II

Migraine

CQ II-1-1

How is migraine classified?

Recommendation

Migraine is classified in accordance to the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta). The ICHD-3beta adopts a hierarchical classification system. Although classification to the first digit level (headache type) or second digit level (subtype) is usually applied to general practice, classification to the third digit level (subform) is recommended for clinical settings such as specialist practice and headache center.

Grade A

Background and Objective

The classification of migraine has evolved with advances in the understanding of the disease concept and pathophysiology of migraine. The International Classification of Headache Disorders 2nd Edition and 3rd edition beta version are intended for use in research and clinical practice in the same manner as the first edition published in 1988, and is based on the most widely accepted disease concept and pathophysiology.

Comments and Evidence

International Classification of Headache Disorders 2nd Edition (ICHD-II) [1] and 3rd edition beta version (ICHD-3beta) [2]

The ICHD-3beta adopts the hierarchical classification system, allowing descriptions of headache disorders using higher hierarchies (subtype, subform) for more specialized levels of research and clinical care.

Use the hierarchy of headache classification which corresponds to the condition and objective of clinical care and research.

Most of the evidence-based treatments for headache were developed based from using the first edition of the International Headache Society classification (1988). Since the major principles concerning the classification and diagnosis of primary headaches have not changed, the evidence obtained from using the first edition remains valid for most of the diagnoses made using the second edition. When looking for patients who will responds to triptan, it is recommended to diagnose the patients according to the diagnostic criteria for migraine with aura and migraine without aura described in the classification.

The ICHD-3beta is one of the most important references that should be read by physicians and researchers with an interest in the diagnosis and treatment of headache patients.

First, all the headaches are classified into major groups. In each group, headaches are subdivided 1, 2 or 3 times into type, subtype, and subform, respectively.

1. "*Migraine*" is a group containing one type of headache (migraine). The subtypes of migraine, such as 1.2 "*Migraine with aura*", are a group of the next level (second digit level). Migraine with aura is further classified into subforms such as 1.2.1 "*Migraine with typical aura*". For general practitioners, in order to select acute phase treatment, diagnosis to the first digit level; in other words, migraine, is usually sufficient. When problem arises with differential diagnosis, then coding to the second or third level may be necessary. Neurologists or headache specialists would be able to correctly diagnose the subform of migraine using the third digit level. This system has proven to be useful at various levels of healthcare system. In the ICHD-3beta, migraine is classified hierarchically as shown in **Table 1**.

An important change from the first edition of the International Classification of Headache Disorder (1988) is the introduction of chronic headache and the accompanying adoption of the diagnostic criteria for medication overuse headache. A provision for chronic migraine is the absence of medication overuse. In the diagnosis of medication overuse headache, the criterion that headache improves after discontinuation of overused medication has to be fulfilled. In June 2006, the Headache Classification Committee of International Headache Society published new criteria that expands the concept of chronic headache as Appendix in Cephalalgia, the official journal of International Headache Society.[3]

First edition of the International Classification of Headache Disorder (IHS classification 1988)[4]

The first edition describes the classification and diagnostic criteria proposed by the International Headache Society in 1988. Since then, international standardization of headache diagnoses was initiated and accumulation of data on diagnosis

Table 1. Classification of migraine in the International Classification of Headache Disorders 3 rd Edition (ICHD-3beta)

1.	Migraine
1.1	Migraine without aura
1.2	Migraine with aura
1.2.1	Migraine with typical aura
1.2.1.1	Typical aura with headache
1.2.1.2	Typical aura without headache
1.2.2	Migraine with brainstem aura
1.2.3	Hemiplegic migraine
1.2.3.1	Familial hemiplegic migraine (FHM)
1.2.3.1.1	Familial hemiplegic migraine type 1
1.2.3.1.2	Familial hemiplegic migraine type 2
1.2.3.1.3	Familial hemiplegic migraine type 3
1.2.3.1.4	Familial hemiplegic migraine, otherloci
1.2.3.2	Sporadic hemiplegic migraine
1.2.4	Retinal migraine
1.3	Chronic migraine
1.4	Complications of migraine
1.4.1	Status migrainosus
1.4.2	Persistent aura without infarction
1.4.3	Migrainous infarction
1.4.4	Migraine aura-triggered seizure
1.5	Probable migraine
1.5.1	Probable migraine without aura
1.5.2	Probable migraine with aura
1.6	Episodic syndromes that may be associated with migraine
1.6.1	Recurrent gastrointestinal disturbance
1.6.1.1	Cyclical vomiting syndrome
1.6.1.2	Abdominal migraine
1.6.2	Benign paroxysmal vertigo
1.6.3	Benign paroxysmal torticollis

and treatment as well as comparative studies became possible. Most of the migraine classification in the first edition have been continued in ICHD-II. The main changes are the abolishment of "*Migraine with acute-onset aura*", and moving "*Ophthalmoplegic migraine*" from the subtype of migraine to the subtype of "*Cranial neuralgias and central causes of facial pain*".

1.7 "*Migrainous disorder* ***not*** *fulfilling above criteria*" was abandoned, and "*Probable migraine*" has been added.

The Ad Hoc Committee classification in 1962[5] classified migraine from the viewpoint that migraine is a vascular headache, and the classification was wide used until the IHS classification was proposed in 1988. Although it is of historic value now, "*classic migraine*" and "*common migraine*" correspond nowadays to *migraine with aura* and *migraine without aura*, respectively. Although *cluster headache* was considered to be one type of migraine, it is now classified into an independent headache group. In addition, *migraine* and *muscle contraction headache* (corresponds to *tension-type headache* in ICHD-II) are grouped together under *Combined headache* and coded independently in ICHD-II.

As seen in Table 1, the classification of migraine has been further developed in the ICHD-3beta.

• References

1) Headache Classification Subcommittee of the International Headache Society: The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004; 24(suppl 1): 9-160.
2) The Headache Classification Committee of International Headache Society: International Classification of Headache Disorders 3rd Edition beta version. Cephalalgia 2013; 33(9): 644-658.
3) Takeshima T, Nakama N, Igarashi H, Hirata Y, Sakani F; New International Headache Classification and Promotion Committee of Japanese Headache Society: On the addition of appendix diagnostic criteria for chronic migraine and medication overuse headache. Japanese Journal of Headache 2007; 34(2): 192-193. (In Japanese)
4) Headache Classification Committee of the International Headache Society: Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988; 8(Suppl 7): 1-96.
5) Ad hoc committee on classification of headache: Classification of headache. JAMA 1962; 179: 127-128.

CQ II-1-2

How is migraine diagnosed?

Recommendation

Migraine is diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta). The ICHD-3beta adopts a hierarchical classification system. In general practice, use of the diagnostic criteria up to the second digit level (subtype) is recommended. In specialist practice and headache centers, diagnosis according to the diagnostic criteria to the second digit level (subtype) or to the highest level of the third digit (subform) is recommended. **Grade A**

Background and Objective

Since the proposal of the diagnostic criteria by the International Headache Society in 1988, international standardization of the diagnosis for migraine was initiated and accumulation of data on diagnosis and treatment as well as comparative studies became possible. The International Classification of Headache Disorders 2nd Edition (ICHD-II) and 3rd Edition beta version (ICHD-3beta)[1)2)] follow the major classification of the first edition. The diagnosis of subtype and subform of migraine is structured on the basis that diagnosis is conducted based on semiology including the characteristics of headache and those of associated symptoms. The classification and diagnostic criteria of the ICHD-II and ICHD-3beta are voluminous. The documents are not intended to be learnt by heart, but to be consulted any time as necessary.

