

Table 3.—Aura/Premonitory and Associated Symptoms of Headaches*

Symptom	Migraine With Aura (n = 41)	Migraine Without Aura (n = 272)	Episodic Tension-type Headache (n = 951)	Chronic Tension-type Headache (n = 107)
Aura/Premonitory				
Scintillating scotoma	90.2	0.0	0.0	0.0
Visual disturbance	22.0	1.5	2.8	4.7
Extremity numbness	7.3	1.1	1.4	1.9
Extremity weakness	2.4	0.0	0.0	0.0
Loss of vigor	31.7	11.4	5.2	6.5
Fatigue	41.5	35.3	24.5	27.1
Others	0.0	4.0	2.0	0.0
Associated				
Nausea	61.0	63.8	6.0	9.8
Vomiting	36.6	24.6	0.5	0.8
Photophobia	43.9	17.9	2.8	5.7
Phonophobia	24.4	17.9	2.0	8.2
Eye congestion	14.6	4.7	3.7	10.7
Lacrimation	14.6	3.0	2.1	7.4
Sore shoulder	65.9	50.5	44.6	59.0
Dizziness/vertigo	46.3	22.9	12.3	23.0
Floating sensation	14.6	6.0	3.0	4.9

*Values are percentages. n indicates the number of valid answers in each headache category.

and the prevalence of migraine was 3.5%.² Although the diagnosis was based on IHS criteria, the sensitivities of questionnaires used in the previous studies required improvement. Validated questionnaires were

used in this study. In addition to an increasing number of migraineurs relating to change of life-styles or environment (or both), the improvement of study methods, including questionnaires and diagnostic procedures,

Table 4.—Headache Triggers*

Trigger	Migraine With Aura (n = 31)	Migraine Without Aura (n = 213)	Episodic Tension-type Headache (n = 412)	Chronic Tension-type Headache (n = 71)
Fatigue	64.5	61.0	47.1	50.7
Mental stress	35.5	30.5	20.1	28.2
Lack of sleep	51.6	45.1	32.0	36.6
Excess sleep	3.2	8.9	5.6	1.4
Change of weather	22.6	20.7	11.4	12.7
Menses	12.9	20.7	11.2	11.3
Release from mental pressure	3.2	3.3	1.9	2.8
Fast/hunger	0.0	0.9	1.2	1.4
Using PC	12.9	6.6	4.9	5.6
Bright light	3.2	4.2	1.2	2.8
Wine	0.0	1.4	1.9	0.0
Chocolate	0.0	0.0	0.7	0.0
Ice cream	0.0	1.4	2.2	0.0
Smoking	3.2	3.3	1.7	2.8
Others	16.1	23.5	14.8	16.9

*Values are percentages. n indicates the number of valid answers in each headache category.

Table 5.—Impact of Headache on Daily Life and Work*

Area of Impact†	Migraine With Aura	Migraine Without Aura	Episodic Tension-type Headache	Chronic Tension-type Headache
Time or days off work				
Yes	25.8	19.5	9.3	16.4
Days, mean (SD), No.	1.8 (0.8)	3.8 (4.8)	2.1 (1.6)	1.6 (0.5)
No	74.2	80.5	90.7	83.6
Unable to do housework				
Yes	27.3	28.0	9.5	8.8
Days, mean (SD), No.	2.0 (1.1)	2.8 (4.4)	2.2 (2.0)	1.5 (0.5)
No	72.7	72.0	90.5	91.2

*Values are percentages unless otherwise indicated.

†Within the previous 3 months.

was one of the reasons why the prevalence of migraine doubled within 10 years. Sakai and Igarashi reported a prevalence of migraine of 8.4% (3.6% in men, 12.9% in women) in Japan based on their nationwide telephone survey.⁵ Since Daisen has predominantly elderly people, 6.0% of crude prevalence of migraine appears to be in accordance with previous findings. Actually, the adjusted prevalence to the national census of Japan in 1995 was 7.3%.

