was predominant in the 30s and 40s age groups in women.

Approximately 5% of migraineurs and 59% of residents with CTTH in Daisen complained of daily or near-daily headache (Table 2). Although it is not listed in the IHS classification system, "chronic daily headache (CDH)" is one of the most important issues. Chronic daily headache consists of transformed migraine, CTTH, new daily persistent headache (NDPH), and hemicrania continua (HC).[21,22] There was no case of NDPH or HC in this survey. Although all subjects categorized to the CTTH group fulfilled the diagnostic criteria of CTTH, some of them may also fulfill the diagnostic criteria for transformed migraine.

Clinical Features of Migraine and Tension-type Headache.—Eighty-five percent of residents with MWA and 65.6% of residents with MWOA stated that their headaches were greater than moderate, which suggested the headaches inhibited daily activities. Approximately half of migraineurs stated that their mean headache duration was less than 4 hours. Duration of headache in Japanese migraineurs may tend to be shorter than that of Caucasians. Sakai and Igarashi reported the prevalence of migraine by the exact IHS criteria was 6.0%, and the prevalence of modified-criteria migraine (less than 4 hours' duration or less than 5 times occurrence of attack) was 2.4%, with an overall prevalence of 8.4%.[5] In a study in Taiwan, the prevalence of migraine was 9.1% when modified criteria for shorter headache duration was included.[14]

In this study, 31.7% of subjects with MWA and 39.0% of subjects with MWOA had only a few attacks per year. The expression of *zuki-zuki* is a Japanese onomatopoeia, indicating moderate to severe throbbing pain. Approximately 40% of subjects with TTH expressed their headache characteristics using *zuki-zuki*. Approximately half of migraineurs had bilateral headaches. Nausea was the most common associated symptom. These features are compatible with earlier findings from Western countries.

Six percent of subjects with ETTH experienced headaches with nausea. These subjects had both IHS-defined ETTH and other headaches with nausea that did not fulfill IHS-defined migraine. These subjects may develop migraine in the future.

Fatigue, mental stress, and lack of sleep were the major triggers in migraineurs. Twenty percent of migraineurs stated menses and change of weather as possible triggers.

Migraine Is One of the Major Health Problems in Japan.—Only 20.3% of migraineurs and 10.4% of subjects with TTH had experienced time or days off work due to headaches. In addition, 27.3% of migraineurs could not do their housework. Health perception was significantly poorer in migraineurs and those with TTH than in nonheadache subjects. Although migraine burdened residents, more than two thirds never consulted a physician for headache. Sakai and Igarashi reported 2.7% of migraineurs visited a physician regularly, and 12.2% visited occasionally.[5] This was confirmed by our door-to-door survey in Daisen, and it emphasized that migraine is one of the major health problems in Japan. Patient education concerning headache syndromes including migraine is necessary in Japan.

Food Preference and Risk of Migraine.—The odds ratio of coffee and tea consumption was significantly higher in migraineurs. Caffeine is widely used and supplemented to headache remedies because caffeine is believed to have some beneficial effects in acute headache treatment. In contrast, chronic use of excess caffeine can cause caffeinism or chronic headaches.[23] Thus, the present results may indicate 2 possibilities: either coffee and tea (probably caffeine) increase the risk of migraine, or in contrast, migraineurs know and use the potential benefits of coffee and tea for protecting or stopping headache attacks. Based on our clinical experience, we tend to support the latter possibility; however, this must remain speculative. Grant reported that the most common foods causing migraine were wheat (78%), oranges (65%), eggs (45%), tea and coffee (40% each), chocolate and milk (37% each), beef (35%), and corn, cane sugar, and yeast (33% each), and when an average of 10 common foods were avoided, there was a dramatic decrease in the number of headaches per month—85% of patients becoming headache-free.[24] In contrast, Medina and Diamond reported that diet appeared to be relatively unimportant in migraine attacks.[25] The present findings suggested that food with a high fat content increased the risk of migraine, and daily fish intake

decreased the risk. Bic et al reported that there was a significant positive correlation between baseline dietary fat intake and headache frequency in migraineurs.[26] In general, the Japanese diet contains lower fat and more fish than Western diets. These observations may provide evidence for a prophylactic diet for migraine; however, further studies including interventions are necessary.

Based on this study, we would emphasize that Japanese migraineurs currently do not adequately use appropriate medical services. Public education concerning headaches is one of the most urgent issues in Japan.

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Genetics of Migraine Headache

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Abstract: Migraine is a common form of chronic headache syndrome. Although the pathogenesis of migraine still remains enigmatic, there has been remarkable progress in genetic research. Point mutations of the P/Q-type Ca^{2+} channel alpha 1 subunit (CACNA1A) gene have been identified in familial hemiplegic migraine (FHM). The CACNA1A gene has been noticed as a possible candidate genetic locus related to common forms of migraine headache. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an autosomal dominant inherited disorder that is often accompanied by migraine-like headache. Point mutations of the notch-3 gene have been identified as the cause of CADASIL. The trigemino-vascular theory is a modern theory of migraine headache that claims that neurogenic inflammation of the meningeal blood vessels is triggered by excitation of trigeminovascular fibers. Neurotransmitters such as serotonin (5HT), CGRP, and substance P likely play major roles in these events during the early stage of migraine attacks. An association study of the allelic variation at Codon 23 (Cys or Ser) of the $5HT_{2C}$-R gene in Japanese samples revealed that the Ser allele frequency in migraine with aura was significantly higher than that in the non-headache controls. However, a negative association of this polymorphism has been reported in Caucasian migraineurs. An increased frequency in the dopamine D2 receptor (DRD2) NcoI C allele has been reported in Caucasian samples. The C677T allelic variation of 5,10-methylenetetrahydrofolate reductase (MTHFR) increased the risk for migraine. Discovery of new genes that are responsible or susceptible to migraine will also open an avenue to develop a new therapeutic strategy for migraine.

