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CONTENTS

Correction: Error in Category
The article titled, "Radiocurable Tumors and Non-Radiocurable Tumors," published in the February issue of the JMAJ (79–83, 47 (2), 2004) was incorrectly included in the category of Interferon Therapy. We regret the error.

JMA's Health Care Activities in Nepal
—Cooperation to build a healthy village community—

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Key words: International health; Public health; School health; Community health; Nepal

Introduction

The Kingdom of Nepal is situated north of India nestled at the foot of the Himalayas and Mt. Everest, and its state religion is Hinduism. Based on a request by His Majesty's Government of Nepal, the Japan Medical Association (JMA) dispatched school and community health experts to implement the School and Community Health Project (SCHP), a health development cooperation project. The project was started in 1992 and this is the eleventh year since its inception.

The objectives, characteristics, transitions in activities, and the significance of the SCHP are discussed below.

Objectives of the Project

Nepal is one of the most poverty-stricken nations in the world, and there are many international agencies and NGOs that undertake development activities in the country. Despite this fact, the maternal and infant mortality rates are extremely high.

Due to the proximity of Mt. Everest and the harsh undulating terrain, the development activities of both the domestic and international aid agencies are adequately implemented in the urban areas, but they are nearly nonexistent in the mountainous areas where access is limited. On my several visits to Nepal, it seemed as if I were seeing the earth's wrinkles from the view from the plane.

The SCHP implemented by the JMA is removed from the urban area and its activities are aimed at building healthy village communities in the rural mountainous region where medical and community health care services are inadequate.

Characteristics of the Project

The project has two distinct features. Firstly, the SCHP is a pioneering endeavor that introduced school health concepts to Nepal for the first time. Secondly, the SCHP adopts a new approach to building healthy villages based on two programs.

1. School health program

Japanese children are taught basic knowl-

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edge about health and hygiene at school, such as "there is invisible bacteria on your hands" or "it's important to wash your hands before you eat". This knowledge is acquired as a hygienic practice at a very young age. These children eventually become adults and have their own children. In turn, their children are taught appropriate hygienic practices at two places, the school and the home. This is an established way of learning about hygienic that I have taken for granted, but it is indicative of the fact that in terms of global standards, school health in modern Japan is highly organized and widespread.

Basic knowledge about health has permeated Japanese society, and hygienic practices have become established. As a result, high health standards have been maintained, contributing to the longevity of the Japanese people. Thus, it is with renewed awareness that an approach that promotes comprehensive health and hygiene education for schoolchildren through school health is greatly effective.

School health was legally established in postwar Japan, and it helped improve the hygienic environment during the postwar restoration period. Using this home-grown approach of utilizing school health as a central means of promoting health, a variety of health activities such as literacy education were combined and used to promote health care in schools and at home with the aim of improving the health of community residents. This is the goal of JMA's international cooperation activities and a distinct feature of this project.

2. Community health program

To improve the health conditions of the region's inhabitants, it is essential to raise the regional community's awareness about health care, to teach them what is important for health, and to put that knowledge to practical use. This is true for both Japan and Nepal.

However, the fundamental difference between Japan and Nepal is the very limited knowledge that the Nepalese people have about health and health care and the very different ideas and values that they have about health. The definition of health varies, but Western medical science has identified what health conditions define human life. However, it is difficult for this knowledge about health and health care to permeate Nepalese society and to evolve into established ideas and practices, unless the people themselves actively pursue health care activities.

Thus, the focus of the project's activities — from school health, literacy education, polio vaccinations, to infectious disease prevention measures against the onset of diarrhea during the rainy season (which contributes to the mortality rate) — is centered on the activities undertaken by community residents. It is a grassroots movement, a bottom-to-top health movement that promotes activities carried out by the community residents themselves.

The grassroots health movement is vital in order to ensure that project activities are sustained in the community after they have formally ended under the project. Additionally, the existence of health care personnel that will support these community activities is also essential in order for the community's awareness and activities that have been fostered to take root and stabilize.

