh] OR cognition disorder* [TI] OR cognitive disorder* [TI]) AND ("Neuropsychological Tests" [Majr] OR neuropsychological test* [TI] OR "Disability Evaluation" [Majr] OR disability evaluation* [TI] OR disability assessment* [TI]) AND ("Liability, Legal" [Mesh] OR legal liability* [TI] OR "Forensic Psychiatry" [Mesh] OR "Decision Making" [Mesh] OR decision making* [TI] OR "Executive Function" [Mesh] OR functional ability* [TI] OR "Mental Competency" [Mesh] OR competency* [TI] OR capacity* [TI])

Ichushi search: July 14, 2015 (Tuesday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Neuropsychological examination/TH OR Neuropsychological examination/TI OR Neuropsychological test/TI) AND (Legal responsibility/TH OR Legal responsibility/TI OR Legal ability to act/TI OR Decision making/TH OR Decision making/TI OR "Executive function (awareness process)"/TH OR Executive function/TI OR Functional ability/TI OR Mental ability/TH OR Mental ability/TI OR Judgment ability/TI OR competence/TI OR capacity/TI)

CQ 5B-2

How can the adult guardianship system be used to protect the rights of people with dementia?

Answer

Individuals with dementia are vulnerable to infringement of their rights due to decline of judging ability. The adult guardianship system is a system that supports all legal activities including asset management and contract related to personal custody for a person who lacks sufficient judgment ability, by appointing an assistant (such as adult guardian) who protects the rights of the persons with dementia. However, there are many issues in the current adult guardianship system including the following: the guardian does not have the right to consent to medical actions; there are insufficient measures against asset embezzlement by the guardian; the utilization rate is low; and there is a shortage of persons willing to take on the role as guardian.

Comments and evidence

Persons with dementia are vulnerable to having their rights infringed due to decline in judgment ability [1, 2]. In order to prevent such infringement of rights, persons with dementia can utilize the programs for supporting independence in daily living and the adult guardianship systems. In both systems, the crucial point is to support daily living while respecting the person's self-determination [3].

1. Outline of the program for supporting independence in daily living

For persons whose ability of judgment is impaired due to dementia, intellectual disability, mental disability, and other causes, and who experience difficulties in managing the contracts of utilizing welfare services by themselves, these persons can utilize the "Program for supporting independence in daily living (former: Community welfare rights protection project)" that provides assistance for using welfare services, management of everyday finance, custody of important documents, and other services based on the contract signed with the person with dementia. However, in order to use this project, there is a condition that "the person himself/herself has the ability to understand the contents of the program and sign a contract".

2. Outline of the adult guardianship system

The adult guardianship system is a system that supports all legal activities including contracts related to asset management and personal custody (taking care of personal affairs) for a person who lacks sufficient judgment ability, by selecting an assistant (such as a guardian) who protects the rights of the person with dementia. There are two systems: a statutory guardianship system and a voluntary guardianship system. The statutory guardianship system is a system that protects and assists the person with dementia (hereinafter referred to as the person) by the following framework: an adult guardian appointed by the family court (adult guardian, curator, or assistant), while considering the interests of the person, acts on behalf of the person to execute legal acts such as contracts (proxy right), give consent when the person conducts legal acts by himself/herself (consent right), or cancel a legal act after the person has committed an unbeneficial legal act without consent from the adult guardian (right to rescind). On the other hand, the voluntary guardianship system operates as follows: to prepare for the future when judgment ability becomes inadequate, the person while still having adequate judgment ability selects a proxy (voluntary guardian), and concludes a contract granting proxy right for legal acts related to the person's own asset management and personal custody (voluntary guardianship contract), which is a notarized document prepared by a notary.

Application to use the statutory guardianship system is filed by the person, spouse, relative within the fourth degree, public prosecutor, or (if there is no relative) the municipal mayor. There are three types of statutory guardianship: guardian, curator, and assistant. In the case of "a general state of lacking judgment capability", a guardian is appointed, and the guardian is able to exercise all proxy rights and rights to rescind. In the case of "markedly inadequate judgment capability", a curator is appointed. The curator is able to exercise rights to consent and rights to rescind on specific matters (debt, lawsuit, approval/waiver of inheritance, new construction/renovation, etc. listed in Civil Code Article 13). In addition, the curator may be granted proxy rights for certain legal acts (such as bank cash management, asset management, long-term care contract, hospitalization contract, etc.) according to the request of the person. In the case of "inadequate judgment capability", an assistant is appointed, and the assistant can exercise rights to consent or rights to rescind for a part of specific matters

according to the request of the person.

However, the proxy rights that a guardian can exercise are limited to asset management and personal custody. For example, the guardian cannot exercise proxy rights regarding divorce/marriage/adoption, consent to medical actions, surety, and guarantor. In addition, there are other issues such as insufficient measures against asset embezzlement by the guardian, low utilization rate per population compared to European and American countries, and shortage of persons willing to take on the role as guardian.

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2) Akanuma Y. How to protect the rights of persons with dementia? Rights protection for dementia. Naika 2012; 109(5): 825-827. (In Japanese)
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PubMed search: July 14, 2015 (Tuesday)

#1 "Dementia" [Mesh] OR dementia [TI] OR "Cognition Disorders" [Mesh] OR cognition disorder* [TI] OR cognitive disorder* [TI] AND ("Legal Guardians" [Mesh] OR adult guardian* [TI]) AND ("Patient Advocacy" [Mesh] OR "Patient Rights" [Mesh] OR advocacy [TI] OR right* [TI])

Ichushi search: July 14, 2015 (Tuesday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Adult guardianship system/TH or Adult guardianship system/TI) AND (Patients' rights protection /TH OR Rights protection/TI OR Patients' rights/TH)

CQ 5B-3

What role does the Prevention of Elder Abuse Act play in preventing abuse to persons with dementia?

Answer

The Prevention of Elder Abuse Act sets forth national responsibilities for preventing elder abuse, protection measures for older people who have been abused, and support measures to prevent abuse of older people by caregivers. Cognitive impairment is a major factor that increases the risk of abuse. Anyone finding an older person who appears to be abused has the obligation to report or the obligation to make efforts to report to the municipalities (Community General Support Centers), depending on the severity of abuse.

Comments and evidence

The "Act on the Prevention of Elder Abuse, Support for Caregivers of Elderly Persons and Other Related Matters" (hereinafter "Prevention of Elder Abuse Act") was approved in November 2005 and enforced in April 2006. To protect the rights of older people, this law sets forth the responsibilities of the country to prevent elder abuse, protection measures for older persons who have been abused, and support measures to prevent abuse of older persons by caregivers (such as by reducing caregiver burden) aiming to promote policies related to support for prevention of elder abuse and support for caregivers [1].

1. Outline of the law

In this law, an elderly person is defined as a person who is aged 65 years or older, and elder abuse is classified into "elder abuse by a caregiver" and "elder abuse by care facility staff". Caregivers are assumed to include family members, relatives, and persons living with the elderly person, who are taking care of the elderly person. Care facility staff is assumed to be employee working in a "care facility" or "care business".

Elder abuse is defined as "an elderly person placed in a state where his/her rights and interests are infringed, or in a state where his/her life, health, or living is impaired by inappropriate treatment from others".

A person finding an older person who appears to be abused has the obligation to report or the obligation to make efforts to report to the municipalities (Community General Support Centers), depending on the severity of abuse. In addition, municipalities are primarily responsible for the prevention of abuse, protection of the older persons, and support for the abuse perpetrators. Even if it is difficult to determine whether a case is abuse, the municipality should take necessary assistant measures according to the Prevention of Elder Abuse Act, when it is speculated that the rights of an older person may be infringed, or his/her life, health, or living may be impaired.

2. Factors for elder abuse

The risk factors for abuse in community-dwelling older persons include (1) factors related to the older person (75 years of age and older, female, ethnicity, poor economic or health status, cognitive impairment, behavioral problems such as aggression and care refusal, high level of dependence due to functional decline, psychiatric illness or psychological problems, poor physical health or frailty); (2) factors related to the perpetrator (psychiatric illness or psychological problems, care burden, and stress) (3) relationship (family disharmony, poor or conflictual relationship), and (4) environmental factors (poor social support, living with others) [2].

3. Situation of response to the Prevention of Elder Abuse Act

Since 2007, the Ministry of Health, Labor and Welfare has reported the "Survey results on the status of responses based on the Act on the Prevention of Elder Abuse, Support for Caregivers of Elderly Persons and Other Related Matters".

4. Limitations of the Prevention of Elder Abuse Act

A survey of long-term care insurance facilities and daycare facilities for dementia finds that cases of suspected abuse constituted approximately 10 to 20%, but speculates that a considerable number of cases did not get notified [3]. Although elder abuse is attracting attention because of the intent, there are many cases in the gray zone that are difficult to prove as

abuse. Also, there is no provision in the current law for self-neglect. The necessity of proposing a law that can deal with a wide range of infringements, including self-neglect, has been pointed out [4]. Regarding elder abuse by care facility staff and others, it is necessary to more clearly define the importance of efforts aiming to improve the quality of care, reduce the occupational stress on workers, and implement appropriate organizational management. On the other hand, dementia care workers need to detect signs of abuse by caregivers and provide appropriate care management and family support [5].

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2) Johannesen M, LoGiudice D. Elder abuse: a systematic review of risk factors in community-dwelling elders. Age Ageing. 2013; 42(3): 292-298.
3) Yoshikawa Y. Elder abuse and physical restraint by care facility workers: 5 years after enactment of the law. Japanese Journal of Gerontology (Ronen Shakai Kagaku) 2012; 34(1): 71-76. (in Japanese)
4) Nomura S. A study of the legal system to prevent and support self-neglected elderly: Issues regarding enactment of law for elderly advocacy including self-neglect. Journal of the Japan Academy for the Prevention of Elder Abuse (Koreisha Gyakutai Boshi Gakkai) 2011; 7(1): 82-99. (in Japanese)
5) Yoshikawa Y. Prevention of elder abuse in dementia care: from the viewpoint of prevention before occurrence. Journal of Japanese Society for Dementia Care (Nihon Ninchishokea Gakkaishi) 2013; 11(4): 765-771. (in Japanese)

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PubMed search: July 14, 2015 (Tuesday)
#1 ("Dementia" [Mesh] OR dementia [TI] OR "Cognition Disorders" [Mesh] OR cognition disorder* [TI] OR cognitive disorder* [TI]) AND "Elder Abuse/prevention and control" [Mesh]

Ichushi search: July 14, 2015 (Tuesday)
#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Elder abuse prevention law/TH OR Elder abuse prevention law/TI) AND ((Elder abuse/TH OR Elder abuse/TI) AND ((SH = Prevention) OR Prevention/TI OR Prevention/TI))

C | Early-onset Dementia

CQ 5C-1

What is early-onset dementia?

Answer

From the medical viewpoint, early-onset dementia refers to onset of dementia younger than 65 years of age. In terms of utilization of support system, the term refers to a person younger than 65 years of age at the time of utilization.

Comments and evidence

In Japan, various terms had been used to describe dementia depending on the time of onset, such as juvenile dementia, presenile dementia, and senile dementia. However, in several diseases such as juvenile Parkinson's disease, "juvenile" refers to onset age younger than 40 years. It was pointed out that since the same term "juvenile" may refer to different age groups depending on the disease, terms such as juvenile dementia and senile dementia perhaps should not be used to avoid confusion [Japan Society for Dementia Research (Ed.) Textbook of Dementia 2008]. Then, since launching of "Policies for early-onset dementia" [1] in 2009 (http://www.mhlw.go.jp/topics/kaigo/dementia/e01.html), the term "early-onset dementia" was clearly described in the 5-year Plan for Promotion of Measures Against Dementia (the Orange Plan) in 2013 and the Comprehensive Strategy to Accelerate Dementia Measures (the New Orange Plan) in 2015. At present, the notation of early-onset dementia as onset of dementia younger than 65 years of age is commonly used at the administrative level.

According to the "Study report on the status of early-onset dementia and infrastructure development as control measures" (2009, Asada et al. [2]), the number of persons with early-onset dementia per 100,000 population was 47.6 [95% confidence interval (CI) 45.5 to 49.7) in the 18–64 year-old population, 57.8 in men, 36.7 in women, and the total number of persons with early-onset dementia nationwide was estimated to be 37,800 (95% CI 36,100 to 39,500). The causative diseases were vascular dementia (39.8%), Alzheimer's disease dementia (25.4%), sequelae of head injury (7.7%), frontotemporal lobar degeneration (3.7%), alcoholic dementia (3.5%), and dementia with Lewy bodies (3.0%).

In addition to being younger, persons with early-onset dementia have life issues that are different from older persons with dementia: they are the main providers of family finance and childcare; the family may have children still attending school, etc. Therefore interventions should take these into consideration [4]. In an environment where services are not fully utilized, active and comprehensive use of systems including informal services should be promoted [3].

Since 2016, early-onset dementia support coordinators have been deployed in each prefecture, who are available for consultation. The purpose of this service is to provide support that meets the needs of each person. In addition to providing consultation service, this office is expected to build a collaborating system with municipalities and related organizations, as well as to disseminate correct knowledge and conduct education activities about early-onset dementia [5].

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1) Ministry of Health, Labour and Welfare. Summary of study results on the status of early-onset dementia and the Ministry of Health, Labour and Welfare policies for measures against early-onset dementia. 2009. http://www.mhlw.go.jp/houdou/2009/03/h0319-2.html (In Japanese)
2) Asada T. Study report on the status of early-onset dementia and infrastructure development as control measures. 2009. (In Japanese)
3) Dementia Care Research Training Obu Center. Handbook on early-onset dementia (revised edition). https: //www.dcnet.gr.jp/support/research/center/list.html?center=2 (In Japanese)
4) Dementia Care Research Training Obu Center. Handbook on support for early-onset dementia (revised edition). https: //www.dcnet.gr.jp/support/research/center/list.html?center=2 (In Japanese)
5) Dementia Care Research Training Obu Center. Manual for placement of support coordinator for early-onset dementia (excerpt). https: //www.dcnet.gr.jp/support/research/center/list.html?center=2 (In Japanese)

■ Search formula

PubMed search: June 27, 2015 (Saturday)

#1 "juvenile dementia" OR "early onset dementia" OR "young onset dementia" OR (("Dementia" [Mesh] OR dementia [TI]) AND (juvenile OR "early onset" OR "young onset" OR "Age Factors" [Mesh])) AND ("economics" [subheading] OR "Economics" [Mesh] OR economic* [TI]) AND ("Social Support" [Mesh] OR "Health Planning" [Mesh] OR "Delivery of Health Care" [Mesh])

Ichushi search: June 27, 2015 (Saturday)

#1 (Early-onset dementia/AL OR ((Dementia/TH OR Dementia/TI) AND Juvenile/AL)) AND (Economics/TH OR Economic/TI) AND (Social support/TH OR Social resource/TI OR Support system/TI OR Health care plan/TH OR Health service provision/TH)

CQ 5C-2

What are the support systems to help persons with early-onset dementia with their economic challenges?

Answer

Public supports including medical payment for services and supports for persons with disabilities under the Services and Supports for Persons with Disabilities Act, accident and sickness benefits, and disability pension are available, but whether the patient is eligible to receive these supports depends on the disease condition, disease stage, and household income.

Comments and evidence

If a person is diagnosed with early-onset dementia while still in employment, the first financial support available is the reduction in copayment (portion paid by patient) of medical expenses under the System of Services and Supports for Persons with Disabilities. If the person takes leave of absence, he/she will receive accident and sickness benefits for a period of 1 year and 6 months. In addition, the person can apply for the Health and Welfare Certificate of Persons with Mental Disabilities from 6 months after the date of the first hospital visit, which allows him/her to benefit from deductions of service fees and taxes. After leaving employment, the person can apply for disability pension from 1 year and 6 months after the date of the first hospital visit. In addition, if the person continues to receive accident and sickness benefits after leaving employment, once he/she applies for extension of the employment insurance benefit (unemployment benefit), he/she will be able to use the disability welfare services. When the payment of accident and sickness benefits is stopped, those who have joined the employment insurance can also receive unemployment insurance benefits for a certain period.

The System of Services and Supports for Persons with Disabilities offers the following benefits. When a person is diagnosed with dementia and receives non-hospitalization-based medical care, by applying at the municipal office to utilize the above System, the copayment portion of medical expenses is reduced to 10% in principle. Accident and sickness benefit is a social security system for persons under medical treatment provided by the Health Insurance Law. When a person who is insured with a health insurance society is under medical treatment and cannot work for more than 3 consecutive days, then from the 4th day at which he/she has not been paid a salary, he/she is entitled to receive a sum of two-thirds of the standard daily wage, for a period of 1 year and 6 months.

Health and Welfare Certificate of Persons with Mental Disabilities under the Mental Health and Welfare Act allows a person with a certain degree of mental disability to receive various assistances, aiming to promote the person's independence and social participation. The Certificate entitles a person to receive two types of services: services that can be received nationwide, and services that can be received depending on region and employer. The former includes deductions in income tax, resident tax, inheritance tax; reduction in automobile tax and automobile acquisition tax; reduction or exemption of utility charges; and social welfare loan. The latter include discounts for railway, bus, taxi fares; discounts for mobile phone fee and water and sewage charges; discount for public facility admission fee; increases of welfare benefit and public assistance for persons with disabilities; and priority to be allocated public housing. The patient may apply for the Health and Welfare Certificate of Persons with Mental Disabilities at the municipal office after 6 months from the date of the first hospital visit. The Certificate is classified from grade 1 to grade 3 according to the degree of disability. Note that at this stage, it is also possible to apply simultaneously for medical payment subsidy under the System of Services and Supports for Persons with Disabilities.

Furthermore, persons who have joined the national or employee pension scheme can receive a disability pension after 1 year and 6 months from the date of the first hospital visit. An insured person of the national pension scheme receives a basic disability pension. An insured person of the employee pension scheme can receive the disability employee pension on top of the basic disability pension. If the disability grade is less than grade 3, the person cannot receive a disability pension, but can receive disability benefit as a lump sum.

In addition, in some cases, some patients are eligible for life insurance and other insurances, reduction or waiver of diaper charge, and childcare system (depending on the municipality).

Also, since July 1, 2015, frontotemporal dementia and semantic dementia have been designated as intractable diseases based on the Intractable/Rare Disease Act. Certain medical assistance is provided if the requirements are met.

Further reading

1) Awata S. Use medical care services, living support services, long-term care insurance services. Japanese Journal of Geriatric Psychiatry (Ronen Seishin Igaku Zasshi) 2015; 26(4): 398-405. (In Japanese)
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4) Ministry of Health, Labour and Welfare. Let's start from knowing: General site on mental health for everyone. http://www.mhlw.go.jp/kokoro/support/promotion_4.html (In Japanese)

Search formula

PubMed search: June 27, 2015 (Saturday)

#1 "juvenile dementia" OR "early onset dementia" OR "young onset dementia" OR (("Dementia" [Mesh] OR dementia [TI]) AND (juvenile OR "early onset" OR "young onset" OR "Age Factors" [Mesh])) AND ("Social Support" [Mesh] OR social support* [TI] OR life support* [TI] OR "Health Planning" [Mesh] OR "Delivery of Health Care" [Mesh])

Ichushi search: June 27, 2015 (Saturday)

#1 (early-onset dementia/AL OR ((Dementia/TH OR Dementia/TI) AND Juvenile/AL)) AND (Social support/TH OR Social resource/TI OR Support system/TI OR Health care plan/TH OR Health service provision/TH)

CQ 5C-3

What are the systems that can be used to support the living of persons with early-onset dementia?

Answer

If a person is diagnosed with any of the 16 specified illnesses of early-onset dementia, he/she can utilize the long-term care insurance system from the age of 40 years. If younger than 40 years, the long-term care insurance system cannot be used. If the person is certified as a person with mental disorder, he/she can utilize facilities based on the Services and Supports for Persons with Disabilities Act.

Comments and evidence

If a person is diagnosed with any of the 16 specified illnesses* of early-onset dementia, he/she can utilize the long-term care insurance system from the age of 40 years. However, these services are difficult to use because most long-term care services are operated with the assumption that the users are older people. For persons of all ages having mental disorders, it is possible to use facilities for mentally disabled persons based on the Services and Supports for Persons with Disabilities Act. However, there is also a problem that these services may be difficult to use because they are not operated with the assumption that users have dementia.

<Specified diseases*>

The Ministry of Health, Labor and Welfare lists the specific diseases as described below, from the viewpoint of clarifying the scope of the diseases and facilitating certification of the level of care/support needed in the long-term care insurance system (Enforcement Order of Long-term Care Insurance Act, Article 2).

A specified disease is a disease that is considered to have a medical relationship with the psychosomatic pathological aging phenomenon. The disease should meet all the requirements listed below. Upon comprehensive consideration, the disease is recognized as one that causes psychosomatic changes with aging, leading to a state requiring long-term care.

1) The disease occurs frequently in older people aged 65 years and older, while it is also found in the age group from 40 to younger than 65 years. In this disease, a relationship of its incidence/prevalence (including similar indicators) with aging is observed, and the medical concept can be clearly defined.
2) A disease that is considered to have a high rate of needing care or support for 3 to 6 months or above .

1. Cancer (terminal stage of cancer)*
   (limited to those judged by a doctor to have no prospect of recovery based on generally accepted medical knowledge.
2. Rheumatoid arthritis*
3. Amyotrophic lateral sclerosis
4. Ossification of the posterior longitudinal ligament
5. Osteoporosis with bone fracture
6. Dementia in early old age
7. Progressive supranuclear palsy, corticobasal degeneration, and Parkinson's disease* (Parkinson's disease-related diseases)
8. Spinocerebellar degeneration
9. Spinal canal stenosis
10. Progeria
11. Multiple system atrophy *
12. Diabetic neuropathy, diabetic nephropathy, diabetic retinopathy
13. Cerebrovascular disease
14. Arteriosclerosis obliterans
15. Chronic obstructive pulmonary disease
16. Osteoarthritis with significant deformation in bilateral knee or hip joints
    (Asterisks denote diseases added in April 2006, after revision)

Further reading

1) Awata S. Use medical care services, living support services, long-term care insurance services. Japanese Journal of Geriatric Psychiatry (Ronen Seishin Igaku Zasshi) 2015; 26(4): 398-405. (In Japanese)
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http://www.mhlw.go.jp/topics/kaigo/nintei/gaiyo3.html (In Japanese)
3) Ministry of Health, Labour and Welfare. Let's start from knowing: General site on mental health for everyone.
http://www.mhlw.go.jp/kokoro/support/promotion_4.html (In Japanese)

Search formula

PubMed search: June 27, 2015 (Saturday)
#1 ("juvenile dementia" OR "early onset dementia" OR "young onset dementia" OR (("Dementia" [Mesh] OR dementia [TI]) AND (juvenile OR "early onset" OR "young onset" OR "Age Factors" [Mesh]))) AND ("Social Support" [Mesh] OR social support* [TI] life support* [TI] OR "Health Planning" [Mesh] OR "Delivery of Health Care" [Mesh])

Ichushi search: June 27, 2015 (Saturday)
#1 (early-onset dementia/AL OR ((Dementia/TH OR Dementia/TI) AND Juvenile/AL)) AND (Social support/TH OR Social resource/TI OR Support system/TI OR Health care plan/TH OR Health service provision/TH)

CQ 5C-4

What kind of consultation support is available for persons with early-onset dementia?

Answer

There are family associations in various districts, counseling bodies commissioned by municipalities, and others. However, the actual situation varies depending on the region, so it is necessary to contact the municipalities.

Comments and evidence

From the disease characteristics of dementia and also from the viewpoint of information exchange and peer counseling, it is important to utilize the consultation counters, participate in family associations of caregiving families, use informal services, and utilize dementia cafes that have been set up in various places in recent years.

In 2009, Ministry of Health, Labour and Welfare set up a call center at the Dementia Care Research Training Obu Center (http://www.mhlw.go.jp/houdou/2009/09/h0930-6.html) as a free consultation telephone service for persons with early-onset dementia.

- Early-onset dementia call center
  http://y-ninchisyotel.net/callcenter/new.html
  Some municipalities also set up independent support centers.
- Tokyo early-onset dementia support center
  http://www.fukushihoken.metro.tokyo.jp/zaishien/ninchishou_navi/kisochishiki/jakunensei/jakunen_center/

■ Further reading

1) Awata S. Use medical care services, living support services, long-term care insurance services. Japanese Journal of Geriatric Psychiatry (Ronen Seishin Igaku Zasshi) 2015; 26(4): 398-405. (In Japanese)
2) Ministry of Health, Labour and Welfare. Summary of the future policies for early-onset dementia.
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■ Search formula

PubMed search: June 27, 2015 (Saturday)
#1 ("juvenile dementia" OR "early onset dementia" OR "young onset dementia" OR (("Dementia" [Mesh] OR dementia [TI]) AND (juvenile OR "early onset" OR "young onset" OR "Age Factors" [Mesh]))) AND ("Referral and Consultation"[Mesh] OR consult[TI] OR consultation[TI] OR referral[TI])

Ichushi search: June 27, 2015 (Saturday)
#1 (early-onset dementia/AL OR ((Dementia/TH OR Dementia/TI) AND Juvenile/AL)) AND (Social support/TH OR Social resource/TI OR Support system/TI OR Health care plan/TH OR Health care service provision/TH) AND (Referral and consultation/TH OR Consultation/TI OR Consultant/TI OR Counseling/TH OR Counseling/TI)

D | Road Traffic Act

CQ 5D-1

What should be done if one finds that a person diagnosed with dementia holds a driver license and is still driving?