Key words: Migraine; Gene; Ca^{2+} channel; CACNA1A; Methylenetetrahydrofolate (MTHFR)

Introduction

Traditionally, headache was considered a mere symptom of disease, and it was not duly recognized as a disease in itself, but with the development of tryptans and other drugs, which exhibit a specific effect on migraine, the clinical entity of chronic headache has come to receive

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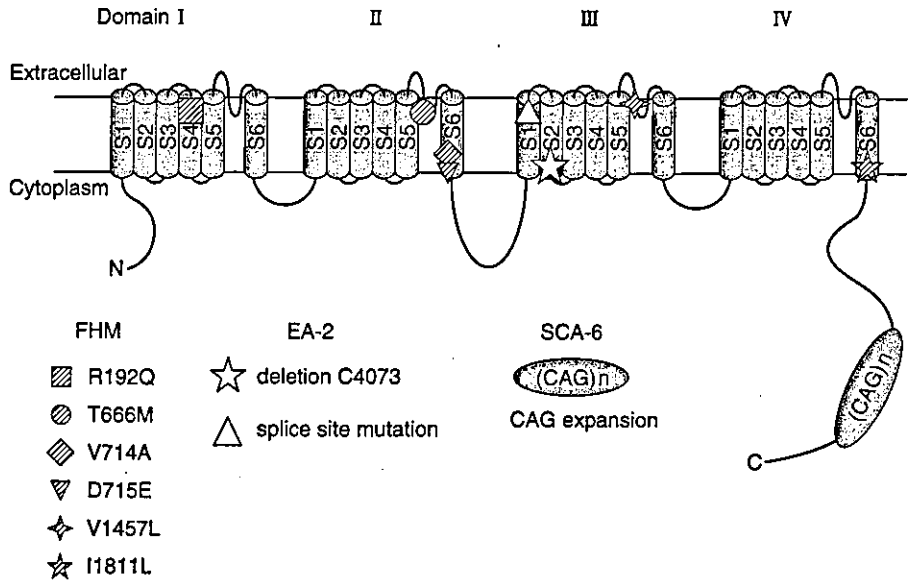

Fig. 1 Structure of the P/Q type Ca^{+2} channel $\alpha 1$ subunit (CACNA1A) and the FHM mutation site
Due to the mutation site of the CACNA1A gene, FHM as well as episodic ataxia 2 (EA2) occur. With genetic cerebellar ataxia (SCA6), the CAG repeats at the C end of this gene increased to more than 20.
A: alanine, D: aspartate, E: glutamate, I: isoleucine, L: leucine, M: methionine, Q: glutamine, R: arginine, T: threonine, V: valine
(Partly adapted from Ophoff, R.A. *et al.*: *Cell* 1996; 87: 543–552)

considerable attention. A study conducted in Daisen-cho, Tottori-prefecture, showed that 28.8% of the population experienced some kind of chronic headache, while 6.0% suffered migraine,[1] a figure that matches the prevalence of high blood pressure.

Efforts are made to understand the pathophysiology of migraine, and research on a genetic level is also progressing recently. The discovery of the mutations of calcium channel gene in familial hemiplegic migraine (FHM) was a breakthrough. Other genes that are also studied as possible migraine-related susceptibility genes include the serotonin receptor, dopamine receptor, and methylene-tetrahydrofolate reductase (MTHFR) genes, as well as the angiotensin-converting enzyme (ACE) gene, etc.

Familial Hemiplegic Migraine

Familial hemiplegic migraine (FHM), which is classified as a subgroup of migraine with aura (MA) by the International Headache Society, fulfills the diagnostic criteria for MA by definition, because it exhibits an aura, in this case hemiplegia, and has a history of at least one first degree relative (parent, sibling or child) with similar attacks. Different families exhibit different symptoms, and it is known that some families exhibit symptoms like nystagmus or cerebellar atrophy, while convulsions or disturbed consciousness may appear in other families. With FHM relatively slight external trauma or a procedure like brain angiography may trigger a severe attack, resulting in irreversible brain damage.

In 1993, Joutel *et al.* linked FHM to chromosome 19p13, and in 1996 Ophoff *et al.*[2] identified a point mutation of the P/Q type Ca^{+2} channel alpha 1 subunit (CACNL1A4; presently called CACNA1A) on chromosome 19 (Fig. 1). Ducros *et al.*[3] analyzed the available genetic data and clinical presentations of FHM

in 28 families with a known family history of FHM. Migraine attacks with hemiplegia appeared in 89% of the members with the CACNA1A mutation, and a third of them experienced particularly severe migraine attacks accompanied by coma or delayed hemiplegia.

The 28 families that were analyzed showed a total of 9 mutation types, including 5 newly identified mutations; 6 of these mutations were related to hemiplegic migraine and cerebellar signs, and 83% of the patients presented with nystagmus or ataxia. The other three gene mutations caused "pure type" hemiplegic migraine (pure hemiplegic migraine)," and it was shown that they do not cause lasting cerebellar signs. Apart from the involvement of chromosome 19, a familial gene locus was also reported on chromosome 1q21–23, and a familial FHM gene locus on chromosome 1q31.

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)

This is an autosomal dominant hereditary disease with onset from a young age to middle age, that presents predominantly with cerebral leukoencephalopathy and recurring infarcts of the cerebral white matter. It does not exhibit high blood pressure, hyperlipidemia or any of the other risk factors for atherosclerosis. It is reported that migraine-like headaches are associated with it at a high frequency in affected families in Europe and America. Approximately half of the cases presented with a migraine-like attack and as the disease progresses, hemiplegia, ataxia, epilepsy, and cognitive dysfunction develop.[4]

There are very few reports on this disease in Japanese, but even so, very few Japanese cases seem to be associated with headache.[5]

If the perivascular presence of granular osmiophilic material (GOM) can be demonstrated on skin biopsy, the diagnosis is confirmed. CADASIL is caused by a point mutation of the Notch 3 gene.

It is reported that Americans of Chinese heritage suffer a hereditary disease similar to CADASIL, called hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS). There is also a report of a large family in Holland that showed symptoms of an autosomal dominant hereditary disease with retino-vascular degeneration, migraine, and Raynaud's phenomenon. In both these conditions, migraine (migraine-like headache) features prominently, and although the gene involved has not been identified, it is linked to chromosome 3p21.[6]

Mitochondrial Gene

The mitochondrial encephalomyopathies like the syndrome of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), are known for their frequent association with headache. There is a view that migraine is either a mitochondrial disease or a symptom of mitochondrial encephalomyopathy. This view is supported by reports suggesting mitochondrial dysfunction of the brain and muscles due to ^{31}P-MRS in migraine patients, while cases of patients with cluster headache and an A3243G MELAS mutation, have also been reported.

It was considered that the mtDNA11084A-G polymorphism, which is frequently found in Japanese, may be a migraine-susceptible gene, but after studying many cases, the frequency of G polymorphisms was found to be the same as that in the control group, and it was concluded that it does not play a role in migraine.[7] The possibility that mitochondria may be involved in migraine is an important one, and we anticipate the results of future studies.