Prevalence of migraine was reported to be 3.0% in China,¹¹ 3.0% in Ethiopia,¹² 9.0% in Malaysia,¹³ 9.1% in Taiwan,¹⁴ 12.1% in France,¹⁵ 13.0% in the United States,⁴ 13.2% in Sweden,¹⁶ 27.5% in Germany,¹⁷ and 29.1% in Thailand.¹⁸ Prevalence of migraine in Daisen was slightly lower than previous findings from the United States or from European countries. Stewart et al reported variation in migraine prevalence by race; ie, prevalence of migraine in Asian Americans was

Table 6.—Impact of Headache on General Health Perception and Sleep

	Health Perception			Sleep	
	Good	Fair	Poor	Good	Poor
Nonheadache (n = 3045),%	24.0	66.6	9.4	79.8	20.2
Migraine with aura (n = 40),%	2.5	77.5	20.0	46.3	53.7
Odds ratio	1.0	16.7	57.6	1.0	4.2
95% confidence interval		2.3–123.5	6.7–492.3		2.3–7.8
P		.006	.0002		<.0001
Migraine without aura (n = 300),%	14.0	76.0	10.0	56.4	43.6
Odds ratio	1.0	3.2	6.6	1.0	2.7
95% confidence interval		2.2–4.6	3.8–11.5		2.1–3.5
P		<.0001	<.0001		<.0001
Episodic tension-type headache (n = 1115),%	13.5	75.1	11.5	66.0	34.0
Odds ratio	1.0	2.5	4.0	1.0	1.9
95% confidence interval		2.1–3.1	3.0–5.5		1.6–2.2
P		<.0001	<.0001		<.0001
Chronic tension-type headache (n = 121),%	11.6	60.3	28.1	65.5	34.5
Odds ratio	1.0	2.2	8.8	1.0	2.1
95% confidence interval		1.2–4.0	4.3–17.7		1.4–3.1
P		.009	<.0001		.0002

Table 7.—Behavior and Pattern of Use of Medical Care for Headaches*

	Migraine With Aura	Migraine Without Aura	Episodic Tension-type Headache	Chronic Tension-type Headache
Consult physician				
No. of residents	41	301	1125	122
Never	61.0	71.8	89.3	68.9
Once	9.8	7.0	3.7	3.3
Couple times	22.0	15.9	4.7	15.6
Consult continuously	7.3	5.3	2.2	12.3
Never consult physician				
No. of residents	14	123	286	39
Too busy	14.3	16.3	14.7	7.7
Headache not severe enough	35.7	29.3	49.7	43.6
Will improve spontaneously after standing	57.1	56.9	51.4	53.8
Headache not serious enough	7.1	15.4	14.3	20.5
OTC medication is effective	21.4	53.7	32.9	41.0
Physician will not help	7.1	0.8	1.4	2.6
Do not know where to go	0.0	2.4	1.7	2.6
No difference between prescribed drug versus OTC	7.1	5.7	4.2	12.8
Other reasons	21.4	8.9	5.6	10.3
Do not consult continuously				
No. of residents	13	69	95	23
Too busy	7.7	15.9	8.4	13.0
Headache not severe enough	38.5	30.4	45.3	43.5
Will improve spontaneously after standing	30.8	27.5	38.9	39.1
Headache not serious enough	7.7	8.7	3.2	4.3
OTC medication is effective	23.1	30.4	25.3	17.4
Headache will not threaten life	7.7	8.7	3.2	4.3
Physician will not help	7.7	4.3	2.1	13.0
Do not know where to go	0.0	5.8	2.1	13.0
No difference between prescribed drug versus OTC	7.7	11.6	3.2	4.3
Physician did not help	0.0	8.7	3.2	13.0
Other reasons	15.4	14.5	12.6	21.7
Use of headache remedy				
No. of residents	32	214	414	78
Always	46.9	27.1	19.3	32.1
Occasionally	37.5	51.4	42.8	41.0
Never	15.6	21.5	37.9	26.9
Remedies	33.3	22.7	27.8	35.7
Prescription	50.0	61.0	61.5	39.3
OTC	16.7	16.3	10.7	25.0
Both	33.3	22.7	27.8	35.7

*Values are percentages. OTC indicates over-the-counter.