Comments and Evidence

The major subtypes of migraine are 1.1 "*Migraine without aura*" and 1.2 "*Migraine with aura*". The major subform is 1.2.1 "*Migraine with typical aura*".

The diagnostic criteria are shown below:

1.1 *Migraine without aura*

• Comments

This type of migraine is a recurrent headache disorder with attacks lasting 4-72 hours. Characteristics of the headache are unilateral, pulsating headache, moderate to severe in intensity, and aggravated by routine physical activity; with nausea, photophobia and phonophobia as associated symptoms.

• Diagnostic criteria

A. At least five attacks fulfilling criteria B–D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

1.2 *Migraine with aura*

• Comments

This type of migraine is a disorder with recurrent attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last for less than 60 minutes. Headache with the characteristics of *migraine without aura* usually follows the aura symptoms. In rare cases, headache may lack migrainous characteristics, or headache may be completely absent.

• Diagnostic criteria

A. At least 2 attacks fulfilling criterion B

B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1-1.2.6

C. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

1.2.1 *Typical aura with migraine headache*

• Comments

Typical aura consists of visual, sensory, and speech symptoms that develop gradually, with duration no longer than one hour. Aura is characterized by a mixture of positive and negative features, is complete reversible, and is associated with a headache fulfilling the criteria for 1.1 "*Migraine without aura*".

• Diagnostic criteria

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least two of the following four characteristics:

1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
2. each individual aura symptom lasts 5-60 minutes[Note 1]
3. at least one aura symptom is unilateral[Note 2]
4. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

Notes:

1. When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 × 60 minutes. Motor symptoms may last up to 72 hours.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

In June 2006, the Headache Classification Committee of International Headache Society reported new criteria that expand the concept of chronic headache as Appendix in Cephalalgia, the official journal of International Headache Society.

The main point of the appendix criteria for chronic migraine is that headache attack that responds to triptan or ergotamine may show no headache characteristic of migraine. However, fulfilling the diagnostic criteria for migraine without aura at least in the past is mandatory. This is based on the evidence from research results that while pure tension-type headache does not respond to triptan, the headache of migraine patients always responds to triptan even though they fulfill the diagnostic diagnosis of tension-type headache.[3)]

This appendix criteria have been developed into ICHD-3beta criteria,[2)] which are shown below.

1.3 *Chronic migraine*[Notes 1,2]

• Diagnostic criteria

A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months[Note 2] and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*

C. On ≥8 days per month for >3 months, fulfilling any of the following[Note 3]:

1. criteria C and D for 1.1 Migraine without aura
2. criteria B and C for 1.2 Migraine with aura
3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. The diagnosis of 1.3 *Chronic migraine* excludes the diagnosis of 2. *Tension-type headache* or its subtypes because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*.
2. The reason for singling out chronic from episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. It is extremely difficult to keep such patients medication-free in order to observe the natural history of the headache. In this situation, attacks with or without aura are both counted, as well as tension-type-like headaches. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 *Medication-overuse headache*. Around 50% of patients apparently with 1.3 *Chronic migraine* revert to an episodic migraine subtype after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 *Chronic migraine*. Equally, many patients apparently overusing medication do not improve after drug withdrawal, and the diagnosis of 8.2 *Medication-overuse headache* may in a sense be inappropriate (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be given both diagnoses. After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse headache* may be rescinded. In some countries, it is usual practice to diagnose 8.2 *Medication-overuse headache* only on discharge.
3. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month. Sample diaries are available at http://www.i-h-s.org.

• References

1) Headache Classification Subcommittee of the International Headache Society: The International Classification of Headache Disorders; 2nd edition. Cephalalgia 2004; 24(suppl 1): 9-160.
2) The Headache Classification Committee of International Headache Society: International Classification of Headache Disorders 3rd Edition beta version. Cephalalgia 2013; 33 (9): 644-658.
3) Takeshima T, Nakama N, Igarashi H, Hirata Y, Sakani F; International Headache Classification Promotion Committee of Japanese Headache Society: On the addition of appendix diagnostic criteria for chronic migraine and medication overuse headache. Japanese Journal of Headache 2007; 34(2): 192-193. (In Japanese)

CQ II-1-3

What is the prevalence of migraine in Japan?

Recommendation

In Japan, the annual prevalence of migraine is 8.4%; comprising migraine with aura 2.6% and migraine without aura 5.8%. The prevalence of migraine is high in women aged 20-40 years. In juveniles, the prevalence is 9.8% among senior high students and 4.8% among junior high students. **Grade A**

Background and Objective

In the past, migraine was thought to be not highly prevalent in Japan. Accompanying the popularization of the international headache classification, epidemiology studies using standardized diagnostic criteria have been conducted in various countries worldwide. In Japan also, epidemiology surveys of the general population have been undertaken.

Comments and Evidence

Sakai and Igarashi[1] conducted a nationwide survey on a sample population aged 15 years or older in Japan and reported an overall prevalence of migraine in the past year of 8.4% (migraine without aura 5.8%, and migraine with aura 2.6%). When stratified by gender and age, the prevalence of migraine was highest among women in their thirties, reaching approximately 20%, while the prevalence in women in their forties was also high at approximately 18%.

In a survey conducted in Daisen, Tottori Prefecture, targeting residents aged 20 years or older, 6.0% of the residents had migraine (migraine with aura 0.9%, migraine without aura 5.2%). The prevalence reported in various countries differs: 3.0% in China, 9.0% in Malaysia, 9.1% in Taiwan, 12.1% in France, 13.0% in the United State, 13.2% in Sweden, 27.5% in Germany, and 29.1% in Thailand. Although the differences are likely due to the differences in survey method, diagnostic sensitivity, lifestyle, and regional characteristics, the estimated prevalence is 5-10% in Asia including Japan and 10-15% in European and American countries. All these figures portray a very high prevalence, indicating that migraine is a disorder requiring control measures. When analyzed by age, the prevalence of migraine is high in young to middle-aged women; with prevalence reaching 17.6% and 18.4% in women in the thirties and forties, respectively.[2]

In a survey of Japanese senior high school students conducted by Suzuki et al.,[3] the prevalence of migraine (including migraine with aura and without aura) was 9.8%, which is almost the same level as reported in other countries.

In a survey of Japanese junior high school students conducted by Ando et al.,[4] the prevalence of migraine was 4.8%; 29.1% of those students had migraine with aura. In addition, approximately one-half of the migraine patients had migraine attacks with short duration, ranging from 1 to 3 hours.