Answer

Since 2002, driving is not permitted if a person is diagnosed with dementia in Japan. From 2014, a voluntary reporting system has been started, and reporting to the Prefectural Public Safety Commission has been approved. C

Comments and evidence

1. Comments

Various medical assessments of driving competency for people with dementia have been examined, but no testing methods have been established for determining and predicting driving ability and competency, with consideration of dementia as the underlying disease. No conclusions have been drawn regarding the conditions and the types of dementia that present danger when persons with dementia continue to drive. The reasons are that dementia has diverse underlying diseases, and that driving ability may be influenced by the severity of dementia. On the other hand, in Japan, the 2002 revision of the Road Traffic Act restricts driving related to dementia.

Currently, if a person aged 75 years or above applying for renewal of the driver license is suspected of dementia after taking the Cognitive Impairment Screening Test for Senior Drivers, and if that person has caused specific traffic violation called "standard actions" within one year, the Public Safety Commission will order the person to undergo a Special Driving Competency Test or to be examined by a family doctor for assessment of dementia. If the result determines that the person has dementia as provided by the Article 5-2 of Long-term Care Insurance Act, the driver license will be revoked.

Under the Revised Road Traffic Act enacted in March 2017, a special screening test is introduced for persons aged 75 years or above who have committed traffic violation of one or more of 18 items, and they are obliged to take the Cognitive Impairment Screening Test for Senior Drivers without waiting for the time of license renewal. And, if the person is assessed as category 1, he/she has to see a doctor for assessment for the presence or absence of dementia. The "Guide for family doctors on writing medical certificate related to renewal of driver's license for older people with dementia" produced by Japan Medical Association was released on March 8, 2017 (http://www.med.or.jp/doctor/report/004984.html). Doctors may refer to this guide when writing a medical certificate.

Furthermore, the voluntary reporting system was started in June 2014. Doctors who are engaged in medical care for dementia can report to the Public Safety Commission when dementia is suspected or when dementia is diagnosed, but they should first of all diagnose appropriately regarding whether or not the person has dementia. When dementia is diagnosed based on evidence, after disclosing the diagnosis of dementia to the patient and the family, the doctor should explain carefully all the details about the patient's need to give up driving, and record in the medical record the patient's and the family's reactions to the explanations. In addition, the doctor should keep in mind to provide guidance to the patient and family on daily living, including the effect of giving up driving on the patient's treatment and daily life, not only just once after notifying the patient to give up driving but to repeat thereafter. Five medical societies related to dementia have jointly released a guideline for using the voluntary reporting system. Doctors may refer to these guidelines (http://dementia.umin.jp/GL_2014.pdf).

■ Further reading

1) Martin AJ, Marottoli R, O'Neill D. Driving assessment for maintaining mobility and safety in drivers with dementia. Cochrane Database Syst Rev. 2013; (5): CD006222.
2) Martin AJ, Marottoli R, O'Neill D. Driving assessment for maintaining mobility and safety in drivers with dementia. Cochrane Database Syst Rev. 2009; (1): CD006222.
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Search formula

PubMed search: July 14, 2015 (Tuesday)

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Ichushi search: July 14, 2015 (Tuesday)

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Chapter 6

Alzheimer's Disease Dementia

Objective

To review recent reports on the diagnosis, treatment, care, and social response for Alzheimer's disease dementia, and to clarify the level of evidence and grading of recommendation.

Concept

Alzheimer's disease is characterized by two pathological changes; neurofibrillary tangles (tauopathy) and amyloid deposition (Aβ amyloidosis; cerebral cortex, cerebral blood vessels), which cause neuronal death, synapse depletion and decreased acetylcholine in the cerebral cortex, hippocampus, and frontobasal region, leading to development of dementia. Typically, the major symptoms are learning and memory impairments starting from slowly progressive episodic memory impairment, progressing to aphasia, executive function impairment, visuospatial function impairment, and social cognitive impairment including personality change. There are also atypical cases with onset symptoms including posterior cortical atrophy, logopenic aphasia, frontal variant with visual construction deficits, aphasia, and frontal lobe function impairment.

Pathology

In autosomal dominant Alzheimer's disease, many mutations have been identified in *APP*, *PSEN1* and *PSEN2*, all of which have been shown to increase Aβ42 production. Increased production together with reduced transport and metabolism of Aβ leads to formation of Aβ42 aggregates (oligomer) that damage synapses, induce neurofibrillary tangles and neuronal death. This process has been suggested to be the mechanism for the development of mild cognitive impairment and dementia (the amyloid β−tauopathy cascade hypothesis).

Progression and course of symptoms

Characteristic symptoms include forgetfulness and memory impairment due to damage of the hippocampus and medial surface of the temporal lobe; verbal amnesia due to damage of the temporal, parietal and occipital regions; visuospatial deficit; apraxia; semantic memory impairment due to damage of the lateral surface of the temporal lobe; as well as reduced disease awareness and spontaneity due to damage of the frontal lobe. Impairment of episodic memory is also a characteristic, and "saving appearance response" and repetition behavior are often observed. In moderate cases, impairment of immediate memory and impairment of long-term memory (starting from recent events) progress, and the number of words that can be used decreases due to semantic memory impairment and aphasia. In severe cases, almost all memories are impaired.

Constitutional impairment is commonly found. Initially, drawing and copying of complex pictures such as clocks and cubes are impaired. Then other symptoms begin to appear including inability of using everyday tools and inability of using multiple objects due to ideational apraxia, inability of imitating oral and visual commands due to ideomotor apraxia, and cortical symptoms such as limb-kinetic apraxia. Dressing apraxia is also a symptom commonly seen in moderate Alzheimer's disease dementia, and these apraxias progress in conjunction with impairment of procedural memory for learned movements. Early stage dementia is recognized by memory decline and reduced ability to execute work and housework. As the disease progresses, lowered initiation of actions, persistence and stubbornness, as well as impulsiveness and disinhibition appear, and self-correction becomes difficult. Many patients have no awareness of the disease, and appear cheerful. Eventually, the patient becomes incapable of self-care such as grooming, dressing, taking meals, toileting, and bathing; and incapable of understanding words and speaking. This progresses to loss of basic motor abilities such as standing, sitting and walking, and the average survival is around 10 years.

In approximately 80% of the patients, behavioral and psychological symptoms of dementia (BPSD) appear as the disease progresses, and these pose a burden on families and caregivers. Depression and apathy in the early stage progress to irritability, abusive language and violence, frustration and agitation, rejection, hallucination, delirium, insomnia, and wandering behaviors. In severe cases, inability to walk, incontinence, myoclonus, parkinsonism, and convulsions are seen. In the United States Alzheimer's Disease Neuroimaging Initiative (ADNI) study, which observed subjects from mild cognitive impairment to the onset of dementia, the time from mild cognitive impairment with impaired memory (amnestic MCI) to onset of dementia was 1 year in 16% of the subjects, 2 years in 24%, and 3 years in 49%.

CQ 6-1

What are the features and key points of diagnosis for neuropsychiatric symptoms in Alzheimer's disease dementia?

Answer

Alzheimer's disease dementia (1) has insidious onset and slow progression; (2) often presents initially as decline in recent memory; (3) as the disease progresses, additional symptoms of disorientation, impaired executive function, and visuospatial impairment appear; (4) followed by apathy, psychiatric symptoms such as depressive symptoms, disease unawareness, and characteristic interpersonal behaviors such as saving appearance response; (5) in presenile-onset dementia cases, cognitive impairment other than memory decline, such as aphasic symptoms, visuospatial impairment, and executive function impairment are often observed in the foreground; (6) marked focal neurological signs are rarely seen from the early stage of disease.

Comments and evidence

1. *Cognitive impairment*

The core symptom is memory impairment. Specifically, the characteristic memory loss is recent memory impairment when classified by the retention time, and episodic memory decline when classified based on content. The patient forgets appointments, cannot recall where things are kept, forget what he/she has said and repeats the same narration. The delayed recall task is the most sensitive tool to detect memory impairment in Alzheimer's disease dementia; characteristically the patient cannot give a correct answer even when given cues [1, 2]. In contrast to recent memory, remote memory is relatively preserved.

In many patients, memory impairment is followed by disorientation, impaired executive function, visuospatial impairment, and language impairment. Disorientation often progresses in the order of time → place → person. Impaired executive function is often recognized from a relatively early stage and interferes with day-to-day operations such as work and housework. The patient has difficulties copying figures due to visuospatial disturbance, and begins to get lost even in the neighborhood. As the disease progresses, apraxia (cannot use objects) also becomes noticeable. With respect to language, in addition to amnesic aphasia causing difficulties in understanding the names of objects, verbal paraphasia is conspicuous and language understanding becomes poor. Fluency and repetition are preserved until the terminal stage, presenting a clinical picture of transcortical sensory aphasia. Although social cognitive impairment is also observed, it is less severe compared to frontotemporal dementia [3]. Regarding daily life functioning, instrumental activities of daily living (IADL) are impaired from a relatively early stage, while impairment of activities of daily activity (ADL) appears after the disease has advanced [4].

2. *Behavioral and psychological symptoms of dementia*

According to studies using the Neuropsychiatric Inventory (NPI) for evaluation, apathy is the most common symptom observed in 30 to 80% of the patients [5-7], and reduced spontaneity and indifference cause problems in daily life. The prevalence of depressive state is also high; major depression according to the DSM criteria is present in 12.7%, and a depressive state based on specific criteria for dementia in 42% [8]. The prevalence is higher in studies of patients visiting hospitals or clinics compared to population-based studies [8]. The frequency of delusion is 36%, and delusion of theft is most frequent (50.9%). Hallucinations are found in 18% of the patients, and visual hallucinations is more common than auditory hallucinations [9]. When the severity of dementia progresses to moderate or above, wandering, agitation, and irritability become conspicuous.

3. *Focal neurological signs*

Except for some cases of familial Alzheimer's disease, definite neurological signs such as extrapyramidal symptoms, myoclonus, and seizures are rarely found from the early stage of Alzheimer's disease dementia. When significant neurological findings are observed from the early stage of the disease, diseases other than Alzheimer's disease dementia should be suspected.

4. *Atypical cases*

Alzheimer's disease dementia that causes atypical symptoms accounts for 6-17% of the total [10-12]. They include a type with visual cognitive impairment in the foreground due to localized atrophy in parietal and occipital lobes, a type with conspicuous behavioral abnormalities and executive function impairment due to severe frontal lobe degeneration, and a type with only prominent language impairment. Among patients with progressive aphasia, those showing logopenic aphasia often have the pathology of Alzheimer's disease [13].

5. Key points for diagnosis

When disease is in the early stage, paying attention to the characteristics of memory impairment and other symptoms is important to distinguish dementia from forgetfulness due to normal aging, depression, and delirium. Patients with forgetfulness due to normal aging are fully aware of the symptom (disease awareness), and the impairment is mild or appropriate to age. Patients with depression often exaggerate their forgetfulness. Patients with senile depression often have physical complaints such as general malaise, headache, stiff shoulders, and constipation in the foreground, while depression may not be remarkable.

Even when cognitive impairment such as memory decline is recognized, delirium should be considered if the onset is sudden, the symptoms change, and impaired consciousness is strongly suspected. Check for environmental changes, physical factors such as electrolyte abnormalities, and drugs that may cause delirium (including anxiolytics, anti-parkinsonian drugs, drugs with anticholinergic effects). Alzheimer's disease dementia has insidious onset and slow progression. If symptoms develop within a short time span of days or hours, vascular disorders and delirium are suspected. Confirm whether or not there are major signs of other diseases [dementia with Lewy bodies (DLB), frontotemporal dementia (FTD)], and make an exclusion diagnosis. A lack of disease awareness, and presence of saving appearance reaction and repetition signs may also help with the diagnosis.

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■ Search formula

PubMed search: July 2, 2015 (Thursday)
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CQ 6-2

What are the diagnostic criteria for Alzheimer's disease dementia?

Answer

The Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) published by the American Psychiatric Association or the diagnostic criteria of the National Institute on Aging–Alzheimer's Association (NIA-AA) is recommended for clinical diagnosis of Alzheimer's disease dementia. For the purpose of strict diagnosis and research, the IWG-2AD advanced research diagnostic criteria for dementia developed by the International Working Group (IWG) is available. A

Comments and evidence

In the Diagnosis and Statistical Manual of Mental Disorders Fifth Edition published by American Psychiatric Association in 2013, the diagnostic criteria for dementia and Alzheimer's disease dementia were completely revised. The term dementia was abolished and was changed to "major neurocognitive disorder". The diagnosis of Alzheimer's disease dementia is based on meeting the criteria for dementia (A), insidious onset and gradual progression of impairment (B), and exclusion of other diseases (D), and is classified as either probable or possible (C). While amyloid PET and cerebrospinal fluid Aβ42 level are described as significant for diagnosis, other tests including genetic analyses (*APP*, *PSEN1/2*, and *APOE ε4*), cerebrospinal fluid total tau and phosphorylated tau levels, cortical atrophy in hippocampus and temporal lobe on MRI, and decreased glucose metabolism in bilateral parietal lobes on FDG-PET are described as tests for future clinical application [1].

In 2011, diagnostic criteria for dementia and Alzheimer's disease dementia were proposed by the Workgroup of the National Institute on Aging (NIA) and the Alzheimer's Association (AA) in the United States. In these diagnostic criteria, Alzheimer's disease is a term that reflects brain pathology. Based on the stage and clinical symptoms, Alzheimer's disease is subdivided into preclinical Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease, and Alzheimer's disease dementia. The proposed major clinical criterion is the presence of slowly progressive, objective cognitive impairment in the memory or non-memory domain. To ensure that the diagnostic criteria can also be used in research, the Workgroup also describes recent advances in amyloid deposition biomarkers including decreased cerebrospinal fluid Aβ42 level and Aβ deposits on PiB amyloid PET, neurodegeneration biomarkers including increased cerebrospinal fluid total tau and phosphorylated tau levels, decreased glucose metabolism on FDG-PET, progressive brain atrophy on MRI, and genetic testing [2].

In 2014, the International Working Group (IWG) and NIA–AA more clearly classified the clinical symptoms of Alzheimer's disease dementia, and proposed the advancing research diagnostic criteria (IWG-2 diagnostic criteria) for Alzheimer's disease adopting biomarker findings [3]. Clinical phenotypes are broadly classified into typical Alzheimer's disease dementia with onset symptom of episodic memory impairment progressing to cerebral cortex symptoms involving other domains, and atypical Alzheimer's disease dementia with atypical onset symptoms including posterior cortical atrophy, logopenic aphasia, and frontal variant. Tests necessary for diagnosis include brain amyloid PET, decreased cerebral spinal fluid Aβ42 level together with increased total tau and phosphorylated tau levels, and genetic testing.

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Search formula

PubMed search: July 22, 2015 (Wednesday)
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CQ 6-3

What are the characteristic image findings of Alzheimer's disease dementia?

Answer

The characteristic image findings of Alzheimer's disease dementia are as follows: (1) CT and MRI depicting atrophy in medial temporal lobe, especially the hippocampus; (2) SPECT and FDG-PET showing decreased blood flow and glucose metabolism in bilateral temporal/parietal lobes and posterior cingulate gyrus, (3) amyloid PET indicating amyloid deposition in frontal lobe, posterior cingulate gyrus, and anterior wedge. A

Comments and evidence

In 20 studies that evaluated the diagnostic accuracy of diagnostic imaging by CT, MRI, SPECT, and PET for Alzheimer's disease dementia, histopathologically diagnosed Alzheimer's disease dementia was differentiated from healthy individuals and non-Alzheimer's disease dementia with a sensitivity of 86.8% [95% confidence interval (CI) 81.9 to 91.7%] and specificity of 78.7% (95% CI 70.3- to 87.1%) [1]. In 12 studies using MRI, Alzheimer's disease dementia due to atrophy of medial temporal lobe was differentiated from healthy subjects with a sensitivity of 85% and specificity of 88% [2]. Moreover, hippocampal atrophy correlated with Braak stage and MMSE score, and was associated with the carrier status of *APOE* ε4 [3]. In a meta-analysis of 49 of 775 studies using cerebral blood flow SPECT, ^{99}mTc-HMPAO SPECT differentiated Alzheimer's disease dementia from frontotemporal dementia with 79.7% sensitivity and 79.9% specificity, Alzheimer's disease dementia from vascular dementia with 74.5% sensitivity and 72.4% specificity, Alzheimer's disease dementia from dementia with Lewy body with 70.2% sensitivity and 76.2% specificity, and Alzheimer's disease dementia from healthy subjects with 76.1% sensitivity and 85.4% specificity [4]. In 119 studies on the diagnostic accuracy of FDG-PET for Alzheimer's disease dementia, Alzheimer's disease dementia was differentiated from healthy subjects with a sensitivity of 90% (95% CI 84% to 94%) and specificity of 89% (95% CI 81% to 96%), and Alzheimer's disease dementia was differentiated from non-Alzheimer's disease dementia (including mild cognitive impairment) with a sensitivity of 92% (95% CI 84% to 96%) and specificity of 78% (95% CI 69% to 85%) [5]. The Dominantly Inherited Alzheimer Network (DIAN) study reported that amyloid deposition depicted by PIB-PET was observed 15 years before the onset age [6]. In a meta-analysis of amyloid PET positivity in Alzheimer's disease dementia and non-Alzheimer's disease dementia, the positive rates were 88% (95% CI 85% to 90%) for Alzheimer's disease dementia, 51% (95% CI 33% to 69%) for dementia with Lewy body, 30% (95% CI 21% to 42%) for vascular dementia, and 12% (95% CI 8% to 18%) for frontotemporal dementia [7]. In a study examining the predictive accuracy of amyloid PET for progression from mild cognitive impairment to Alzheimer's disease dementia, the sensitivity was 94.7% (95% CI 89.8 to 97.7%) and specificity was 57.2% (95% CI 50.1 to 64.2%), and both sensitivity and specificity increased by long-term follow-up [8].

For proper use of amyloid PET, see CQ6-6.

Amyloid PET and FDG-PET are not covered by health insurance in Japan.

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Search formula

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CQ 6-4

Is *APOE* genetic testing useful for the diagnosis of Alzheimer's disease dementia?

Answer

The *APOE* gene ε4 allele is a powerful genetic risk factor for the onset of Alzheimer's disease dementia in Japanese. Homozygous carriers of ε4 allele are known to have a higher risk of onset than heterozygous carriers this allele. Currently, routine testing *APOE* gene polymorphism is not recommended. In accordance with the Ethical Guidelines for Human Genome/Gene Analysis Research, explanations to patients and obtaining consent, support by genetic counseling, and conducting genetic testing at specialized facilities are recommended for genetic testing. C

Comments and evidence

The ε4 allele of apolipoprotein E (*APOE*) gene polymorphism is a risk factor for the development of Alzheimer's disease dementia [1], and the onset rate increases as the number of ε4 alleles increases [2]. However, there are also cases where ε4/ε4 carriers do not develop Alzheimer's disease. Therefore, *APOE* ε4 allele should be understood as a genetic risk factor, not a causative gene. Routine testing for *APOE* gene polymorphisms is not recommended in the guidelines of the American Academy of Neurology and the European Federation of Neurological Societies [3, 4]. Furthermore, DSM-5 published by the American Psychiatric Association has not clarified the significance of *APOE* genetic analysis [5]. The NIA–AA diagnostic criteria for Alzheimer's disease dementia revised in 2011 state that carrier state of *APOE* ε4 allele does not have sufficient specificity for the diagnosis of Alzheimer's disease dementia [6]. Regarding disclosure of *APOE* genotyping result, although test-related stress is reduced in adults who were informed that their *APOE* gene ε4 testing result was negative, adults with strong psychological stress before undergoing genetic testing tended to have strong psychological stress also after disclosure. Disclosure of *APOE* genotyping result did not pose a significant psychological risk in the short term [7].

Regarding genetic testing, the Ministry of Education, Culture, Sports, Science and Technology; the Ministry of Health, Labor and Welfare; and the Ministry of Economy, Trade and Industry published the "Ethical Guidelines for Human Genome/Gene Analysis Research" (partially revised on November 25, 2014). See also "Guidelines on Genetic Diagnosis of Neurological Diseases, 2009" developed by the Japanese Society of Neurology [8].

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Search formula

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CQ 6-5

What are the useful biomarkers for the diagnosis of Alzheimer's disease dementia?

Answer

Many large-scale prospective studies have provided evidence for decreased Aβ42 level and increased total tau or phosphorylated tau level in cerebrospinal fluid (CSF) as biomarkers for the diagnosis and prediction of onset of Alzheimer's disease dementia. The Dominantly Inherited Alzheimer Network (DIAN) study, an observational study of autosomal dominant Alzheimer's disease, reports that Aβ42 decreases from 25 years and total tau increases from 15 years before the estimated onset age. The NIA-AA criteria recommend use of these biomarkers for research in Alzheimer's disease dementia and mild cognitive impairment, while the IWG-2 advancing research diagnostic criteria for Alzheimer's disease dementia include these markers as tests required for diagnosis. A

Comments and evidence

Decrease in cerebrospinal fluid (CSF) Aβ42 level correlates with the amount of Aβ deposition in brain. Increases in CSF total tau and phosphorylated tau levels reflect neurofibrillary tangles and neuronal death. The evidence of these biomarkers has been confirmed by many large-scale multicenter prospective studies. When used alone, Aβ42 has the best accuracy (sensitivity 81-96%, specificity 77-89%), and a combination of Aβ42 and total tau or phosphorylated tau may further improve the accuracy of diagnosis (sensitivity 60-92%, specificity 47-93%). Moreover, these markers have been reported to be predictive markers for the development of Alzheimer's disease dementia from a healthy state or from mild cognitive impairment (MCI) (combination of Aβ42 with total tau or phosphorylated tau; sensitivity 83-98%, specificity 38-90%).

The Alzheimer's Disease Neuroimaging Initiative (ADNI), which was started in 2004 in the United States aiming to elucidate the factors associated with early diagnosis and onset of Alzheimer's disease dementia, has generated a large volume of evidence in biomarker research [1]. The Dominantly Inherited Alzheimer Network (DIAN) study has revealed that CSF Aβ42 level decreases in autosomal dominant Alzheimer's disease from 25 years before the estimated age of dementia onset, thus establishing CSF Aβ42 as the biomarker showing the earliest change. An increase in CSF tau level is detected 15 years before dementia onset and is considered to be a secondary marker for neuronal injury [2]. In 2011, NIA–AA incorporated elevated CSF tau level as a biomarker for "probable AD dementia with evidence of the AD pathophysiological process" in the new diagnostic criteria for Alzheimer's disease dementia [3]. Furthermore, in 2014, in the advancing research diagnostic criteria for Alzheimer's disease (IWG-2 criteria), a combination of decreased Aβ42 with increased total tau or phosphorylated tau has been included as a marker that reflects Alzheimer's disease pathological findings required for the diagnosis of Alzheimer's disease dementia [4]. While a clinical diagnosis can be made using major clinical diagnostic criteria alone, biomarker measurements are recommended for clinical research and interventional studies.

The issues of using CSF biomarkers for clinical diagnosis include variability of measured values among facilities, and fluctuation of values depending on sampling methods and storage conditions. Therefore, standardization of CSF handling, measurement methods and cut-off points is considered necessary, and standard measurement methods have been proposed [5]. Although the differentiation of Alzheimer's disease dementia from normal controls has high diagnostic sensitivity and specificity, overlap occurs with other dementia subtypes. Especially since CSF Aβ42 level also decreases in dementia with Lewy bodies, differentiation is difficult using CSF Aβ42 alone [6]. In Japan, total tau measurement in CSF is covered by health insurance for the diagnosis of Creutzfeldt-Jakob disease, and phosphorylated tau measurement in CSF is covered by insurance for differential diagnosis of dementia.

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Search formula

PubMed search: July 23, 2015 (Thursday)
#1 ("Alzheimer Disease/diagnosis" [Majr] OR (Alzheimer* [TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI]))) AND ("Biological Markers" [Majr] OR biological marker* [TI] OR biomarker* [TI] OR "Hematologic Tests" [Mesh] OR hematologic test* [TI] OR blood test* [TI] OR "Cerebrospinal Fluid" [Mesh] OR "cerebrospinal fluid" [TI] OR CSF [TI] OR "cerebrospinal fluid" [subheading])

Ichushi search: July 23, 2015 (Thursday)
#1 ((Alzheimer's disease/TH OR Alzheimer's disease/TI) OR (Alzheimer/TI) AND Dementia/TH OR Dementia TI)) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI) AND (Biological marker/MTH OR Biological marker/TI OR Biomarker/TI OR Blood test/TH OR Hematological test/TI OR Blood test/TI OR Cerebrospinal fluid test/TH or Cerebrospinal fluid test/TI)

CQ 6-6

Is amyloid PET examination useful for the diagnosis of Alzheimer's disease dementia?

Answer

The positive rates of amyloid PET examination are approximately 98% for Alzheimer's disease dementia, approximately 68% for mild cognitive impairment (MCI), and 33% in healthy older persons. Amyloid PET negativity is useful for differentiating non-Alzheimer's disease dementia. In the NIA-AA criteria and IWG-2 advancing research diagnostic criteria for Alzheimer's disease, amyloid PET examination is required as a biomarker of brain amyloid deposition. Participation in clinical studies requires consent, and general clinical use should conform to appropriate guidelines.

Amyloid PET examination is not covered by health insurance in Japan. A

Comments and evidence

Many studies have demonstrated the disposition of amyloid β (Aβ) before onset of Alzheimer's disease dementia. Aβ deposition is one of the required items in NIA-AA diagnostic criteria and IWG-2 AD advancing research criteria. However, amyloid deposition is observed in 10.4% of people aged 50 years and in 43.8% of healthy older people at age 90. Moreover, Aβ deposition is also observed in dementia-related diseases other than Alzheimer's disease dementia, such as dementia with Lewy bodies. Therefore, although amyloid PET is useful for differentiating Alzheimer's disease dementia from non-Alzheimer's disease dementia, when amyloid PET is used in clinical diagnosis, attention is required in patient selection and interpretation of results. Furthermore, the needs for consent, disclosure, counseling, education, and psychological support are emphasized.