9.2% in women and 4.1% in men, while in Caucasians it was 20.4% in women and 8.6% in men.¹⁹ The difference of migraine prevalence among communities might be caused from differences in diagnostic accuracy and methods of subject samplings, or from differences in genetic and environmental factors. The migraine prevalence of Asian Americans is quite similar to our present results.

The predominance of females is significant in the present results as in previous studies that implicated pathophysiological relations to hormonal activity. The female to male ratio of prevalence of MWA was $0.7/0.4 = 1.75$ and of MWOA, $8.1/1.9 = 4.2$. Female predominance of migraine was more pronounced in MWOA than in MWA, in accord with earlier observations.^{5,20} As shown in the Figure, migraine

Table 8.—Food Preference and Migraine, Adjusted by Age and Gender

	Migraine (n = 340)			Tension-type Headache (n = 1226)		
	Odds Ratio	95% CI	P	Odds Ratio	95% CI	P
Breakfast						
Daily	1.1	0.7–1.7	.79	0.9	0.7–1.2	.42
Couple times/week	1.0	0.6–2.0	.90	1.0	0.7–1.5	.86
Rare/never	1.0			1.0		
Green-yellow vegetable						
Everyday	0.8	0.6–1.1	.14	0.8	0.7–0.92	.003
Every other day	0.9	0.7–1.2	.57	0.8	0.7–0.97	.02
Occasionally/never	1.0			1.0		
Fruits						
Everyday	1.0	0.8–1.3	.97	0.7	0.6–0.9	.0001
Every other day	1.1	0.8–1.4	.70	0.8	0.7–1.0	.02
Occasionally/never	1.0			1.0		
Fresh vegetable						
Everyday	1.1	0.7–1.6	.67	0.8	0.7–1.0	.09
Every other day	1.0	0.8–1.3	.86	0.9	0.8–1.1	.28
Occasionally/never	1.0			1.0		
Eggs						
Everyday	1.0	0.7–1.3	.83	0.8	0.7–1.0	.053
Every other day	0.9	0.6–1.2	.37	0.8	0.7–1.0	.03
Occasionally/never	1.0			1.0		
Fish						
Everyday	0.7	0.5–1.0	.04	0.8	0.7–1.0	.02
Every other day	1.0	0.7–1.3	.90	0.9	0.7–1.0	.14
Occasionally/never	1.0			1.0		
Meat						
Everyday	1.1	0.8–1.4	.56	1.0	0.8–1.2	.98
Every other day	1.0	0.8–1.5	.78	1.0	0.9–1.2	.75
Occasionally/never	1.0			1.0		
Milk						
Everyday	1.1	0.5–1.3	.55	0.8	0.7–0.9	.01
Every other day	1.1	0.5–1.5	.66	0.9	0.7–1.0	.12
Occasionally/never	1.0			1.0		
Soybeans and related foods (Tofu and Nattou)						
Everyday	0.8	1.2–2.3	.39	0.8	0.6–1.1	.10
Every other day	0.9	1.0–1.8	.63	0.8	0.6–1.1	.10
Occasionally/never	1.0			1.0		
Oil/fat						
Everyday	1.7	0.6–1.2	.002	1.1	0.9–1.3	.32
Every other day	1.3	0.8–1.4	.10	1.0	0.8–1.2	.96
Occasionally/never	1.0			1.0		
Seaweed						
Everyday	0.9	0.5–1.2	.38	0.9	0.7–1.0	.10
Every other day	1.1	0.7–1.1	.56	0.9	0.7–1.0	.08
Occasionally/never	1.0			1.0		
Potatoes						
Everyday	0.7	1.7–3.5	.18	0.7	0.5–0.9	.01
Every other day	0.9	1.0–2.7	.35	0.8	0.7–1.0	.02
Occasionally/never	1.0			1.0		
Coffee/tea						
Everyday	2.4	0.6–1.9	<.0001	1.1	0.9–1.3	.32
Every other day	1.6	0.8–2.2	.08	1.0	0.8–1.3	.89
Occasionally/never	1.0			1.0		
Night meal						
Everyday	1.0	0.6–1.9	.90	0.9	0.7–1.3	.70
Every other day	1.3	0.8–2.2	.27	1.1	0.8–1.5	.55
Occasionally/never	1.0			1.0		