In Japan, a small proportion of migraine patients consult medical facilities, even though migraine causes disability in everyday life.[1)-4)]

• References

1) Sakai F, Igarashi H: Prevalence of migraine in Japan: a nationwide survey. Cephalalgia 1997; 17(1): 15-22.
2) Takeshima T, Ishizaki K, Fukuhara Y, Ijiri T, Kusumi M, Wakutani Y, Mori M, Kawashima M, Kowa H, Adachi Y, Urakami K, Nakashima K: Population-based door-to-door survey of migraine in Japan: the Daisen study. Headache 2004; 44(1): 8-19.
3) Suzuki S, Hirata K, Tatsumoto M, Hoshiyama E, Kobayashi H: The prevalence and character of primary headache in Japanese high school students. Rinsho Shinkeigaku 2005; 45(10): 717-723.
4) Ando N, Fujimoto S, Ishikawa T, Teramoto J, Kobayashi S, Hattori A, Togari H: Prevalence and features of migraine in Japanese junior high school students aged 12-15 yr. Brain Dev 2007; 29(8): 482-485.

• Search terms and secondary sources

- Search database: PubMed (2011/11/4)
  migraine and (prevalence or epidemiology) and (Japan or Japanese) 60

CQ II-1-4-1

What hypotheses have been proposed for the pathophysiology of migraine?

Recommendation

The definite pathophysiological mechanisms of migraine have not been established. In the past, the vascular theory, neuronal theory, and trigeminovascular theory were proposed as the pathological hypotheses of migraine. Currently, the trigeminovascular system, the descending pain modulatory network in the brainstem, and various peptides are considered to play important roles in migraine. Especially, serotonin and its receptor (5-HT1B/1D receptor) as well as calcitonin gene-related peptide (CGRP) released from the trigeminal nerve endings may be closely associated with the pain in migraine attacks. On the other hand, aura of migraine is considered to be a phenomenon due to cortical spreading depression (CSD). **Grade A**

Background and Objective

Various hypothesis for the pathophysiology of migraine have been proposed. Literature was searched with the aim to verify the pathophysiological hypothesis of migraine based on scientific evidence.

Comments and Evidence

The pathophysiology of migraine has not been definitively established, although the vascular theory, the neuronal theory and the trigeminovascular theory were proposed in the past. Currently, visual aura is no longer considered a phenomenon due to cerebral vasoconstriction, and headache attack is not regarded as a phenomenon caused by cerebral vasodilation. The aura of migraine is now believed to be a phenomenon due to cortical spreading depression (CSD). As for the origin of headache, the theory of peripheral origin from cerebral blood vessels and trigeminal nerve endings, and the theory of central origin from the brainstem have been proposed, but a conclusion is yet to be arrived. In addition, the involvement of both central sensitization and peripheral sensitization in pain has been proven. Many reports have shown that nitric oxide (NO), histamine, serotonin, glutamic acid, dopamine, orexin, and various neuropeptides including calcitonin gene-related peptide (CGRP) are involved in the pathology of migraine attacks. In these reports, however, human data are mixed with results of animal studies. As a result, the evidence-based pathophysiological mechanisms that can explain all the neural symptoms observed during migraine attacks and the accompanying physiological changes have not been elucidated. Many phenomena observed in humans cannot be verified by animal experiments. In the future, it is necessary to further accumulate findings in humans to better elucidate the pathophysiological mechanisms based on scientific evidence. Therefore, several representative references with a review nature are given here.[1)-6)]

• References

1) Edvinsson L: Pathophysiology of primary headaches. Curr Pain Headache Rep 2001; 5(1): 71-78.
2) Welch KM: Contemporary concepts of migraine pathogenesis. Neurology 2003; 61(8 Suppl 4): S2-8.
3) Olesen J, Burstein R, Ashina M, Tfelt-Hansen P: Origin of pain in migraine: evidence for peripheral sensitisation. Lancet Neurol 2009; 8(7): 679-690.
4) Ho TW, Edvinsson L, Goadsby PJ: CGRP and its receptors provide new insights into migraine pathophysiology. Nat Rev Neurol 2010; 6(10): 573-582.
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6) Gupta S, Nahas SJ, Peterlin BL: Chemical mediators of migraine: preclinical and clinical observations. Headache 2011; 51(6): 1029-1045.

• Search terms and secondary sources

- Search database: PubMed (2011/11/8)
  Migraine
  & pathogenesis or pathophysiology or mechanism or hypothesis 14683

CQ II-1-4-2

What are the types of auras in migraine?

Recommendation

Apart from the typical aura observed in migraine with aura, migraine aura also includes the aura observed in hemiplegic migraine and migraine with brainstem aura.

Typical aura observed in migraine consists of visual symptoms, sensory symptoms, and speech symptoms. Aura in hemiplegic migraine includes motor weakness in addition to the typical aura. Aura in migraine with brainstem aura includes dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, and decreased level of consciousness.

Grade A

Background and Objective

This section explains the types of aura in migraine by describing the typical aura observed in migraine with aura, aura in hemiplegic migraine, and aura in migraine with brainstem aura.

Comments and Evidence

1. Typical aura

This type of aura is totally reversible focal neurological symptoms occurring immediately before or at the same time as pain starts in a migraine attack, which usually develops gradually over 5-20 minutes and lasts for less than 60 minutes. The first edition of International Headache Classification (1988) lists typical aura as visual symptoms, sensory symptoms, weakness, and speech symptoms. In the International Classification of Headache Disorders 2nd Edition (ICHD-II), typical aura consists of visual symptoms, sensory symptoms, and speech symptoms.[1)2)]

Visual aura is fully reversible symptoms including positive features (for example, flickering lights, spots or lines) and/or negative features (loss of vision). This is the most common type of aura, and often presents as fortification spectrum. In other words, a zigzag figure near the fixation point gradually spreads in a right or left direction and assumes a laterally convex shape with an angulated scintillating edge, resulting in absolute or relative scotoma. Next in frequency are sensory disturbances, which is fully reversible sensory symptoms including positive features (pins and needles spreading slowly from the point of origin and affecting the body and face to various extents) and/or negative features (numbness). Numbness may occur in its wake, but numbness may also be the only symptom. Less frequent are speech disturbances, usually fully reversible dysphasic but often hard to categorize.

2. Aura of hemiplegic migraine

Aura of hemiplegic migraine consists of fully reversible motor weakness and at least one symptom of the typical aura. The duration of each aura is 5 minutes or longer and less than 24 hours.

3. Aura of migraine with brainstem aura

Migraine with brainstem aura is described as migraine with aura symptoms clearly originating from the brainstem, but no motor weakness. According to the ICHD 3rd edition (beta version),[3)] the diagnostic criteria include: aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible; and at least two of the following brainstem symptoms: dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, and decreased level of consciousness but no motor or retinal symptoms.

Aura has at least two of the following four characteristics: 1. at least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession; 2. each individual aura symptom lasts 5-60 minutes; 3. at least one aura symptom is unilateral; 4. the aura is accompanied, or followed within 60 minutes, by headache.

• References

1) Headache Classification Subcommittee of the International Headache Society: The International Classification of Headache Disorders; 2nd edition. Cephalalgia 2004; 24(suppl 1): 9-160.

2) Headache Classification Committee of International Headache Society: International Classification of Headache Disorders 2nd Edition (ICHD-II). Japanese Journal of Headache 2004; 31(1): 13-188. (In Japanese)
3) Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013; 33(9): 629-808.