In 2013, the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association jointly developed the world's first appropriate use criteria for amyloid PET that can be used in clinical practice [1]. Experts concluded that use of amyloid PET requires the following: (1) a cognitive complaint with objectively confirmed cognitive impairment; (2) Alzheimer's disease as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert; and (3) when knowledge of the presence or absence of amyloid-beta pathology is expected to increase diagnostic certainty and alter management. The document also provides examples of appropriate and inappropriate use. Furthermore, an update of the criteria expands the following topics: (1) defining dementia experts and their use of proper documentation to demonstrate the medical necessity of an amyloid PET scan; (2) identifying a specific subset of individuals with mild cognitive impairment for whom an amyloid PET scan is appropriate; and (3) developing educational programs for appropriate use of amyloid PET [2].

Recommendation from the Italian Interdisciplinary Working Group for the clinical use of amyloid imaging limits the use to patients with objective cognitive impairment of unknown cause, in whom amyloid PET results are expected to be useful for diagnostic accuracy and treatment [3]. In Japan, use of amyloid PET should comply with the Guidelines for Proper Use of Amyloid PET Imaging Agent Synthesis Device (released in April 2015) developed by the Joint Working Group of the Japanese Society of Nuclear Medicine, Japan Society for Dementia Research, and Japanese Society of Neurology [4]. According to the guidelines, proper use is defined as follows: (1) dementia patients with atypical clinical symptoms, in whom a definitive diagnosis is required for appropriate treatment; and (2) patients with atypical onset age (onset age younger than 65 years), in whom a definitive diagnosis is required for appropriate treatment. Use for mild cognitive impairment is not recommended.

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Search formula

PubMed search: July 23, 2015 (Thursday)

#1 ("Alzheimer Disease/diagnosis" [Majr] OR (Alzheimer* [TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI]))) AND ("Positron-Emission Tomography" [Mesh] OR "positron emission tomography" OR PET [TI]) AND (Amyloid [Mesh] OR amyloid* [TI])

Ichushi search: July 23, 2015 (Thursday)

#1 ((Alzheimer's disease/TH OR Alzheimer's disease/TI) OR (Alzheimer/TI) AND Dementia/TH OR Dementia TI)) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI) AND ("amyloid pet"/TI OR Amyloid PET/TI OR ((Positron emission tomography/TH OR PET/TI OR Positron emission tomography OR Positron emission tomography) AND (Amyloid/TH OR Amyloid/TI)))

CQ 6-7

What are the pharmacotherapy and treatment algorithms for Alzheimer's disease dementia?

Recommendation

The currently available drugs for improving cognitive function in Alzheimer's disease dementia are the three cholinesterase inhibitors (ChEIs); donepezil, galantamine, and rivastigmine, as well as the NMDA receptor antagonist memantine. Scientific evidence of efficacy has been demonstrated for both classes of drugs, and their use is recommended.

1A

Comments and evidence

1. Cholinesterase inhibitors (ChEIs)

Currently, three ChEIs are available; namely, donepezil, galantamine, and rivastigmine. A Cochrane Systematic Review analyzed 10 randomized controlled trials (RCTs) in patients with mild to severe Alzheimer's disease dementia. Treatment with ChEIs improves the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-cog) by 2.37 points on average with good clinician-rated global clinical state, and efficacy for activities of daily living (ADL) and behaviors was also observed. Similar effects were observed in patients with severe Alzheimer's disease dementia, although evidence was inadequate because there were only two RCTs. Adverse events such as nausea, vomiting, and diarrhea were significantly more frequent compared to the placebo group. In conclusion, although there are some differences in mechanism of action among the three drugs, there are no remarkable differences in effectiveness, and ChEIs are recommended for mild to moderate Alzheimer's disease dementia [1].

In a systematic review of 96 publications on 59 clinical trials of ChEIs and memantine, treatment of dementia with ChEIs and memantine was significantly effective, but clinical improvements in cognitive function and global assessment were mild [2]. The systematic review and meta-analysis reported by Hansen et al. [3] showed no difference in efficacy between the three ChEIs on cognitive function, but found slight differences in the effects on global function and behavioral disorder as well as the frequency of adverse events. In a systematic review and meta-analysis of global reports on the three ChEIs and memantine, all four drugs, including galantamine capsule 32 mg/day, were efficacious for cognitive function. Only donepezil 10 mg/day and galantamine 24 mg/day were effective for behavioral disorders. Donepezil 5 mg/day had no effect on functional outcome. There were significantly more dropouts from clinical trials and more adverse events in the ChEIs group than in the placebo group [4].

A systematic review of seven RCTs on rivastigmine capsule (6-12 mg/day) and patch (9.5 mg/day) showed that both formulations reduced the rates of cognitive decline and ADL decline in mild to moderate Alzheimer's disease dementia, with good clinician-rated global clinical state. There were fewer side effects using the patch than using the capsule [5]. A 24-week RCT of rivastigmine patch conducted in Japan reported improvement in ADAS-J cog at a dose of 18 mg/day with rare serious adverse events [6].

Although treatment with donepezil for very mild Alzheimer's disease dementia does not prevent the progression of hippocampus atrophy [7], administration of donepezil to patients with mild cognitive impairment for one year has been reported to decrease the progression of hippocampal atrophy by 45% [8].

2. NMDA receptor antagonist: memantine

In a RCT conducted by the Memantine Study Group in which 252 patients with moderate to severe Alzheimer's disease dementia were treated with memantine 20 mg/day for 28 weeks, global function was assessed by Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), ADL was assessed by Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev), and cognitive function was assessed by Severe Impairment Battery (SIB). Significant improvements were observed in all the scales, and memantine was considered to be effective [9]. In a Cochrane Systematic Review of two RCTs on memantine for moderate to severe Alzheimer's disease dementia, mild improvements were found in assessments by SIB, ADCS-ADLsev, Neuropsychiatric Inventory (NPI), and CIBIC-Plus. Patients with severe Alzheimer's disease dementia were less likely to develop irritability, and the drug was well tolerated [10].

Doody et al. [11] conducted a meta-analysis of six RCTs, and reported that memantine was effective for Alzheimer's disease

dementia of all stages. Especially, efficacy was observed for behavioral disorders in moderate to severe dementia, and for cognitive function in mild to moderate dementia. In a meta-analysis of nine RCTs for moderate to severe Alzheimer's disease dementia conducted by Wilkinson et al. [12], memantine 20 mg/day was effective for cognitive function, ADL, and global assessment scale, and ameliorated clinical worsening [12]. A meta-analysis of 13 RCTs for mild to severe Alzheimer's disease dementia conducted by Jiang et al. [13] confirmed that memantine was beneficial for cognitive function, mental status, ADL, and clinical global impression, and while the drug did not increase the number of all adverse events, serious adverse events or death, the risk of somnolence was elevated. Similarly, phase II and phase III clinical trials in Japanese patients have shown memantine to be effective for moderate to severe Alzheimer's disease dementia [14].

In a meta-analysis of three RCTs on memantine for mild to moderate Alzheimer's disease dementia, no improvements in ADAS-cog, CIBIC-Plus, ADCS-ADLsev, and NPI were found in patients with mild Alzheimer's disease dementia, and efficacy was not proven [15].

3. Severe Alzheimer's disease dementia

Four RCTs on donepezil, one RCT on galantamine, and one meta-analysis were identified. The RCT reported by Winblad et al. [16] showed improvements in SIB and ADCS-ADLsev after 6-month treatment with 5-10 mg of donepezil. In the donepezil group, although there were many cases of discontinuation due to adverse events, the drug was effective in maintaining cognitive function and ADL even in patients with severe Alzheimer's disease dementia [16]. In the RCT reported by Black et al. [17], donepezil was effective when assessed by SIB, CIBIC-Plus and Mini-Mental State Examination (MMSE), but no effect was observed when evaluated by ADCS-ADLsev, NPI, Caregiver Burden Questionnaire (CBQ) and Resource Utilization for Severe Alzheimer Disease Patients (RUSP). In a Japanese multicenter trial consisting of a 6-month RCT followed by a 52-week open-label study reported by Homma et al. [18], efficacy and safety were maintained for at least 1 year, and the effect was sustained in the group that continued taking donepezil 10 mg/day without interruption. In a Japanese RCT in patients with severe Alzheimer's disease dementia, there were no significant differences in SIB and CIBIC-Plus scores between doses of 23 mg/day and 10 mg/day, indicating that the appropriate dose in Japan is 10 mg/day [19].

In one RCT for severe Alzheimer's disease dementia, galantamine 24 mg/day improved cognitive function (SIB) but did not improve ADL [20]. In a meta-analysis on the efficacy of ChEIs and memantine in relation to severity of Alzheimer's disease dementia, all the drugs tested slightly improved cognitive function, ADL, and BPSD regardless of disease severity, and the improvement of ADL by memantine was more marked in severe patients [21].

4. Combination of ChEIs with memantine

In a RCT in which patients with moderate to severe Alzheimer's disease dementia already receiving oral donepezil were given memantine 20 mg in combination for 24 weeks, significant improvements in SBT, ADCS-ADL19, and CIBIC-Plus scores were observed [22]. In the same RCT, when abnormal behaviors were evaluated using NPI, using memantine in combination significantly decreased NPI scores compared to donepezil alone. Among 12 items in NPI, significant improvements were seen in agitation/aggression, appetite, and irritability/lability [23]. The DOMINO-AD study enrolled 295 patients with moderate to severe Alzheimer's disease dementia who were treated with donepezil 10 mg for 3 months, followed by random allocation to with or without memantine in combination for 52 weeks. Differences in MMSE and Bristol Activity of Daily Living Scale (BADLS) scores were observed between the continued donepezil group and discontinued donepezil group, and between the donepezil-with-memantine group and donepezil-with-placebo group, but the differences did not reach statistical significance. Therefore, the beneficial effect of using a combination of donepezil with memantine was not proven [24]. In a sub-analysis of a follow-up study for 3 years after completion of the DOMINO-AD study, the risk of admission to nursing homes increased in the group that discontinued donepezil during the first year [25]. Therefore, caution should be exercised in discontinuing drug treatment.

In a RCT in which patients with moderate to severe Alzheimer's disease dementia already treated with ChEIs were given memantine 28 mg in combination for 24 weeks, combination with memantine significantly improved SIB, CIBIC-Plus, NPI, and verbal frequency test scores, but there was no significant difference in ADCS-ADL19 score [26]. There are few systematic reviews of combination therapies [27, 28]. Farrimond et al. [27] reported a systematic review and meta-analysis of three RCTs that evaluated combined memantine and ChEIs therapy for moderate to severe Alzheimer's disease dementia, which showed minor improvements in global score, cognitive function, behavior, and mood.

No benefits of combined ChEIs and memantine therapy were found in patients with mild to moderate Alzheimer's disease dementia [29].

It has been pointed out that in addition to RCT, long-term observational studies are important for determining the effects of anti-dementia drugs in delaying the progression of Alzheimer's disease dementia [30]. A longitudinal observational study

that followed 201 patients with Alzheimer's disease dementia for 6 years reported that use of ChEIs prolonged the time to functional impairment and death, while memantine prolonged the time to death [31].

5. Methods of using various drugs

For insurance-covered medical care in Japan, all drugs are gradually up-titrated while paying attention to adverse effects. Titration up to 10 mg of donepezil is approved for severe Alzheimer's disease dementia. Memantine is indicated for moderate to severe Alzheimer's disease dementia and can be used in combination with ChEIs. Regarding the rivastigmine patch, in addition to the conventional three-step titration method, a one-step titration method from 9 mg/day to 18 mg/day for well-tolerated cases can also be used. For details of adverse effects, refer to the package insert of each drug and CQ3A-6.

6. Treatment algorithm

(1) Mild: Select and administer one of the ChEIs considering the characteristics of each drug. Consider changing to another ChEIs when there is no or inadequate response to the drug being used, when the effect is attenuated, or when the drug has to be discontinued due to adverse effects.

(2) Moderate: Select and administer one ChEIs or memantine considering the characteristics of each drug. Change to another ChEIs or to memantine, or consider using ChEIs and memantine in combination (if combination is not used), when there is no or inadequate response to the drug being used, when the effect is attenuated, or when the drug has to be discontinued due to adverse effects.

(3) Severe: Consider using donepezil 5-10 mg, or memantine, or a combination of both. Consider also discontinuation if both drugs are ineffective or the drugs cannot be continued due to adverse effects. However, there are cases in which cognitive impairment progresses rapidly after drug withdrawal. Treatment discontinuation has to be judged with caution.

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■ Search formula

PubMed search: July 23, 2015 (Thursday)
#1 ("Alzheimer Disease/drug therapy" [Majr] OR (Alzheimer* [TI] AND ("drug therapy" [TI] OR chemotherapy [TI] OR pharmacotherapy [TI] OR "pharmacological therapy" [TI]))) AND (Algorithms [Mesh] OR algorithm* [TI] OR NMDA antagonist* [TI] OR "Receptors, N-Methyl-D-Aspartate/antagonists and inhibitors" [Mesh] OR "N-Methylaspartate/antagonists and inhibitors" [Mesh] OR "Cholinesterase Inhibitors" [Mesh] OR cholinesterase inhibitor* [TI])

Ichushi search: July 22, 2015 (Wednesday)
#1 ((Alzheimer's disease/TH OR Alzheimer's disease/TI) OR (Alzheimer/TI) AND Dementia/TH OR Dementia TI)) AND ((SH = Pharmacotherapy) OR Pharmacotherapy/TH OR Drug treatment/TI OR Pharmacotherapy/TI OR Antipsychotics/TH OR Therapeutic drug/TI) AND (Algorithm/TH OR Algorithm/TI OR Algorithm/TI OR "NMDA Receptor Antagonists"/TH OR "NMDA Receptor Antagonist"/TI OR NMDA receptor antagonist/TI OR NMDA antagonist/TI OR NMDA receptor blocker/TI OR NMDA receptor inhibitor/TI OR (("NMDA Receptors"/TH) AND (SH = Antagonist·Inhibitor)) OR ("NMDA Receptor"/TI AND (Antagonize/TI OR Inhibit/TI)) OR ((N-Methylaspartate/TH) AND (SH = Antagonist·Inhibitor)) OR ((N-Methylaspartate/TI) AND (Antagonize/TI OR Inhibit/TI)) OR "Cholinesterase Inhibitors"/TH OR "Cholinesterase Inhibitors"/TI)

CQ 6-8

What are the effects of non-pharmacological therapies for Alzheimer's disease dementia?

Answer

The therapeutic effects of non-pharmacological therapies depend largely on the patient's preference and the capability of the practitioner. Therefore, it is not meaningful to decide whether a therapy is superior or inferior. It is important that the patient participate willingly in therapy, and it is desirable to use multiple therapies as needed. C

Comments and evidence

Non-pharmacological therapies should be given priority over pharmacotherapy in the treatment of behavioral and psychological symptoms of dementia (BPSD). However, it should be noted that even non-pharmacological therapies may have negative effects. See CQ3A-7-1, 2 and CQ4C-1 for non-pharmacological therapies for dementia in general, and CQ3B-1-7 for the effects of non-pharmacological therapies for BPSD.

1. Approach focusing on cognition

Cognitive stimulation (therapy) was originally developed from reality orientation, but now includes various miscellaneous elements. Although certain effects on cognitive function can be expected in patients with Alzheimer's disease dementia, the evidence level is low [1].

A meta-analysis has reported that cognitive training is beneficial for improving overall cognitive function in Alzheimer's disease dementia [2]. However, the validity of this analysis remains questionable due to the issues of quality of the trials and heterogeneity among studies [3].

2. Approaches focusing on aspects other than cognition

There are few RCTs on reminiscence therapy for Alzheimer's disease dementia, and it is difficult to confirm whether this therapy is effective [4, 5].

Exercise therapy attenuates worsening of physical function and activities of daily living (ADL) in Alzheimer's disease dementia [6, 7]. In addition, although the possibility that exercise therapy may slow the decline in cognitive function has been suggested [8], heterogeneity between studies is high [7].

Music therapy is considered to be effective to some extent in improving BPSD, including anxiety, but the level of evidence is low because of the issues of quality of research and heterogeneity among studies [9, 10].

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analysis. Ageing Res Rev. 2013; 12(2): 628-641.
(References 1, 4-7, 9 and 10 were identified through manual search)

■ Search formula

PubMed search: July 2, 2015 (Thursday)

#1 ("Alzheimer Disease/therapy" [Majr] OR (Alzheimer [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI]))) NOT ("Alzheimer Disease/drug therapy" [Mesh] OR (Alzheimer [TI] AND ("drug therapy" [TI] OR chemotherapy [TI] OR "endocrine therapy" [TI])))

Ichushi search: July 2, 2015 (Thursday)

#1 ((Alzheimer's disease/TH OR Alzheimer's disease/TI) OR (Alzheimer/TI) AND Dementia/TH OR Dementia TI)) AND ((SH = Therapeutic use, Treatment, Surgical treatment, Transplantation, Dietary therapy, Psychological therapy, Radiation therapy) OR Treatment/TI OR Therapy/TI)) NOT ((Alzheimer's disease/TH OR Alzheimer's disease/TI OR ((Alzheimer/TI) AND (Dementia/TH OR Dementia/TI))) AND ((SH = Pharmacotherapy) OR Pharmacotherapy/TH OR Pharmacological action/TH OR Pharmacotherapy/TI OR Drug treatment/TI OR Chemotherapy/TI))

CQ 6-9

What are the key points in care for Alzheimer's disease dementia?

Answer

It is important to respect the patient's intentions and respond with respect and empathy. Since there is no established care method specially for Alzheimer's disease dementia, care for dementia in general can be applied to Alzheimer's disease dementia. The concept of person-centered care and techniques such as validation have been proposed.

Comments and evidence

Obtaining medical evidence in the field of care is a difficult task, and a low level of evidence does not mean that care is ineffective. Respecting the intentions of a patient with dementia and responding with respect and empathy are related to the patient's dignity as a person, and is a principle that should be observed regardless of the existence of evidence. Refer to CQ3A-7-1 and CQ4C-1-5 for care and guidance support for dementia in general.

Regarding caregivers' attitudes to patients with dementia, the general principles recommended by the American Psychiatric Association (APA) treatment guidelines are as follows [1]:

- recognize patient's decline in capacity, avoid over-expectation
- pay attention to rapid progression and emergence of new symptoms
- keep requests and demands simple,
- change requests if the patient becomes overly upset or angered
- avoid difficult tasks that may lead to frustration
- do not confront patients to face their impairment
- remain calm, firm, and supportive
- avoid unnecessary changes
- explain in detail and provide cues to maintain patient's orientation

Explain interventions also to caregivers. RCTs focusing on Alzheimer's disease dementia have reported that providing education/support and stress management to caregivers reduce patients' behavioral and psychological symptoms of dementia (BPSD), care burden, and caregivers' depression, subsequently delaying admission to care facilities [2-5]. However, heterogeneity among studies is high due to factors such as diversity of intervention methods. Currently, the evidence level is low.

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(References 2-5 were identified through manual search)

■ Search formula

PubMed search: July 2, 2015 (Thursday)

#1 ("Alzheimer Disease/therapy" [Majr] OR (Alzheimer [TI] AND (therapy [TI] OR therapeutic [TI] OR treatment [TI]))) AND ("Counseling" [Mesh] OR counsel* [TI] OR "Patient Care" [Majr] OR care [TI] OR intervention [TI])

Ichushi search: July 2, 2015 (Thursday)

#1 ((Alzheimer's disease/TH OR Alzheimer's disease/TI) OR (Alzheimer/TI) AND (Dementia/TH OR Dementia/TI)) AND (Patient management/TH OR Counseling/TH OR Care/TI OR Counseling/TI)

CQ 6-10

What kind of social support is available for Alzheimer's disease dementia?

Answer

In order to reduce the care burden, active utilization of social support is necessary from the early stage of disease. It is desirable to have some knowledge about the available systems and social support.

Comments and evidence

Refer to CQ5C-1 to 4 for details of financial support and daily living support for early-onset dementia.

1. Public long-term care

Persons aged 40 years and above who have dementia-related diseases are eligible to use long-term care insurance services [1].

In-home long-term care support (home services) including visiting services (such as home-visit long-term care and home-visit nursing), day services/daycare (day rehabilitation), and short stay services are important [1, 2]. For home-visit long-term care, home helpers visit the homes of persons with dementia to provide care for daily living. For day services/daycare, persons with dementia visit facilities during the day and receive care or rehabilitation. For short stay services, persons with dementia are admitted to facilities that provide facility care support for a short period of time. Group home (communal long-term care for dementia) belongs to in-home long-term care support within the long-term care insurance system [1]. Other in-home care support includes home-visit rehabilitation and home-visit bathing service [3].

There are three types of facility care support: long-term care welfare facilities for older people (special nursing homes for older people), long-term care health facilities for older people (health facilities for older people), and long-term care sanatorium-type medical facility (medical care facilities) [1]. In addition, as one of the community-based services, multifunctional long-term care in small group home allows the provision of day service, home-visit services and overnight stay services in one facility [1].

2. Medical care

Daycare provided by medical care insurance includes daycare for persons with severe dementia. In-patient facilities include dementia treatment wards [1].

3. Organization for persons affected by dementia

As an organization for persons affected by dementia, the "Alzheimer's Association Japan" is a private organization for persons with dementia and their families, and is an active organization with branches in all the prefectures. Activities include "telephone helpline service for dementia" [1].

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■ Search formula

PubMed search: July 2, 2015 (Thursday)

#1 ("Alzheimer Disease" [Majr] OR Alzheimer [TI]) AND ("Social Support" [Mesh] OR social support* [TI] OR "Health Resources" [Mesh] OR health resource* [TI] OR social resource* [TI] OR health care system* [TI] OR healthcare system* [TI] OR "Social Welfare" [Mesh] OR "social welfare" [TI] OR "welfare system" [TI])

Ichushi search: July 2, 2015 (Thursday)

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Chapter 7

Dementia with Lewy bodies

CQ 7-1

What are the diagnostic criteria and key points for early diagnosis of dementia with Lewy bodies (DLB)?

Answer

For clinical diagnosis of DLB, the revised diagnostic criteria of the DLB International Workshop are used. The diagnostic criteria for DLB are also provided in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Memory impairment may not be noticeable in the early stage of the disease. The key point for early diagnosis is to look for the presence or absence of decline of cognitive functions other than memory (such as attention, executive function, and visuospatial cognition), REM sleep behavior disorder, parkinsonism, autonomic symptoms, olfactory disturbance, depressive symptoms, and other symptoms.

In June 2017, new DLB diagnostic criteria were published.

C

Comments and evidence

In 1995, the first DLB International Workshop proposed the term "dementia with Lewy bodies" (DLB) and its clinical diagnostic criteria [1]. The diagnostic criteria were revised at the third workshop, and further revised in 2017 [2]. Probable DLB (almost definite) can be diagnosed if two or more of the core features are present. In the presence of only one core clinical feature, probable DLB can also be diagnosed if one or more of the indicative biomarkers are present. The DSM-5 published in 2013 shows the diagnostic criteria for major neurocognitive disorder (dementia) with Lewy bodies and mild neurocognitive disorder (mild cognitive impairment) with Lewy bodies [3].

In DLB, since memory impairment is often unremarkable in the early stage of the disease, it is important to examine whether there are disorders other than memory impairment, such as attention disorder, impaired executive function, and visuospatial impairment. Moreover, diverse clinical symptoms may manifest in addition to cognitive impairment. Paying attention to these clinical symptoms provides important clues for early diagnosis of DLB. REM sleep behavior disorder is often seen from the prodromal stage [4]. Furthermore, studies that compared early and prodromal stages of DLB with those of Alzheimer's disease have reported that parkinsonism [4-6], gait disorder [6], autonomic symptoms [4, 7], olfactory dysfunction [4, 7], hallucinations [4-6], delirium [5, 6], sleep disturbance and psychiatric symptoms [7] occur more frequently in DLB. Since many factors such as hypersensitivity to antipsychotic drugs, syncope, and falls are directly related to poor prognosis in DLB, an accurate diagnosis from the early stage is important for appropriate disease management.

References

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Search formula

PubMed search: July 5, 2015 (Sunday), August 18, 2015 (Tuesday)
#1 "Lewy Body Disease/diagnosis" [Mesh] OR ((Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI])) AND ("Early Diagnosis" [Mesh] OR early OR "diagnostic criteria" OR "diagnostic accuracy" OR "diagnostic classification" [TI] OR "Diagnosis, Differential" [Mesh] OR "differential diagnosis")

Ichushi search: July 6, 2015 (Monday)
#1 (Lewy body disease/TH OR Lewy body disease/TI OR Lewy body disease/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis)OR Diagnosis/TH OR Diagnosis/TI) AND (Early diagnosis/TH OR Early/TI OR Diagnostic criteria/AL)

CQ 7-2

What are the clinical and pathological differences between dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD)?

Answer

(1) Lewy body disease (LBD) is a disease concept that includes all the diseases containing Lewy bodies from the pathological aspects. (2) There is no evidence that there is fundamental difference between DLB and PDD. DLB and PDD can be viewed as a disease spectrum called LBD. (3) As an operational criterion used in research, it has been proposed to diagnose DLB when dementia precedes parkinsonism, and PDD when parkinsonism precedes dementia for one year or longer.

Comments and evidence

1. Terminology issue of DLB and PDD

At the first DLB International Workshop in 1995, the term DLB was proposed for dementia characterized by the neuropathological feature of the appearance of Lewy bodies with α-synuclein as the main component [1]. On the other hand, if dementia occurs after the onset of motor symptoms of Parkinson's disease (PD), this condition has been called "Parkinson's disease with dementia (PDD)". In the International Workshop, PDD is defined as cases in which parkinsonism has been present for one year or longer before the onset of dementia, and DLB as cases in which the onset of dementia is before the onset of parkinsonism or within one year after onset of parkinsonism (1 year rule) [1]. This one-year rule continues to be adopted subsequently in the third workshop [2]. However, note that this rule is only an operational criterion used in research.