Susceptibility Genes in General Migraine

FHM and CADASIL are hereditary diseases that are associated with migraine-like headaches and are caused by an abnormality of a

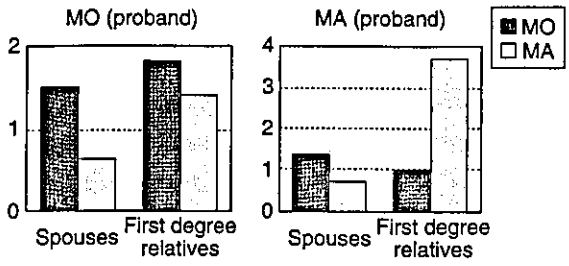

Fig. 2 Relative risk for migraine among spouses and first degree relatives
MA: Migraine with aura, MO: Migraine without aura
(Partly adapted from Russell, M.B. *et al.*: *Cephalalgia* 1996; 16: 305–309)

specific gene. On the one hand, many genetic studies in common form of migraine are under way. The familial occurrence of migraine is empirically well known, and it is assumed that genetic factors, as well as environmental factors like diet, etc. play a role.

Russell *et al.*[8] conducted a study on familial migraine and found that, compared to the general population, patients with migraine with aura (MA), had a 3.8 times higher frequency of first degree relatives with MA and a 0.8 times higher frequency of spouses with MA; while patients with migraine without aura (MO) had a 1.9 times higher frequency of first degree relatives with MO and a 1.5 times higher frequency of spouses with MO (Fig. 2). Genetics seems to play the most important role in MA, while genetic and environmental factors both play a role in MO.

Serotonin (5-hydroxytriptamine; 5-HT)-Related Genes

Serotonin plays a major role in the clinical presentation of migraine and the serotonin receptor gene is actively investigated. Serotonin receptors are classified into subtypes $5HT_1$ through $5HT_7$. Sumatriptan (succinate), a drug that is specifically used for the treatment of migraine, is an agonist of the $5HT_{1B/1D}$ receptor subtypes; stimulation of the $5HT_{1B}$ receptor causes vasoconstriction in the brain, while stimulation of the $5HT_{1D}$ receptor inhibits neurogenic inflammation, thus, by inhibiting neural activity it exerts an aborting effect on migraine attacks. Based on such facts as that the $5HT_{2C}$ receptor agonist m-chlorophenyl piperazine (mCPP) induces a high incidence of migraine attacks in migraine patients, and that the $5HT_{2C}$ receptor antagonists methylsergide and pizotyline are effective as prophylactic agents against migraine attacks, it is thought that the $5HT_{2C}$ receptor, with its gene locus on chromosome Xq24, is involved in the induction of migraine attacks.

The study by Burnet *et al.*[9] of the Cys/Ser polymorphisms of the $5HT_{2C}$ receptor codon23, could not establish a significant relation with migraine, but the domestic study by Kusumi *et al.*[10] showed that the frequency of the Ser allyl was significantly increased in MA. These results can be attributed to racial differences, but it is not clear how the function of the receptor is changed by the Ser type, and we are anticipating the progress of future research.

Ogilvie *et al.* have also studied the relation between serotonin transporter gene polymorphism and migraine, and reported a significant relationship with both MA and MO.

Dopamine Receptor Gene

Peroutka *et al.* studied dopamine receptor (DRD2) gene polymorphism, and reported that the C/C type is significantly increased in migraine.[11] According to the studies by Kusumi *et al.*[10] this gene was not involved in migraine.

Methylene-Tetrahydrofolate Reductase Gene

Methylene-tetrahydrofolate reductase (MTHFR), an enzyme involved in the metabolism of homocysteine, is known for its C677T (Ala->Val) gene polymorphism. The T-mutation causes significantly increased blood levels of homocysteine, and the homozygous T/T presence is receiving attention as a risk factor for coronary

artery disease and cerebrovascular disease.

The authors' study[12] showed that the frequency of the T/T type was high in MA. In other words, the T/T type MTHFR gene is a risk factor for hereditary migraine.

Also, when the blood homosysteine value was measured in migraine patients, it was found to be slightly, yet significantly, increased. Abnormalities in the MTHFR gene are presumably involved in the altered trigeminal nerve activity associated with migraine, and the modified threshold for the onset of migraine.

Angiotensin Converting Enzyme

The angiotensin converting enzyme (ACE) gene is related to blood pressure via the metabolic enzymes of the angiotensin system, but it is also known for its involvement in the metabolism of the trigger substance, substance P.

There are both insertion (I) and deletion (D) mutations of the Alu base-pair sequence of the ACE gene; with the D type the blood levels of ACE are increased, and the homozygous D type (DD type) is attracting attention as a risk factor for myocardial infarction. When the presence of this polymorphism was investigated in migraine patients, the frequency of the DD type was significantly elevated in MA. In Europe, Paterna *et al.* reported similar results in MO patients.[13]

Endothelin Receptor Gene

Endothelin-1 (ET-1) is a potent vasoconstrictor substance and it is known that blood levels of ET-1 are elevated during a migraine attack. During the intermission of attacks of migraine, the levels of ET-1 have been reported to be both decreased and increased.

There are two types of ET-1 receptors, namely ET-A and ET-B. The ET-A receptor mediates the response to ET-1 and the production of nitric oxide (NO), which is involved in migraine, is suppressed. A study of the ET genes involved in migraine, the ET-A and ET-B receptor genes, showed that polymorphisms of the ET-A receptor gene played a significant role.

Other Genes

The NO synthase (NOS) gene was studied as a migraine-related candidate, but a significant relationship was not established. Study of the prothrombin gene 20210A→G polymorphism, which is involved in blood coagulation, showed that it does not play a role in migraine. It is reported that the insulin receptor gene, which is located close to the CACNA of FHM (19p13.3/2) plays a role in migraine.

The Genetic Locus of Migraine with Aura Is 4q24

It was reported that a genome-wide sequence analysis using 350 types of microsatellite markers was performed on a sample of Finnish migraine patients and the gene was located on chromosome 4q24.[14] Future identification of the gene as such is anticipated.

Conclusion

Genetic research of hereditary disorders that present as specific kinds of migraine has been successful, as in the identification of the genes that cause FHM and CADASIL.

Apart from familial migraine, families that demonstrate hereditary (familial) disorders with pathognomonic symptoms are meticulously examined clinically to establish separate syndromes, followed by a genetic search. It is therefore likely that new genetic mutations will continue to be identified.

On the one hand, based on the biochemical evidence involved in migraine, the use of single nucleotide polymorphisms (SNP) or microsatellite markers are progressing in the mutual analysis of possibly related candidate genes, and the susceptibility genes of migraine are gradually established. One aim of the molec-

ular genetic research of migraine is to understand the molecular level of clinical migraine in order to develop a more selective approach to the treatment of migraine.

