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.

■ References

1) Mathias JL, Burke J. Cognitive functioning in Alzheimer's and vascular dementia: a meta-analysis. Neuropsychology. 2009; 23(4): 411-423.
2) Dubois B, Feldman HH, Jacova C, Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014; 13(6): 614-629.
3) Bora E, Walterfang M, Velakoulis D. Theory of mind in behavioural-variant frontotemporal dementia and Alzheimer's disease: a meta-analysis. J Neurol Neurosurg Psychiatry. 2015; 86(7): 714-719.
4) Delva F, Auriacombe S, Letenneur L, et al. Natural history of functional decline in Alzheimer's disease: a systematic review. J Alzheimers Dis. 2014; 40(1): 57-67.
5) Lyketsos CG, Steinberg M, Tschanz JT, et al. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. Am J Psychiatry. 2000; 157(5): 708-714.
6) Lyketsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA. 2002; 288(12): 1475-1483.
7) Hirono N, Mori E, Tanimukai S, et al. Distinctive neurobehavioral features among neurodegenerative dementias. J Neuro-psychiatry Clin Neurosci. 1999; 11(4): 498-503.
8) Chi S, Wang C, Jiang T, et al. The prevalence of depression in Alzheimer's disease: a systematic review and meta-analysis. Curr Alzheimer Res. 2015; 12(2): 189-198.
9) Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. Am J Psychiatry. 2005; 162(11): 2022-2030.
10) Lopez OL, Becker JT, Klunk W, et al. Research evaluation and diagnosis of probable Alzheimer's disease over the last two decades: I. Neurology. 2000; 55(12): 1854-1862.
11) Galton CJ, Patterson K, Xuereb JH, et al. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. Brain. 2000; 123(Pt 3): 484-498.
12) Snowden JS, Stopford CL, Julien CL, et al. Cognitive phenotypes in Alzheimer's disease and genetic risk. Cortex. 2007; 43(7): 835-845.
13) Teichmann M, Kas A, Boutet C, et al. Deciphering logopenic primary progressive aphasia: a clinical, imaging and biomarker investigation. Brain. 2013; 136(Pt 11): 3474-3488.

■ Search formula

PubMed search: July 2, 2015 (Thursday)
#1 ("Alzheimer Disease/diagnosis" [Majr] OR (Alzheimer [TI] AND (diagnosis [TI] OR diagnostic [TI]))) AND (sign [TI] OR signs [TI] OR symptom [TI] OR symptoms [TI] OR symptomatology [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 (Characteristics/TI OR Signs/TI OR Symptoms/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI)

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.

References

1) American Psychiatric Association. Diagnostic and statistical manual of mental disorders Fifth Edition: DSM-5. Arlington, VA: American Psychiatric Association; 2013.
2) McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7(3): 263-269.
3) Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014; 13(6): 614-629. Erratum in: Lancet Neurol. 2014 Aug; 13(8): 757.

Search formula

PubMed search: July 22, 2015 (Wednesday)
#1 ("Alzheimer Disease/diagnosis" [Majr] OR (Alzheimer* [TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI]))) AND ((criteria [TI] AND diagnosis* [TI]) OR "Diagnosis, Differential" [Mesh] OR "Diagnostic Errors" [Mesh] OR "Sensitivity and Specificity" [Mesh] OR "differential diagnosis" [TI] OR sensitivity [TI] OR specificity [TI] OR diagnostic error* [TI]

Ichushi search: July 22, 2015 (Wednesday)
#1 Alzheimer's disease/TH OR Alzheimer's disease/TI) AND ((Criteria/TI AND Diagnosis/TI) OR ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI) AND (Differential diagnosis/TH OR Differential diagnosis/TI OR Misdiagnosis/TH OR Misdiagnosis/TI OR Sensitivity and specificity/TH OR Sensitivity/TI OR Specificity/TI))

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.