• Search terms and secondary sources

- Search database: PubMed (2011/12/21)
  Migraine 24757
  & aura 3464
  & diagnosis 1886

CQ II-1-4-3

What is the proposed mechanism for aura in migraine?

Recommendation

At present, aura in migraine is considered to be caused by cortical spreading depression (CSD) or spreading oligemia. **Grade B**

Background and Objective

Several hypotheses for the physiopathology of migraine have been proposed. For aura, research so far suggests that aura manifests because of the occurrence of cortical spreading depression (CSD) in the cerebrum. Aura of migraine is explained by referring to some review articles.

Comments and Evidence

In the past, the typical aura of migraine was thought to be caused by local contraction of cerebral blood vessels.[1] Cortical spreading depression (CSD) was first observed in an animal study,[2] and this phenomenon was suggested to resemble the process of spreading of fortification spectrum. Subsequent study reported the phenomenon of spreading oligemia. During migraine attack, regional cerebral blood flow in the occipital lobe is lowered (oligemia), and the reduced blood flow spreads anteriorly in the cerebrum at a speed of 2–3 mm/minute.[3] Since spreading oligemia and CSD both propagate at almost the same speed, and are both almost independent of the vascular territory, it is currently hypothesized that spreading oligemia is caused by abnormal neural activities such as CSD. Currently, the neural theory that typical aura occurs due to abnormality activities of cerebral cortical neurons is being advocated.

With recent advances in functional neuroimaging, the involvement of CSD in visual aura has been demonstrated in humans using functional MRI, and the hypotheses proposed are gradually being tested and verified.[4]

The mechanisms for aura in migraine with brainstem aura and aura in hemiplegic migraine have not been elucidated at present.

• References

1) Graham JR, Wolff HG: Mechanism of migraine headache and action of ergotamine tartrate. Arch Neurol Psychiatry 1938; 39(4): 737-763.
2) Leo AAP: Spreading depression of activity in the cerebral cortex. J Neurophysiol 1944; 78: 359-390.
3) Olesen J, Larsen B, Lauritzen M: Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 1981; 9(4): 344-352.
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• Search terms and secondary sources

- Search database: PubMed (2011/9/1)
  Migraine 24757
  & aura 3464
  & pathophysiology 1427 or mechanism 213

CQ II-1-4-4

What is the proposed mechanism for pain in migraine?

Recommendation

No definitive mechanism has been established for the pathophysiology of pain in migraine. Two main hypotheses regarding the genesis of pain have been proposed: the peripheral origin theory of pain generated from cerebral blood vessels and trigeminal nerve endings, and the central origin theory of pain generated from the brainstem. Currently, the trigeminovascular system, the descending pain modulatory system in the brainstem, and various peptides are considered to play important roles in migraine pain. Especially, there is high probability that serotonin and its receptor (5-HT1B/1D receptor) and calcitonin gene-related peptide (CGRP) released from the trigeminal nerve endings are closely associated with pain in migraine attack. **Grade A**

Background and Objective

Regarding the genesis of pain in migraine, the central origin theory and the peripheral origin theory have been proposed from the past. Literature was searched to clarify the origin of pain and its physiopathology based on scientific evidence.

Comments and Evidence

The definitive mechanisms of the pathophysiology of pain in migraine remain to be established. For the genesis of pain also, two hypotheses have been proposed; the central origin theory of pain generated in the superior brainstem and the peripheral theory of pain generated from cerebral blood vessels and trigeminal nerve endings, but no conclusion has been arrived. Nevertheless, currently headache attack as a phenomenon caused by cerebral vasodilation is no longer considered valid. Recent research has shown that sensitization, which is the perception of pain caused by innocuous stimuli, occurs both peripherally and centrally. There is no dispute that skin allodynia caused by central sensitization of central nociceptive neurons and peripheral sensitization caused by trigeminovascular activation (neurogenic inflammation) are both prominently involved in migraine pain. Moreover, nitric oxide (NO), histamine, serotonin, glutamic acid, dopamine, and various chemical mediators including calcitonin gene-related peptide (CGRP) are involved in the pathology of migraine. In addition, the existence of the nociceptive receptor TRPV1 (transient receptor potential cation channel, subfamily V, member 1) has been demonstrated, and considered to be related to the pathology of migraine.

However, since previous reports contain a mixture of human and animal study data, they do not provide evidence-based pathophysiological mechanisms that can explain all the neural symptoms observed during migraine attacks as well as the accompanying physiological changes. Further elucidation of the pathophysiological mechanism based on scientific evidence is necessary. Therefore, several representative references with a review nature are given here.[1)-8)]

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1) Sanchez del Rio M, Reuter U, Moskowitz MA: Central and peripheral mechanisms of migraine. Funct Neurol 2000; 15 (Suppl 3): 157-162.
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• Search terms and secondary sources

- Search database: PubMed (2011/11/8)
  Migraine
  & pathogenesis or pathophysiology or mechanism or hypothesis 14683

CQ II-1-4-5

How is migraine related to serotonin abnormality?

Recommendation

The involvement of platelet serotonin (5-hydroxytriptamine: 5-HT) abnormality in the pathology of migraine was hypothesized. However, subsequent examinations of plasma or serum serotonin levels yielded no consensus, and there are few reports on serotonin and its metabolism. On the other hand, serotonin receptors; 5-HT1B receptor and 5-HT1D receptor, are widely distributed in the trigeminovascular system consisting of intracranial large caliber blood vessels, trigeminal peripheral nerve endings, trigeminal ganglion, and subnucleus caudalis of the spinal trigeminal nucleus. Since the advent of triptan (5-HT1B/1D receptor agonist), the relationship between migraine and serotonin receptor has been highlighted. Grade A

Background and Objective

Serotonin abnormality in migraine was debated mainly in the 1960s. The majority of serotonin is present in the platelets. A few reports described the release of large amounts of serotonin from platelets, and others described the induction of migraine attack by intravenous injection of serotonin. However, subsequent studies did not lead to a unified opinion, and there are few reports of serotonin studies in humans. Literature was searched to clarify the role of abnormalities in serotonin, including serotonin receptors, in the pathology of migraine.

Comments and Evidence

The relationship between serotonin and migraine was advocated from the 1960s. A low serotonin state in the central nervous system during the period in between attacks and the release and increase of serotonin during attack suggest an association between serotonin and migraine pathology. However, a consistent mechanism of serotonin kinetics (in blood or in platelet) during interictal and ictal periods has not yet been established. On the other hand, the serotonin receptor 5-HT1B/1D is widely distributed in the trigeminovascular system. Since triptan (5-HT1B/1D receptor agonist) is effective for the relief of migraine attack, there is no doubt that 5-HT1B/1D receptor plays an important role in migraine attack. Recent studies in humans have demonstrated increased 5-HT synthesis and augmented activity of 5-HT1A receptor in the raphe nucleus during migraine attacks. Here, only important references are provided.[1)-11)]

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• Search terms and secondary sources

- Search database: PubMed (2011/11/8)
  Migraine
  & {serotonin} 2928

CQ II-1-4-6

How does cerebral blood flow change during migraine attack?