We expect that the medical consultation of migraine will also include genetic testing in the future in order to rationalize the diagnostic process and allow selection of the most effective therapeutic drugs.

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特集 慢性疾患の予後決定因子—インフォームド・コンセントを得るために

慢性頭痛の予後決定因子

竹島多賀夫* 荒木治子 中島健二

要旨

本邦における片頭痛の年間有病率は6～8.4%，緊張型頭痛は約22%である。一次性頭痛は通常生命を脅かすことはなく，慢性頭痛の罹患率は加齢とともに低下し，治癒する患者が少なくないと考えられる。片頭痛の追跡調査で16年後には約1/3が治癒したと報告されている。

一方，片頭痛患者の一部は，脳血管障害や白質病変の罹患率が有意に上昇していることも明らかになりつつある。発作頻度が高い片頭痛患者に対しては，発作時の適切な急性期治療に加えて，脳障害の蓄積を防ぐための予防的治療法が必要である可能性が指摘されている。

急性期治療薬の乱用により薬剤乱用頭痛を併発すると治療に難渋することが多く，適切な予防療法を実施することが重要と考えられる。また，一次性頭痛に並存する疾患として，心血管系疾患，てんかん，うつ病などの神経疾患や喘息，アレルギー性疾患が注目されており，一次性頭痛の治療薬選択に際しては並存する疾患を考慮することも重要である。

はじめに

片頭痛や緊張型頭痛などの一次性頭痛は，通常生命を脅かすことはない。しかしながら，頭痛発作を繰り返して日常生活に支障をきたし，患者のQOLを阻害する疾患である。適切な治療がなされないと，患者はしばしば頭痛の治療を諦めてしまい，社会生活上の困難から進路や職業の選択にも悪影響を及ぼしうるのである。世界保健機関の調査では，現在知られている日常生活に支障をきたす疾患の中で，片頭痛による患者への負荷の強さは全疾患中の第19位に位置付けられている。

本稿では，一次性頭痛の診療に際してよりよい患者-医師関係を築き，良質な医療を提供するために必要な知識，すなわち頭痛の疫学的事項，診断基準，予後を悪化させる要因などについて概説する。

慢性頭痛の特徴と診断

片頭痛は前兆の有無により，前兆のない片頭痛(migraine without aura)と前兆のある片頭痛(migraine with aura)に細分類される。片頭痛とは，特徴的な拍動性，片側性頭痛と悪心や光過敏などの随伴症状により特徴付けられる臨床的症候群である。頭痛発作は通常4～72時間持続するが，頭痛がない期間はなんら支障がなく，エピソーディックな疾患であることも重要な特徴の一つである。

診断には，国際頭痛学会の診断基準[1]が用いられている。標準化された片頭痛の診断がなされるようになり，研究成果や治療成績の国際的な比較も可能になった。

目の前にいる頭痛患者を片頭痛と診断するに際して，まず考慮すべきことは，その患者の頭痛が，

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一次性の頭痛であるか，二次性頭痛なのか，あるいはその両方か，ということを明確にすべきである。つまり，まず器質疾患による頭痛の鑑別を正確に行う必要がある。ただし，器質疾患の除外で事足れりとしてはならない。一次性頭痛の種類についても鑑別を行い，国際頭痛学会の診断基準に沿った適切な診断を行い，科学的な根拠に基づいて最適な治療を行うことが望まれている。

前兆のない片頭痛の診断基準を表1に示した。

片頭痛における前兆（aura）は，大脳皮質または脳幹に由来する完全可逆性の局在神経徴候をさす。閃輝暗点や視野欠損など視覚症状，手足のチクチク感や感覚鈍麻などの感覚症状，および失語を含む言語障害が典型的前兆として分類されている。前兆として脱力がある場合には，新しい国際頭痛学会診断基準では「典型的前兆」には含めず，運動障害を片麻痺性片頭痛や脳底型片頭痛の前兆に分類するように改訂された。

緊張型頭痛では通常，圧迫するような，あるいは締め付けるような両側性の軽度～中等度の頭痛が数十分～数日間持続する。日常的な動作による頭痛の増悪は認めず，悪心を伴わない。頭痛の頻度によって，稀発反復性緊張型頭痛，頻発反復性緊張型頭痛，および慢性緊張型頭痛に分類し，おのおの頭蓋周囲の圧痛を伴うものと，伴わないものに細分類する。

頻発反復性緊張型頭痛の診断基準を表2に示した。頻発緊張型頭痛は前兆のない片頭痛に伴って起こることが多く，頭痛日記などを用いて特定することが望ましい。

慢性頭痛の疫学

SakaiとIgarashi[2]の日本全国調査では，片頭痛の年間有病率は8.4%，われわれが実施した鳥取県大山町の調査[3]では，住民の6.0%が片頭痛（前兆のある片頭痛0.9%，前兆のない片頭痛5.2%）に罹患していた。世界各国における有病率はさまざまで，中国3.0%，台湾9.1%，フランス12.1%，米国13.0%[4]，ドイツ27.5%などの報告がある。

図1に年代別の片頭痛有病率（大山町調査）を

表1　1.1前兆のない片頭痛（migraine without aura）の診断基準（文献[1,11]より抜粋）

A．B～Dを満たす頭痛発作が5回以上ある(注1)。
B．頭痛の持続時間は4～72時間（未治療もしくは治療が無効の場合）(注2,3,4)
C．頭痛は以下の特徴の少なくとも2項目を満たす
　1．片側性(注5,6)
　2．拍動性(注7)
　3．中等度～重度の頭痛
　4．日常的な動作（歩行や階段昇降などの）により頭痛が増悪する，あるいは頭痛のために日常的な動作を避ける
D．頭痛発作中に少なくとも以下の1項目を満たす
　1．悪心または嘔吐（あるいはその両方）
　2．光過敏および音過敏(注8)
E．その他の疾患によらない(注9)