References

1) Cure S, Abrams K, Belger M, et al. Systematic literature review and meta-analysis of diagnostic test accuracy in Alzheimer's disease and other dementia using autopsy as standard of truth. J Alzheimers Dis. 2014; 42(1): 169-182.
2) Scheltens P, Fox N, Barkhof F, et al. Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. Lancet Neurol. 2002; 1(1): 13-21.
3) Liu Y, Yu JT, Wang HF, et al. APOE genotype and neuroimaging markers of Alzheimer's disease: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2015; 86(2): 127-134.
4) Yeo JM, Lim X, Khan Z, et al. Systematic review of the diagnostic utility of SPECT imaging in dementia. Eur Arch Psychiatry Clin Neurosci. 2013; 263(7): 539-552.
5) Bloudek LM, Spackman DE, Blankenburg M, et al. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. J Alzheimers Dis. 2011; 26(4): 627-645.
6) Benzinger TL, Blazey T, Jack CR Jr, et al. Regional variability of imaging biomarkers in autosomal dominant Alzheimer's disease. Proc Natl Acad Sci U S A. 2013; 110(47): E4502-E4509.
7) Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA. 2015; 313(19): 1939-1949.
8) Ma Y, Zhang S, Li J, et al. Predictive accuracy of amyloid imaging for progression from mild cognitive impairment to Alzheimer disease with different lengths of follow-up: a meta-analysis. Medicine. 2014; 93(27): e150.

Search formula

PubMed search: July 22, 2015 (Wednesday)

#1 ("Alzheimer Disease/diagnosis" [Majr] OR (Alzheimer* [TI] AND (diagnosis [TI] OR diagnoses [TI] OR diagnostic [TI]))) AND ("Diagnostic Imaging" [Mesh] OR "magnetic resonance imaging" OR "single-photon emission computed tomography" OR "positron emission tomography" OR "amyloid imaging" OR "tau imaging" OR MRI OR SPECT OR PET)

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 = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI) AND (Diagnostic imaging/TH OR MRI/TI OR Magnetic resonance imaging OR Magnetic resonance tomography OR Magnetic resonance imaging OR Nuclear magnetic resonance imaging OR PET/TI OR Positron emission tomography OR Positron emission tomography 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)

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].

References

1) Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A. 1993; 90(5): 1977-1981.
2) Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology. 1993; 43(8): 1467-1472.
3) Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia(an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001; 56(9): 1143-1153.
4) Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol. 2007; 14(1): e1-26.
5) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: DSM-5. Arlington, VA: American Psychiatric Association; 2013.
6) McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7(3): 263-269.
7) Green RC, Roberts JS, Cupples LA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. N Engl J Med. 2009; 361(3): 245-254.
8) "Guidelines on Genetic Diagnosis of Neurological Diseases" Preparation Committee (Ed.). Japanese Society of Neurology (Supervision). Guidelines on Genetic Diagnosis of Neurological Diseases, 2009. Tokyo: Igaku Shoin; 2009. (In Japanese)

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 ("Apolipoproteins E" [Mesh] OR "Apolipoproteins E" [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 = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH OR Diagnosis/TI) AND ("Apolipoproteins E"/TH OR "Apolipoproteins E"/TI OR "Apolipoprotein E"/TI OR ApoE [TI])

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.

References

1) Weiner MW, Veitch DP, Aisen PS, et al. 2014 Update of the Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception. Alzheimers Dement. 2015; 11(6): e1-e120.
2) Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012; 367(9): 795-804.
3) McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7(3): 263-269.
4) Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014; 13(6): 614-629.
5) Molinuevo JL, Blennow K, Dubois B, et al. e clinical use of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper

from the Alzheimer's Biomarkers Standardization Initiative. Alzheimers Dement. 2014; 10(6): 808-817.
6) Ewers M, Mattsson N, Minthon L, et al. CSF biomarkers for the differential diagnosis of Alzheimer's disease. A large-scale international multicenter study. Alzheimers Dement. 2015; 11(11): 1306-1315.

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.

References

1) Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. Alzheimers Dement. 2013; 9(1): e1-e16.
2) Johnson KA, Minoshima S, Bohnen NI, et al. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Alzheimers Dement. 2013; 9(4): e106-e109.
3) Guerra UP, Nobili FM, Padovani A, et al. Recommendations from the Italian Interdisciplinary Working Group (AIMN, AIP, SINDEM) for the utilization of amyloid imaging in clinical practice. Neurol Sci. 2015; 36(6): 1075-1081.
4) Ministry of Health, Labour and Welfare Study Group "Multicenter clinical study on the clinical use of amyloid imaging as a method of risk prediction of Alzheimer's disease onset". Guidelines for Proper Use of Amyloid PET Imaging Agent Synthesis Device, first edition, 2015. (in Japanese)

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.