2. Similarities and differences between DLB and PDD

A conference held in 2006 which examined the boundary issues between PDD and DLB concluded that "the differing temporal sequence of symptoms and clinical features of PDD and DLB justify distinguishing these disorders. However, a single Lewy body disorder model was deemed more useful for studying disease pathogenesis because abnormal neuronal α-synuclein inclusions are the defining pathologic process common to both PDD and DLB" [3]. The diagnostic criteria for PDD have also been proposed [4].

Lewy bodies containing α-synuclein as the major component are frequently found in neurons of the brain and in autonomic nervous system. According to the distribution pattern, Lewy body disorder is classified into the diffuse type (neocortical type), limbic type, brainstem type, and cerebral type (Lewy bodies are scarcely seen in the brainstem). Many patients with LBD also have concomitant pathology of Alzheimer's disease, and are classified into Alzheimer type, usual type, and pure type (in decremental order of concomitant Alzheimer's pathology). Lewy body pathology spreads in different patterns, including spread from the medulla oblongata ascending to the cerebral cortex, progression from the amygdala to cerebral cortex or brainstem, and descending spread from the cerebral cortex to brainstem. Such pathological diversity probably accounts for the broad spectrum of LBD phenotypes.

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Search formula

PubMed search: July 5, 2015 (Sunday), August 18, 2015 (Tuesday)

#1 ("Lewy Body Disease/diagnosis" [Mesh] OR ((Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic[TI])))) AND (("Parkinson Disease" [Mesh] AND (Dementia [Mesh] OR "Cognition Disorders" [Mesh])) OR "Parkinson's disease dementia" OR "Parkinson disease dementia" OR PDD) OR (("Lewy Body Disease/diagnosis" [Mesh] OR (("Lewy body" OR "Lewy bodies") AND "Dementia/diagnosis"[Majr])) AND ("Parkinson Disease/diagnosis" [Mesh] OR ("Parkinson disease" AND diagnosis [TI])) AND (criteria OR "Diagnosis, Differential" [Mesh] OR "Incidence" [Mesh] OR "differential diagnosis" [TI] OR "pathologic diagnosis"))

Ichushi search: July 6, 2015 (Monday)

#1 (Lewy body disease/TH OR Lewy body disease/TI) AND (Parkinson disease/TH OR Parkinson disease/TI OR Parkinson disease/TI) AND (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI)

CQ 7-3

What are the characteristic laboratory and imaging biomarker of dementia with Lewy bodies (DLB)?

Answer

DLB is characterized by reduced uptake on dopamine transporter scintigraphy and metaiodobenzylguanidine (MIBG) myocardial scintigraphy. On CT/MRI, the medial temporal lobe is relatively preserved. Cerebral SPECT and FDG-PET show decreased blood flow and glucose metabolism in the occipital lobe. A

Comments and evidence

In DLB, decreased uptake is observed on ^{123}I-MIBG myocardial scintigraphy and dopamine transporter scintigraphy. In particular, ^{123}I-MIBG myocardial scintigraphy is useful for differentiation from other parkinsonism-related diseases (such as multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration) [1], while dopamine transporter scintigraphy is highly useful for differentiation from Alzheimer's disease [2]. A report shows that a combination of ^{123}I-MIBG myocardial scintigraphy and dopamine transporter scintigraphy can differentiate DLB from Alzheimer's disease dementia with 96.1% sensitivity and 90.7% specificity [3].

When using dopamine transporter (DAT) scintigraphy in diagnosis, careful attention has to be given to the following.

(1) Differentiation between DLB and other parkinsonism-related diseases (including progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration) is difficult because both are presynaptic disorders of nigrostriatal dopaminergic neurons.

(2) Vascular parkinsonism shows normal to mild loss in DAT uptake in the striatum. Drug-induced parkinsonism shows normal findings, but it is necessary to confirm the history of the causative drugs use such as anti-dopaminergic agents.

(3) Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and other drugs (drugs with stimulant effect such as cocaine, amphetamine, methylphenidate, and modafinil) affect the imaging result because of interaction of the ligand with drugs that have mechanisms of action on dopamine transporters and serotonin transporters. Therefore, suspending medication or using alternative drugs should be considered before examination. Anti-parkinsonian drugs such as cholinesterase inhibitors, levodopa and MAOB inhibitors have little effects on the results [4].

(4) Pregnant women and persons who are allergic to excitatory substances such as cocaine are general contraindications. Breastfeeding is a relative contraindication [4].

(5) For patients with liver dysfunction, alcohol hypersensitivity, urinary disorder, or allergic constitution, the examination has to be administered with caution and after obtaining consent.

The hippocampus and parahippocampal gyrus are relatively preserved on brain MRI, but brainstem atrophy may be diagnosed by statistical analysis such as Voxel-based Specific Regional Analysis System for Alzheimer's Disease (VSRAD) [5]. On cerebral blood flow scintigraphy, both Alzheimer's disease and DLB show decreased blood flow in the occipital lobe, posterior cingulate gyrus, and precuneus. Whereas hippocampal blood flow is reduced in Alzheimer's disease, it is relatively preserved in DLB. Compared to Alzheimer's disease, DLB is also characterized by showing earlier decreases in blood flow and metabolism in the primary visual cortex [6]. Study has shown that if the diagnosis of DLB is difficult by brain SPECT alone, combining with ^{123}I-MIBG myocardial scintigraphy increases the diagnostic accuracy [7].

In summary, characteristic abnormalities for DLB are found in ^{123}I-MIBG myocardial scintigraphy, dopamine transporter scintigraphy, MRI combined with VSRAD, and cerebral blood flow scintigraphy. When diagnosis is difficult using a single examination, a combination of multiple examinations is expected to increase diagnostic accuracy.

Furthermore, while amyloid PET shows increased uptake in DLB similar to that in Alzheimer's disease, cholinesterase-PET (ChE-PET) is known to demonstrate decreased ChE uptake mainly in the occipital lobe in DLB [8].

Regarding cerebrospinal fluid (CSF) biomarkers, there are many reports of low CSF α-synuclein levels in DLB as in Parkinson's disease, but the usefulness of this marker has not been established. A report has shown that CSF levels of phosphorylated α-synuclein and α-synuclein oligomers are elevated in DLB as in Parkinson's disease [9]. In addition, low CSF Aβ42 level has been reported in DLB compared to controls [10].

New diagnostic criteria for DLB have been published in June 2017 (see CQ7-1). Among these criteria, the following

indicative biomarkers have been added: (1) reduced uptake in basal ganglia demonstrated by dopamine transporter scintigraphy; (2) reduced uptake on ^{123}I-MIBG myocardial scintigraphy; and (3) REM sleep without atonia (RWA) confirmed by polysomnography (PSG). In particular, abnormal muscle tone during REM sleep is a highly specific phenomenon for patients with Lewy body pathology, and is recognized as an important sign even if the other biomarkers are negative.

References

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Search formula

PubMed search: July 5, 2015 (Sunday), August 18, 2015 (Tuesday)

#1 ("Lewy Body Disease/diagnosis" [Mesh] OR ((Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic[TI]))) AND "Diagnostic Imaging" [Mesh] OR "3-Iodobenzylguanidine/diagnostic use" [Mesh] OR "Dopamine Plasma Membrane Transport Proteins" [Mesh]) OR "magnetic resonance imaging" OR "single-photon emission computed tomography" OR "positron emission tomography" OR DAT scan* OR neuroimaging OR MRI OR SPECT OR MIBG OR PET) OR "Lewy Body Disease/cerebrospinal fluid" [Majr] OR ("Lewy Body Disease/radionuclide imaging" [Mesh] OR (("Lewy body" [TI] OR "Lewy bodies" [TI]) AND dementia [TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI]))) AND ("Fluorodeoxyglucose F18/diagnostic use" [Mesh] OR "3-Iodobenzylguanidine/diagnostic use" [Mesh] OR "Dopamine Plasma Membrane Transport Proteins/analysis" [Majr] OR Metaiodobenzylguanidine OR meta-iodobenzylguanidine OR MIBG)

Ichushi search: July 6, 2015 (Monday)

#1 (Lewy body disease/TH OR Lewy body disease/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis)OR Diagnosis/TH) AND (Diagnostic imaging/TH OR "Dopamine Plasma Membrane Transport Proteins"/TH OR DAT scan OR DAT-scan OR DAT imaging OR MRI/TI OR magnetic resonance imaging OR magnetic resonance tomography OR Magnetic resonance imaging OR Nuclear magnetic resonance imaging OR SPECT/TI OR Single photon emission computed tomography OR Single photon emission computed tomography OR Single photon computed tomography OR Single photon emission computed tomography OR Single photon emission computed tomography OR Iobenguane/TH OR MIBG OR PET/TI OR Positron emission tomography)

CQ 7-4

What are the clinical course and prognosis of dementia with Lewy bodies (DLB)?

Answer

Reports have indicated that there is no difference in the progression of cognitive impairment between DLB and Alzheimer's disease. There are reports indicating that the time from initial consultation or diagnosis to hospital admission or death is shorter in patients with DLB. C

Comments and evidence

Several studies have compared the clinical course and prognosis of DLB and Alzheimer's disease. Many of them report no differences between DLB and Alzheimer's disease in terms of progression of cognitive impairment [1-6] and progression of declined functional abilities [1, 2]. The result of a recent meta-analysis also confirms no difference in the progression of cognitive impairment [7]. On the other hand, there are reports showing that the DLB group has a shorter time from the first hospital visit to end point (admission to institutional, admission to hospital, or death) [6], and a shorter survival duration from onset of dementia [5, 8] or from diagnosis [9]. In any case, careful attention should be paid to the complications such as pneumonia, which worsen the outcome.

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■ Search formula

PubMed search: July 5, 2015 (Sunday), August 18, 2015 (Tuesday)
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Ichushi search: July 6, 2015 (Monday)
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CQ 7-5

What is the treatment strategy planned for dementia with Lewy bodies (DLB)?

Answer

Regarding treatment strategy for DLB, symptomatic treatment for each of the diverse clinical symptoms is recommended. The strategy should include pharmacotherapy and non-pharmacological therapies. A

Comments and evidence

DLB may manifest diverse symptoms including cognitive impairment, hallucinations, delusion, depressive symptoms, apathy, abnormal REM sleep behavior and other behavioral and psychological symptoms of dementia (BPSD), extrapyramidal symptoms, and autonomic symptoms. Because of the diversity of symptoms, it is important to determine the major symptoms that should be the target of treatment, and then plan the treatment strategy.

Since DLB has high risk of drug-induced adverse events, non-pharmacological interventions such as care and environmental adaptation are particularly important. While donepezil has been used for treating cognitive impairment, symptomatic drugs should be used for BPSD, motor deficits, and autonomic dysfunction [1].

References

1) McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005; 65(12): 1863-1872.

Search formula

PubMed search: July 5, 2015 (Sunday), August 18, 2015 (Tuesday)

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Ichushi search: July 6, 2015 (Monday)

#1 (Lewy body disease/TH OR Lewy body disease/TI) AND (Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment)OR Treatment/TH OR Treatment/TI OR Therapy/TI)

CQ 7-6

Are there any drugs for the treatment of cognitive impairment in dementia with Lewy bodies (DLB)?

Recommendation

Cholinesterase inhibitors have been reported to be effective for cognitive impairment in DLB patients. 1B

Comments and evidence

The usefulness of cholinesterase inhibitors for cognitive impairment in DLB has been reported [1]. In Japan, donepezil (Aricept®) is covered by health insurance for the treatment of cognitive impairment in DLB. In a meta-analysis of randomized controlled trials (RCT), both cholinesterase inhibitors and memantine are safe and improve Clinician's Global Impression of Change (CGIC), but only cholinesterase inhibitors enhance cognitive function [1]. According to the results of a meta-analysis in 2015 analyzing 17 large-scale studies on Lewy body disease, cholinesterase inhibitors are useful in improving cognitive function without worsening motor function [2].

1. Cholinesterase inhibitor (ChEI)

a. Donepezil

Four open-label trials have shown the efficacy of donepezil in improving cognitive function in DLB patients. In Japan, a randomized controlled trial showed that oral donepezil at doses of 5 mg and 10 mg improved Mini Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI)-2 scores (hallucination and cognitive function) [3]. Although there was no significant difference in NPI-10 score, effectiveness was observed in change of dementia symptoms. Improvement in caregiver's burden was also found in the high-dose (10 mg) group. Furthermore, in a multicenter open label long-term study (52 weeks), change in cognitive function and improvement of NPI-4 score were also observed [4] [See CQ7-7 for details of the effects of donepezil on BPSD). Subsequently, a 56-week long-term study confirmed the tolerability and maintenance of cognitive function improvement in patients treated with donepezil 5 mg and 10 mg [5]. A placebo-controlled double-blind study (phase III) in DLB patients demonstrated improvement in MMSE score with 10 mg, but not with 5 mg of donepezil [6].

On the other hand, a randomized controlled trial has shown the effectiveness of donepezil for cognitive function also in PDD [7].

b. Rivastigmine

In a RCT conducted in patients with DLB, although the improvements of MMSE score and global clinical evaluation were not significant in patients treated with oral rivastigmine, the effect of improving attention was particularly remarkable [8]. A RCT of rivastigmine in patients with PDD has shown significant improvement in multiple cognitive function evaluation tests including the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) [9]. Regarding the efficacy on cognitive impairment in PDD, rivastigmine was highly recommended by the European Federation of Neurological Society (EFNS) (clinical evidence class I, recommended level A) and American Academy of Neurology (AAN) (evidence level class II, recommendation level B) [10].

c. Galantamine

A 24-week open-label study of galantamine in DLB patients showed improvement in global clinical impression and in cognitive function (ADAS-cog) [11].

2. NMDA receptor antagonist: memantine

A 24-week placebo-controlled RCT of memantine in 72 DLB or PDD patients showed improvement in a cognitive function test requiring attention (A Quick Test of Cognitive Speed; AQT) and in CGIC [12]. However, the results of a meta-analysis on memantine for Lewy body disorders reported by Matsunaga et al.[13] showed no significant improvement in cognitive function.

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Search formula

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#1 ("Lewy Body Disease" [Mesh] OR Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND ("Cognition Disorders/therapy" [Mesh] OR ((cognition disorder* OR cognitive disorder*) AND (therapy OR therapeutic OR treatment))) OR ("Lewy Body Disease/drug therapy" [Majr] OR (("Lewy body" [TI] OR "Lewy bodies" [TI]) AND (donepezil OR rivastigmine)) OR ("Dementia/drug therapy" [Majr] AND "Parkinson Disease/complications" [Mesh])) AND ("Cognition/drug effects" [Majr] OR ((cognitive function* OR cognitive assessment* OR cognitive subscale*) AND improve*))

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#1 (Lewy body disease/TH OR Lewy body disease /TI) AND (Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment)OR Treatment/TH OR Treatment/TI OR Therapy/TI)

CQ 7-7

Are there any treatments for behavioral and psychological symptoms of dementia (BPSD) and REM sleep behavior disorder (RBD) in dementia with Lewy bodies (DLB)?

Recommendation

(1) Although *Yokukansan* and atypical antipsychotics have been reported to be therapeutic drugs for BPSD, sufficient consideration for safety is required. (2) The effectiveness of clonazepam for RBD has been reported. Some case reports have indicated that *Yokukansan*, ramelteon, and donepezil are effective when clonazepam cannot be used. 2C

Comments and evidence

Patients with DLB may show hypersensitivity to antipsychotic drugs. Therefore, non-pharmacological interventions should take priority over pharmacotherapy for the treatment of BPSD. Donepezil, a therapeutic drug for cognitive impairment in DLB, may also be effective against BPSD [1].

If there is no response to the above interventions, symptomatic drugs for BPSD are used. *Yokukansan* has been shown to be effective in improving NPI total score, hallucinations, delusion, depression, and anxiety symptoms [2]. Although *Yokukansan* does not cause extrapyramidal symptoms or anticholinergic symptoms, hypokalemia may occur occasionally which requires attention. In addition, a report indicates the effectiveness of memantine against BPSD such as delusion, hallucinations, abnormal nocturnal behaviors, and abnormal appetite in patients with DLB [3]. Antipsychotics have been used for BPSD in DLB. However, as noted above, patients with DLB may have hypersensitivity to antipsychotics; therefore use of these drugs requires special caution [4]. Haloperidol is contraindicated for Parkinson's disease, and should also be avoided in patients with DLB in principle.

Among atypical antipsychotics, quetiapine and aripiprazole that have mild adverse effects on the extrapyramidal system are considered to be relatively safe [4], but there is little evidence. Although there are reports on the effectiveness of atypical antipsychotics for BPSD in DLB, discontinuation due to adverse effects is not uncommon. When using these drugs, it is necessary to use the minimum dose and always pay attention to the occurrence of adverse events.

Clonazepam has been reported to be effective for the treatment for RBD. However, special attention should be paid to over-sedation and falls when used in patients with DLB. Case reports have indicated that *Yokukansan* [5], ramelteon [6], and donepezil [7] were effective when clonazepam cannot be used due to adverse effects. There is little evidence for the effect of clonazepam on insomnia in DLB. In patients with DLB, attention should be paid to the effects of sleep medications causing dizziness, falls and hang-over. Two cases of insomnia in DLB responding to ramelteon have been reported [8]. A report also indicates the effectiveness of *Yokukansan* in improving total time and efficiency of sleep, and reducing the number of arousals during sleep [9].

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#1 ("Lewy Body Disease" [Mesh] OR Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND (("behavioral psychological symptom dementia" OR BPSD) AND (therapy OR therapeutic OR treatment)) OR "Behavioral Symptoms/therapy" [Mesh] OR (("REM sleep" OR sleep disorder*) AND (therapy OR therapeutic OR treatment)) OR "Sleep Disorders/therapy"[Mesh]) OR ((((("Lewy Body Disease/psychology" [Mesh] OR ((("Lewy body" [TI] OR "Lewy bodies" [TI]) AND dementia[TI]) AND (mental impairment* OR behavioural symptom* [TI]))) AND ("Lewy Body Disease/drug therapy" [Majr] OR "Delusions/drug therapy" [Majr] OR "Psychotic Disorders/drug therapy" [Majr] OR ("Dementia/drug therapy" [Majr] AND "Dementia/psychology" [Mesh]))) OR ("REM Sleep Behavior Disorder/drug therapy" [Majr] OR ("REM Sleep Behavior Disorder/drug therapy" [Mesh] AND "REM Sleep Behavior Disorder/physiopathology"[Mesh]))) AND ("Nootropic Agents" [Mesh] OR "Antipsychotic Agents" [Mesh] OR "Drugs, Chinese Herbal" [Mesh] OR "Dibenzothiazepines" [Mesh] OR "Anticonvulsants" [Mesh] OR "Clonazepam" [Mesh] OR "Cholinesterase Inhibitors" [Mesh]))

Ichushi search: July 6, 2015 (Monday)

#1 (Lewy body disease/TH OR Lewy body disease/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment)OR Treatment/TH OR Treatment/TI OR Therapy/TI) AND (Behavioral psychological symptoms /TH OR Behavioral psychological symptoms/TI OR Behavioral symptoms /TH OR Behavioral symptoms /TI OR Psychiatric symptoms/TH OR Psychiatric symptoms/TI OR Sleep disorder/TH OR Sleep disorder/TI)

CQ 7-8

Are there any treatments for autonomic symptoms (such as orthostatic hypotension, constipation, sweating, urination disorder) in dementia with Lewy bodies (DLB)?

Recommendation

For autonomic symptoms in DLB, drugs for the treatment of autonomic symptoms in Parkinson's disease (PD) are used while paying attention to deterioration of cognitive function and psychiatric symptoms. Non-pharmacological therapies are also used. 2C

Comments and evidence

There are no randomized controlled trials (RCT) for autonomic symptoms in DLB, but treatments for orthostatic hypotension, constipation, abnormal sweating, and urinary disorder are given according to those used for the treatment of these conditions in PD [1]. In a study of 29 patients with DLB, urinary incontinence (97%) and constipation (83%) were the most common, while hypotension was found in 66%, and a history of syncope in 28% [2].

Not only orthostatic hypotension, but postprandial hypotension also occurs frequently. Especially in older patients, dehydration is a common triggering factor, which requires attention. For the treatment of orthostatic hypotension, apart from non-pharmacological interventions such as salt intake, head-up tilt in bed, and wearing compressive stockings [3], pharmacotherapy using droxidopa, midodrine, and fludrocortisone is effective.

For constipation, adequate dietary fiber and water intake, and use of laxatives such as magnesium oxide, lubiprostone, senna, sennoside, and *Daikenchuto* are useful. In addition, prescribe mosapride and domperidone to improve gastrointestinal peristalsis. In DLB, pay attention to paralytic ileus as in PD.

Regarding urinary disorder in DLB, avoid using anticholinergic drugs as far as possible because these drugs may deteriorate cognitive function. Oxybutynin should not be used because this drug readily passes into the central nervous system and its anticholinergic action on the central nervous system has the risk of worsening cognitive impairment [4]. Paroxetine, a selective serotonin reuptake inhibitor (SSRI), and milnacipran, a serotonin-norepinephrine reuptake inhibitor (SNRI), are sometimes useful. Donepezil has been reported to improve attention in patients with dementia, and at the same time suppress the micturition reflex via central muscarinic M2 receptor [5]. Use of the adrenoreceptor antagonists such as urapidil, tamsulosin, and naftopidil may be considered in cases of difficulty in urination due to enlarged prostate.

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#1 ("Lewy Body Disease" [Mesh] OR Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND ("Autonomic Nervous System Diseases/therapy" [Mesh] OR "Constipation/therapy" [Mesh] OR "Hyperhidrosis/ therapy" [Mesh] OR "Dysuria/therapy" [Mesh] OR ((autonomic dysfunction* OR orthostatic hypotension* OR constipation* OR hyperhidrosis OR dysuria) AND (therapy OR therapeutic OR treatment))) OR (("Parkinson Disease/therapy" [Majr] OR Parkinson's disease*) AND (((orthostatic hypotension* OR GI symptom* OR GI complaint*) AND improve*) OR "Urination Disorders/drug therapy" [Majr] OR "Urinary Bladder Diseases/drug therapy" [Majr]))

Ichushi search: July 6, 2015 (Monday)
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CQ 7-9

What are the suitable treatments for parkinsonism in dementia with Lewy bodies (DLB)?

Recommendation

Levodopa is recommended for parkinsonism in DLB patients, but high doses should be avoided because of the risk of worsening psychiatric symptoms and involuntary movements (such as dyskinesia). Use of dopamine agonist tends to worsen psychiatric symptoms, and therefore require special caution. 2C

Comments and evidence

Although there is no randomized controlled trial (RCT) for the treatment of parkinsonism in patients with DLB, levodopa is recommended according to the recommendation for Parkinson's disease (PD) [1, 2]. However, response to levodopa in DLB is generally inferior to that in PD [2]. Note that high doses should not be used because there is little benefit in improving motor symptoms, while there is a risk of exacerbating psychiatric symptoms. When levodopa is used, start from a low dose and up-titrate gradually to the minimally required dose. Anticholinergic drugs such as trihexyphenidyl have the risk of impairing cognitive function and should be avoided in principle [2].

Using high-dose levodopa from the early stage tends to induce not only psychiatric symptoms such as hallucination, but also motor complications such as dyskinesia and wearing-off symptoms [3],. Therefore, start from a low dose and pay attention to whether psychiatric symptoms are worsened. Since psychiatric symptoms such as hallucination and impulse control disorder are easily induced in patients with DLB, dopamine agonists may be used with special caution [4]. In the case of difficulty with rolling over in bed due to wearing off symptoms at night or in early morning, rotigotine patch has been reported to be effective for the group of diseases causing atypical parkinsonism including PD with dementia [5], but avoid using this drug if there is any deterioration in psychiatric symptoms such as hallucination.

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#1 ("Lewy Body Disease" [Mesh] OR Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND ("Parkinsonian Disorders/therapy" [Mesh] OR "Neurologic Manifestations/therapy" [Mesh] OR((Parkinsonian disorder* OR Parkinsonism OR dyskinesia OR motor dysfunction*) AND (therapy OR therapeutic OR treatment))) OR ("Parkinson Disease/drug therapy" [Majr] OR ((Parkinson disease* [TIAB] OR Parkinson's disease*[TIAB]) AND (therapy [TIAB] OR intervention* [TIAB]))) AND ("Lewy Body Disease/drug therapy" [Mesh] OR (("Lewy body" [TI] OR "Lewy bodies" [TI]) AND dementia [TI] AND (therapy [TI] OR management[TI]))OR "Dyskinesias" [Majr] OR dyskinesia* [TI])

Ichushi search: July 6, 2015 (Monday)

#1 (Lewy body disease/TH OR Lewy body disease/TI) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment)OR Treatment/TH OR Treatment/TI OR Therapy/TI) AND (Parkinsonism/TH OR Parkinsonism/TI OR Parkinson disease/TI OR Involuntary movement/TH OR Involuntary movement/TI OR Dyskinesia/TH OR Dyskinesia/TI)

CQ 7-10

What are the non-pharmacological interventions for dementia with Lewy bodies (DLB)?