注：
1）1.1「前兆のない片頭痛」と2.1「稀発反復性緊張型頭痛」は，ときに鑑別が困難であると思われる。したがって，発作を5回以上経験していることを診断の要件とした。発作回数が5回未満の例は，それ以外の1.1「前兆のない片頭痛」の診断基準を満たしていても，1.6.1「前兆のない片頭痛の疑い」にコード化すべきである。
2）片頭痛発作中に入眠してしまい，目覚めた時には頭痛を認めない患者では，発作の持続時間を目覚めた時刻までとみなす。
3）小児では片頭痛発作の持続時間は，1～72時間としてよいかもしれない（ただし，プロスペクティブな日記研究により，小児においては未治療時の発作持続時間が2時間未満でありうることのエビデンスは，プロスペクティブな頭痛日記により確認する必要がある）。
4）発作が3カ月を超える期間にわたり15日/月以上生じている場合には，1.1「前兆のない片頭痛」としてコード化するとともに，1.5.1「慢性片頭痛」としてコード化する。
5）幼児の片頭痛は両側性である場合が多い。成人にみられる片側性の頭痛パターンは思春期の終わりか成人期の初めに現れるのが通例である。
6）片頭痛は通常，前頭側頭部に発生する。小児における後頭部痛は，片側性か両側性かを問わずまれであり，診断上の注意が必要である。器質性疾患によるものが多いと考えられる。
7）拍動性頭痛（pulsating）とは，ズキンズキンする（throbbing），あるいは，心臓の拍動に伴い痛みが変化することを意味する。
8）幼児の光過敏および音過敏は，行動から推測できるものと思われる。
9）病歴および身体所見・神経所見より頭痛分類5～12を否定できる，または，病歴あるいは身体所見・神経所見よりこれらの疾患が疑われるが，適切な検査により除外できる，または，これらの疾患が存在しても，初発時の発作と当該疾患とは時間的に一致しない。

表2　2.2 頻発反復性緊張型頭痛 (Frequent episodic tension-type headache) の診断基準 (文献[1,11]より抜粋)

A．3カ月以上にわたり，平均して1カ月に1日以上，15日未満（年間12日以上180日未満）の頻度で発現する頭痛が10回以上あり，かつB～Dを満たす
B．頭痛は30分～7日間持続する
C．頭痛は以下の特徴の少なくとも2項目を満たす
　1．両側性
　2．性状は圧迫感または締め付け感（非拍動性）
　3．強さは軽度～中等度
　4．歩行や階段の昇降のような日常的な動作により増悪しない
D．以下の両方を満たす
　1．悪心や嘔吐はない（食欲不振を伴うことはある）
　2．光過敏や音過敏はあってもどちらか一方のみ
E．その他の疾患によらない(注1)

注：
1．病歴および身体所見・神経所見より頭痛分類5～12を否定できる，または，病歴あるいは身体所見・神経所見よりこれらの疾患が疑われるが，適切な検査により除外できる，または，これらの疾患が存在しても，初発時の発作と当該疾患とは時期的に一致しない。

2.2.1　頭蓋周囲の圧痛を伴う頻発反復性緊張型頭痛

診断基準：
A．頭痛は，2.2「頻発反復性緊張型頭痛」の診断基準A～Eを満たす
B．触診により頭蓋周囲の圧痛が増強する

2.2.2　頭蓋周囲の圧痛を伴わない頻発反復性緊張型頭痛

診断基準：
A．頭痛は，2.2「頻発反復性緊張型頭痛」の診断基準A～Eを満たす
B．触診により頭蓋周囲の圧痛が増強しない

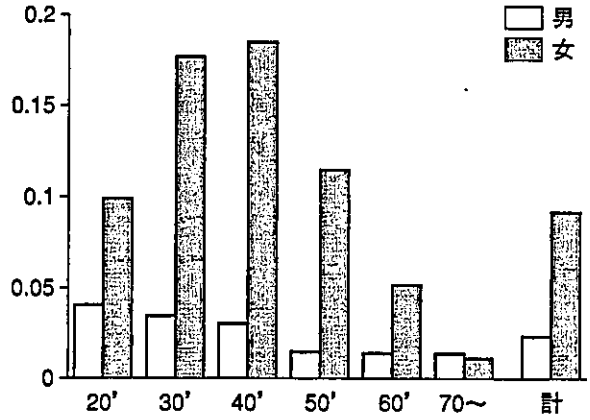

図1　鳥取県大山町の片頭痛有病率
（文献[3]より引用し改変）

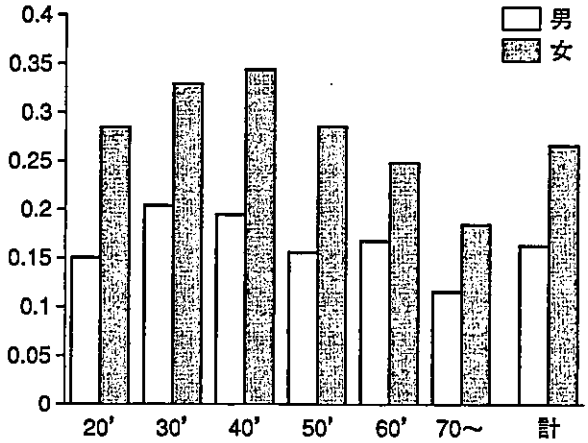

図2　鳥取県大山町の緊張型頭痛有病率
（文献[3]より引用し改変）

示した。片頭痛は若年～中年の女性に多く，30歳代，40歳代女性の片頭痛の有病率はおのおの17.6%，18.4%も及んでいた。男性の片頭痛罹患率は加齢とともに一様に下がるが，女性では20歳代から30歳，40歳代で上昇し，その後低下する。これは女性ホルモンの活動性が関与していることを伺わせるものとして注目される。有病率の性比（女性/男性）をみると，前兆のある片頭痛2.4，前兆のない片頭痛4.2，反復性緊張型頭痛1.6，慢性緊張型頭痛1.8であった。いずれの慢性頭痛も女性に多いが，前兆のない片頭痛で，女性優位がもっとも顕著であることも女性ホルモンの関与を示すものと考えられている[3]。

緊張型頭痛は，もっともありふれた一次性頭痛であり，生涯有病率は30～78%[1]とされている。社会的にも経済的にも多くの影響を及ぼしているにもかかわらず，あまり研究が進んでいない。以前は主として心因性とみなされていたが，少なくとも重症サブタイプでは，神経生物学的病態を有する疾患と理解されるようになってきている。大山町の一般人口の年間の有病率は21.8%で，片頭痛よりやや高齢に患者が分布している（図2）。

予後と予後決定因子

一次性頭痛は直接的に生命を脅かす疾患ではな

い。したがって，図1，2のごとく加齢とともに有病率が低くなることより，片頭痛，緊張型頭痛ともに年齢とともに治癒ないし軽減する患者が少なくないことを示している。

また，片頭痛患者が加齢とともに頭痛の性質が変化してきて，緊張型頭痛様の頭痛となることも多い。このようなケースを以前は連合性頭痛，あるいは混合性頭痛と称していたが，現在の国際頭痛学会の分類では片頭痛と緊張型頭痛の合併として取り扱っている。このような緊張型頭痛様に変化した片頭痛をtransformed migraineとして，緊張型頭痛とは区別して扱うべきであるとの主張もある。これらを考慮しても，加齢とともに片頭痛・緊張型頭痛の一部は治癒してゆくと考えられる。