■ References

1) Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006; (1): CD005593.
2) Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008; 148(5): 379-397.
3) Hansen RA, Gartlehner G, Webb AP, et al. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging. 2008; 3(2): 211-225.
4) Tan CC, Yu JT, Wang HF, et al. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014; 41(2): 615-631.
5) Birks JS, Chong LY, Grimley Evans J. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev. 2015; 9: CD001191. [Epub ahead of print]
6) Nakamura Y, Imai Y, Shigeta M, et al. A 24-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of the rivastigmine patch in Japanese patients with Alzheimer's disease. Dement Geriatr Cogn Dis Extra. 2011; 1(1): 163-179.
7) Wang L, Harms MP, Staggs JM, et al. Donepezil treatment and changes in hippocampal structure in very mild Alzheimer disease. Arch Neurol. 2010; 67(1): 99-106.
8) Dubois B, Chupin M, Hampel H, et al. Hippocampus Study Group. Donepezil decreases annual rate of hippocampal atrophy in suspected prodromal Alzheimer's disease. Alzheimers Dement. 2015; 11(9): 1041-1049.
9) Reisberg B, Doody R, Stoer A, et al; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003; 348(14): 1333-1341.
10) McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev. 2006; (2): CD003154.
11) Doody RS, Tariot PN, Pfeiffer E, et al. Meta-analysis of six-month memantine trials in Alzheimer's disease. Alzheimers Dement. 2007; 3(1): 7-17.
12) Wilkinson D, Wirth Y, Goebel C. Memantine in patients with moderate to severe Alzheimer's disease: meta-analyses using realistic definitions of response. Dement Geriatr Cogn Disord. 2014; 37(1-2): 71-85.
13) Jiang J, Jiang H. Efficacy and adverse effects of memantine treatment for Alzheimer's disease from randomized controlled trials. Neurol Sci. 2015; 36(9): 1633-1641.
14) Nakamura Y, Kitamura S, Homma A, et al. Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer's disease: results of a pooled analysis of two randomized, double-blind, placebo-controlled trials in Japan. Expert Opin Pharmacother. 2014; 15(7): 913-925.
15) Schneider LS, Dagerman KS, Higgins JP, et al. Lack of evidence for the efficacy of memantine in mild Alzheimer disease. Arch Neurol. 2011 Aug; 68(8): 991-998.
16) Winblad B, Kilander L, Eriksson S, et al; Severe Alzheimer's Disease Study Group. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet. 2006 Apr 1; 367(9516): 10571065. Erratum in: Lancet. 2006; 368(9548): 1650. Lancet. 2006; 367(9527): 1980.
17) Black SE, Doody R, Li H, et al. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology. 2007; 69(5): 459-469.
18) Homma A, Imai Y, Tago H, et al. Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52-week, open-label, multicenter, extension study in Japan. Dement Geriatr Cogn Disord. 2009; 27(3): 232-239.
19) Homma A, Atarashi H, Kubota N, et al. Efficacy and Safety of Sustained Release Donepezil High Dose versus Immediate Release Donepezil

Standard Dose in Japanese Patients with Severe Alzheimer's Disease: A Randomized, Double-Blind Trial. J Alzheimers Dis. 2016; 52(1): 345-357.
20) Burns A, Bernabei R, Bullock R, et al. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease(the SERAD study): a randomised, placebo-controlled, double-blind trial. Lancet Neurol. 2009; 8(1): 39-47.
21) Di Santo SG, Prinelli F, Adorni F, et al. A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of Alzheimer's disease. J Alzheimers Dis. 2013; 35(2): 349-361.
22) Tariot PN, Farlow MR, Grossberg GT, et al; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004; 291(3): 317-324.
23) Cummings JL, Schneider E, Tariot PN, et al; Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. Neurology. 2006; 67(1): 57-63.
24) Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med. 2012; 366(10): 893-903.
25) Howard R, McShane R, Lindesay J, et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD)trial: secondary and post-hoc analyses. Lancet Neurol. 2015; 14(12): 1171-1181.
26) Grossberg GT, Manes F, Allegri RF, et al. The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. CNS Drugs. 2013; 27(6): 469-478.
27) Farrimond LE, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. BMJ Open. 2012; 2(3). pii: e000917.
28) Matsunaga S, Kishi T, Iwata M. Combination therapy with cholinesterase inhibitors and memantine for Alzheimer's disease: A systematic review and meta-analysis. Int J Neuropsychopharmacol. 2015; 1-11.
29) Porsteinsson AP, Grossberg GT, Mintzer J, et al; Memantine MEM-MD-12 Study Group. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res. 2008; 5(1): 83-89.
30) Rountree SD, Atri A, Lopez OL, et al. Effectiveness of antidementia drugs in delaying Alzheimer's disease progression. Alzheimers Dement. 2013; 9(3): 338-345.
31) Zhu CW, Livote EE, Scarmeas N, et al. Long-term associations between cholinesterase inhibitors and memantine use and health outcomes among patients with Alzheimer's disease. Alzheimers Dement. 2013; 9(6): 733-740.