Answer

Non-pharmacological interventions are also important for DLB, and appropriate care and environmental adjustment are recommended. D

Comments and evidence

Non-pharmacological interventions such as appropriate care and environmental improvement are also important in the management of DLB. However, although non-pharmacological interventions may be effective in improving behavioral and psychological symptoms of dementia (BPSD) and functional abilities in patients with DLB, there are no research reports proving them so far. Since cognitive impairment and visual hallucination are worsened by decline in arousal and attention levels [1], social interaction and environmental stimulation may be effective. For BPSD in DLB, using a person-centered approach to improve caregiver's burden should be tried first [2]. For dementia in general, removal of any trigger of agitation (pain, fear, hallucination, delusion, environment) is recommended [3]. The results of a meta-analysis show that giving advice on care to caregivers, supporting caregivers, and acquiring stress management skills are effective to reduce BPSD [4], and these approaches may also be useful in patients with DLB. Parkinsonism is a risk of falls in DLB patients [1, 5]. Although some reports have shown that gait rehabilitation training is useful as a non-pharmacological intervention for falls and gait disturbances in patients with Parkinson's disease, there is little evidence for DLB.

References

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Search formula

PubMed search: July 5, 2015 (Sunday), August 19, 2015 (Wednesday)

#1 ("Lewy Body Disease/therapy" [Mesh] OR ((Lewy body disease* OR "Lewy body dementia" OR "dementia with Lewy body") AND (therapy OR therapeutic OR treatment OR rehabilitation OR intervention*))) AND ("Rehabilitation" [Mesh] OR rehabilitation* OR "Psychotherapy" [Mesh] OR "Social Support" [Mesh] OR psychosocial intervention*) OR (("Lewy Body Disease/therapy" [Mesh] OR (("Lewy body" [TI] OR "Lewy bodies" [TI]) AND dementia [TI] AND (therapy [TI] OR management [TI]))) AND (specific intervention* OR nonpharmacologic OR cognitive-behavioral intervention*)) OR ("Dementia/therapy" [Majr] AND "Phototherapy" [Mesh])

Ichushi search: July 6, 2015 (Monday)

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Chapter 8

Frontotemporal Lobar Degeneration

History

Frontotemporal lobar degeneration (FTLD), with Pick's disease as the prototype, is a progressive non-Alzheimer's disease often with the presenile onset and is characterized by degeneration and loss of neurons mainly in the frontal and temporal lobes, causing marked behavioral abnormalities, psychiatric symptoms, and language impairment, while various degrees of motor disorders may emerge during the course of disease. The concept, name, and classification of FTLD have changed over the years, and terms such as frontal lobe degeneration of non-Alzheimer type and frontal lobe dementia were once used in the past.

Clinical classification

The term FTLD is used in cases with a definitive pathological and genetic diagnosis, while frontotemporal dementia (FTD) is used in cases with a clinical diagnosis. The term FTLD is adopted as the disease name in designated intractable diseases in Japan. In this guideline, FTLD is used and also includes clinically diagnosed cases.

FTLD is a classified clinically into three types: behavioral variant frontotemporal dementia (bvFTD) with mainly prefrontal atrophy; semantic dementia (SD) with localized atrophy mainly in the temporal pole and middle/inferior temporal gyrus; and progressive non-fluent aphasia (PNFA), which is left-dominant and shows localized atrophy around the fissure of Sylvius. Refer to CQ2-6 for the classification by type of aphasia.

Also, parkinsonism and motor neuron symptoms may be observed in patients with FTLD during the course of disease. The disease type showing motor neuron symptoms is called frontotemporal dementia with motor neuron disease (FTD-MND).

Pathological classification

Pathologically, specific proteins aggregate and deposit as inclusion bodies in neurons and glial cells. Tau protein, TAR DNA-binding protein of 43 kD (TDP-43), and fused in sarcoma (FUS) protein have been identified as the main components of the inclusion bodies [1].

Tau protein is one of the microtubule-binding proteins and is broadly classified by the number of repeats in the microtubular binding region at the C-terminal side into three-repeat tau protein and four-repeat tau protein. Tauopathy is a general term for diseases in which abnormal accumulation of phosphorylated tau protein is considered to be an essential pathogenic mechanism. The subgroup of FTLD that exhibits tauopathy is called FTLD-tau. FTLD-tau comprises cases showing accumulation of mainly three-repeat tau protein (Pick disease) and those showing accumulation of mainly four-repeat tau protein. Corticobasal degeneration, progressive supranuclear palsy, and argyrophilic grain dementia are broadly interpreted as four-repeat tauopathy with FTLD.

TDP-43 protein and FUS protein exist mainly in the nucleus, and both possess diverse functions such as transcription, splicing, RNA transport, and stabilization. In FTLD, both TDP-43 protein and FUS protein disappear from the nucleus and are observed as extracellular aggregates, and these disease types are called FTLD-TDP and FTLD-FUS, respectively. See CQ1-8 for a detailed description of pathology.

Relationship between clinical classification and pathological classification

It has been reported that more than half of bvFTD cases are FTLD-TDP type, while approximately 70% of PNFA cases are FTLD-tau type (PSP, CBD, Pick disease), and approximately 80% of SD are FTLD-TDP type [2].

Diagnosis

For diagnostic criteria, see CQ8-1.

Family history

Family history is evident in 30 to 50% of the cases in European and American countries but is almost absent in Japan. In familial cases, mutations have been identified in several genes, including the *tau* gene, the *TARDBP* gene, the *FUS* gene, and the *progranulin* gene. Abnormal expansion of a hexanucleotide repeat in intron 1 of the *C9orf72* gene is the most frequent cause in European and American countries, but very rarely in Japan.

Treatment

FTLD is a progressive degenerative disease, and curative treatment that can modify the natural course has not been developed. When patients show motor neuron symptoms, pay special attention to the onset of respiratory failure and dysphagia. Parkinsonism and repeated falls may be observed, but levodopa preparations have limited use or are often ineffective.

References

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CQ 8-1

What are the diagnostic key points and diagnostic criteria for frontotemporal lobar degeneration (FTLD)?

Answer

Among various types of frontotemporal lobar degeneration (FTLD), the criteria developed by the International Behavioral Variant Frontotemporal Dementia Criteria Consortium (FTDC) in 2011 are recommended for the diagnosis of behavioral variant frontotemporal dementia (bvFTD). For semantic dementia (SD), the use of the clinical diagnostic characteristics for semantic dementia proposed in 1998 is recommended, with additional reference to the clinical diagnostic features for semantic variant progressive aphasia proposed in 2011. B

Comments and evidence

FTLD is classified clinically into behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA). Among them, bvFTD and SD are included as designated intractable diseases in Japan.

1. Diagnostic criteria for bvFTD

The FTDC diagnostic criteria reported by Rascovsky et al. [1] are used. The sensitivity of the FTDC criteria is 93% for possible bvFTD and 80% for probable bvFTD, and the positive predictive value of cases diagnosed as possible bvFTD is 90% [2]. Harris et al. [3] studied mainly early-onset cases and reported high reliability, with 95% sensitivity and 82% specificity for possible bvFTD, and 85% sensitivity and 95% specificity for probable bvFTD.

The major false-positive cases are Alzheimer's disease dementia, while dementia with Lewy bodies also constitutes a certain percentage [2].

For the FTDC criteria, although the κ values (indicating interrater agreement rate) are high, with 0.81 for possible bvFTD and 0.82 for probable bvFTD, there are some differences in agreement rate among individual items [4].

For characteristic image findings, see CQ8-2. Family history is evident in 30-50% of the patients in European and American countries but in almost none of the Japanese patients.

In the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), the term "neurocognitive disorder (NCD)" is introduced to replace the term "dementia. FTLD is called major or mild frontotemporal NCD, and broadly classified into behavioral variant and language variant. For diagnostic criteria of behavior variant, the criteria adopted are almost the same as the above-mentioned FTDC criteria.

2. Diagnostic criteria of SD and characteristics of aphasia

According to the diagnostic criteria of Gorno-Tempini et al. [5] the diagnostic procedure is first to diagnose progressive aphasia and then classify into semantic, non-fluent/grammatical, and logopenic (for classification based on aphasia, see CQ2-6). SD manifests semantic aphasia (loss of word meaning). However, in SD with predominantly right temporal lobe atrophy, some patients show conspicuous semantic deficits other than semantic aphasia (for example, semantic memory impairment related to well-known buildings and faces) or behavioral disorders in the early stage. Consequently, there is less consensus compared to the bvFTD diagnostic criteria. The diagnostic criteria for designated intractable diseases adopt the Gorno-Tempini diagnostic criteria for semantic variants characterized by aphasia, together with the diagnostic criteria of Neary et al. [6] based on the evidence of characteristic semantic memory impairment regardless of the presence or absence of progressive aphasia.

In SD, impairment of object naming and word comprehension is consistent, and patients have difficulties with the same objects and words under different test settings and in daily life. Surface dyslexia is observed in reading kanjis that have different pronunciations, especially in idioms, where the words are read differently from the original kanjis.

Some patients develop impairment in recognizing the face of a known person, or cognitive impairments across multiple modalities such as visual and auditory comprehension of an object. These patients cannot recognize the faces of well-known persons, friends, or relatives whom they meet only occasionally. When they see these faces, they would say, "I can't remember anything" or "I don't know". The fact that recognition is not helped by providing sound or touch cues would indicate that

the condition is different from the usual agnosia.

For clinical diagnosis of SD, after identifying the characteristic aphasia, differentiate from other diseases such as Alzheimer's disease dementia carefully from image and other clinical findings.

3. Characteristics of aphasia observed in PNFA

Diagnostic criteria of nonfluent/agrammatic aphasia characteristic of PNFA have been reported by Gorno-Tempini et al. [5]. As mentioned above, when using these criteria, first diagnose whether progressive aphasia is present. Nonfluent/agrammatic aphasia is characterized by (1) agrammatism in speech, and (2) apraxia of speech characterized by inconsistent speech sound errors and distortions (pronunciation not found in the Japanese language); at least one of the above should be present. While single-word comprehension is spared, comprehension of grammatically complex sentences is impaired. Other features are effortful speech, difficulty in initiating speech, halting speech, and inconsistent speech errors.

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■ Search formula

PubMed search: July 10, 2015 (Friday)

#1 "Frontotemporal Lobar Degeneration/diagnosis" [Mesh] OR (("frontotemporal lobar degeneration" [TI] OR "frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR bvFTD [TI]) AND Dementia/diagnosis [Mesh]) OR (("frontotemporal lobar degeneration" OR "frontotemporal dementia" OR FTD OR FTLD bvFTD) AND (diagnosis OR diagnoses OR diagnostic))

Ichushi search: July 10, 2015 (Friday)

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CQ 8-2

What are the characteristics of image findings of frontotemporal lobar degeneration (FTLD)?

Answer

Among FTLD disorders, behavioral variant frontotemporal dementia (bvFTD) shows MRI/CT findings of localized atrophy in the frontal and temporal lobes, predominantly in the frontal lobe. On SPECT/PET, decreased metabolism/decreased blood flow is observed in the frontal lobe and anterior temporal lobe, while the parietal and occipital lobes are spared.

Semantic dementia (SD) shows MRI/CT findings of atrophy in the temporal lobe predominantly involving the anterior region and inferior temporal gyrus. Usually, atrophy is asymmetrical. As the disease progresses, frontal lobe atrophy also appears. On SPECT/PET, decreased metabolism/decreased blood flow in the temporal lobe predominantly involving the anterior region and in the inferior temporal gyrus is observed.

Progressive non-fluent aphasia (PNFA) shows MRI/CT findings of atrophy in the left frontal lobe predominantly from the posterior region to the insula. On SPECT/PET, decreased metabolism/decreased blood flow in the left frontal lobe predominantly from the posterior region to the insula is observed.

Imaging examination is useful for the diagnosis of FTLD, but a diagnosis cannot be made with images alone. B

Comments and evidence

1. General head MRI/CT and SPECT/PET findings [1)]

For bvFTD, atrophy on MRI/CT and decreased metabolism and blood flow on SPECT/PET are observed in the frontal lobes and anterior temporal lobes. For SD, atrophy on MRI/CT and decreased metabolism/blood flow on SPECT/PET are observed in temporal lobes predominantly in the anterior region and in the inferior temporal gyrus. For PNFA, atrophy on MR/CT and decreased metabolism/blood flow are observed in the left frontal lobe predominantly from the posterior region to the insula.

2. Brain volumetric imaging

Brain volumetric imaging is useful for the differentiation of Alzheimer's disease dementia, dementia with Lewy bodies, and FTLD [2)].

In bvFTD, atrophy is observed in the frontal lobes involving the medial, dorsolateral, and orbitofrontal regions, as well as the anterior temporal lobes. Atrophy in the frontal lobe, especially the medial surface, progresses from the earliest stage [1)]. The results of a meta-analysis show that bvFTD is characterized by atrophy in the prefrontal cortex, in particular, atrophy of the regions corresponding to superior and middle frontal gyrus, anterior cingulate gyrus, insula, caudate nucleus, and putamen [3)].

SD is characterized by left-right asymmetric inferior temporal gyrus-dominant anterior temporal atrophy or decreased blood flow/metabolism. The orbitofrontal cortex, insula, and caudate nucleus are also affected. In a longitudinal observational study, temporal lobe atrophy progresses from the earliest stage, and atrophy in the frontal lobe, insula, caudate nucleus, and thalamus progress in the same manner.

PNFA is characterized by atrophy or decreased blood flow/metabolism in the posterior frontal lobe, including Broca's area and the superior premotor cortex, as well as in the insula. Lesions in the superior temporal gyrus and striatum are also observed.

3. Diffusion tensor imaging [4)]

In bvFTD, bilateral and widespread lesions in the white matter tracts are observed. The lesions are severe in the superior longitudinal fasciculus, anterior cingulate fasciculus, anterior corpus callosum, uncinate fasciculus, and inferior longitudinal fasciculus, and are especially severe, usually in the anterior aspect of superior longitudinal fasciculus and inferior longitudinal fasciculus. In SD, left-dominant degeneration in the uncinate fasciculus and inferior longitudinal fasciculus is observed, and anterior-dominant degeneration in the anterior corpus callosum and arcuate fasciculus is also found. In PNFA, degeneration is observed in the left superior longitudinal fasciculus, especially in the arcuate bundle projecting to the inferior frontal lobe.

4. Resting-state functional MRI [4]

In bvFTD, decreased connectivity of the salience network, including the anterior cingulate gyrus and the anterior insula has been reported.

5. Genetic mutation and brain volumetric imaging [5]

Compared to patients with mutations in *tau* and *progranulin* genes and patients with sporadic disease, patients with mutations in *C9orf72* gene show atrophy in the anterior temporal lobe, parietal lobe, occipital lobe, and cerebellum. Patients with *Tau* gene mutations are characterized by atrophy in the anteromedial temporal lobe, and patients with *progranulin* gene mutations are characterized by asymmetric atrophy in the temporoparietal lobe. In addition, the speed of atrophy of the brain as a whole is faster in patients with *progranulin* gene mutations than in patients with *C9orf72* or *tau* gene mutations.

6. Comparison of brain imaging findings with underlying pathological findings [6]

There is a limitation to estimate underlying pathology based on atrophy patterns observed on MRI. In recent years, highly sensitive tau PET imaging capable of visualizing tau pathology has become available in some facilities, and further studies are awaited [7, 8].

7. Phenocopy syndrome [1]

Some bvFTD cases show no apparent atrophy on MRI, and they are termed "bvFTD phenocopy syndrome". Clinical progression in these patients is known to be very slow. FDG-PET also does not show any abnormalities. Various underlying diseases, such as developmental disorders, are speculated.

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■ Search formula

PubMed search: July 8, 2015 (Wednesday)

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Ichushi search: July 10, 2015 (Friday)

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CQ 8-3

Are there effective drugs for frontotemporal lobar degeneration (FTLD)?

Recommendation

The use of selective serotonin reuptake inhibitor (SSRI) is recommended for the purpose of improving behavioral disorders in FTLD (off-label). 2C

Comments and evidence

Because FTLD is a clinical syndrome and has diverse underlying pathologies, there are few studies on pharmacotherapy. The available studies are small-scale trials, which do not necessarily provide sufficient evidence [1, 2]. A review reported by Nardell and Tampi [2] suggests that SSRIs, trazodone, and amphetamines may be effective in improving some behavioral symptoms, but none of the medications had an impact on cognition. The authors also pointed out various issues of the studies reviewed, such as the use of different diagnostic criteria, inconsistent evaluation indicators, and use of indicators such as Mini-Mental State Examination (MMSE) which are not sensitive to FTLD symptoms. Trazodone has been shown to be effective in a double-blind, randomized control trial (RCT) [3].

Regarding SSRI, since the report of Swartz et al. [4] in 1997, some reports have shown that these drugs are effective for disinhibition, stereotyped behavior, and abnormal eating behavior, while other reports observed no effectiveness. In Japan, an open-label trial has reported the effectiveness of SSRI for repetitive behavior, stereotyped behavior, and compulsive complaint in FTLD [5]. Lanctot et al. [6] used PET to investigate the mechanism of action of SSRI for FTLD, and reported significant decreases in serotonin 5-HT_{1A} receptor binding potential in all the brain regions examined in FTLD patients compared with controls. Using electroencephalography and magnetoencephalography, Hughes et al. [7] reported recovery of the activity of inferior frontal gyrus in FTLD patients treated with SSRI.

Views on the usefulness of cholinesterase inhibitors (ChEIs) remain divided [1, 2]. There are reports of no effectiveness of ChEIs and reports of worsening of disinhibition. Thus caution is required when administering ChEIs. A recent review concludes that the efficacy of ChEIs for FTD cannot be confirmed and that ChEIs are associated with more gastrointestinal adverse effects [8]. Besides, two RCTs failed to demonstrate the usefulness of memantine, an NMDA receptor antagonist, compared with placebo.

Nasal oxytocin at a dose of 24 IU has been reported to improve the behavioral score of Neuropsychiatric Inventory (NPI) and reduce episodes of anger and fear compared with placebo [9]. Preparation of a large-scale and long-term clinical trial is ongoing [10].

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Search formula

PubMed search: July 10, 2015 (Friday)

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Ichushi search: July 9, 2015 (Thursday)

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CQ 8-4

Are there effective non-pharmacological therapies for frontotemporal lobar degeneration (FTLD)?

Recommendation

Non-pharmacotherapy therapies such as care and behavioral therapy based on FTLD symptomatology are recommended.

2C

Comments and evidence

The characteristics described in the diagnostic criteria for behavioral variant frontotemporal dementia (bvFTD) are essential in developing treatment strategies for behavioral disorders of FTLD.

Although there is little evidence, non-pharmacological therapies are useful and are the mainstay of treatment. In particular, by utilizing the patient's preserved functions and taking into account the characteristic symptoms and the patient's lifestyle, it may be possible to mitigate behavioral abnormalities and reduce the burden on caregivers [1].

Shinagawa et al. [2] reviewed case reports, expert opinions, and clinical trials (excluding retrospective studies) of non-pharmacological management [2]. Ikeda et al. [3] studied six patients with FTLD, and reported that care that utilized the patient's preserved episodic memory, procedural memory, and visuospatial cognitive function was effective and resulted in the improvement of quality of life (QOL). Mioshi et al. [4] and McKinnon et al. [5] showed that a learning program comprising mainly of cognitive appraisal and coping strategies improved the burden on caregivers.

Ikeda et al. [6] conducted a detailed assessment of behavioral disorders and behavioral interventions given to patients under hospitalized observation, and reported the effectiveness of conducting individualized family guidance based on behavioral disorder assessments of the patients and improvement of families' attitude toward the patients.

Lough et al. [7] reported that the compulsive behaviors of a patient with FTLD were changed to socially acceptable behavior in response to behavioral modification techniques. Tokikawa et al. [8] reported that the introduction of a daycare program for a patient with FTLD resolved the patient's obsessive-compulsive behaviors by acquiring a stereotyped behavior pattern. However, this report also pointed out the problems of newly acquired emotional compulsive behaviors such as coming to daycare, even on holidays, and not able to wait for the pick-up person.

Tokimasa et al. [9] compared the cooking activities of 2 patients with FTLD and five patients with Alzheimer's disease dementia. In patients with Alzheimer's disease dementia, because of episodic memory impairment and apraxia, constant supervision is needed from the early stage, and acquisition of generalized compensation method is difficult. On the other hand, in patients with FTLD, after cautiously forming an intimate relationship, helping the patients form the habit of doing activities of daily living (ADL) utilizing stereotyped behavior is a crucial point for care.

In daycare and institutional care, reports have emphasized that to respond to severe mental symptoms; there is a need for one-on-one response at least when care is initiated [6, 8, 10]. The usefulness of group homes where meticulous care can be provided has been reported [11].

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PubMed search: July 10, 2015 (Friday)

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CQ 8-5

What kind of instructions should be given to families and caregivers of frontotemporal lobar degeneration (FTLD) patients?

Answer

Family and caregiver education based on FTLD symptomatology is recommended. C

Comments and evidence

In FTLD, psychiatric symptoms and behavioral disorders such as disinhibition, asocial behaviors, stereotypic behaviors, abnormal eating behaviors, and increased emotional susceptibility become evident from an earlier stage compared to Alzheimer's disease dementia [1-3]. Due to these various behavioral disorders, caregivers of FTLD patients have a more significant care burden than caregivers of Alzheimer's disease dementia patients [4-7]. Based on the assessments of patients' behavioral abnormalities and language impairment, it is vital to help patients' families understand the disease conditions of individual patients and to provide them guidance on interventions. Also, FTLD has been designated an intractable disease in Japan since July 1, 2015, and it is imperative to explain and provide guidance on how to apply for a subsidy of medical expenses.

Kumamoto et al. [7] studied two FTLD patients and found that behavioral abnormalities exhibited by these patients, particularly behaviors of stuffing food into the mouth, poor table manners, resistance to care, and restlessness, were associated with substantial care burden [7]. Therefore, for family caregivers, individual guidance and support are required according to the patient's conditions. Understanding of the disease condition by the family changes the way caregivers interact with the patients, and the burden on caregivers is often significantly reduced [8].

Nunnemann et al. [9] pointed out that there are very few publications on the burden, problems, and needs of caregivers of FTLD patients. Specific problems include delayed diagnosis, young-onset age, behavioral disturbances, lack of information and suitable care facilities, caregivers' depression, social isolation, and personal needs. Research is needed to identify the real needs of caregivers of FTLD patients.

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Search formula

PubMed search: July 10, 2015 (Friday)

#1 ("Frontotemporal Lobar Degeneration" [Majr] OR "frontotemporal lobar degeneration" [TI] OR "frontotemporal dementia" [TI] OR FTD [TI] OR FTLD [TI] OR bvFTD [TI] OR Pick disease* [TI] OR Picks disease* [TI] OR "frontal lobe dementia" [TI] OR "frontotemporal lobe dementia" [TI] OR "frontal variant frontotemporal dementia" [TI]) AND (care OR education OR burden OR support*) AND (caregiver* OR family)

Ichushi search: July 10, 2015 (Friday)

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Chapter 9

Progressive Supranuclear Palsy (PSP)

Objective

To describe the history, core symptoms, pathology, and etiology of progressive supranuclear palsy (PSP).

Disease Overview

PSP is a group of diseases that exhibit parkinsonism and is a neurodegenerative disease that develops after middle age. The prevalence was 5.3-5.8 per 100,000 population according to most reports in the world. but recently a prevalence of 17-20 per 100,000 has been reported with ageing of the population. The main symptoms are supranuclear ocular motor dysfunction, dorsiflexion of the neck (cervical dystonia), akinesia, subcortical dementia, and impulsive behavioral disorder. In recent years, pathological studies have identified various disease types. Biochemical studies have shown that PSP is one of the diseases belonging to 4-repeat tauopathy (4RT), but the mechanism of tau accumulation and the pathogenesis of neuronal loss remain unclear. Many cases are sporadic, but hereditary PSP is also found. Most hereditary PSP cases are autosomal dominant. There are no obvious risk factors for disease development, but education history is the only weak risk factor. Tau haplotype analysis has indicated that PSP is associated with the H1 haplotype, while the frequency of H2 haplotype is low. However, from the studies of tau haplotypes in Japan, the Japanese population has exclusively H1 haplotype. According to Williams et al.[1], Richardson syndrome (PSP-RS) tends to be more common in men, but there is no gender difference in PSP-parkinsonism (PSP-P). The disease duration is 5.9 years for Richardson syndrome and 9.1 years for PSP-P. The most frequent causes of death are aspiration pneumonia, asphyxia, malnutrition, and trauma. Falls within 1 year of onset, dysphagia in early stage, and urinary incontinence are poor prognostic factors. There is no effective curative therapy, and only symptomatic therapies are available.

History and Classification

In 1964, Steele et al.[2] reported PSP as a disease entity with main clinical symptoms of axial rigidity, akinesia, tendency to fall, cognitive impairment, and supranuclear ocular motor dysfunction in the vertical direction; as well as pathological findings of neurogenic changes in the globus pallidus, substantia nigra, subthalamic nucleus, eye movement-related nucleus, tegentum, dentate nucleus, and inferior olivary nucleus. The first diagnostic criteria for PSP were conducted by Litvan et al.[3] in 1996. Then in 2007 and 2009, Williams et al.[1] classified PSP cases into Richardson syndrome (54%) that exhibits classical PSP; PSP-parkinsonism (PSP-P; 32%) which shows a clinical picture resembling Parkinson's disease with left-right asymmetric symptoms partially responsive to L-dopa; and atypical PSP (14%) that includes pure akinesia with gait freezing (PAGF), PSP with corticobasal syndrome (PSP-CBS), and PSP with progressive non-fluent aphasia (PSP-PNFA) (2009). Researchers in Japan and overseas have also reported a cerebellar variant of PSP (PSP-C)[4]. New diagnostic criteria have been proposed by the International Movement Disorder Society[5]. At present, the disease concept of PSP tends to be expanding, and elucidation of the pathogenesis is expected to control the etiology of PSP.

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CQ 9-1

What are the features of dementia symptoms in progressive supranuclear palsy (PSP)?

Answer

- The characteristic dementia symptoms of classical PSP (also termed Richardson syndrome; PSP-RS) are generally referred to as subcortical dementia. The symptoms include slowed thinking, impulsiveness, stubbornness, and perseveration.
- One-third of the patients with PSP-RS present dementia, personality change, emotional disorder, and memory impairment as onset symptoms.