頭痛の治癒を規定する因子の科学的な調査は少ない。Eriksen と Russell[5]はデンマークにおいて，前兆のある片頭痛患者53人の予後を16年間追跡調査した。頭痛発作が2年以上なければ治癒したと定義すると，16年後には36%（男性55%，女性31%）の患者が治癒しており，予後は比較的良好であった。感覚障害または失語性の前兆の患者の25%，視覚性前兆のみの患者の41%が治癒しており，視覚性前兆のみの方が治癒率が高い傾向であったが，統計学的な有意差はなかったと報告されている。

片頭痛が若年者の脳梗塞の原因としてもっとも重要なもののひとつであることは周知であるが，片頭痛を有することが脳血管障害のリスクにどの程度影響するかについては明確でなかった。Igarashi ら[6]は，片頭痛患者91例において脳MRI検査を実施し，36例（39.6%）においてT2強調像，プロトン密度画像で白質に異常信号を認め，非頭痛対照より有意に高いことを報告した。

Kruit ら[7]のオランダにおける疫学調査の結果によれば，片頭痛患者全体の脳梗塞有病率は8.1%で，非片頭痛対照の5.0%と有意差は認めなかったが，椎骨脳底動脈系（後頭循環系）の小脳梗塞に関しては，片頭痛患者は非片頭痛患者の7.1倍にオッズ比が上昇しており（有病率5.4%対0.7%），前兆のある片頭痛患者では13.7倍（95% CI，1.7〜112），片頭痛発作が月に1回以上ある患者群では9.3倍（95% CI，1.1〜76），前兆のある片頭痛で発作が月に1回以上あれば15.8倍（95% CI，1.8〜140）まで有意にオッズ比が増加していた。また，女性片頭痛患者では，発作頻度が高くなるに伴い脳MRIで検出される深部白質病変が増加していることを示した。片頭痛患者の少なくとも一部においては，片頭痛と関連して脳梗塞や深部白質病変が増加していることが明らかになりつつある。

これらの研究成果より，片頭痛は慢性進行性の脳疾患として理解するべきであって，治療目標も単なる発作時の対症治療だけではなく，脳梗塞や深部白質病変などの脳の病変の蓄積を予防することが重要であり，危険因子の調整と予防的治療や，急性期治療薬の早期適用など疾患の進行を予防するための新しい治療戦略が重要な研究であるとの指摘がなされている[8]。

頭痛診療に際して，もっとも難渋するもののひとつに慢性連日性頭痛がある。慢性連日性頭痛は，国際頭痛学会の分類では採用されていない名称であるが，難治性頭痛として予後や治療を考える際には有用な疾病グループの概念である。通常，1日4時間以上の頭痛が月に15日以上，6カ月間以上の期間にわたり起こっているものを慢性連日性頭痛として取り扱う。

Silberstein の分類[9]では，慢性片頭痛，慢性緊張型頭痛，新規発症持続性連日性頭痛（new daily-persistent headache；NDPH），持続性片側頭痛（hemicrania continua）の4型があり，それぞれ薬剤乱用を伴うものと伴わないものに分類されていた。国際頭痛学会分類[1]では，これらの四つの下位頭痛分類が採用されているが，薬剤乱用を伴わないことが条件になっており，薬剤乱用を伴う場合には薬物乱用頭痛（medication-overuse headache；MOH）に分類する方式が採用された。MOHを併発すると難治になっていくことが多いので，急性期治療薬の過剰使用傾向があれば適切な予防療法を実施する必要がある。

最近，片頭痛に合併しやすい疾患が注目[10]されている。偶然の合併ではなく病態に何らかの関与が想定される疾患，すなわちcomorbid diseasesとして，心血管系疾患のほか，うつ病や喘息，ア

表3　片頭痛に並存しやすい疾患 (comorbid diseases)[10]

心血管系疾患	
	高血圧，低血圧
	レイノー現象
	僧房弁逸脱症
	狭心症・心筋梗塞
	脳卒中
精神疾患	
	うつ病
	躁病
	パニック障害
	不安障害
神経疾患	
	てんかん
	頭位性めまい
消化器疾患	
	機能性腸疾患
その他	
	喘息
	アレルギー

表4　片頭痛予防薬 (文献[10]より引用し改変)

抗痙攣薬	
	バルプロ酸
抗うつ薬	
	三環系抗うつ薬 (TCAs)
	トリプタノール
β遮断薬	
	プロプラノロール，メトプロロール，ナドロール，アテノロール，チモロール
Caチャネル遮断薬	
	ベラパミル，ロメリジン
その他	
	NSAIDs，リボフラビン，マグネシウム，feverfew，Botox

レルギー性疾患が特に検討されている。comorbid diseasesの一覧を表3に示した。これらの疾患は片頭痛の病因を考えるうえで興味深いことはいうまでもないが，治療方針を考えるうえでも重要である。すなわち，片頭痛あるいは並存疾患の治療薬は他方に悪影響を及ぼさないものを選択する必要があり，可能であれば片頭痛と並存疾患の両方を同時に治療できる薬剤の選択が望まれるからである。片頭痛の予防療法薬として使用される薬剤を表4に示した。

おわりに

慢性頭痛の治療に際しては，頭痛発作時の対症的治療ばかりでなく，予後や薬剤乱用頭痛の合併，連日性頭痛への移行，並存疾患の存在の有無にも配慮した治療法の選択，特に予防療法についても積極的に検討することが重要と思われる。

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神経疾患の医療手順：片頭痛*

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Key Words : algorithm, critical pathways, diagnostic criteria, guideline, migraine headache

はじめに

片頭痛は，特徴的な拍動性，片側性頭痛と悪心や光過敏などの随伴症状により特徴づけられる臨床的症候群であり，エピソーディックな疾患である[1]．通常生命を脅かすことはないが，繰り返す頭痛発作により，日常生活に支障をきたし患者のQOLを阻害する疾患である．疫学的研究によれば片頭痛の有病率は高く，本邦では，成人の6.6～8.4％と報告[2,3]されている．世界保健機関（WHO）の調査では，現在知られている日常生活に支障をきたす疾患の中で片頭痛による患者への負荷の強さは第19位に位置づけられており，多くの疾患のなかでも対策が急がれるものの一つである．片頭痛は前兆の有無により「migraine without aura」，「migraine with aura」に細分類されるが，本稿ではこれらの訳語として，「前兆のない片頭痛」と「前兆のある片頭痛」を用いる[4]．おのおの「前兆を伴わない片頭痛」，「前兆を伴う片頭痛」と同義である．