Thus, two approaches aimed at building a healthy village community have been simultaneously pursued in this project. The first is to support community to implement health activities and the second is to develop a cadre of health care personnel who will be responsible for promoting these health activities in the community.

In Japan, physicians, nurses, and staff members of health centers are usually thought of as health care personnel. However, there is no hospital or an adequately equipped health center in the mountain village of Nepal where the JMA is presently active.

Then where do parents take their fevered child for medical assistance? In Nepal, evil spirits that have taken possession of the body are strongly believed to be the cause of disease

and illness. The parents will take their sick child to a traditional healer with religious powers living in the village who is called Dhami Jhakri.

The Dhami Jhakri are traditional healers with knowledge of herbal medicine and prayers to cast out evil spirits that have been passed down from previous generations. They are highly trusted by the villagers and they are looked on as the health caretaker of the village; and in fact, they have acted as the region's health care personnel for generations. But they are also aware through their experience that there are diseases that cannot be cured through prayers and herbal medicine.

Subsequently, the project has implemented training for the Dhami Jhakri. By teaching them Western medical knowledge and first-aid treatment measures, they are able to treat a dehydrated child suffering from diarrhea by quickly providing oral rehydration. An emergency first-aid kit containing oral rehydration salt is distributed to the Dhami Jhakri at the end of their training period. Such measures strengthen the training impact and alliance with the traditional village healers. Thus, the communication between the Dhami Jhakri and health post has been increasingly active.

3. Other project activities

In addition to the training activities for the Dhami Jhakri that was introduced earlier, other types of activities have also been implemented under this project.

His Majesty's Government of Nepal has established health posts, which are staffed by qualified personnel. In order to develop qualified manpower to work in the health post, the project awards scholarships to the youth that are selected from the village to study health and medical care. Other activities include training of community health volunteers and advocacy activities by visiting the Ministry of Health and local government offices to introduce and further understanding of the project's activities.

Transitions in the Project's Activities

I would like to explain in further detail the type of activities actually undertaken by the project, the transitions that they have undergone in the course of their actual implementation, and a few of the major activities of the project.

1. Phase I activities

The SCHP was started in 1992 in Khopasi Village located 40 km southeast of the capital, Kathmandu. A primary health care center (Khopasi PHC center), at the level of a public health facility, was constructed under the project in conjunction with the program to develop health care personnel. Utilizing the school that was located adjacent to the Khopasi PHC center as a base, Nepal's first school health program was begun in addition to the health activities carried out by the village residents.

The Khopasi PHC center transports emergency patients, conducts medical examinations by a Nepalese physician, functions as a public health center and safeguards the health of the community residents. The operating cost of the facility used to be assisted by the project, but the facility is presently managed by an organization of village residents.

2. Phase II activities

The project's activities, which targeted Khopasi Village, were implemented until 1996. Since 1997, the experiences of these health activities were introduced to the mountain villages where the Nepalese government and other international NGOs could not reach. The road leading to these mountain villages are unpaved and it takes about two to three days on foot to reach one village. It is an activity that is implemented in the deepest reaches of the mountains and it is an unimaginable situation in Japan. I have had the experience of walking four hours one way to reach a mountain village. On the way, I was shocked to see a woman climbing a very narrow mountain path with

construction materials on her back.

Village meetings are the first activities that are conducted at these remote mountain villages. At these meetings, the villagers are encouraged to think about the prevailing conditions in their village and to discuss what their village has and what is needed.

It was a surprise to find that each village believed that the most important facility in their community was the school. This fact had significant meaning to our activities. In this way, the project's activities that targeted these mountain villages did not include building new facilities, but rather, the existing village schools were used as the center of the project's various health activities.

- **The significance of school health in the mountainous region**

  The major school health activities that were implemented in the mountain villages were mainly the installation of school toilets to improve the sanitary environment and health promotion activities through the Child Initiative Program.

  Installation of school toilets: Although there were toilets at the schools, they were poorly maintained and extremely unhygienic. Under the SCHP, the new toilets were used to demonstrate, to teach, and to develop hygiene habits among the students. The project also installed drinking water facilities where the children could wash their hands as well as use the toilets.