Comments and evidence

PSP-RS accounts for approximately one-half of the PSP cases. The clinical features of the cognitive symptoms are described below.

- Initial symptoms of PSP:

Two-thirds of the cases present motor symptoms and ocular motor-related symptoms as onset symptoms. One-third of the cases present dementia symptoms or psychiatric symptoms at onset. These symptoms include depression, irritability, aggression, emotional lability, apathy, slowed thinking, and memory impairment. Approximately one-half of them manifest behavioral disorders as onset symptoms.

- Features of behavioral disorders and cognitive impairment in PSP:

The basic symptoms are attention deficit, indifference, and reduced level of interest to the surrounding. These symptoms were called subcortical dementia in the past, and they show features of frontotemporal dementia including slowed thinking, attention deficit, executive impairment, amnesia, apathy, reduced vocabulary, and depression. The speed of response becomes marked reduced due to slowed thinking. Initially it seems that the patient has no response to a question, but after a while he/she would give an accurate response. The behavioral disorders are mainly impulsive behavioral disorders and socially inappropriate behaviors such as compulsive eating, addiction to gambling, and impulse buying. Some of the behaviors are considered to be drug-induced, but there is no consensus. Tendency to fall and "applause sign" are manifestations of behavioral disorder and cognitive impairment. In the study of Yatabe et al. using Neuropsychiatric Inventory (NPI) and Stereotypy Rating Inventory (SRI), there were no differences between frontotemporal lobar degeneration (FTD) and PSP.

■ Further reading

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CQ 9-2

Are there useful therapies for cognitive impairment in progressive supranuclear palsy (PSP)?

Recommendation

Although no therapies for PSP have been developed, there are symptomatic treatments for individual symptoms but no treatment specific for cognitive symptoms. 2C

Comments and evidence

No curative therapies and no therapies for symptom relief and prevention specifically for PSP have been developed. At present, symptoms are treated individually. Although drugs that are useful for other diseases are being used for the treatment of PSP, the efficacy of most of these drug for PSP has not been proven [1, 2].

Pharmacotherapy for psychiatric symptoms of PSP

According to the report of Liepelt et al. [3] in 2010, among the cholinesterase inhibitors, only rivastigmine has been found to improve cognitive function, but the trial was a small observational study. Clinical trials of drugs for PSP reported since the last guideline failed to show good results [2, 3]. Recently, trial of mesenchymal stem cell transplantation has been started, and experimental therapeutic methods are being developed [4].

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Chapter 10

Corticobasal Degeneration

History

In 1968, Rebeiz et al. reported corticobasal degeneration (CBD) as a clinicopathologically independent disease. Pathologically, CBD manifests strong asymmetric cerebral cortical atrophy in the frontoparietal lobe, together with degeneration in the basal ganglia and substantia nigra. Histologically, accumulation of abnormal phosphorylated tau is observed in neurons and glial cells. CBD is characterized by astrocytic plaque, and is classified as 4-repeat tauopathy (4RT), like progressive supranuclear palsy (PSP).

The typical clinical features of CBD are cerebral cortical signs including progressive and asymmetric apraxia, as well as extrapyramidal signs including muscle stiffness. Currently, these signs are referred to as corticobasal syndrome (CBS). Recently, CBD is used when the disease is pathologically diagnosed, and CBS is used when the disease is clinically diagnosed.

Diagnosis

In the diagnostic criteria of Armstrong et al. (2013), clinical symptoms of CBD were extracted from brain banks and published articles reporting at least 5 pathologically proven cases, and four clinical phenotypes associated with CBD pathology were proposed (CQ10-1). Furthermore, the four clinical phenotypes and other features were combined to create clinical research criteria for "probable sporadic CBD" that corresponds to pure CBD, and clinical criteria for "possible CBD" that includes tauopathy other than CBD (CQ10-1). However, subsequent validation study shows that the sensitivity of the new classification is not different from the conventional diagnostic criteria. Furthermore, the specificity is not high. Therefore, search for clinical diagnostic criteria with higher sensitivity and specificity or biomarkers will be a challenge for future research. The definitive diagnosis of CBD is pathological diagnosis.

CQ 10-1

What are the features of cognitive impairment in corticobasal degeneration (CBD), and what are the test methods?

Answer

In CBD, cognitive impairment often appears, and impaired executive function, behavioral and personality changes such as disinhibition, visuospatial disorder, and non-fluent aphasia are observed. A useful test for differentiating CBD from other diseases has not been established. D

Comments and evidence

1. Features of cognitive impairment in CBD

The clinical phenotypes of CBD proposed in the clinical diagnostic criteria of CBD by Armstrong et al. [1] in 2013 consist of the following: (1) corticobasal syndrome (CBS), (2) frontal behavioral-spatial syndrome (FBS), (3) non-fluent/agrammatic variant of primary progressive aphasia (naPPA), and (4) progressive supranuclear palsy syndrome (PSPS). Apart from these types, cases with a clinical picture resembling Alzheimer's disease dementia have also been reported. Among the clinical symptoms of pathologically confirmed CBD cases, general cognitive impairment is the most frequently seen cerebral cortical symptom, and is found in 52% of the patients at onset and in 70% during the course of disease [1]. Among the four CBD phenotypes, FBS manifests impaired executive function, behavioral/personality changes such as disinhibition, and visuospatial deficit. Moreover, naPPA manifests effortful, non-fluent speech, and apraxia of speech with distorted speech production and agrammatism. These symptoms appear before onset of dementia [1].

Lee et al. [2] studied 18 patients with histopathologically confirmed CBD, and found 4 clinical syndromes: progressive non-fluent aphasia (5 patients), behavioral variant frontotemporal dementia (5 patients), executive-motor (7 patients), and posterior cortical atrophy (1 patient). They reported that behavioral or cognitive problems were the initial symptoms in 15 of 18 patients.

2. Methods for assessing cognitive impairment in CBD

Scales used to assess cognitive impairment in CBD include Mini Mental State Examination (MMSE), Addenbrooke's Cognitive Examination (ACE) [3], Dementia Rating Scale (DRS), Frontal Assessment Battery (FAB) [4], and Neuropsychiatric Inventory (NPI). A meta-analysis examined whether several higher brain function tests were useful in differentiating parkinsonian disorders, but evaluation of these tests was difficult due to inadequate sample size [5].

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■ Search formula

PubMed search: June 23, 2015 (Tuesday), July 7, 2015 (Tuesday), July 13, 2015 (Monday), August 12, 2015 (Monday)
#1 (("Dementia/diagnosis" [Mesh] OR (dementia [TI] AND (diagnosis [TI] OR diagnostic [TI])) OR "Cognition Disorders/diagnosis" [Mesh] OR ("cognition disorder*" [TI] AND (diagnosis [TI] OR diagnostic [TI]))) AND "corticobasal degeneration") OR ((corticobasal [TI] OR ("Basal Ganglia/pathology" [Mesh] AND "Cerebral Cortex/ pathology" [Mesh] AND "Neurodegenerative Diseases/pathology" [Mesh]) OR "Primary Progressive Nonfluent Aphasia" [Majr] OR "progressive nonfluent aphasia" [TI]) AND ("Cognition Disorders/etiology" [Majr] OR "Cognition" [Majr] OR cognition [TI] OR cognitive feature* OR behavioral feature* OR cognitive mechanism* OR "emotion processing" OR "Emotions" [Majr]))

Ichushi search: June 23, 2015 (Tuesday)
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CQ 10-2

Are there effective pharmacological and non-pharmacological therapies for cognitive impairment in corticobasal degeneration (CBD)?

Recommendation

No pharmacological and no non-pharmacological therapies have been confirmed to be effective for treating cognitive impairment in CBD. When Alzheimer's disease is considered to be the underlying pathology for CBS, cholinesterase inhibitor or N-methyl-D-aspartate (NMDA) receptor antagonist may be tried. Rehabilitation is recommended for language disorders, behavioral disorders, and visuospatial deficits. 2D

Comments and evidence

1. Pharmacotherapy for cognitive impairment

Regarding pharmacotherapy for cognitive impairment in CBD, no effective drugs with an adequate level of evidence have been reported. For CBS, cholinesterase inhibitors have been tried based on the personal opinions of experts [1, 2]. The effect of NMDA receptor antagonist is unknown.

2. Pharmacotherapy for behavioral and psychological disorders

There is little evidence of pharmacotherapy for behavioral and psychological symptoms in CBD. Sertraline hydrochloride, which is a selective serotonin reuptake inhibitor (SSRI) may be effective for depression [1]. Cholinesterase inhibitors are used for apathy and anxiety, but these symptoms are difficult to treat [1].

3. Non-pharmacological therapies

Although evidence of a certain level is lacking, physiotherapy, occupational therapy, and speech therapy may be effective for cognitive impairment in CBD [1, 2]. Cognitive behavioral therapy may be effective in some cases of depression in CBD, according to expert opinion [2].

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■ Search formula

Pharmacotherapy

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Non-pharmacological therapies

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Ichushi search: June 23, 2015 (Tuesday)

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Chapter 11

Argyrophilic Grain Dementia

CQ 11-1

What is the frequency of argyrophilic grain disease (AGD)?

Answer

The frequency of AGD in older people is estimated to be approximately 5-9%, and this disease is by no means rare. AGD is also known to be associated at high frequencies with other degenerative diseases, especially with corticobasal degeneration (CBD). C

Comments and evidence

AGD is a degenerative disease characterized pathologically by argyrophilic granular structures in the brain. Argyrophilic grains were first reported by Braak and Braak [1] in 1987. Since argyrophilic grains were first found in autopsied brains from persons with dementia, the condition was called argyrophilic grain dementia (or dementia with grains). However, as argyrophilic grains were also present in persons without dementia, the disease is now generally called AGD. There are few studies on the frequency of AGD and its relationship with dementia. The frequency of AGD in older people is estimated to be approximately 5-9%, and is therefore by no means rare. AGD is known to be associated at high frequencies with other degenerative diseases including Alzheimer's disease and dementia with Lewy body [2, 3]. In particular, AGD coexists with progressive supranuclear palsy and corticobasal degeneration at frequencies of 19% and 41%, respectively.[4] Tatsumi et al. [5] reported that argyrophilic grains were observed in 100% of corticobasal degeneration cases.

References

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Search formula

PubMed search: June 19, 2015 (Friday), August 125, 2015 (Tuesday)

#1 ((argyrophilic grain disease* OR ("argyrophilic grain" AND ("Dementia" [Mesh] OR dementia OR "Cognition Disorders" [Mesh] OR cognition disorder*))) AND ("Morbidity" [Mesh] OR morbidity [TI] OR prevalence [TI])) OR (argyrophilic grain* AND ("Dementia/pathology" [Mesh] OR "Nerve Degeneration/pathology" [Mesh]) AND ("Morbidity" [Mesh] OR morbidity OR prevalence OR incidence)) OR ("Dementia/pathology" [Mesh] AND argyrophilic grain disease* [TI]) OR (argyrophilic grain* [TI] AND "Dementia/pathology" [Majr])

Ichushi search: June 19, 2015 (Friday)

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CQ 11-2

How is a clinical diagnosis made for argyrophilic grain dementia?

Answer

The clinical features of argyrophilic grain dementia are as follows: (1) elderly onset; (2) although onset symptom is memory impairment, behavioral and psychological symptoms such as stubbornness, irritability, delusion, personality change, and violent behavior are observed; (3) progresses slowly; (4) cholinesterase inhibitors have limited effectiveness; (5) left-right asymmetrical atrophy of the anterior side of medial temporal lobe, mainly at the ambient gyrus, (6) degree of atrophy of parahippocampal gyrus measured by volumetry tends to increase proportional to the Mini Mental State Examination (MMSE) score; (7) functional imaging shows left-right asymmetrically decreased uptake at the medial temporal lobe, (8) for cerebral spinal fluid biomarkers, amyloid-β (Aβ)42, tau and phosphorylated tau are normal in most cases.

C

Comments and evidence

In a study of the pattern of progression of argyrophilic grains in serial autopsy brains from older persons, the progression of argyrophilic grains was classified into: stage 1; localization in the ambient gyrus only, stage 2; progression to the medial side of temporal lobe, and stage 3; progression to involve the frontobasal region and anterior cingulate gyrus. Among stage 3 cases, 71% had dementia, 21% had mild cognitive impairment, and 8% had some psychiatric symptoms. The stage of progression tended to increase with aging, suggesting that argyrophilic grains are aging-related changes [1, 2]. In another study, stage 3 cases were extracted, and the left-right differences of atrophy at the anterior side of medial temporal lobe on morphological images and those of functional decline on functional images were examined. Left-right asymmetry was observed in 90.8% of the cases by histopathological examination, in 42.6% by morphological CT and MR images, and in all cases by functional SPECT and PET images [3].

Clinical signs of patients with argyrophilic grain dementia confirmed at autopsy include not only memory impairment [4], but also irritability, stubbornness, and delusional jealousy [5]. In argyrophilic grain dementia cases, tau and phosphorylated tau levels in cerebrospinal fluid are mostly normal, with a few cases showing levels slightly above the cut-off; and Aβ42 level is also normal, with only a few cases showing low levels [6]. Based on the above findings, the clinical features of argyrophilic grain dementia are listed above in "Answer" section.

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■ Search formula

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Ichushi search: June 19, 2015 (Friday)

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CQ 11-3

What kinds of treatments are available for argyrophilic grain dementia?

Recommendation

There are no specific therapies for argyrophilic grain dementia. In practice, argyrophilic grain dementia is treated according to the therapies used for Alzheimer's disease dementia. However, cholinesterase inhibitors for argyrophilic grain dementia cannot be expected to be as effective as for Alzheimer's disease dementia and dementia with Lewy body.

2D

Comments and evidence

There are no therapies specifically for argyrophilic grain dementia. Even if this disease is clinically suspected, treatments are given according to those used for Alzheimer's disease dementia. In this disease, loss of cholinergic neurons in the basal nucleus of Meynert is mild [1]. Therefore, cholinesterase inhibitors for this disease cannot be expected to be as effective as for Alzheimer's disease dementia and dementia with Lewy body.

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■ Search formula

#1 ((argyrophilic grain disease* AND (Therapy [Mesh] OR therapy [TI] OR therapeutic [TI] OR treatment [TI])) OR "argyrophilic grain" AND ("Dementia/therapy" [Mesh] OR(dementia AND (therapy OR therapeutic OR treatment)) OR "Cognition Disorders/therapy" [Mesh] OR ("cognition disorder*" AND (therapy OR therapeutic OR treatment)))) OR (argyrophilic grain* AND (therapy [Mesh] OR therapy [TI] OR therapeutic [TI] OR treatment [TI] OR "Dementia/therapy" [Mesh]))

Ichushi search: June 21, 2015 (Sunday)
#1 (Argyrophilic grain dementia/AL OR ((Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI) AND (Argyrophilic grain/AL OR Argyrophilic cell/TH OR Argyrophilic cell/AL))) AND ((SH = Therapeutic use, treatment, drug treatment, surgical treatment, transplantation, dietary treatment, psychiatric treatment, radiologic treatment, nursing, rehabilitation, prevention) OR Treatment/TH OR Treatment/TI OR Therapy /TI)

Chapter 12

Senile Dementia of the Neurofibrillary Tangle Type

CQ 12-1

What kind of disease is senile dementia of the neurofibrillary tangle type (SD-NFT)?

Answer

SD-NFT is a subtype of senile dementia characterized by numerous neurofibrillary tangles (NFTs) mainly in the hippocampus but very few senile plaques. This disease is often diagnosed clinically as Alzheimer's disease dementia.

Comments and evidence

1. Concept

SD-NFT is a subtype of senile dementia characterized by the presence of numerous NFTs mainly in the hippocampus, and the incidence increases with aging. SD-NFT is reported to constitute 1.7-5.6% of autopsy cases of dementia in older people and account for 20% of dementia cases in those over 90 years of age [1]. Among the dementia cases in the Hisayama study, 2.9% was classified as SD-NFT, and the percentage was 4.9% when limited to autopsy cases [2]. On the other hand, the term "primary age-related tauopathy (PART)" has been proposed as a pathological term for the condition in which NFTs are chiefly distributed in the medial temporal lobe while senile plaques are absent or very scarce [3, 4]. Clinically, this is perceived as a concept of spectrum including the states from normal cognitive function to dementia through mild cognitive impairment.

2. Clinical features

SD-NFT is considered to be a pathological condition of accelerated aging process of the brain. The clinical features are as follows [1, 3, 5]:

(1) Common in the late old age
(2) Progresses slowly
(3) Memory impairment as onset symptom
(4) Other cognitive impairments and personality changes are relatively mild
(5) Rare appearance of delirium and extrapyramidal symptoms
(6) Imaging study shows atrophy of hippocampal region and expansion of inferior horn of lateral ventricle.

3. Differential diagnosis

Many cases of SD-NFT are diagnosed during life as Alzheimer's disease dementia, and many pathological findings of SD-NFT overlap with those of argyrophilic grain dementia and vascular lesions.

Although SD-NFT shares many common clinical features with late-onset Alzheimer's disease dementia, such as memory impairment as the core symptom and lesions enhanced in the medial temporal lobe, SD-NFT is a more slowly progressive disease, and amyloid PET is useful for differentiation.

Both argyrophilic grain dementia and SD-NFT are classified as late-onset tauopathy, and the two share common features including lesion in the medial temporal lobe and memory impairment as onset symptom. However, in argyrophilic grain dementia, although memory impairment is the main feature, other symptoms such as irritability, behavioral abnormalities, and personality change are a characteristic feature and useful for differentiation. In addition, the medial temporal lobe atrophy in argyrophilic grain dementia is asymmetric, which is also a differentiation feature. The medial temporal lobe atrophy is anterior-dominant in argyrophilic grain dementia but is relatively prominent at the posterior side in SD-NFT . These features are helpful in differential diagnosis [1, 3, 5].

4. Treatment

In clinical practice, SD-NFT is often diagnosed as Alzheimer's disease dementia and treated with cholinesterase inhibitors. There are currently no therapies that have proven efficacy for SD-NFT [1, 3, 5].

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Chapter 13

Huntington Disease

CQ 13-1

What are the features and diagnosis of cognitive symptoms in Huntington disease?

Answer

Among the cognitive impairments in Huntington's disease, memory function and executive function are particularly affected. Psychiatric symptoms such as depression, anxiety, irritability, apathy, and perseveration are often observed. The definitive diagnosis is by genetic diagnosis. B

Comments and evidence

Huntington's disease is an autosomal dominant hereditary disease, manifesting adult-onset chorea and psychiatric symptoms as the main symptoms. The causative gene of Huntington's disease is the huntingtin (*HTT*) gene located in the short arm of chromosome 4 (4q16.3). The gene consists of an unstable repeated CAG sequence, and abnormal expansion of this sequence leads to the development of Huntington's disease. While the number of CAG repeats in a normal allele is less than 26, an increase in number of repeats to over 36 is considered to cause Huntington's disease. In addition, the onset age becomes younger and the disease becomes more severe in successive generations (genetic anticipation), and inheritance from the father may result in more severe disease. Core dementia symptoms are personality changes and cognitive impairment. On the other hand, affective symptoms such as emotional lability, losing temper, irritability, stubbornness and apathy are present to various degrees [1]. The definitive diagnosis is by genetic testing [2, 3], and this genetic test (*HTT* gene CAG repeat sequence analysis) is covered by health insurance in Japan.

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Search formula

PubMed search: May 28, 2015 (Thursday)
#1 "Huntington Disease/diagnosis" [Mesh]

Ichushi search: May 28, 2015 (Thursday)
#1 (Huntington disease OR "Huntington Disease") AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Symptom OR Feature OR Syndrome OR Sign OR Finding)

Chapter 14

Vascular Dementia

CQ 14-1

What are the diagnostic criteria for vascular dementia (VaD)?

Answer

Representative diagnostic criteria for VaD include the International Statistical Classification of Diseases and Related Health Problems (ICD-10) published by the World Health Organization (WHO), the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) published by American Psychiatric Association, the diagnostic criteria for ischemic vascular dementia proposed by Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) in California, and the NINDS-AIREN diagnostic criteria published by the National Institute of Neurological Disorders and Stroke (NINDS) and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN).

In the statement for healthcare professionals from the American Heart Association/ American Stroke Association (AHA/ASA), the prodromal stage of VaD is termed vascular mild cognitive impairment (VaMCI, or VCI-no dementia), and the term vascular cognitive impairment (VCI) is proposed to include the spectrum of severity from the prodromal stage to VaD. A

Comments and evidence

VaD is a subtype of dementia caused by cerebrovascular disorder, with heterogeneous underlying pathology. The NINDS-AIREN diagnostic criteria, which was developed for research, have high specificity and are widely used clinically, but the low sensitivity is a drawback [1].

In 2011, AHA/ASA proposed an inclusive term "vascular cognitive impairment (VCI)" from the viewpoint of treatment priority [2]. VCI includes VaD and VCI-no dementia or vascular mild cognitive impairment (VaMCI). Note that although the term VCI in the broad sense includes not only the prodromal stage but also the dementia stage, "VCI-no dementia" is also used to describe the prodromal stage [2, 3].

On the other hand, in DSM-5 published in 2013, dementia is positioned as a major neurocognitive disorder. Within this category, VaD is classified as "major vascular neurocognitive disorder" [4].

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Search formula

PubMed search: June 18, 2015 (Thursday)
#1 "Dementia, Vascular/diagnosis" [Mesh] OR ("vascular dementia" AND (diagnosis OR diagnostic)) OR ("vascular cognitive impairment" AND (diagnosis OR diagnostic)) OR ("Vascular Diseases/complications" [Mesh] AND "Cognition Disorders/diagnosis" [Mesh])

Ichushi search: June 18, 2015 (Thursday)
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CQ 14-2

How are the types of vascular dementia (VaD) classified?

Answer

According to the NINDS-AIREN diagnostic criteria, VaD is classified into the following types: (1) multi-infarct dementia (MID), (2) strategic single infarct dementia, (3) small vessel disease dementia, (4) hypoperfusion vascular dementia, (5) hemorrhagic vascular dementia, and (6) others. A

Comments and evidence

VaD is a type of dementia caused by cerebrovascular disorder, and its underlying pathology is heterogeneous.

The NINDS-AIREN diagnostic criteria which were developed for research classify VaD into the following clinical subtypes [1].

(1) Multi-infarct dementia (MID)
(2) Strategic single infarct dementia
(3) Small vessel disease dementia
(4) Hypoperfusion vascular dementia
(5) Hemorrhagic vascular dementia
(6) Others

In small vessel disease dementia, lacunar infarction, white matter lesions (leukoaraiosis), cerebral hemorrhage, and microbleeds are observed in the territory of penetrating arteries as a result of arteriolosclerosis, while cerebral amyloid angiopathy is observed in cortical regions. Small vessel disease dementia that develops as a result of arteriolosclerosis is called subcortical vascular dementia. Subcortical vascular dementia is divided into two types: multiple lacunar infarct dementia when lacunar infarcts are the main cause, and Binswanger disease when white matter lesions are the main cause.

MID is mainly caused by multiple large and small cerebral infarcts in the cortical region. The clinical course is characterized by acute onset or step-wise deterioration, and the symptoms include aphasia, apraxia, agnosia, visuospatial deficit, constitutional impairment and executive dysfunction, together with motor paralysis. Strategic single infarct dementia is caused by cerebral infarcts in areas important for higher brain function. These include the cortical region in the dominant hemisphere such as the angular gyrus and territories of the anterior cerebral artery, the middle cerebral artery, and the posterior cerebral artery, and the subcortical region in the thalamus or basal forebrain.

References

1) Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993; 43(2): 250-260.

Search formula

PubMed search: June 18, 2015 (Thursday)

#1 "Dementia, Vascular/diagnosis" [Mesh] OR ("vascular dementia" AND (diagnosis OR diagnostic)) OR ("vascular cognitive impairment" AND (diagnosis OR diagnostic)) OR ("Vascular Diseases/complications" [Mesh] AND "Cognition Disorders/diagnosis" [Mesh])

Ichushi search: June 18, 2015 (Thursday)

#1 (Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH) AND Diagnostic criteria/AL OR Judgment criteria/AL OR Criteria/TI OR Evaluation criteria/TH OR Classification/TH OR Classification/TI OR ICD classification/TH OR DSM/TH)

CQ 14-3

What are the imaging features of vascular dementia (VaD)?

Answer

Small vessel disease dementia, the most common type of VaD, is characterized by lacunar infarcts and white matter lesions. If the extent and distribution of a lesion adequately explain the neurological symptoms, it is considered to be the culprit lesion of dementia. On the other hand, the temporal relationship between stroke and onset of dementia may support the culprit lesion in some cases, including multi-infarct dementia and strategic single infarct dementia. Hereditary vascular dementia includes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). They show extensive white matter lesions, lacunar infarcts, microbleeds, and brain atrophy, and are characterized by white matter lesion in the temporal pole. A

Comments and evidence

The most common type of VaD is cerebral small vessel disease dementia. Although lacunar infarcts and white matter lesions are characteristic of this disease, patients may remain asymptomatic even after lacunar infarcts have occurred, and do not necessarily show a course of cognitive impairment characterized by stepwise deterioration of dementia after stroke. In such cases, if the extent, distribution, and location of the small blood vessel lesion adequately explain the neurological symptoms (neuroimaging-supported), the lesion is considered to be the culprit lesion of dementia. On the other hand, the temporal relationship between stroke and dementia may provide support for a culprit lesion of dementia (temporally supported) as evidence for diagnosis, and multi-infarct dementia and strategic single infarct dementia belong to this type [1, 2].