Recommendation

Change in cerebral blood flow during migraine attack is discussed focusing on cortical spreading depression (CSD). In an attack of migraine with visual aura, reduced cerebral blood flow in the occipital lobe is observed. In an attack of migraine without aura, the opinion is divided. In addition, regional cerebral blood flow has been shown to increase during headache attack. **Grade B**

Background and Objective

The change in cerebral blood flow during migraine attack was originally discussed focusing on cortical spreading depression (CSD). To prove the hypothesis, regional cerebral blood flow has been measured using Xe/CT, SPECT, PET, transcranial Doppler (TCD), or functional MRI. Literature was searched to clarify the scientific evidence for regional cerebral blood flow during migraine attacks.[1)-10)]

Comments and Evidence

The articles searched and cited are all reports of human studies, in which cerebral blood flow was measured using noninvasive imaging methods such as Xe/CT, SPECT, PET, TCD, and functional MRI. However, due to the small number of cases in each study and the resolution limitation of imaging techniques, the timing of imaging during attack remains an issue. While the results of previous clinical studies concur on a reduction of cerebral blood flow in the occipital lobe in migraine with aura, the opinions regarding migraine without aura are divided. Moreover, increase in cerebral blood flow has also been shown during headache attack. In migraine with aura, because headache attack starts from the time when cerebral blood flow is lowered, vasodilation in the brain alone is not considered the cause of headache. Furthermore, in hemiplegic migraine, which is a special type of migraine associated with hemiplegia, consistent results have not been obtained for regional cerebral blood flow in the affected hemisphere.

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• Search terms and secondary sources

- Search database: PubMed (2011/10/30)
  Migraine
  & {cerebral blood flow} 999

CQ II-1-5

What are the precipitating/aggravating factors of migraine?

Recommendation

The precipitating factors of migraine (from epidemiological studies) include the following:

- Psychological factors: stress, mental strain, fatigue, sleep (too much or too little)
- Endogenous factors: menstrual cycle
- Environmental factors: weather change, temperature change, frequent travels, odor
- Dietary factors: hunger, alcohol (for other food groups, since response differs individually, there is no need to restrict intake)

Grade B

Background and Objective

Many migraine patients are aware that attack occurs easily under specific conditions. Since migraine may be prevented by avoiding the precipitating/aggravating factors in daily life, it is important that individual patients know the factors that precipitate/aggravate their own migraine. Literature was searched to identify the precipitating/aggravating factors of migraine.

Comments and Evidence

Approximately 75% of migraine patients have some kind of precipitating factors.[1] The common migraine precipitating/aggravating factors identified in various epidemiological studies include stress, mental strain, fatigue, sleep, menstrual cycle, weather change, temperature change, frequent travels, odor, hunger, and alcohol.[1)-8)] Apart from alcohol, the other factors are also precipitating factors of tension-type headache.

Stress is one of the most prominent precipitating factors.[1] Stress triggers migraine in approximately 60% of the patients, and 25% of these patients feel that headache occurs when they are relieved from stress.[2] While lack of sleep is perceived as the trigger in approximately 30% of the migraine patients, too much sleep is implicated in 25%.[2] Weather is cited as the precipitating factor in 53% of the migraine patients, and 11% of the patients felt that weather is the precipitant in two-thirds of the headache attacks.[1]

Among alcoholic beverages, red wine is a famous precipitating/aggravating factor. Histamine that is related to pain, and alcohol and polyphenol that possess vasodilating effect are probably involved in the precipitating/aggravating effect. In a study on a group of migraine patients who believed that red wine provoked migraine and a group who did not, migraine was triggered by red wine only in the group that believed that red wine provoked migraine.[9] This finding suggests that the precipitating factors may differ depending on individual patients with migraine. Even from the old days, foods containing amines represented by tyramine, such as cheese, chocolate, citrus fruits, and nuts are well known to precipitate migraine.[9] In a survey conducted in England, 16 to 18% of respondents cited chocolate or cheese as precipitating factor.[10)11)] A double-blind placebo controlled study in 20 patients who believed that chocolate provoked migraine found that chocolate ingestion triggered migraine attacks in many patients.[12] On the other hand, a double-blind study using chocolate and placebo in patients with chronic headache (including migraine and tension-type headache) found no difference in the rate of migraine provocation between chocolate and control even in patients who believed that chocolate was a precipitating factor.[13] Despite the fact that dietary factors are widely known, few patients have actually experienced the precipitating/aggravating factrs.[14] While a large number of foods have been implicated as precipitating/aggravating factors, they do not apply to all the patients. Even in the same patient, a given food does not always provoke headache. Few patients mention specific foods apart from alcohol. Therefore unnecessary dietary restriction may have the opposite effect of lowering patients' QOL. The American Headache Society publishes views on triggers of migraine on its website.[15]

According to a survey conducted by Takeshima et al.,[3] persons with migraine consume more fatty/oily foods, coffee, and tea than persons without headache. From these data, regular consumption of a well balanced diet is recommended. Although there is no correlation between obesity and the prevalence of migraine, study has shown that obesity is associated with chronic progression of migraine.[16]

Despite recent advances in the treatment of migraine, many patients still do not achieve symptomatic relief. However,

even in such patients, lifestyle improvement, for example through sleep and dietary guidance and stress management, may mitigate symptoms, and maintenance of appropriate weight may present chronification of migraine.

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• Search terms and secondary sources

- Search database: PubMed (2012/4/30)
  (migraine or headache) & “trigger factor” 28
  (migraine or headache) & “precipitating factor” 51
  (migraine or headache) & “risk factor” 583
  migraine & food 462
  migraine & diet 260
  migraine & glucose 122
  migraine & wine 39
  migraine & chocolate 44
  migraine & cheese32
- Search database: Ichushi Web for articles published in Japan (2012/4/30)
  (migraine) and (food) 40
- Secondary source, 1 reference added by manual search (No. 15)

CQ II-1-6-1

What is the prognosis of migraine (including chronification of migraine)?

Recommendation

Most migraine patients show a tendency of improvement with age. It is also known that approximately 3% of the patients per year show deterioration of symptoms, with increases in frequency of headache attacks and number of days with headache. The known risk factors for chronification of migraine include (1) congenital factors, (2) headache conditions, (3) comorbidities, and (4) external factors. Especially, (3) and (4) contain elements that are modifiable, and therapeutic interventions may lead to improved outcome. **Grade A**

Background and Objective

Literature was searched to identify the risk factors associated with the outcome and chronification of migraine, and to clarify the current assumptions of the biological mechanism for the chronification of migraine

Comments and Evidence

The outcome of migraine can be broadly classified into four patterns: A. no change; B. partial remission (symptomatic improvement); C. remission; D. progression. For D. progression, apart from increases in intensity and frequency of attacks, chronification defined as overlap of chronic headache and increase in number of days with headache are also classified in this category.[1)]