  By 2000, toilets were installed at all the schools in the project area. Understanding and developing the habit of washing one's hands after using the toilet played a great role in a region where the onset of diarrhea led to deaths. Thus, installing toilets at the schools served as a significant means of teaching this important habit to schoolchildren.

  Activities of the Child Initiative Program: The Child Club, which is like a student council, was formed at each school. Students who were the most interested in health activities were selected by the school and assumed a leadership role for the school's health activities. Neither the teachers nor the project implemented the activities. The Child Club members assumed the responsibility of school health activities with the help of teachers and the project. The objective was to ensure the sustainability of these activities. In Nepal, teachers are frequently transferred to different schools, thus, teacher-centered activities often tend to be discontinued when the teacher leaves.

  The Child Club continues to actively initiate health activities, performs plays, and writes songs to enhance the understanding of good health by the lower grade students. In their plays, parents, local health workers, the Dhami Jhakri, and other immediate members of the community appear. Basic hygiene habits such as "wash your hands before eating" or "if you eat a variety of vegetables, you won't come down with the sickness where you can't see at night" are introduced.

  Because many of the village people do not go to school, knowledge and understanding of health matters among the adult population is exceedingly poor. Thus, the goal of teaching health knowledge and hygiene habits to schoolchildren is that these children look after the health of their siblings and their families and grow up to be future leaders for improved community health. Without the involvement of children, changing the health habits and awareness of the community is difficult due to the harsh environment that surrounds the Nepalese people.

  The school health activity also distributes first-aid kits to schools and organizes a campaign promoting the use of antihelminth medication to all the schools in the region.

- **Importance of literacy education**

  Another project activity that is implemented in the mountain villages is adult literacy for women.

  Numerous community health development activities are presently implemented in many developing countries. Among these activities,

the role of a mother in community health development is often reported. This is because the mother is the caretaker of the family and children. Thus, this project focuses on the empowerment of women and promotes adult literacy as an entry point for promoting community health activities.

The literacy rate is 59 percent for men and 29 percent for women in Nepal, which remains low. In recent years, it has been found that there is a strong link between the infant mortality rate and adult literacy. Subsequently, literacy education textbooks that include health topics have begun to be used.

The literacy program in the project targets women from 15 to 49 years of age. In the first year of the program a six-month basic literacy course is implemented, and in the second year, a post-literacy course that includes topics on health and nutrition is given to introduce a more practical aspect to the program. The study period for both the basic and the advanced courses are six months each, and it takes the mothers an average of two years to complete the entire program. This is due to the fact that many are engaged in farm work and during the busy agricultural period, they are unable to continue their studies.

A course on home gardening is another important program in addition to the literacy program. The aim was to enable those who participated in the literacy course and their families to experience the actual benefits derived from their study, in addition to improving the family's nutritional intake. This program has promoted the understanding of the communities and families about the importance of women's literacy.

The mothers, who have completed the two-year literacy program, are given guidance on forming community self-help groups. Having studied about health and health activities in the literacy program, these women's groups get together to maintain and develop home gardening, first-aid skills, install simple toilets, generate joint revenue by raising goats and pigs, as well as manage mutual support activities. Presently, the self-help groups in each community have developed into the core leadership of their community's health activities. Under the auspices of this project, the self-groups meet regularly for discussions and their activities are assisted by the project.

3. Phase III activities

The Project's activities comprised of the school health program and the community health program began to gradually expand their targeted communities from 1997. An increased number of women's groups have been formed. All the schools in the targeted project region have installed toilets. In 2000, the focus was placed on strengthening the capacities of community groups in each community, not only because the project encouraged the community residents to develop independent activities, but due to the gradual deterioration of public safety throughout Nepal.

Attempts at overthrowing the monarchial system and terrorist acts by a Maoist group have been carried out throughout the country. The police station was attacked and destroyed in the project region; and law and order have swiftly deteriorated over the past few years.