The MRI features of VaD include lacunar infarct, white matter lesion, cerebral hemorrhage (deep type, subcortical type), multiple cortical infarcts, microbleeds, cortical micro-infarct, localized brain surface hemosiderin deposition, perivascular space enlargement, watershed infarct, and cortical laminar necrosis. Lacunar infarct is an infarct with a diameter of 3 to 13 mm occurring in the territory of penetrating arteries, and is observed as hypointensity on T1-weighted MRI, hyperintensity on T2-weighted image, and hypointensity with a rim of hyperintensity on FLAIR image [3]. White matter lesion is observed as normal to hypointensity on T1-weighted image, and hyperintensity on T2-weighted and FLAIR images. White matter lesions are relatively infrequent in the occipital lobe and temporal lobe, although CADASIL and CARASIL are characterized by lesions in the temporal pole [4, 5].

Iadecola [2] described the correlation of image abnormalities with clinical subtypes. Changes in cerebral small blood vessels caused by arteriolosclerosis and amyloid angiopathy are difficult to visualize by conventional MRI. However, since detailed brain imaging has accurately detected vascular lesions caused by cerebral small vessel disease, clinical and imaging findings together have provided insight on the concept of cerebral small vessel disease [6, 7].

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Search formula

PubMed search: June 18, 2015 (Thursday)

#1 ("Dementia, Vascular/diagnosis" [Mesh] OR ("vascular dementia" AND (diagnosis OR diagnostic)) OR ("vascular cognitive impairment" AND (diagnosis OR diagnostic)) OR ("Vascular Diseases/complications" [Mesh] AND "Cognition Disorders/diagnosis" [Mesh])) AND ("Diagnostic Imaging" [Mesh] OR CT [TIAB] OR "computed tomography" OR MRI OR "magnetic resonance imaging" OR SPECT OR "single-photon emission computed tomography" OR PET OR "positron emission tomography")

Ichushi search: June 18, 2015 (Thursday)

#1 (Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH) AND (Diagnostic imaging/TH OR CT/TI OR Computer tomography OR Computer tomography OR MRI/TI OR magnetic resonance imaging OR magnetic resonance tomography OR Magnetic resonance imaging OR Nuclear magnetic resonance imaging OR SPECT/TI OR Single photon emission computed tomography OR Single photon emission computed tomography OR Single photon computed tomography OR Single photon emission computed tomography OR Single photon emission computed tomography OR PET/TI OR Positron emission tomography OR Positron emission tomography)

CQ 14-4

What is the condition when vascular dementia (VaD) coexists with Alzheimer's disease dementia?

Answer

Alzheimer's disease dementia and cerebrovascular disorders have common risk factors, and they tend to coexist. There is a disease concept of Alzheimer's disease with cerebrovascular disorder (CVD) (AD with CVD), or mixed dementia. In the advanced stage of Alzheimer's disease dementia, CVD has little effect on cognitive function. In the early stage of Alzheimer's disease dementia, however, CVD is a factor that promotes cognitive impairment. B

Comments and evidence

The proportion of patients with mixed dementia; Alzheimer's disease dementia coexisting with VaD, increases with aging. The percentage of mixed dementia among all dementia cases varies widely from 0 to 55% even in pathological reports [1]. In general, when cerebrovascular disorder and Alzheimer pathology coexist with either one of them capable of causing dementia, the condition is called mixed dementia. However, there is also opinion that mixed dementia should be defined as the co-existence of both diseases (Alzheimer's disease with CVD). This difference in definition may be a reason for the widely variable frequency reported [1].

Patients with mixed brain pathologies such as Alzheimer's disease dementia, CVD, and dementia with Lewy body are 2.8 times more likely to manifest dementia compared to those with only one disease [2]. CVD has little effect on cognitive function in the advanced stage of Alzheimer's disease dementia, but CVD is a factor that promotes cognitive impairment in the early stage of Alzheimer's disease dementia [3].

References

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Search formula

PubMed search: June 18, 2015 (Thursday)

#1 (("Dementia, Vascular" [Mesh] OR "vascular dementia" OR "vascular cognitive impairment" OR ("Vascular Diseases/ complications" [Mesh] AND "Cognition Disorders" [Mesh])) AND ("Alzheimer Disease" [Mesh] OR alzheimer*)) OR ("Alzheimer Disease" [Majr] AND "Cerebrovascular Disorders" [Majr]) OR ("mixed dementia" [TI] AND "Dementia" [Mesh])

Ichushi search: June 18, 2015 (Thursday)

#1 ((Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI OR Cardiovascular disorder/MTH OR Cardiovascular disorder/TI) AND (Alzheimer's disease/TH OR Alzheimer's disease/TI OR Alzheimer type/TI)) OR (Mixed dementia/TI OR Mixed dementia/TI OR Mixed type dementia/TI OR Mixed type dementia/TI OR Mixed dementia/TI OR Mixed dementia/TI)

CQ 14-5

What are the clinical course and prognosis of vascular dementia (VaD)?

Answer

The typical clinical course of VaD starts with post-stroke dementia in which dementia develops after a stroke, followed by stepwise deterioration of cognitive function after each stroke episode. However, cerebral small vessel disease has a slowly progressive course and may be difficult to differentiate from degenerative dementia.

Patients with VaD has significantly shorter survival than persons without dementia. Although survival has been reported to be shorter in VaD patients than in those with Alzheimer's disease dementia, there is no sufficient scientific evidence. C

Comments and evidence

In VaD, cognitive impairment typically deteriorates in a stepwise manner after or associated with each stroke episode. Dementia that develops after the first stroke is called post-stroke dementia. In community epidemiological studies, post-stroke dementia occurs in 30% of stroke patients, and the prevalence increases from 7% after 1 year to 48% after 25 years [1]. Some cases of post-stroke dementia are caused by Alzheimer's disease dementia, accounting for 19-61% of post-stroke dementia.

The survival of patients with VaD is worse than control subjects without dementia [2-4]. Compared to Alzheimer's disease dementia, survival of VaD is significantly poorer in some reports [5-8], but not significantly different in others [4, 9], with inconsistent results. The average survival time after onset of VaD was 5.1 years for males and 6.7 years for females, and survival after onset of Alzheimer's disease dementia patients was 5.0 years for males and 7.8 years for females, showing a tendency of shorter overall survival in VaD patients [5]. In the Hisayama study that followed 828 older people for over 17 years, 275 persons developed dementia and 164 were autopsied. The results showed that the 10-year survival rate was lower in dementia with Lewy bodies (2.2%), while there was no significant difference between Alzheimer's disease dementia (18.9%) and VaD (13.2%) [4].

Many reports have shown age and severity of stroke to be predictors of cognitive impairment after stroke. In the Efficacy of Nitric Oxide in Stroke (ENOS) trial that analyzed 1,572 stroke patients, 38% showed cognitive decline within 3 months, and was associated with not only age and stroke severity, but also hypertension, atrial fibrillation, and brain atrophy [10].

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Search formula

PubMed search: June 18, 2015 (Thursday)

#1 ("Dementia, Vascular" [Majr] OR "vascular dementia" [TI] OR "vascular cognitive impairment" [TI] OR ("Vascular Diseases/complications" [Majr] AND "Cognition Disorders" [Majr])) AND ("Prognosis" [Mesh] OR "Disease Progression" [Mesh] OR prognosis [TI] OR prole [TI] OR course[TI] OR outcome[TI] OR "natural history" [TI])

Ichushi search: June 18, 2015 (Thursday)

#1 (Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND (Prognosis/TH OR Prognosis/TI OR Natural course/TI)

CQ 14-6

What are the systemic complications and associated symptoms of vascular dementia (VaD)?

Answer

(1) VaD is often accompanied by gait disturbance, falls, urinary disorder, pseudobulbar paralysis, and mood disorders such as depression. In addition to stroke, VaD may be complicated by systemic vascular disorders such as ischemic heart disease and peripheral artery disease.

(2) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is associated with migraine with aura, mood disorder (depression), and arteriosclerotic changes in the fundus.

(3) Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is associated with not only dementia but also alopecia (baldness) and low back pain associated with spondylosis deformans.

Comments and evidence

The most widely used diagnostic criteria for VaD are the diagnostic criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [1]. The NINDS-AIREN diagnostic criteria describe specific systemic complications and associated symptoms including early presence of gait disturbance, unstable gait and frequent falls, early presence of urinary disorder, pseudobulbar palsy, personality disorder, abulia, depression, and emotional incontinence. On the other hand, "features that make the diagnosis of VaD unlikely" include (1) early onset of memory deficit or cognitive impairments including aphasia, apraxia, and agnosia, in the absence of corresponding focal lesions on brain imaging; (2) absence of neurological signs; and absence of cerebrovascular lesions on brain CT or MRI. Compared to Alzheimer's disease dementia, VaD is often accompanied by impaired physical functions such as neurologic deficit symptoms.

Depression is significantly more common in VaD than in Alzheimer's disease dementia, suggesting that VaD may worsen depression [2-4]. The manifestation of depression after onset of stroke is attracting attention as post-stroke depression.

CADASIL, which is a hereditary VaD, is known to be accompanied by migraine with aura, mood disorder (depression), and arteriosclerotic changes in the fundus [5].

Furthermore, CARASIL, also a hereditary VaD, is known to be associated with not only dementia but also alopecia and lower back pain associated with spondylosis deformans [6].

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Search formula

PubMed search: June 27, 2015 (Saturday)

#1 "Dementia, Vascular/complications" [Majr] OR ("vascular dementia" [TI]AND complication* [TI]) OR ("vascular cognitive impairment*" [TI] AND complication* [TI])

Ichushi search: June 27, 2015 (Saturday)

#1 (Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND (Complication/TI OR Associated symptom/TI)

CQ 14-7

What are the risk factors for vascular dementia (VaD) and how are they controlled?

Recommendation

(1) VaD risk factors include aging, lack of exercise, a history of stroke (especially recurrent), hypertension, diabetes, dyslipidemia, obesity, atrial fibrillation, and smoking.
(2) For prevention of VaD, antihypertensive therapy for midlife hypertension is recommended. 1B However, no consensus has been reached regarding the target blood pressure reduction.
(3) Smoking cessation is recommended for VaD prevention. 1B
(4) Physical exercise is recommended for VaD prevention. 2C
(5) Continuous weight control from midlife (prevention of obesity) is recommended for VaD prevention. 2C

Comments and evidence

The Hisayama Study in Japan identified aging, low score in Hasegawa Dementia Scale, a history of stroke, and high systolic blood pressure as significant risk factors for VaD, while high hematocrit also tended to be a risk. In particular, midlife hypertension has been shown to be a strong risk factor for VaD [1, 2], and midlife hypertension should be treated actively from the viewpoint of dementia prevention.

On the other hand, among the large-scale randomized trials of antihypertensive drugs conducted mainly in older people, 6 trials also assessed cognitive function as an outcome measure. Among these 6 trials, 4 trials found no definitive effects of antihypertensives on the risk of dementia and on cognitive function [3], while the remaining 2 trials showed usefulness of these agents in reducing the risk of dementia in one trial (Syst-Eur trial) [4] and demonstrated efficacy for post-stroke dementia in the other trial (PROGRESS trial) [5, 6].

As described above, there is inadequate scientific evidence for antihypertensive treatment and the optimal target of blood pressure reduction in older people. Therefore, no conclusions have been reached regarding the effect of antihypertensive treatment for late-life hypertension on the prevention of dementia. However, antihypertensives are prescribed because there is no evidence that they deteriorate cognitive function.

Diabetes is a risk factor for stroke, but glycemic control alone does not prevent the recurrence of stroke, and control of other risk factors including hypertension is important. There is insufficient scientific evidence that using insulin therapy for glycemic control improves cognitive function [7]. Statin use reduces stroke by 17% [98], but the effects on cognitive function are inconsistent among reports [9]. In one study, use of strong statins for more than 1 year reduced new-onset dementia (hazard ratio 0.71, 95% confidence interval 0.61 to 0.82) [10], but dementia was not classified into subtypes in that study. In addition, a cohort study in residents aged over 60 years in Taiwan showed that the use of strong statins reduced the incidence of new-onset dementia [hazard ratio 0.73 (95% confidence interval 0.65 to 0.81)]. The effect was not significant when analysis was focused only on VaD [hazard ratio: 0.92 (95% confidence interval 0.72-1.18)].

A meta-analysis (19 prospective studies with follow-up periods of 2 to 30 years) has revealed that smoking is a risk factor of VaD, as is for Alzheimer's disease dementia [11]. The relative risk of VaD in current smokers is 1.78-fold compared with those who have never smoked, and this result is almost the same as that for Alzheimer's disease dementia (1.79-fold) [11]. Although further studies are needed to determine the extent of VaD risk reduction by smoking cessation, smoking cessation is desirable for VaD prevention.

In terms of physical activity, a prospective study of 749 older people observed for an average of 3.9 years evaluated the effects of exercise in 54 persons who developed Alzheimer's disease dementia and 27 people who developed VaD. In this analysis, exercise and walking reduced the risk of developing VaD [12]. Therefore, moderate physical activity is desirable.

In relation to eating habits, antioxidants (vitamins E and C) and fish-derived lipids (consumption of fatty fish) protect against VaD, while fried fish, elevated homocysteine, and low levels of folic acid and vitamins B_{12} increase the risk of VaD [13]. However, for older people with high blood levels of homocysteine, the risk of dementia cannot be reduced by supplementation with vitamin B complex [14].

It has been shown that both underweight and obesity correlate with dementia (U-shape phenomenon) [15]. In particular, obesity (BMI ≥ 30) increases the risk of developing VaD by a factor of 5.01 in a prospective study of 10,136 persons aged 40

to 45 years with a mean follow-up period of 36 years. However, in a short-term (3-5 years) study in older people, the correlation between obesity and VaD is poor [15]. Therefore, continuous weight control (prevention of obesity) from midlife is desirable for VaD prevention.

Atrial fibrillation increases the risk of dementia through various mechanisms [16]. Although there are few studies that classify and analyze VaD and Alzheimer's disease dementia separately, many reports have shown that the risk of dementia is increased 2 to 3 times in patients with atrial fibrillation associated with stroke.

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Search formula

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Ichushi search: June 27, 2015 (Saturday)
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CQ 14-8

What is antithrombotic therapy for vascular dementia (VaD)?

Recommendation

There is little evidence for the use of antithrombotic drugs for primary prevention of dementia. However, appropriate anticoagulant therapy is desirable for dementia prevention only in patients with atrial fibrillation.

To prevent dementia after noncardiogenic cerebral infarction, consider using antiplatelet drugs. 2C

Comments and evidence

The effectiveness of antiplatelet drugs for dementia is not consistent across several observational studies. In the Aspirin for Asymptomatic Atherosclerosis (AAA) trial, 3,350 subjects were given aspirin 100 mg or placebo for over 5 years, but no significant difference in cognitive function was demonstrated between two groups [1]. In another cohort study of 3,809 community-dwelling persons, the odds ratio for cognitive decline after 6 years of aspirin use was 0.97 (95% confidence interval 0.82-1.15) [2]. Therefore, previous studies have not confirmed the usefulness of prescribing antiplatelet drugs at least for a period of 6 years for primary prevention of dementia. On the other hand, in a study in which 70 patients with multi-infarct dementia were randomized into an aspirin group and a no-aspirin group and followed every year for 3 years, cognitive function was preserved in the aspirin group. However, study limitations such as lack of placebo control and small sample size have been pointed out [3]. In the South London Stroke Register that analyzed 4,413 patients with ischemic stroke but no atrial fibrillation, aspirin and dipyridamole combination therapy showed a tendency of protection against cognitive impairment [relative risk, 0.8 (95% confidence interval 0.68 to 1.01)] [4]. Thus, although antiplatelet therapy may not be useful for primary prevention of dementia, this therapy may be considered for prevention of dementia after ischemic stroke.

In the PRoFESS trial, a study was performed in patients with ischemic stroke comparing treatment using aspirin and dipyridamole combination therapy and clopidogrel monotherapy. After a mean follow-up period of 2.4 years, there was no difference in cognitive decline between two treatment groups [5]. Therefore, the effect of combination therapy with antiplatelet drugs and the class effect (difference in dementia prevention effect by antiplatelet drugs with different mechanisms of action) for dementia prevention remain unclear.

In the SPS3 trial, patients with symptomatic lacunar infarction were followed for an average of 3 years, and cognitive function was compared between aspirin monotherapy and combination therapy with two antiplatelet drugs. No dementia prevention effect was observed for dual antiplatelet therapy [6].

In cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is a hereditary vascular dementia, cerebral hemorrhage may develop during the course of disease, and administration of antiplatelet drugs may increase the risk of cerebral hemorrhage [7]. Even in sporadic vascular dementia, it is necessary to pay attention to bleeding complications when using antiplatelet drugs.

In a 3000-day observational study of 2,693 patients with no history of stroke or dementia who received warfarin for atrial fibrillation, the groups with poor warfarin control [time in therapeutic range (TTR) <25%, 26-50%, and 51-75%] had dementia hazard ratios of 5.34, 4.10, and 2.57, respectively, compared to the good warfarin control group (TTR >75%) [8]. In patients with atrial fibrillation, appropriate anticoagulant therapy for dementia prevention is desirable.

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■ Search formula

PubMed search: June 28, 2015 (Sunday)
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CQ 14-9

Are there effective drugs for cognitive impairment in vascular dementia (VaD)?

Recommendation

For the treatment of core symptoms of VaD, the cholinesterase inhibitors; namely, donepezil 2B, galantamine 2B and rivastigmine 2C; as well as the N-methyl-D-aspartate (NMDA) receptor antagonist memantine 2B are recommended (off-label).

Comments and evidence

In a double-blind randomized clinical trial conducted in patients with VaD, the donepezil group showed significant improvement in cognitive function compared to the placebo group. In particular, strong evidence was obtained for short-term treatment of approximately 24 weeks for mild to moderate VaD. In the future, establishment of evidence for the usefulness of long-term administration is awaited [1]. For cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a hereditary VaD, although administration of donepezil was not effective to improve cognition overall, usefulness was noted for executive function only [2].

Treatment with galantamine achieved significant improvement in cognitive function compared to the placebo group in a double-blind randomized clinical trials conducted in VaD patients [3] and in Alzheimer's disease dementia patients with cerebrovascular disorders [4].

In a double-blind randomized clinical trial in VaD patients, rivastigmine significantly improved some cognitive function assessment items compared to the placebo group [5].

Treatment with memantine, an NMDA receptor antagonist, resulted in significant improvement in cognitive function compared to the placebo group in double-blind randomized clinical trials in patients with VaD and in patients with Alzheimer's disease dementia and cerebrovascular disease [6, 7].

The above four drugs may be effective to certain extent for VaD, but one cannot exclude the possibility that the observed effectiveness may be mediated by the effect on coexisting Alzheimer's dementia.

As for other therapeutic agents, several clinical trials have shown that nicergoline improves cognitive function in VaD. In Japan, nicergoline is covered by health insurance for "improvement of decreased motivation due to chronic cerebrovascular disorder associated with sequelae of cerebral infarction". Amantadine is covered by insurance for sequelae of cerebral infarction, and may be considered for use to improve motivation and initiative in VaD. *Ginkgo biloba* has been reported to be effective for the treatment of dementia including VaD in several clinical trials [8]. Moreover, risperidone at low doses (mean 0.95 mg/day) reduces aggression, agitation and psychiatric symptoms associated with VaD [9]. Tiapride is covered by health insurance for "improvement of aggressive behaviors, mental agitation, wandering, and delirium associated with sequelae of stroke".

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CQ 14-10

What is the clinical position of cerebral amyloid angiopathy (CAA)?

Answer

(1) Cerebral amyloid angiopathy is related to the development of dementia.
(2) There is no known effective treatment for cerebral amyloid angiopathy, but if hypertension coexists, antihypertensive therapy is recommended to prevent cerebral hemorrhage.

Comments and evidence

Cerebral amyloid angiopathy is a pathological vascular change, which almost always occurs in Alzheimer's disease dementia. However, apart from being a direct cause of bleeding in the brain lobes, symptoms are rarely observed and hence the condition did not attract much attention. However, image and pathological analyses have clearly demonstrated that cerebral amyloid angiopathy is associated with various cerebrovascular disorders such as cortical micro-infarcts and cortical microbleeds [1, 2]. Furthermore, report has indicated that it is an independent factor of not only stroke but also dementia [3]. In a systematic review that analyzed the findings of four population-based studies; the Cambridge City over-75s Cohort (CC75C) study, the MRC Cognitive Function and Aging Study (MRC-CFAS), the Honolulu-Asia Aging study, and the Vantaa 85+ study, CAA was observed in 55% to 59% of patients with dementia but in only 28% to 38% of non-dementia patients. Severe CAA was observed in 37% to 43% of patients with dementia but only 7 to 24% of non-dementia patients, with clear differences between the two groups. [3]

In a multicenter randomized study conducted in 6,105 patients with cerebrovascular disease comparing cerebrovascular events during treatment with antihypertensive medications versus placebo for a mean period of 3.9 years, intracerebral hemorrhage associated with CAA was observed in a total of 16 patients. Cerebral hemorrhage was reduced by 77% in patients receiving antihypertensives compared with patients receiving placebo (3 patients in the antihypertensive group, 13 patients in the placebo group) [4]. There is no known effective treatment for CAA, but if patients also have hypertension, antihypertensive therapy is recommended for prevention of intracerebral hemorrhage.

In patients with CAA, acute inflammatory reaction mediated by autoimmune reaction against vascular wall amyloid β may occur concomitantly, causing acute impairment of consciousness and cognitive deterioration. This condition is called CAA-related inflammation (CAA-ri) [5]. As suggested from the pathological mechanism of CAA-ri, administration of immunosuppressive drugs such as corticosteroids and cyclophosphamide is effective in the acute phase [6].

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Search formula

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Chapter 15

Prion Disease

CQ 15-1

What are the clinical features of sporadic Creutzfeldt-Jakob disease (CJD)?

Answer

Sporadic CJD is the most common form of prion disease, constituting approximately 70% of all cases. Classic cases are characterized by a course of rapidly progressive dementia, cerebellar ataxia, pyramidal and extrapyramidal signs, and myoclonus, progressing to akinetic mutism over weeks.

Comments and evidence

The annual incidence of prion disease in Japan is approximately 1 case per 1 million [1, 2]. The mean age at onset is 67.9 years. Typical cases are termed classic CJD, and manifest as rapidly progressive dementia, myoclonus, cerebellar ataxia, visual disturbances, pyramidal signs and extrapyramidal symptoms, progressing to akinetic mutism in 3 to 6 months on average. The diagnostic criteria of sporadic CJD have been reported [3, 4].

The analysis of brain samples from patients with sporadic CJD has led to characterization of the protease K-resistant prion protein (PrP), which is distinguished into type 1 and 2 by Western blot analysis. Combining this typing with the PrP gene codon 129 polymorphism (MM type; homozygous for methionine, MV type; heterozygous for valine, VV type, homozygous for valine), sporadic CJD is classified into 6 types; MM1, MM2, MV1, MV2, VV1 and, VV2. The MM2 type is further classified by clinicopathological findings into MM2-cortical and MM2-thalamic types [5]. MM1 is the most common type of sporadic CJD, with a clinical course of the classic type. For details, see references 5 and 6.

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CQ 15-2

What are the electroencephalographic, cerebrospinal fluid, and MRI findings of sporadic Creutzfeldt-Jakob disease (CJD)?

Answer

In typical cases, electroencephalogram (EEG) shows slow and/or irregular waves in the early stage, then periodic sharp wave complexes (PSWCs) will emerge when myoclonus appears, and is followed by disappearance of PSWCs and flattening of waves at the end stage. In the cerebrospinal fluid (CSF), the appearance, cell count, and protein level are normal in most cases, while 14-3-3 protein and total tau protein increase. Abnormal prion proteins in the CSF can be detected by real-time quaking-induced conversion (RT-QuIC) method. Further, hyperintensity is observed in the in cerebral cortex and basal ganglia (putamen, caudate nuclei) on diffusion-weighted or FLAIR MRI, and in the medial thalamus in some cases.

A

Comments and evidence

In prion disease, the EEG shows slowing and irregularity in the early stage of the disease, then PSWCs emerge at the same time as myoclonus appears. Finally, PSWCs disappear and the EEG flattens in the end stage [1]. Hyperintensity is observed in the cerebral cortex, basal ganglia (putamen, caudate nuclei), and the thalamus in some cases, on diffusion-weighted or FLAIR MRI [2, 3]. CSF examination typically shows a normal appearance and cell count, and protein levels are normal in most cases; however 14-3-3 and total tau proteins are increased in the CSF [4]. In recent years, the RT-QuIC method has been developed, which enables the detection of abnormal prion proteins (PrP^{Sc}) in the CSF with approximately 70% sensitivity [5, 6].

The Ministry of Health, welfare and Labour Prion Study Group has established a diagnosis support system. Utilization of this system is recommended [7, 8].

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Search formula

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CQ 15-3

What are the types and features of genetic prion disease in Japan?

Answer

Genetic prion diseases are classified as genetic Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler Scheinker (GSS) disease, and fatal familial insomnia (FFI). In Japan, genetic prion diseases commonly include V180I (CJD), P102L (GSS), E200K (CJD), and M232R (CJD) mutations of the prion protein gene (*PRNP*). CJD with V180I and M232R are found more commonly in sporadic cases; therefore, genetic testing is required for diagnosis. Patients with V180I mutation often have late onset and typically manifest slowly progressive dementia. Patients with P102L mutation have cerebellar ataxia at onset with slow progression, and patients with E200K mutation show a clinical course similar to classic sporadic CJD. In recent years, one type with autonomic failure as the main symptom has been reported.

Comments and evidence

In Japan, the common mutations of *PRNP* include V180I (CJD), P102L (GSS), E200K (CJD), and M232R (CJD). The frequencies of these mutations differ significantly from those in Europe and America [1, 2]. V180I is the most common mutation in Japan and Korea, and M232R and P105L (GSS) mutations are unique to Japan [3, 4]. Genetic prion disease is usually autosomal dominant, and almost all cases with P105L mutation are familial. However, genetic testing is required for diagnosis of cases with V180I and M232R mutations because these rarely exhibit a family history.