疾病対策として，病態の理解，正確な診断法と有効な治療法の確立，これらの研究成果を有効に診療に生かすためには，標準的な診断基準と治療ガイドラインの作成，これらを統合した医療手順の作成が必要である．本稿では，日常生活に支障がある片頭痛患者が外来受診した際に，正しく片頭痛と診断され，必要かつ十分な検査が適切に施行され，合理的に薬剤が選択され，適切に治療されるための手順について論じたい．国際頭痛学会の診断基準[1]および，内外の片頭痛治療ガイドライン[5,6]からレビューし，データや文献資料が不十分な事項についてはわれわれの提言も含めて記述する．

I．片頭痛の診断

正確な片頭痛の診断には，国際頭痛学会の診断基準が用いられるべきである．国際頭痛学会の診断基準に従って標準化された片頭痛の診断を行うことにより，片頭痛の研究成果や治療成績を国際的に比較することが可能となり，多くのメリットが期待しうる．

片頭痛診断に際して，まず考慮すべきことは，その頭痛が，一次性頭痛か，二次性頭痛か，あるいはその両方か？ということである．片頭痛の特徴を有する頭痛が初発し，頭痛の原因となることが知られている他疾患と時期的に一致する場合には，原因疾患に応じて二次性頭痛として分類することになる．頭痛診断のコアアルゴリズムを**Fig. 1**に示した．適切な問診と注意深い神経学的

* Critical pathways of Neurological Diseases : Migraine Headache.

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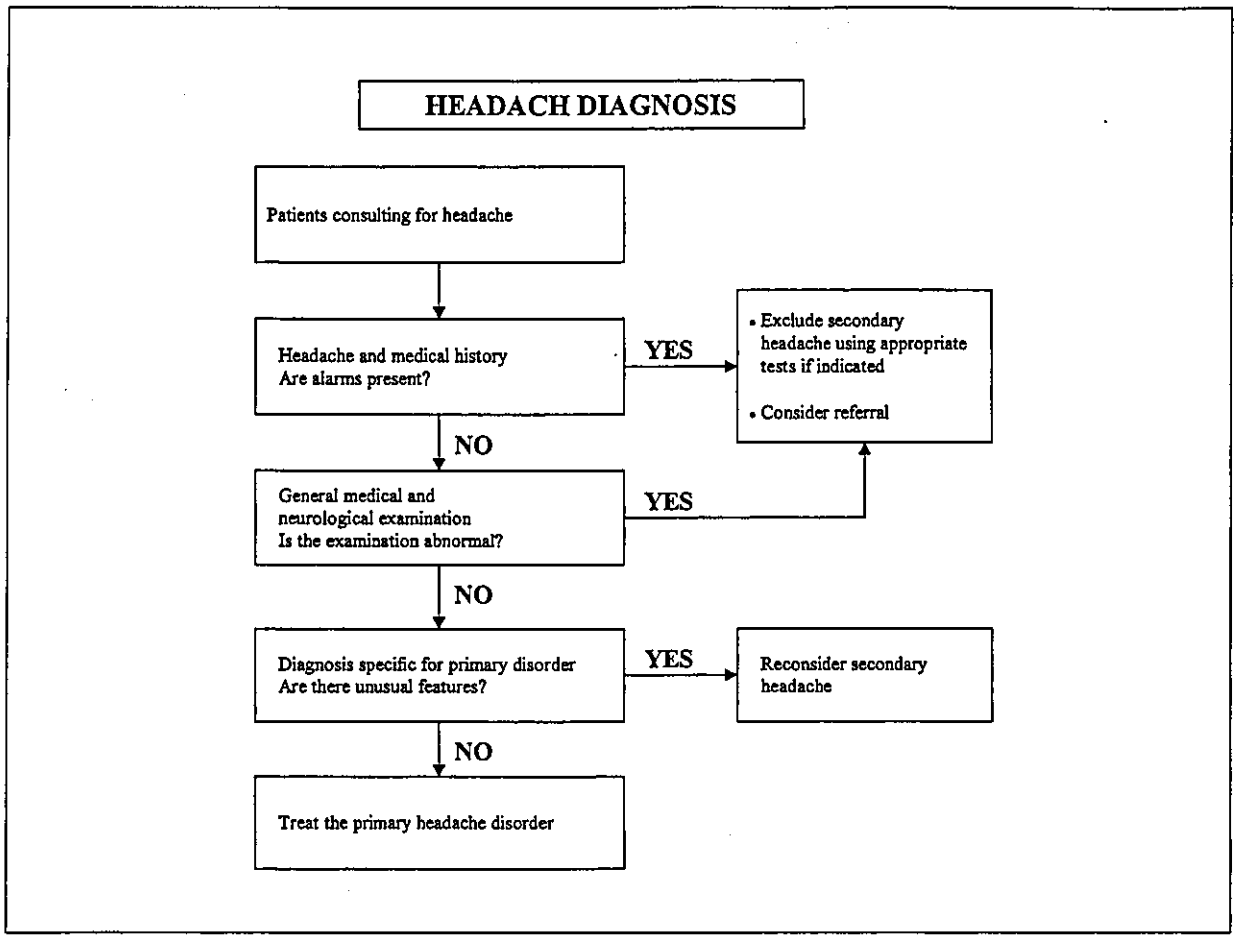

Fig. 1 Core algorithm for headache diagnosis

診察により器質疾患の除外を十分に行い，器質疾患の可能性があれば適切な検査を実施する必要がある[7]．また，器質疾患が疑われるならば施設によってはより専門的な施設や専門医に紹介することも検討する．**Table 1**に国際頭痛学会の分類と診断基準第2版（ICHD-II）に準拠して，一次性頭痛の分類と，二次性頭痛の大分類を示した[1]．

1．前兆のない片頭痛

「前兆のない片頭痛」は，特異的な頭痛の症状と随伴症状により特徴づけられる臨床的症候群である．頭痛発作は通常4～72時間持続し，頭痛は片側性，拍動性で，中等度～重度の強さであり，日常的な動作により頭痛が増悪することが特徴的である．また，随伴症状として悪心や光過敏・音過敏を伴う．片頭痛を疑う最も重要なポイントはエピソーディックな頭痛発作を繰り返していることと，頭痛発作により生活に支障をきたしているということである．また，随伴症状として悪心があることも片頭痛を疑うポイントの一つである．片頭痛が疑われれば，適切な問診により，診断基準をみたすことを確認する．診断基準には適切な方法で器質疾患が除外されていることも含まれている．前兆のない片頭痛の診断基準を**Table 2**に示した．