■ 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].

References

1) Woods B, Aguirre E, Spector AE, et al. Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane Database Syst Rev. 2012; 2: CD005562.
2) Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev. 2013; (6): CD003260.
3) Alves J, Magalhaes R, Thomas RE, et al. Is there evidence for cognitive intervention in Alzheimer disease? A systematic review of efficacy, feasibility, and cost-effectiveness. Alzheimer Dis Assoc Disord. 2013; 27(3): 195-203.
4) Woods B, Spector AE, Jones CA, et al. Reminiscence therapy for dementia. Cochrane Database Syst Rev. 2005; (2): CD001120.(Woods B, Spector A, Jones C, Orrell M, Davies S. Reminiscence therapy for dementia. Cochrane Dementia and Cognitive Improvement Group, Cochrane Database Syst. Rev. 2009; 1)
5) Huang HC, Chen YT, Chen PY, et al. Reminiscence therapy improves cognitive functions and reduces depressive symptoms in elderly people with dementia: A meta-analysis of randomized controlled trials. J Am Med Dir Assoc. 2015; 16(12): 1087-1094.
6) Pitkala K, Savikko N, Poysti M, et al. Efficacy of physical exercise intervention on mobility and physical functioning in older people with dementia: a systematic review. Exp Gerontol. 2013; 48(1): 85-93.
7) Forbes D, Forbes SC, Blake CM, et al. Exercise programs for people with dementia. Cochrane Database Syst. Rev. 2015; (4): CD006489.
8) Farina N, Rusted J, Tabet N. The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review. Int Psychogeriatr. 2014; 26(1): 9-18.
9) Vink AC, Bruinsma MS, Scholten RJPM. Music therapy for people with dementia. Cochrane Database Syst Rev. 2004; (3): CD003477.(Vink AC, Bruinsma MS, Scholten RJPM. Music therapy for people with dementia. Cochrane Database Syst. Rev. 2013; 9)
10) Ueda T, Suzukamo Y, Sato M, et al. Effects of music therapy on behavioral and psychological symptoms of dementia: a systematic review and meta-

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.

■ References

1) APA Work Group on Alzheimer's Disease and other Dementias, Rabins PV, Blacker D, et al. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. Am J Psychiatry. 2007; 164(12 Suppl): 5-56.
2) Livingston G, Johnston K, Katona C, et al. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatry. 2005; 162(11): 1996-2021.
3) 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.
4) Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. Am J Psychiatry. 2012; 169(9): 946-953.
5) 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.

(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].

■ References

1) Miyake Y. Social resources (Chapter 4: Treatment and Care). Tahira T (Ed.) Latest Medical Supplement, Alzheimer's Disease Dementia, 2nd revision. Osaka: Saishin Igakusha; 2014: 184-193. (In Japanese)
2) Awata S. Mechanism in the community to support persons with dementia. Bio Clin. 2014; 29(7): 635-639. (In Japanese)
3) Endo H. Integrated medical care, collaboration (Chapter 4: Treatment and Care). Tahira T (Ed.) Latest Medical Supplement, Alzheimer's Disease Dementia, 2nd revision. Osaka: Saishin Igakusha; 2014: 184-193. (In Japanese)

■ 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)

#1 ((Alzheimer's disease/TH OR Alzheimer's disease/TI) OR (Alzheimer/TI) AND (Dementia/TH OR Dementia/TI)) AND (Social response/TI OR Social support/TH OR Social support/TI OR Health care resource /TH OR Health care resource /TI OR Social resource/TI OR Health care service/TI OR Health service/TI OR Social welfare/TH OR Social welfare/TI OR Welfare system/TI)