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.

Acknowledgments: This study was supported in part by grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology, Government of Japan (T. T.), Health and Labor Sciences Research Grants (T. T. and K. N.), and a grant from AstraZeneca Japan. Appreciation is expressed to the local public health nurses of Daisen for their cooperation.

REFERENCES

- Mishima K, Takeshima T, Okada H, et al. Epidemiology of headache in a small island in San-in, Japan. *Auton Nerv Syst.* 1996;33:298-305.
- Shimomura T, Kowa H, Takahashi K. Epidemiologic study of migraine in west Tottori. *Jpn J Headache.* 1992;19:93-95.
- Stewart WF, Schechter A, Rasmussen BK. Migraine prevalence: a review of population-based studies. *Neurology.* 1994;44(suppl 4):S17-S23.
- Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. *Neurology.* 2002;58:885-894.
- Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. *Cephalalgia.* 1997;17:15-22.
- 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.
- Urakami K, Igo M, Takahashi K. An epidemiologic study of cerebrovascular disease in western Japan: with special reference to transient ischemic attacks. *Stroke.* 1987;18:396-401.
- Urakami K, Adachi Y, Takahashi K. A community-based study of parental age at the birth of patients with dementia of the Alzheimer type. *Arch Neurol.* 1989;46:38-39.
- Kusumi M, Nakashima K, Nakayama H, Takahashi K. Epidemiology of inflammatory neurological and inflammatory neuromuscular diseases in Tottori Prefecture, Japan. *Psychiatry Clin Neurosci.* 1995;49:169-174.
- Nakashima K, Yokoyama Y, Shimoyama R, et al. Prevalence of neurological disorders in a Japanese town. *Neuroepidemiology.* 1996;15:208-213.
- Wang SJ, Liu HC, Fuh JL, et al. Prevalence of headaches in a Chinese elderly population in Kinmen: age and gender effect and cross-cultural comparisons. *Neurology.* 1997;49:195-200.
- Tekle-Haimanot R, Seraw B, Forsgren L, Ekblom K, Ekstedt J. Migraine, chronic tension-type headache, and cluster headache in an Ethiopian rural community. *Cephalalgia.* 1995;15:482-488.
- Alders EE, Hentzen A, Tan CT. A community-based prevalence study on headache in Malaysia. *Headache.* 1996;36:379-384.
- Wang SJ, Fuh JL, Young YH, Lu SR, Shia BC. Prevalence of migraine in Taipei, Taiwan: a population-based survey. *Cephalalgia.* 2000;20:566-572.
- Henry P, Michel P, Brochet B, et al. A nationwide survey of migraine in France: prevalence and clinical features in adults. *Cephalalgia.* 1992;12:229-237.
- Dahlof C, Linde M. One-year prevalence of migraine in Sweden: a population-based study in adults. *Cephalalgia.* 2001;21:664-671.
- Gobel H, Petersen Braun M, Soyka D. The epidemiology of headache in Germany: a nationwide survey of a representative sample on the basis of the headache classification of the International Headache Society [see comments]. *Cephalalgia.* 1994;14:97-106.
- Phanthumchinda K, Sithi-Amorn C. Prevalence and clinical features of migraine: a community survey in Bangkok, Thailand. *Headache.* 1989;29:594-597.
- Stewart WF, Lipton RB, Liberman J. Variation in migraine prevalence by race. *Neurology.* 1996;47:52-59.
- Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia.* 1992;12:221-228.
- Silberstein SD, Lipton RB, Solomon S, Mathew NT. Classification of daily and near-daily headaches:

- proposed revisions to the IHS criteria. *Headache*. 1994;34:1-7.
22. Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: field trial of revised IHS criteria. *Neurology*. 1996;47:871-875.
 23. Seltzer S. Foods, and food and drug combinations, responsible for head and neck pain. *Cephalalgia*. 1982;2:111-124.
 24. Grant EC. Food allergies and migraine. *Lancet*. 1979;1:966-969.
 25. Medina JL, Diamond S. The role of diet in migraine. *Headache*. 1978;18:31-34.
 26. Bic Z, Blix GG, Hopp HP, Leslie FM, Schell MJ. The influence of a low-fat diet on incidence and severity of migraine headaches. *J Womens Health Gen Based Med*. 1999;8:623-630.

Genetics of Migraine Headache

JMAJ 47(3): 140–145, 2004

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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

This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 128, No. 11, 2002, pages 1640–1644).

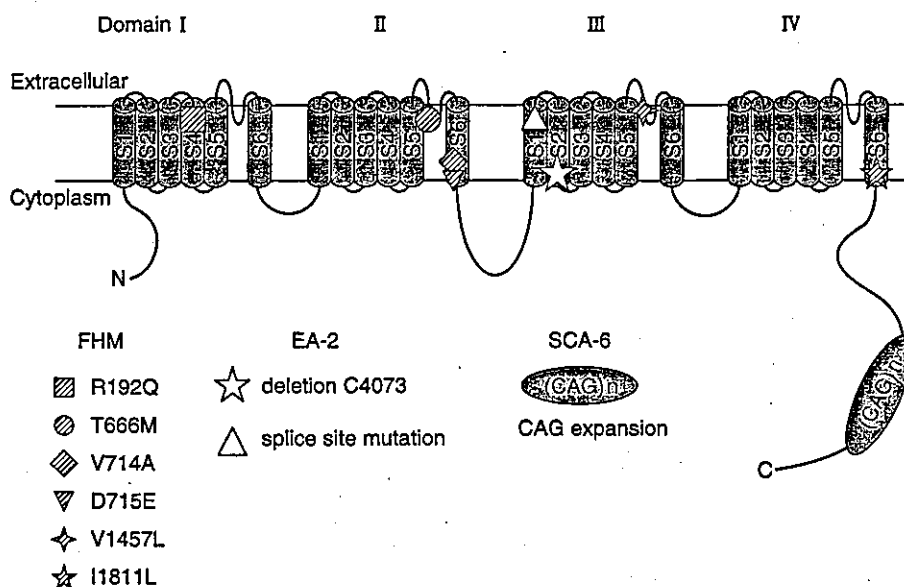


Fig. 1 Structure of the P/Q type Ca^{+2} channel $\alpha 1$ subunit (CACNA1A) and the FHM mutation site

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 (CACNA1A; 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 ³¹P-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

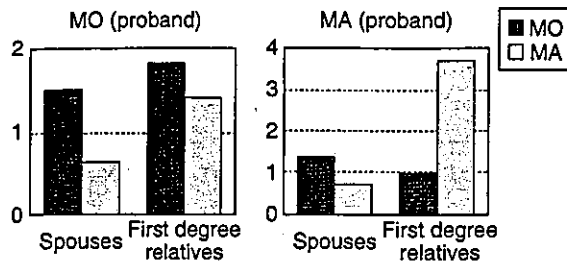


Fig. 2 Relative risk for migraine among spouses and first degree relatives

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-hydroxytryptamine; 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 5HT₁ through 5HT₇. 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 stimu-

lation 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 allele 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' study¹²⁾ 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 homocysteine 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.