2．前兆のある片頭痛

「前兆のある片頭痛」は，頭痛発作と，これに先行または随伴する局所神経症状によって特徴づけられる症候群である．前兆は，脳幹または大脳皮質に由来する完全可逆性の局所神経徴候であり，眠気や生あくびなど非特異的な症状は前兆には含めない．

典型的前兆には視覚症状，感覚症状，言語症状があるが，これらの神経症状は徐々に進展し，1時間以上持続することはない．前兆には陽性徴候

Table 1 The International Classification of Headache Disorders (2nd Edition)

1. [G43] Migraine
1.1 [G43.0] Migraine without aura
1.2 [G43.1] Migraine with aura
1.2.1 [G43.10] Typical aura with migraine headache
1.2.2 [G43.10] Typical aura with non-migraine headache
1.2.3 [G43.104] Typical aura without headache
1.2.4 [G43.105] Familial hemiplegic migraine (FHM)
1.2.5 [G43.105] Sporadic hemiplegic migraine
1.2.6 [G43.103] Basilar-type migraine
1.3 [G43.82] Childhood periodic syndromes that are commonly precursors of migraine
1.3.1 [G43.82] Cyclical vomiting
1.3.2 [G43.820] Abdominal migraine
1.3.3 [G43.821] Benign paroxysmal vertigo of childhood
1.4 [G43.81] Retinal migraine
1.5 [G43.3] Complications of migraine
1.5.1 [G43.3] Chronic migraine
1.5.2 [G43.2] Status migrainosus
1.5.3 [G43.3] Persistent aura without infarction
1.5.4 [G43.3] Migrainous infarction
1.5.5 [G43.3] Migraine-triggered seizure
1.6 [G43.83] Probable migraine
1.6.1 [G43.83] Probable migraine without aura
1.6.2 [G43.83] Probable migraine with aura
1.6.5 [G43.83] Probable chronic migraine
2. [G44.2] Tension-type headache (TTH)
2.1 [G44.2] Infrequent episodic tension-type headache
2.2 [G44.2] Frequent episodic tension-type headache
2.3 [G44.2] Chronic tension-type headache
2.4 [G44.28] Probable tension-type headache
3. [G44.0] Cluster headache and other trigeminal autonomic cephalalgias
3.1 [G44.0] Cluster headache
3.2 [G44.03] Paroxysmal hemicrania
3.3 [G44.08] Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT)
3.4 [G44.08] Probable trigeminal autonomic cephalalgia
4. [G44.80] Other primary headaches
4.1 [G44.800] Primary stabbing headache
4.2 [G44.803] Primary cough headache
4.3 [G44.804] Primary exertional headache
4.4 [G44.805] Primary headache associated with sexual activity
4.5 [G44.80] Hypnic headache
4.6 [G44.80] Primary thunderclap headache
4.7 [G44.80] Hemicrania continua
4.8 [G44.2] New daily-persistent headache (NDPH)

5. [G44.88] Headache attributed to head and/or neck trauma
6. [G44.81] Headache attributed to cranial or cervical vascular disorder
7. [G44.82] Headache attributed to non-vascular intracranial disorder
8. [G44.4 or G44.83] Headache attributed to a substance 2 or its withdrawal
9. Headache attributed to infection
10. [G44.882] Headache attributed to disorder of homoeostasis
11. [G44.84] Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures
12. [R51] Headache attributed to psychiatric disorder
13. [G44.847, G44.848 Cranial neuralgias and central causes of facial pain or G44.85]
14. [R51] Other headache, cranial neuralgia, central or primary facial pain

Table 2 Diagnostic criteria of migraine without aura

1.1 Migraine without aura

Description :
Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/ or photophobia and phonophobia.

Diagnostic criteria :
A. At least 5 attacks[1] fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)[2;3;4]
C. Headache has at least two of the following characteristics :
   1. unilateral location[5;6]
   2. pulsating quality[7]
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following :
   1. nausea and/or vomiting
   2. photophobia and phonophobia[8]
E. Not attributed to another disorder[9]

Notes :
1. Differentiating between 1.1 *Migraine without aura* and 2.1 *Infrequent episodic tension-type headache* may be difficult. Therefore at least 5 attacks are required. Individuals who otherwise meet criteria for 1.1 *Migraine without aura* but have had fewer than 5 attacks should be coded 1.6.1 *Probable migraine without aura*.
2. When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children, attacks may last 1-72 hours (although the evidence for untreated durations of less than 2 hours in children requires corroboration by prospective diary studies).
4. When attacks occur on 15 days/month for >3 months, code as 1.1 *Migraine without aura* and as 1.5.1 *Chronic migraine*.
5. Migraine headache is commonly bilateral in young children ; an adult pattern of unilateral pain usually emerges in late adolescence or early adult life.
6. Migraine headache is usually frontotemporal. Occipital headache in *children*, whether unilateral or bilateral, is rare and calls for diagnostic caution ; many cases are attributable to structural lesions.
7. *Pulsating* means throbbing or varying with the heartbeat.
8. In young children, photophobia and phonophobia may be inferred from their behaviour.
9. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

および陰性徴候が混在し，完全に可逆性である．ICHD-IIでは運動麻痺（脱力）は典型的前兆からは除外して，片麻痺性片頭痛に分類するように定義されている．前兆のある片頭痛の診断基準を**Table 3**に示した．

II. 片頭痛の急性期治療

片頭痛発作の頻度，程度，生活への支障度は患者ごとに異なっているが，急性期治療法として重要なポイントは，1）確実に鎮痛できる，2）不

Table 3 Diagnostic criteria of migraine with aura

1.2 Migraine with aura

Description :
Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly ; headache lacks migrainous features or is 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 attributed to another disorder[1]

Note :
1. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

1.2.1 Typical aura with migraine headache

Description :
Typical aura consisting of visual and/or sensory and/or speech symptom. Gradual development, duration no longer than one hour, a mix of positive and negative features and complete reversibility characterise the aura which is associated with a headache fulfilling criteria for 1.1 Migraine without aura.

Diagnostic criteria :
A. At least 2 attacks fulfilling criteria B-D
B. Aura consisting of at least one of the following, but no motor weakness :
   1. fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
   2. fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
   3. fully reversible dysphasic speech disturbance
C. At least two of the following :
   1. homonymous visual symptoms[1] and/or unilateral sensory symptoms
   2. at least one aura symptom develops gradually over >5 minutes and/or different aura symptoms occur in succession over >5 minutes
   3. each symptom lasts >5 and <60 minutes
D. Headache fulfilling criteria B-D for 1.1 Migraine without aura begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder[2]

Notes :
1. Additional loss or blurring of central vision may occur.
2. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.