According to the evolution of headache prevalence with age published by the American Migraine Prevalence and Prevention Study (AMPP), the prevalence in men was 9% in the 30-39 year group, decreasing to 5.9% in the 50-59 year group, and further to 2.1% at 60 years.[2)] In women also, the prevalence reached 38.1% in the 30-39 age group, and decreased to 6.4% after 60 years of age. These figures suggest that many patients achieve remission with age, in both men and women. There are few longitudinal studies on the long-term outcome of migraine. Lyngberg et al.[3)] studied 64 migraine patients and reported that 42% showed complete or partial remission after 12 years, 38% showed no change, and 20% evolved to transformed migraine. A 30-year prospective cohort study conducted in Switzerland also shows that migraine tends to remit in the long term.[4)] However, regarding the change in disease state one year after onset, 83.29% show no change, 9.85% show partial remission, and 3.26% show complete remission.[1)] However, in 2.97% of the patients, the frequency of headache attacks increases and headache-related disability becomes more severe.[1)] In other words, although the overall percentage is low, migraine progresses in some patients who gradually complain of more chronic headache over time. Even on days without migraine attack, these patients experience headache symptoms similar to tension-type headache. As a result, the number of days without headache becomes even less. As explained in a different section, the headache symptoms of patients with episodic migraine become chronic, and are eventually diagnosed as chronic migraine when headache occurs on 15 days or more per month (see "CQII-1-8; What kind of disease is chronic migraine?"). The mechanisms leading to progression or chronification remain unclear. However, epidemiological studies identified several risk factors related to chronification of migraine (note: these epidemiological studies often target chronic daily headache). These risk factors are listed below.[5)-10)]

(1) Congenital factors

1. Family history

The risk of onset in a child increases when the mother has chronic daily headache.

2. Prenatal exposure

Mother's drinking and smoking during gestation are risk factors.

(2) Headache conditions

1. The number of days with headache at baseline

Migraine tends to become chronic when the number of days with headache at baseline is high.

(3) Comorbid conditions

1. Obesity

The prevalence of chronic daily headache (including chronic migraine) is increased three-fold in persons with BMI 25-29 and five-fold in those with BMI 30 or above, compared to normal-weight individuals.

2. Snoring and sleep apnea
3. Psychiatric disorder or stressful life

   Mood disturbances such as depression and anxiety have been related to chronic migraine. Stressful life events (such as moving and losing job) are triggers of alteration in migraine.
4. Temporomandibular disorder

(4) External factors

1. Analgesic overuse

   The focus here is not on the aggravation of medication-overuse headache, but on the relationship between analgesics and chronification of migraine. Although this may not be an issue in Japan, use of opioid and barbiturate is a risk for migraine chronification. Triptan and NSAIDs contribute to chronification when given to patients with headache on 10 days or more per month.
2. Caffeine consumption
3. Traumatic injury to the head

   The incidence of cutaneous allodynia (CA) in terms of semiology is known to increase accompanying chronification of migraine. CA is considered to be a phenomenon indicating the presence of central sensitization in second-order trigeminal neurons (subnucleus caudalis of the spinal trigeminal nucleus) or above. The periaqueductal gray (PAG) modulates pain transmission in the subnucleus caudalis of the spinal trigeminal nucleus. The possibility that PAG dysfunction changes the threshold of headache leading to chronification of headache is hypothesized. In this connection, iron deposition in the PAG has been demonstrated by high-resolution MRI in patients with episodic migraine and patients with chronic daily headache, and the degree of deposition is proportional to the disease stage.[11] Whether iron deposition in the PAG is a cause or the result of migraine chronification is not clear. However, several studies using voxel-based morphometry of MRI in patients with chronic migraine reported changes in volume of brain tissues in these patients, indicating a possibility of the presence of organic changes in the central nervous system structures.[12)-15)]

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• Search terms and secondary sources

- Search database: PubMed (2011/12/7)
  migraine & chronification 63

CQ II-1-6-2

To what extent does migraine impair the healthy life expectancy and QOL of patients?

Recommendation

The healthy life expectancy and QOL of patients with migraine are significantly compromised in terms of physical, mental and social functions, compared with healthy individuals without headache. When compared with other chronic diseases, migraine patients experience greater impairment in QOL in some domains. **Grade B**

Background and Objective

Migraine is a chronic disease, and is known to cause a wide variety of functional disabilities from the physical, mental and social aspects. According to a survey conducted by World Health Organization (WHO), migraine is ranked as the 19th disease (7th for women alone) that shortens healthy life expectancy.[1] Many attempts have been made to quantitatively evaluate the quality of life (QOL) of migraine patients by comprehensively assessing functional disability from various aspects. To evaluate the deleterious impact of migraine on QOL, tools that assess overall health-related quality of life (HRQoL) such as the Short Form Health Survey (SF)-20[2] and SF-36,[3] as well as tools specific for migraine such as the Migraine Disability Assessment (MIDAS),[4][5] Headache Impact Test-6 (HIT-6),[5] and Migraine-Specific Quality of Life Questionnaire (MSQ)[6] have been developed and used. This section examines the QOL impairment in migraine patients, focusing on reports of QOL studies in migraine patients using representative evaluation methods.

Comments and Evidence

Healthy life expectancy refers to the number of years that a person can expect to live healthily and independently both physically and mentally. The WHO publishes the years of life lived with disability (YLDs) for various diseases, and migraine is ranked as number 19. In the Global Burden of Disease (GBD) Study, diseases were classified by the severity of disease sequelae into seven disability classes; class I to class VII. Parkinson disease and deafness are classified as class IV, Alzheimer and other dementias as well as blindness as class VI, and severe migraine together with quadriplegia, terminal stage cancer and others as the most severe class VII.[7]

In a survey of migraine patients using SF-20 and SF-36, HRQoL score was significantly lower in migraine patients compared with healthy population without chronic disease.[3] In a large-scale telephone interview survey conducted in the United States and United Kingdom comparing persons who had migraine with a non-migraine control group[8], HRQoL scores both in the mental health and physical health components were significantly lower in subjects with migraine. A correlation was observed between the degree of disability in HRQoL and migraine attack frequency. The comorbid rate of migraine and depression was significantly high, and each independently impaired HRQoL.[8] Although migraine is an episodic disease, migraine patients have lower QOL and perceive greater emotional stress even between attacks compared with non-headache controls.[9] In an evaluation using the MIDAS questionnaire, the mean MIDAS total score was 23.4 (n = 234) in patients who had migraine without aura and 79.2 (n = 150) in patient who had chronic migraine, both groups showing lower HRQoL.[10] Compared to subjects with episodic migraine, those with chronic migraine reported significantly higher health care resource utilization rate, significantly lower HRQoL, and higher levels of anxiety and depression.[11] Iigaya et al.[12] developed the Japanese version of the MIDAS questionnaire and reported its reliability and validity.

When the eight SF-36 subscales were analyzed, patients with migraine had almost the same degree of HRQoL impairment as patients with other chronic primary headaches.[10] In some of the subscales, patients with migraine had more severely impaired QOL compared to patients with other chronic diseases such as hypertension and diabetes.[3] Since QOL depends to some extent on culture and lifestyle, scales suitable for measuring QOL in Japanese have been established and used for the evaluation of drug treatment.[13]

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• Search terms and secondary sources

- Search database: PubMed (2012/3/17)
  {Migraine} or {vascular headache} or {hemicrania} 69836
  & Quality of Life 1755
  & disability 1575
- Search database: Ichushi Web for articles published in Japan (2012/3/17)
- Secondary source, 2 references added by manual search (Nos. 1 and 7)

CQ II-1-7

What are the comorbid disorders associated with migraine?