REFERENCES

- 1) Takeshima, T., Ishizaki, K., Fukuhara, Y. *et al.*: Prevalence and QOL of migraine: Daisen study. *Japanese Journal of Headache* 2002; 29(1): 66–68. (in Japanese)
- 2) Ophoff, R.A., Terwindt, G.M., Vergouwe, M.N. *et al.*: Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca²⁺ channel gene CACNL1A4. *Cell* 1996; 87: 543–552.
- 3) Ducros, A., Denier, C., Joutel, A. *et al.*: The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *N Engl J Med* 2001; 345: 17–24.
- 4) Dichgans, M., Mayer, M., Uttner, I. *et al.*: The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol* 1998; 44: 731–739.
- 5) Uchino, M., Uyama, E., Maeda, Y. *et al.*: CADASIL – Clinical analysis of CADASIL and CADASIL-like disorders in Japan. *Rinsho Shinkeigaku* 2000; 40(12): 1247–1250. (in Japanese)
- 6) Ophoff, R.A., DeYoung, J., Service, S.K. *et al.*: Hereditary vascular retinopathy, cerebroretinal vasculopathy, and hereditary endo-
theliopathy with retinopathy, nephropathy, and stroke map to a single locus on chromosome 3p21.1-p21.3. *Am J Hum Genet* 2001; 69: 447–453.
- 7) Takeshima, T., Fukuhara, Y., Adachi, Y. *et al.*: Leukocyte mitochondrial DNA A-to-G polymorphism at 11084 is not a risk factor for Japanese migraineurs. *Cephalalgia* 2001; 21: 987–989.
- 8) Russell, M.B., Iselius, L. and Olesen, J.: Migraine without aura and migraine with aura are inherited disorders. *Cephalalgia* 1996; 16: 305–309.
- 9) Burnet, P.W., Harrison, P.J., Goodwin, G.M. *et al.*: Allelic variation in the serotonin 5-HT_{2C} receptor gene and migraine. *Neuroreport* 1997; 8: 2651–2653.
- 10) Kusumi, M., Adachi, Y., Kowa, H. *et al.*: Association study of 5-HT_{2C} and DRD2 gene in migraine. *Japanese Journal of Headache* 1999; 26(1): 42–44. (in Japanese)
- 11) Peroutka, S.J., Wilhoit, T. and Jones, K.: Clinical susceptibility to migraine with aura is modified by dopamine D2 receptor (DRD2) *NcoI* alleles. *Neurology* 1997; 49: 201–206.
- 12) Kowa, H., Yasui, K., Takeshima, T. *et al.*: The homozygous C 677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. *Am J Med Genet* 2000; 96: 762–764.
- 13) Paterna, S., Di Pasquale, P., D'Angelo, A. *et al.*: Angiotensin-converting enzyme gene deletion polymorphism determines an increase in frequency of migraine attacks in patients suffering from migraine without aura. *Eur Neurol* 2000; 43: 133–136.
- 14) Wessman, M., Kallela, M., Kaunisto, M.A. *et al.*: A susceptibility locus for migraine with aura, on chromosome 4q24. *Am J Hum Genet* 2002; 70: 652–662.

慢性頭痛の予後決定因子

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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、治療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、エピソード的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、ということを確認にすべきである。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な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「典型的な前兆」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 Igarashi²⁾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、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^{1,2)}より抜粋)

- A. B～Dを満たす頭痛発作が5回以上ある⁽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)^(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^(5,6)
 - 2. 拍動性⁽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⁽⁸⁾
- E. その他の疾患によらない⁽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ことが多い。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¹¹⁾より抜粋)