For details, refer to reference 5.

References

1) Nozaki I, Hamaguchi T, Sanjo N, et al. Prospective 10-year surveillance of human prion diseases in japan. Brain. 2010; 133(10): 3043-3057.
2) Nakamaura Y, Ae R, Takumi I, et al. Descriptive epidemiology of prion disease in Japan: 1999-2012. J Epidemiol. 2015; 25(1): 8-14.
3) Shiga Y, Satoh K, Kitamoto T, et al. Two different clinical phenotypes of Creutzfeldt-Jacob disease with a M232R substitution. J Neurol. 2007; 254(11): 1509-1517.
4) Iwasaki Y, Kizawa M, Hori N, et al. A case of Gerstmann-Straussler-Scheinker syndrome with the P105L prion protein gene mutation presenting with ataxia and extrapyramidal signs without spastic paraparesis. Clin Neurol Neurosurg. 2009; 111(7): 606-609.
5) Health Welfare and Labor Sciences Research Grant for Research Project for Combating Intractable Diseases (Research Project for Combating Intractable Diseases). Study Group on Prion Disease and Late-onset Virus Infections (ed.) Clinical Practice Guidelines for Prion Disease 2017. (In Japanese)

Search formula

PubMed search: June 30, 2015 (Tuesday)

#1 ("Prion Diseases/genetics" [Mesh] OR (genetic AND prion disease*) OR (genetic AND gerstmann-straussler-scheinker disease*) OR (genetic AND "fatal familial insomnia")) AND ("Japan" [Mesh] OR japan [TIAB])

Ichushi search: June 30, 2015 (Tuesday)

#1 (Prion disease/TH OR Prion disease/TI OR Fatal familial insomnia /TI OR Gerstmann-Straussler-Scheinker/TI)AND((SH = Genetics) OR Genetics/TH OR Hereditary/TI OR Hereditary disease/TH) AND (Japan/TH OR Japan/TI OR This country/TI OR Our country/TI OR Our country/TI)

CQ 15-4

What are the types and features of acquired (infectious) prion disease in Japan?

Answer

Two types of acquired prion diseases have been confirmed in Japan; variant Creutzfeldt-Jakob disease (variant CJD; vCJD) and dura mater graft-associated CJD. Cases of dura mater graft-associated CJD in Japan constitute over half of all cases worldwide. Surprisingly, some cases showed disease onset over 30 years after dura mater transplantation. Two-thirds of these cases are the non-plaque type and show a clinical feature similar to classic CJD. One-third of the cases are plaque-type and manifest as relatively slowly progressive ataxia.

Comments and evidence

Acquired prion diseases are classified into Kuru, vCJD, and iatrogenic CJD [1, 2].

Variant CJD exhibits a younger onset compared with the other prion diseases, with a mean age at onset of 29 years. Patients manifest psychiatric symptoms such as frustration and depression at an early stage; therefore, the disease is often misdiagnosed as psychiatric diseases. As the disease progresses, cognitive impairment and motor symptoms such as ataxic gait, gradually emerge. Hyperintensity in the medial-dorsal thalamus (pulvinar sign) is observed on diffusion-weighted MRI. Periodic sharp wave complexes (PSWCs) on EEG are typically not observed.

In Japan, all cases of acquired CJD, except one case of vCJD, are dura mater grafting-associated CJD, with 154 confirmed cases (Surveillance Committee, September 2017). The dura mater used in all identifiable cases was cadaveric dura mater Lyodura® from B. Braun, Germany. The cases in Japan constitute over half of the cases worldwide [3]. After Lyodura® was discontinued (March 1997), the disease has not been found in patients who undergo dura mater grafting. Although the incidence of patients with dura mater grafting-associated CJD has decreased, some cases have presented with disease up to 30 years after surgery [3]. Two-thirds of dura mater grafting-associated CJD cases have clinicopathological findings similar to classic CJD, and one-third of the cases manifest an ataxic gait with relatively slow progression, and no PSWCs is observed on electroencephalogram in the early stage. Pathological examination of the brain shows plaque-like deposition of abnormal prion protein [4].

For patients with CJD caused by dura mater grafting, the patient/family association has set up a CJD support network (http://www.cjdnet.jp/). Utilization of this network is recommended.

■ References

1) Health Welfare and Labor Sciences Research Grant for Research Project for Combating Intractable Diseases. Study Group on Prion Disease and Late-onset Virus Infections and Study Group Related to Surveillance and Infection Control of Prion Disease. Clinical Practice Guideline for Prion Disease 2017. (In Japanese)
2) Health Welfare and Labor Sciences Research Grant for Research Project for Combating Intractable Diseases. "Study Group on Prion Disease and Late-onset Virus Infections" (ed.) Prion Disease and Late-onset Virus Infections. Tokyo: Kanehara Shuppan: 2010. (In Japanese)
3) Hamaguchi T, Sakai K, Noguchi.-Shinohara M, et al. Insight into the frequent occurrence of dura mater graft-associated Creutzfeldt-Jakob disease in Japan. J Neurol Neurosurg Psychiatry. 2013; 84(10): 1171-1175.
4) Noguchi-Shinohara M, Hamaguchi T, Kitamoto T, et al. Clinical features and diagnosis of dura mater graft associated Creutzfeldt Jakob disease. Neurology. 2007; 69(4): 360-367.

■ Search formula

PubMed search: June 30, 2015 (Tuesday)

#1 ("Prion Diseases/transmission" [Mesh] OR ((acquired OR transmission* OR "dura mater graft associated" OR infectious OR iatrogenic) AND ("Prion Diseases" [Mesh] OR prion disease*)) OR (variant Creutzfeldt-Jakob disease* OR "variant CJD" OR vCJD OR kuru [TIAB])) AND ("Japan" [Mesh] OR japan [TIAB])

Ichushi search: June 30, 2015 (Tuesday)

#1 (Prion disease/TH OR Prion disease/TI OR Creutzfeldt-Jakob disease/TI OR CJD/TI OR Kuru/TI) AND (Acquired/TI OR Acquired/TH OR Infectious/TI OR Infectious/TH OR Iatrogenic/TI OR ((Dura mater/TH OR Dura mater/TI) AND grafting)) AND (Japan/TH OR Japan/TI OR This country/TI OR Our country/TI OR Our country/TI)

CQ 15-5

What are the infection control measures and effective sterilization methods for prion disease?

Answer

For medical devices that have been used in high-risk procedures for patients known to have prion disease (see Guideline [1]), the currently recommended method is to remove as much as possible the blood and tissue fragments attached to the device, then immerse in 3% sodium dodecyl sulfate (SDS) solution and boil at 100°C for 3-4 minutes. After washing manually or in a washer-disinfector, sterilize in a pre-vacuum autoclave at 134°C for 10 minutes.

Comments and evidence

Prion disease can be transmitted not only after disease onset but also during the incubation period via medical devices that have been in contact with high-risk infectious sites or through blood (for variant CJD). The Japanese guidelines for prevention of prion disease currently recommend disinfection and sterilization methods for surgical instruments that have been used in patients with prion disease (http://prion.umin.jp/guideline/cjd_2008all.pdf) [1].

■ References

1) Health Welfare and Labor Sciences Research Grant; Research Project for Combating Intractable Diseases. Study Group on Prion Disease and Late-onset Virus Infections. Guidelines for Prevention of Prion Disease (2008 edition).
http://prion.umin.jp/guideline/index.html (In Japanese)

■ Search formula

PubMed search: June 30, 2015 (Tuesday)
#1 ("Prion Diseases" [Mesh] OR prion disease* [TI]) AND ("Decontamination" [Mesh] OR "Communicable Disease Control" [Mesh] OR decontamination OR precaution* OR infection control*)

Ichushi search: June 30, 2015 (Tuesday)
#1 (Prion disease/TH OR Prion/TI) AND (Infection prevention/TH OR Infection control/TI OR Infection control/TI OR Infection prevention/TI OR Infection prevention/TI OR Decontamination/TH OR Sterilization/TI OR Disinfection/TI OR Decontamination/TI)

Chapter 16

Medical Diseases and Others

CQ 16-1

What are the features of cognitive impairment due to vitamin deficiency?

Answer

Vitamin B_1 deficiency leads to the development of Wernicke encephalopathy, an acute metabolic encephalopathy with main symptoms of impaired consciousness, eye movement disorder, and motor ataxia. If not responding to treatment, Wernicke encephalopathy may convert irreversibly to Korsakoff syndrome and manifests symptoms such as disorientation, amnesia, confabulation (storytelling), and lack of disease awareness.

Vitamin B_{12} deficiency causes memory impairment and psychiatric symptoms, and folate deficiency has been reported to cause cognitive impairment similar to that of vitamin B_{12}. In recent years, vitamin D deficiency has also been suggested to cause cognitive impairment.

Comments and evidence

Vitamin B_1 deficiency is often caused by alcoholism or an unbalanced diet. As the condition progresses, patients develop Wernicke encephalopathy with the triad of impaired consciousness, eye movement disorders, and ataxic gait [1]. However, only few cases satisfy all the three main features. Other symptoms such as delirium, weakness, apathy, impaired recognition of the surrounding situation, and impaired concentration may also be observed; and may even lead to coma and death [2, 3]. It has been reported that Wernicke encephalopathy converts to Korsakoff syndrome in 85% of the cases. In these cases, memory impairment more severe than recent memory, anterograde amnesia, and confabulation are observed, but procedural memory is often preserved [3].

Vitamin B_6 deficiency can also cause pellagra-like symptoms (see below).

In vitamin B_{12} deficiency and folic acid deficiency, cognitive impairment may be caused by hyperhomocysteinemia.

In vitamin B_{12} deficiency, even in the absence of anemia and macrocytosis, cognitive impairments such as slowed thinking, memory impairment, and attention deficit; psychiatric symptoms such as depressive symptoms, delusions, hallucinations, and delirium; and neurological symptoms such as motor, sensational and autonomic symptoms are observed [4].

Although the neuropsychiatric symptoms in folate deficiency are the same as those in vitamin B_{12} deficiency, it has been reported that decrease in blood folate level is associated with cognitive impairment [5], but no consensus has been reached.

Niacin (nicotinic acid, nicotinamide) deficiency has been known as pellagra from the past (four "Ds": dermatitis, diarrhea, dementia, death) [6].

In recent years, vitamin D deficiency has been found to be quite common in older people. Although a meta-analysis has reported a relationship between low vitamin D and memory disorder and executive dysfunction [7], there is no consistent opinion.

References

1) Koyama K. Symptoms of Wernicke's encephalopathy. Vitamin. 2012; 86(11): 620-624. (In Japanese)
2) Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol. 2007; 6(5): 442-455.
3) Kopelman MD, Thomson AD, Guerrini I, et al. The Korsakoff syndrome: clinical aspects, psychology and treatment. Alcohol. 2009; 44(2): 148-154.
4) Lachner C, Steinle NI, Regenold WT. The neuropsychiatry of vitamin B12 deficiency in elderly patients. J Neuropsychiatry Clin Neurosci. 2012; 24(1): 5-15.
5) Michelakos T, Kousoulis AA, Katsiardanis K, et al. Serum folate and B12 levels in association with cognitive impairment among seniors: results from the VELESTINO study in Greece and meta-analysis. J Aging Health. 2013; 25(4): 589-616.
6) Niwa A. Chapter 3 Diagnosis of dementia, 4 Examinations. Nakajima K (ed.) Dementia Handbook. Tokyo: Igaku Shoin; 2013: 131. (In Japanese)
7) Annweiler C, Montero-Odasso M, Llewellyn DJ, et al. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. J Alzheimers Dis. 2013; 37(1): 147-171.

Search formula

PubMed search: June 27, 2015 (Saturday), July 21, 2015 (Tuesday)

#1 (("Dementia" [Mesh] OR dementia OR "Cognition Disorders" [Mesh] OR cognition disorder* OR "cognitive impairment") AND ("Avitaminosis" [Mesh] OR avitaminosis OR "vitamin deficiency")) OR (((("Thiamine" [Mesh] OR "Vitamin B 1" [TI] OR "Vitamin B1" [TI]) AND ("Korsakoff Syndrome" [Mesh] OR Wernicke Korsakoff Syndrome* [TI] OR Korsakoff Psychosis* [TI])) OR "Vitamin B 6" [Mesh] OR "Vitamin B 6" [TI] OR "Vitamin B6" [TI] OR "Vitamin B 6 Deficiency" [Mesh] OR "Vitamin B 12" [Mesh] OR "Vitamin B 12" [TI] OR "Vitamin B12" [TI] OR "Vitamin B 12 Deficiency" [Mesh] "Vitamin D" [Mesh] OR "Vitamin D" [TI] OR "Vitamin D Deficiency" [Mesh] OR "Folic Acid" [Mesh] OR "folic acid" [TI] OR folate [TI]) AND ("Executive Function" [Mesh] OR cognitive function* [TI]) OR (("Avitaminosis" [Mesh] OR avitaminosis [TI]) AND ("Hyperhomocysteinemia" [Mesh] OR hyperhomocysteinemia* [TI]) AND ("Cognition Disorders" [Mesh] OR "cognition disorder*" [TI] OR "cognitive impairment" [TI] OR "cognition disorder*" OR cognitive impairment" OR "cognitive decline" [TI]))

Ichushi search: June 27, 2015 (Saturday), July 21, 2015 (Tuesday)

#1 ((Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive decline/TI) AND (Vitamin deficiency/TH OR Vitamin deficiency/TI)) OR ((Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive decline/TI) AND (((Thiamine/TH OR Thiamine/TI OR Thiamin/TI OR Vitamin B1/TI OR "Vitamin B1"/TI OR "Vitamin B 1"/TI) AND (Korsakoff syndrome/TH OR Korsakoff syndrome/TI OR Korsakoff syndrome/TI OR Korsakoff psychosis/TI)) OR "Vitamin B6"/TH OR "Vitamin B6"/TI OR Vitamin B6/TI OR Vitamin B6 deficiency/TH OR "Vitamin B12"/TH OR "Vitamin B12"/TI OR Vitamin B12/TI OR Vitamin B12 deficiency/TH OR "Vitamin D"/TH OR "Vitamin D"/TI OR Vitamin D/TI OR Vitamin D deficiency/TH OR "Folic Acid"/TH OR "Folic Acid"/TI OR Folic acid/TI OR Folic acid deficiency/TH OR ((Vitamin deficiency/TH OR Vitamin deficiency/TI) AND (Hyperhomocysteinemia/TH OR Hyperhomocysteinemia/TI))))

CQ 16-2

What are the features of cognitive impairment due to hypothyroidism?

Answer

Overt hypothyroidism causes cognitive impairment and depressive symptoms. Many reports have shown no clear effect of subclinical hypothyroidism on cognitive function, but opinion is divided. In Hashimoto's encephalopathy, acute psychiatric symptoms such as impaired consciousness, delirium, and hallucination; cognitive impairment; and chronic symptoms such as depression and anxiety are observed. C

Comments and evidence

In overt hypothyroidism, a wide range of cognitive functions are impaired, and impairments of general intelligence, attention and concentration, memory, perceptual function, language, and executive function are observed. Especially, memory impairment and verbal memory are consistently reported [1-3]. Many studies have concluded that there is an association between overt hypothyroidism and depressive symptoms.

Subclinical hypothyroidism generally does not cause depressive symptoms, anxiety, or widespread or severe cognitive impairment, but no consensus has been established [2].

Hashimoto's disease (chronic thyroiditis) is the most common cause of hypothyroidism. In Hashimoto's encephalopathy, cognitive impairment, word-finding difficulty, epileptic seizures, behavioral disorders, myoclonus, gait ataxia, aphasia, tremor, hyperreflexia, motor deficit, psychotic symptoms, depressive symptoms, confusion, and sleep disorder have been reported [4]. In particular, patients who are positive for anti-N-terminal of α-enolase (NAE) antibody often presents with an acute encephalopathy type, with high frequencies of consciousness disturbance and various psychiatric symptoms and cognitive impairment. In contrast, patients with a chronic course often have depressive symptoms, anxiety, and cerebellar ataxia.

■ References

1) Japan Thyroid Association. Guidelines for the Diagnosis of Thyroid Diseases 2013. http://www.japanthyroid.jp/en/guidelines.html
2) Samuels MH. Psychiatric and cognitive manifestations of hypothyroidism. Curr Opin Endocrinol Diabetes Obes. 2014; 21(5): 377-383.
3) Dugbartey AT. Neurocognitive aspects of hypothyroidism. Arch Intern Med. 1998; 158(13): 1413-1418.
4) de Holanda NC, de Lima DD, Cavalcanti TB, et al. Hashimoto's encephalopathy: systematic review of the literature and an additional case. J Neuropsychiatry Clin Neurosci. 2011; 23(4): 384-390.
5) Yoneda M. Hashimoto's encephalopathy. Japanese Journal of Molecular Psychiatry (Bunshi Seishinigaku) 2013; 13(3): 178-184. (In Japanese)

■ Search formula

PubMed search: June 27, 2015 (Saturday), July 7, 2015 (Tuesday), September 12, 2015 (Saturday)

#1 (("Dementia" [Mesh] OR dementia OR "Cognition Disorders" [Mesh] OR "cognition disorder*" OR "cognitive impairment") AND ("Hypothyroidism" [Mesh] OR hypothyroid* OR "Hashimoto's disease" OR "Hashimoto disease")) OR (("Executive Function" [Mesh] OR "Cognition" [Mesh] OR cognitive function* OR "Cognition Disorders" [Mesh] OR cognition disorder* OR cognitive disorder* OR cognitive impairment*) AND ("Hypothyroidism" [Mesh] OR hypothyroid* OR "Hashimoto Disease" [Mesh] OR "hashimoto encephalopathy" OR "hashimoto's encephalopathy" OR Hashimoto's disease* OR Hashimoto disease*)) OR ("Thyroid Diseases/diagnosis" [Majr] AND manifestation [TI])

Ichushi search: June 27, 2015 (Saturday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive decline/TI) AND (Hypothyroidism/TH OR Hypothyroidism/TI OR Hashimoto disease/TI)

CQ 16-3

What are the features of cognitive decline due to neurosyphilis?

Answer

Neurosyphilis is a neurological infection caused by *Treponema pallidum*, which infiltrates the nervous system after the initial infection. In late syphilis, which develops more than 15 to 20 years after the initial infection, long-term chronic meningovasculitis as well as the spread of infiltration and inflammation to the brain parenchyma, cause progressive paralysis manifesting with dementia, and tabes dorsalis due to damage of the dorsal funiculus and/or dorsal nerve roots. Dementia symptoms include disorientation, memory disturbance and judgment disability, as well as hallucination, delusion, irritability, and convulsion.

Comments and evidence

After infection occurs *via* sexual contact or blood transfusion, syphilis can infiltrate the central nervous system and cause progressive paralysis, mainly manifesting dementia 15-20 years after the initial infection. As a result of long-term chronic meningovasculitis, bacterial infiltration and/or inflammatory spread to the central nervous system, dementia symptoms in progressive paralysis are observed as disorientation, memory disturbance, and decline in judgment and calculation capacity, followed by manifestations of anti-social speech and behaviors and abnormal behaviors. Furthermore, patients show psychiatric symptoms such as hallucination, delusion, and depression. Symptoms are diverse, and it is difficult to distinguish neurosyphilis from other dementias. Clinical diagnosis is made by serum non-treponema tests such as VDRL and RPR, syphilis-specific antigen test (TPHA), and cerebrospinal fluid examination (TPHA and FTA-Abs in cerebrospinal fluid) [1, 2].

Treatment includes penicillin G (18-24 million units/day) administered by continuous intravenous infusion or intravenous infusion every 4 hours for 10-14 days. However, some patients show minor improvement with sequelae.

For details, refer to the "Guideline for Diagnosis and Treatment of Sexually Transmitted Diseases" (http://jssti.umin.jp/pdf/guideline-2011.pdf).

References

1) Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. JAMA. 2014; 312(18): 1905-1917.
2) Ghanem KG. REVIEW: Neurosyphilis: a historical perspective and review. CNS Neurosci Ther. 2010; 16: e157-e168.

Search formula

PubMed search: June 30, 2015 (Tuesday)

#1 ("Neurosyphilis" [Mesh] OR neurosyphilis OR "general paresis" OR "progressive paralysis") AND ("Dementia" [Mesh] OR dementia[TI] OR "Cognition Disorders" [Mesh] OR "cognition disorder*" OR "cognitive dysfunction")

Ichushi search: June 30, 2015 (Tuesday)

#1 (Syphilis-nerve/TH OR Neurosyphilis/TI)AND(Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI OR Cognitive decline/TI)

CQ 16-4

What are the features of cognitive impairment caused by hepatic encephalopathy (HE)?

Answer

In hepatic encephalopathy (HE), attention, information processing ability, and visuomotor coordination are impaired from an early stage. Occasionally these symptoms are accompanied by focal neurological signs such as parkinsonism and/or choreic movement.

Comments and evidence

HE is characterized as a group of neuropsychiatric symptoms caused by acute or chronic liver dysfunctions. HE occurs when the portal venous shunt produces toxic substances such as ammonia produced by hepatocellular injury, and the toxins enter the systemic circulation without detoxication in the liver [1, 2].

The current trend is to interpret the disease as a continuum and use the following clinical rating: (1) lack of cognitive impairment (UNIMPAIRED); (2) acute confusional syndrome (unstable); and (3) persistent chronic cognitive impairment (stable). In the continuous approach, patients may move from one situation to another interchangeably [3]. Severity is evaluated categorically and graded based on the state of consciousness, intellectual function, behavior, and neuromuscular signs into 5 stages (stage 0 to 4) [4].

Acute episodic HE is an acute confusional syndrome that can progress to coma in severe cases. Bilateral symmetrical hyperintensities in the globus pallidus and ventral midbrain are observed on T1-weighted MRI. In cases of acute exacerbation of chronic hepatitis, bilateral symmetrical hyperintensities have been observed in the thalamus, posterior limb of internal capsule, and white matter around the lateral ventricle on diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) MRI.

Minimal HE is present in approximately 55% of cirrhosis patients. They show abnormalities on comprehensive neuropsychological test but not on neurological examination. It is associated with impaired driving skills and a significantly higher risk of motor vehicle crashes, due to attention and visuomotor coordination deficits.

Even in patients with prolonged chronic cognitive impairment, motor symptoms such as parkinsonism, choreic movements, and myelopathy are observed in the late stages.

■ References

1) Taniguchi E, Kawaguchi T, Sakata M, et al. Lipid prole is associated with the incidence of cognitive dysfunction in viral cirrhotic patients: a data-mining analysis. Hepatol Res. 2013; 43(4): 418-424.
2) Seyan AS, Hughes RD, Shawcross DL. Changing face of hepatic encephalopathy: role of inflammation and oxidative stress. World J Gastroenterol. 2010; 16(27): 3347-3357.
3) Cordoba J. New assessment of hepatic encephalopathy. J Hepatol. 2011; 54(5): 1030-1040.
4) Bajaj JS. Review article: the modern management of hepatic encephalopathy. Aliment Pharmacol Ther. 2010; 31(5): 537-547.

■ Search formula

PubMed search: June 30, 2015 (Tuesday)

#1 ("Hepatic Encephalopathy" [Mesh] OR "Liver Diseases/complications" [Mesh] OR "Liver Diseases" [Majr]) OR "hepatic encephalopathy" OR "liver dysfunction" [TI] OR liver disease* [TI]) AND ("Dementia" [Mesh] OR dementia [TI] OR "Cognition Disorders" [Mesh] OR "cognition disorder*" OR "cognitive dysfunction")

Ichushi search: June 30, 2015 (Tuesday)

#1 (Hepatic encephalopathy/TH OR Hepatic encephalopathy/TI OR hepatic coma/TI OR portal systemic encephalopathy/TI OR portal systemic encephalopathy/TI OR Liver disease/ TH OR Liver dysfunction/TI OR Abnormal liver function/TI OR Liver dysfunction/TI) AND (Dementia/TH OR Dementia/TI OR Cognitive impairment/TH OR Cognitive impairment/TI OR Cognitive function impairment/TI OR Cognitive decline/TI)

CQ 16-5

What are the features, diagnosis, and treatment strategies for dementia symptoms of idiopathic normal pressure hydrocephalus (iNPH)?

Answer

Psychomotor speed, attention, working memory, and memory function are the cognitive functions that tend to be impaired in iNPH and which can be improved by removing cerebrospinal fluid. For diagnosis and treatment strategy, refer to "Clinical Practice Guideline for Idiopathic Normal Pressure Hydrocephalus, 2nd Edition" (2011). B

Comments and evidence

In patients with iNPH, psychomotor speed decreases, and attention and working memory are impaired even in mild cases. For diagnosis and treatment policy, refer to the "Clinical Practice Guideline for Idiopathic Normal Pressure Hydrocephalus, 2nd Edition" (2011) [1].

■ References

1) Japanese Society of Normal Pressure Hydrocephalus, Clinical Practice Guideline for Idiopathic Normal Pressure Hydrocephalus Development Committee (Ed.) Clinical Practice Guideline for Idiopathic Normal Pressure Hydrocephalus, 2nd edition. Tokyo: Medical Review Co. Ltd.: 2011. http://minds.jcqhc.or.jp/n/med/4/med0038/G0000352/0001 (In Japanese)

■ Search formula

PubMed search: May 28, 2015 (Thursday)
#1 "Hydrocephalus, Normal Pressure" [Mesh] AND ("idiopathic normal pressure hydrocephalus" OR iNPH)

Ichushi search: May 28, 2015 (Thursday)
#1 Hydrocephalus-normal pressure/TH AND (Idiopathic normal pressure hydrocephalus/AL OR "idiopathic normal pressure hydrocephalus"/AL OR iNPH/AL)