Recommendation

The comorbid disorders of migraine include hypertension, heart diseases, cerebrovascular diseases, depression, bipolar disorder, anxiety disorder, epilepsy, asthma, allergic diseases, and autoimmune diseases. **Grade B**

Background and Objective

Comorbid disorders of migraine are an important concept when considering the etiology, pathophysiology and treatment of migraine. The relationship of comorbid disorders with migraine may be (1) incidental coexistence; (2) comorbid disorder causing migraine or migraine causing comorbid disorder; (3) common risk factors causing migraine and comorbid disorder; (4) given hereditary and environmental factors triggering specific cerebral conditions, and the conditions causing migraine and comorbid disorder.[1)]

Studies on migraine comorbidities, such as case series and epidemiological surveys, have been conducted from various viewpoints.

Comments and Evidence

Migraine is a disease with high prevalence, and often coexists incidentally with other diseases that also have high prevalence. Even if incidental, when planning treatments for migraine and the comorbid disorders, it is important to select drugs that do not exert adverse effects on both conditions.

Many case series have reported a high percentage of hypertension in migraine patients, but the results are not consistent. Large-scale epidemiological studies often found no correlation between migraine and hypertension. The prevalence of hypertension is high, hence the number of patients with both conditions is large, even though the association is incidental.[2)3)]

Although reports have suggested an association between migraine and heart diseases such as mitral valve prolapse, ischemic heart disease and arrhythmia, no large-scale studies have been conducted. Furthermore, there is a lack of evidence on the correlation after adjusting for risk factors of ischemic diseases, including smoking and hypertension. A high comorbid rate of patent foramen ovale (PFO) in patients who have migraine with aura has been reported, but concrete evidence on the effect of PFO closure on migraine has not been obtained.[4)-6)]

Many studies have investigated the association between migraine and cerebrovascular disorders, especially ischemic cerebrovascular disorder. This aspect is discussed in detail elsewhere in this guideline: "CQII-1-9 "Is migraine a risk factor of cerebral infarction?" (page 85).

Several studies have examined the relationship between migraine and psychiatric diseases such as major depression, bipolar disorder, and anxiety disorder, and the majority demonstrated no significant correlation.[2)7)] The relationship with epilepsy has been much debated in terms of etiology,[8)9)] but consistent data showing a correlation is lacking. The correlation between migraine and other diseases such as restless legs syndrome,[10)-12)] asthma,[3)13)] allergic diseases,[3)14)] autoimmune diseases,[3)] **Ménière** disease,[14)15)] endometriosis,[16)17)] biliary tract disorders,[18)] kidney stone,[3)] thyroid disease,[3)] fibromyalgia,[3)19)20)] and chronic fatigue syndrome [21)] has received attention, and further accumulation of data is necessary.

Comorbid disorders are important in understanding the pathology of migraine. On the other hand, understanding comorbid condition is also essential when conducting migraine treatment, especially prophylactic therapy.

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- Search database: PubMed (2012/1/3)
  migraine and (comorbid or comorbidity) 934

CQ II-1-8

What kind of disease is chronic migraine?

Recommendation

Chronic migraine is a condition that starts off as episodic migraine but migraine attacks increase in frequency during the course of disease resulting in headache occurring on many days of a month. The diagnosis should be made according to the diagnostic criteria of the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta). **Grade A**

Background and Objective

Literature was searched to clarify the diagnosis and epidemiological characteristics of chronic migraine.

Comments and Evidence

Chronic migraine[Notes 1,2] should be diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders 3rd Edition (ICHD-3beta), as described below.

Diagnostic criteria:

A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months[Note 2] and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*

C. On ≥8 days per month for >3 months, fulfilling any of the following[Note 3]:

1. criteria C and D for 1.1 Migraine without aura
2. criteria B and C for 1.2 Migraine with aura
3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. The diagnosis of 1.3 *Chronic migraine* excludes the diagnosis of 2. *Tension-type headache* or its subtypes because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*.
2. The reason for singling out chronic from episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. It is extremely difficult to keep such patients medication-free in order to observe the natural history of the headache. In this situation, attacks with or without aura are both counted, as well as tension-type-like headaches. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 *Medication-overuse headache*. Around 50% of patients apparently with 1.3 *Chronic migraine* revert to an episodic migraine subtype after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 *Chronic migraine*. Equally, many patients apparently overusing medication do not improve after drug withdrawal, and the diagnosis of 8.2 *Medication-overuse headache* may in a sense be inappropriate (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be given both diagnoses. After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse headache* may be rescinded. In some countries, it is usual practice to diagnose 8.2 *Medication-overuse headache* only on discharge.
3. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month. Sample diaries are available at http://www.i-h-s.org.
   The headache observed in patients with chronic migraine does not necessarily manifest typical properties of migraine, and is known to commonly show the properties of tension-type headache. Even in this type of headache, since headache is often improved by treatment with triptan, it is different from the usual tension-type headache and is interpreted as mild

migraine presenting as tension-type headache-like headache.[2)3)] In addition, patients with chronic migraine often use many acute headache medications, with some in a state of overuse.

The prevalence of chronic migraine differs depending on the diagnostic criteria used, and is estimated to range from 1.4 to 2.2%. Patients with chronic migraine has more severe disability, lower QOL, and higher comorbidity rate of psychiatric disorders such as depression, compared with patients with episodic migraine.[4)] The risk factors for chronification of migraine are described in another section: CQ II-1-6-1: What is the prognosis of migraine (including chronification of migraine)? (page 77).

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• Search terms and secondary sources

- Search database: PubMed (2011/12/7)
  chronic migraine 3108

CQ II-1-9

Is migraine a risk factor of cerebral infarction?

Recommendation

In women younger than 45 years of age, the presence of migraine with aura may slightly increase the risk of cerebral infarction. However, the annual incidence of ischemic stroke in this age group is very low. However, the risk is increased by smoking and oral contraceptive. Migraine without aura does not increase the risk. **Grade A**

Background and Objective

Many analytical epidemiological studies have examined the relationship between migraine and cerebrovascular diseases. In addition, cross-sectional studies using MRI have reported increased rates of cerebral deep white matter lesion and infratentorial lesions in patients with migraine compared with controls.[1)2)]