- A. 3カ月にわたり、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

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、女性優位がもつ

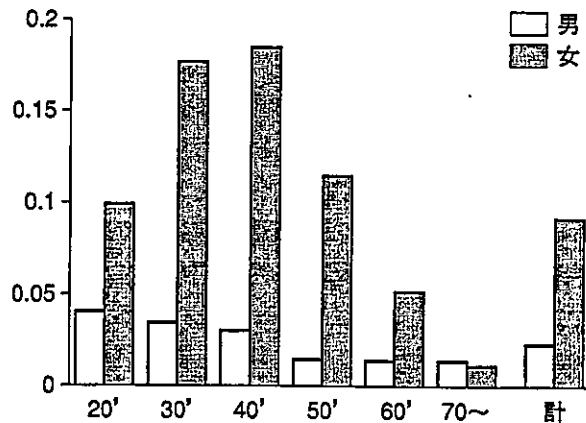


図1 鳥取県大山町の片頭痛有病率 (文献⁹⁾より引用し改変)

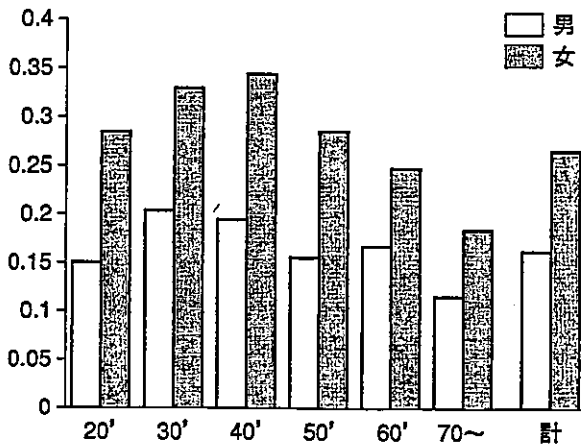


図2 鳥取県大山町の緊張型頭痛有病率 (文献⁹⁾より引用し改変)

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⁹⁾。

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%⁹⁾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 Russell⁶⁾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⁷⁾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 強調画像、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⁹⁾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
機能的腸疾患
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チャンネル遮断薬
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

ア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る、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。

文 献

- 1) Headache classification subcommittee of the international headache society. The international classification of headache disorders, 2nd edition. Cephalalgia 24 (Suppl 1): 1-160, 2004
- 2) Sakai F, Igarashi H: Prevalence of migraine in Japan: a nationwide survey. Cephalalgia 17: 15-22, 1997
- 3) Takeshima T, Ishizaki K, Fukuhara Y, et al: Population-based door-to-door survey of migraine in Japan: The Daisen Study. Headache 44: 8-19, 2004
- 4) Lipton RB, Scher AI, Kolodner K, et al: Migraine in the United States: Epidemiology and patterns of health care use. Neurology 58: 885-894, 2002
- 5) Eriksen MK, Thomsen LL, Russell MB: Prognosis of migraine with aura. Cephalalgia 24: 18-22, 2004
- 6) Igarashi H, Sakai F, Kan S, et al: Magnetic resonance imaging of the brain in patients with migraine. Cephalalgia 11: 69-74, 1991
- 7) Kruit MC, Van Buchem MA, Hofman PA, et al: Migraine as a risk factor for subclinical brain lesions. JAMA 291: 427-434, 2004
- 8) Lipton RB, Pan J: Is migraine a progressive brain disease? JAMA 291: 493-494, 2004
- 9) Silberstein SD, Lipton RB, Sliwinski M: Classification of daily and near-daily headaches: Field trial of revised IHS criteria. Neurology 47: 871-875, 1996
- 10) Silberstein SD, Goadsby PJ: Migraine: preventive treatment. Cephalalgia 22: 491-512, 2002
- 11) 国際頭痛学会・頭痛分類委員会 (日本頭痛学会・新国際分類普及委員会訳): 国際頭痛分類第2版 (ICHD-II) 日本語版, 日本頭痛学会誌 (印刷中)

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、エピソード的な疾患である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⁵⁾および、内外の片頭痛治療ガイドライン^{6,7)}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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