Comments and Evidence

According to a systematic review and meta-analysis of 11 case-control studies and 3 cohort studies reported by Etminan et al.[3)] in 2005, the relative risk of ischemic stroke was 2.16 (95% confidence interval: 1.89 to 2.48) in all people with migraine, 2.27 (1.61 to 3.19) in people who had migraine with aura, 1.83 (1.06 to 3.15) in people who had migraine without aura, 8.72 (5.05 to 15.05) in migraine patients using oral contraceptives, 2.36 (1.92 to 2.90) in migraine patients aged below 45 years (male and female), and 2.76 (2.17 to 3.52) in female migraine patients aged below 45 years. In another systematic review and meta-analysis of 13 case-control studies, 10 cohort studies and 2 cross-sectional studies reported by Schürks et al.[4)] in 2009, the relative risk of ischemic stroke was 1.73 (1.31 to 2.29) in all people with migraine, 2.16 (1.53 to 3.03) in people who had migraine with aura, 1.23 (0.90 to 1.69) in people who had migraine without aura, 2.08 (1.13 to 3.84) in female migraine patients (including with and without aura), 1.37 (0.89 to 2.11) in male migraine patients, 2.65 (1.41 to 4.97) in migraine patients aged below 45 years of age, 3.65 (2.21 to 6.04) in female migraine patients aged below 45 years of age, 9.03 (4.22 to 19.34) in smoking migraine patients, 7.02 (1.51 to 32.68) in female migraine patients using oral contraceptives. The relative risk of transient ischemic attack in migraine patients was 2.34 (1.90 to 2.88), and the relative risk of hemorrhagic stroke was 1.18 (0.87 to 1.60). A meta-analysis of 13 case control studies and 8 cohort studies reported by Spector et al.[5)] in 2010 showed that the odds ratio of ischemic stroke was 2.30 (1.91 to 2.76) in all people with migraine, 2.51 (1.52 to 4.14) in people who had migraine with aura, 1.29 (0.81 to 2.06) in people who had migraine without aura, and 2.89 (2.42 to 3.45) in female migraine patients.

The results of the above studies show that the risk of ischemic stroke in people who have migraine with aura is increased approximately two-fold, the risk is further increased in young women, smokers, and oral contraceptive users. However, the absolute annual incidence of ischemic stroke in women younger than 45 years is extremely low at 5 to 10 per 100,000 population.[6)] Further accumulation of studies is necessary to arrive at a conclusion of whether migraine alone is a clinically significant risk factor of cerebrovascular diseases.

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• Search terms and secondary sources

- Search database: PubMed (2011/9/14)
  migraine and risk and (stroke or cerebrovascular or infarction or infarct or hemorrhage) 798

CQ II-1-10

Is it safe for migraine patients to use low-dose oral contraceptives?

Recommendation

Estrogen-containing oral contraceptives are in principle contraindicated in women who have migraine with aura, and other contraceptive methods are recommended. Although these oral contraceptives are not contraindicated in women who have migraine without aura, caution has to be exercised in administration and observation is necessary.

Grade B

Background and Objective

Hormonal contraception is one of the most effective contraception methods, and include low-dose combined oral contraceptive (OC) containing estrogen and progestogen, progestin-releasing intrauterine contraceptive device (IUD), and progestin-only pill (not yet approved in Japan). In Japan, OC is the most widely used method.

Migraine is prevalent in women reaching sexual maturity. Apart from contraception, use of combined OC is often considered for the purpose of treating gynecological and dermatological diseases. Literature was searched to examine the tolerability and safety of OC use in migraine patients.

Comments and Evidence

Combined OC exhibits contraceptive effect by acting on the hypothalamic-pituitary-ovarian endocrine system to suppress follicle development and ovulation, and by exerting effects on the cervical mucosa and endometrium.

Combined OC are generally taken for 21-24 consecutive days, followed by 3-7 days of no pills or placebo pills. During this period, the endometrium sloughs off resulting in withdrawal bleeding. For women who desire no bleeding, continuous taking of OC without a pill-free period is also possible.[1] The types of hormone contained in combined OC differ depending on the formulation, which may be one-phase pills containing the same doses of hormones every day or multiple-phase pills containing different amounts of hormones on different days.

Headache has been reported to be one of the most common adverse effects associated with taking OC.[2] Use of OC may aggravate preexisting headache or induce new onset of headache.[3] In the ICHD-II, *Exogenous hormone-induced headache* and *Estrogen-withdrawal headache* are defined. However, in most of the patients with aggravated and new onset headache, the headache occurs during early cycles of OC use, and with continued use, the difference between OC use and control becomes insignificant.[3]

Headache associated with OC use tends to occur during the placebo or pill-free period, and the impact on headache has been reported to differ depending on the administration regimen. To control headache during the pill-free period, continuous OC regimen[4] and estrogen supplementation during the pill-free period have been used.[5]

A large number of studies have been conducted to examine the impact of OC on migraine, some of which have various issues. For example, the observation period and interval between OC administration and headache onset are not well defined in some studies, combined oral contraceptive and progestin-only pill are not differentiated in others, and the majority of the studies are case-control research.

In a large-scale cross-sectional study, the incidence of migraine among 13,944 women using OC was approximately 18%, and the odds ratio of OC use compared with non-OC use was 1.4 (95% confidence interval: 1.2-1.7).[6] A prospective cohort study in patients who had migraine without aura comparing subjects using and those not using OC reports that use of OC exerts only subtle differences on the course of migraine.[7]

In several retrospective studies, use of OC aggravates the frequency and intensity of migraine in 24.1-34.8% of patients who had migraine without aura, and in 18.6-69.2% of patients who had migraine with aura.[8]-[11]

In a metaanalysis of 13 case-control studies and 10 cohort studies reported in 2009, the relative risk of cerebral infarction was 7.02 (1.51-32.68) in patients with migraine (including with and without aura) using OC, while the risk was 10.0 (1.4-73.7) in migraine with aura accompanied by OC use and smoking.[12] The current WHO medical eligibility criteria for

contraceptive use (WHOMEC) classifies migraine with local neurological signs as category 4 (unacceptable health risk),[13] and the UK eligibility criteria for contraceptive use (UKMEC) published by the Faculty of Family Planning and Reproductive Health Care (FFPRHC) also classified migraine with aura as category 4 (unacceptable health risk) and a past history (≥ 5 years ago) of migraine with aura as category 3 (risks outweigh advantages).[14] In Japan, the package insert of OC also lists migraine with aura as a contraindication.

Other than barrier contraception method, the contraception methods that can be used for patients who have migraine with aura in Japan include copper-bearing IUD [both WHOMEA and UKMEC classify as category 1 (no restriction for use)] and levonorgestrel-releasing IUD [WHOMEA classifies as category 3 (risks outweigh advantages) for continuation, while UKMEC classifies as category 2 (advantages outweigh risks)]. When initiating OC in patients who had migraine without aura, the presence of other risk factors such as smoking, obesity, and ischemic attack has to be investigated. In the case of continuation of OC, attention has to be given to new onset of risk factors. When there is aggravation of attack frequency and intensity or new onset of aura or persistent headache, suspension of OC should be considered. WHOMEC classifies continuation in age ≥35 years as category 4 (unacceptable health risk), whereas UKMEC does not provide age stratification, and classifies continuation as category 3 (risks outweigh advantages). In the case of using OC not for contraception but for treatment of disease, careful evaluation of risk and benefit in individual patient is necessary.

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  Oral contraceptives & headache 851
  Contraceptive & headache 869
  migraine & contraceptives 504
  Migraine & oral contraceptives 494
  Migraine & contraception 187
  2.1 and stroke 149
- Search database: Ichushi Web for articles published in Japan
  (migraine TH or migraine AL) and (oral contraceptive TH or pill AL) 14
  (headache TH or headache AL) and (oral contraceptive TH or pill AL) 53