However, the women's groups that have been supported by the project have fortunately continued to progress towards sustained self-reliance in their activities. Despite the stringent circumstances that prevail, these groups have become the nucleus of community health activities; and the project has supported their efforts at independently managing the activities that were promoted in the project. Presently, effort has been dedicated to fostering human resources that will help enable women groups and schools in the same community as well as community organizations to coordinate their efforts in a major alliance.

Significance of the Project

In concluding this discussion about the activities in Nepal, I would like to discuss the significance of the project. The objective of the JMA medical assistance project is to develop a sustainable program where the village people can continue to carry out the activities following the end of the project. The idea is for community residents to continue to undertake activities without external assistance.

To ensure the sustainability of the activities, the SCHP's solution has been to foster human resources. Human resources in this context refer to the local professionals, the Dhami Jhakri, and the community residents. The project's objectives were to support the activities implemented by the community in conjunction with the residents and to raise the community's awareness using schools and other facilities in the community.

In international cooperation, implementing activities that draw out the potential capabilities of community residents is known as empowerment. Thus, the significance of this project lies in the fact that it illustrates the huge potential of empowerment oriented health promotion activities.

Moreover, the school health program has the greatest potential among these activities. Promoting the school health program as a means of health promotion is probably a measure that is uniquely Japanese. However, introducing this Japanese concept especially to developing countries does not imply that the Japanese school health system is simply exported to these countries. It is important that the concept is adapted to suit the needs and environment of that country before it is introduced. In this respect, this activity was based completely on trial and error.

Thus, the JMA's project activities reflect the history of school health in Nepal. JMA's activities have continued for the past decade, they have been coordinated and pursued with the central and regional governments of Nepal, international organizations such as UNICEF and WHO, international and local NGOs, and other organizations.

Consequently, the school health program has gradually become widely recognized and accepted throughout Nepal. In 2001, the government of Nepal established a school health division within its Ministry of Health. Furthermore, a plan is under review to implement a "School Health Program Based on the JMA Model" in the model regions. The JMA plans on continuing its assistance activities under this project with the hope and anticipation that the seeds that it has planted, especially in school health, will take root and spread throughout Nepal.

Another significance of this project is that it is a jointly implemented cooperation project between a nongovernmental organization, the JMA and a government agency, the Japan International Cooperation Agency (JICA). The SCHP has been implemented with the cooperation of JICA since its start in 1992. Generally, international cooperation is largely implemented by government agencies and NGOs. Due to the different budgets that are available for each organization, construction projects such as building bridges are implemented by government agencies and the NGOs are usually involved in assisting grassroots activities that support local communities.

The SCHP is a cooperation project that has been implemented by two organizations with expertise in different areas. In retrospect, if assistance from either the JMA or JICA were excluded, the outcome of the project would not have been as successful as it has been. International cooperation activities that have been pursued based on this type of joint cooperation between a NGO and a government agency has produced highly effective results; and it has helped reduce ODA costs. That is why it has been the focus of great interest in view of the prevailing economic conditions over the past few years. It is hoped that the method of cooperation that was adopted in the SCHP will serve as a point of reference for future international

cooperation activities implemented by Japan as well as other countries.

Conclusion

The goal of development cooperation activities is to eliminate the need for assistance. The objective of the SCHP is to promote activities that will enable the community groups to become self-reliant. It is hoped that when the Japanese health experts in Nepal, who presently share the trials and tribulations of the project with the village residents, leave the country, the health concepts disseminated in this project will remain and continue to be practiced by the village residents in their endeavor to build a healthy community. It is to this end that the Japanese project leaders continue to implement these activities in conjunction with the residents of the community. Sharing the joys and hardships with community residents in this kind of project represents the fundamental basis of what medicine should be.

Classification of Chronic Headache

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Abstract: Most patients with chronic headache suffer from chronic functional headaches, consisting of migraine, tension-type headache, and cluster headache as three major causes. However, there are rare types of chronic functional headache such as chronic paroxysmal hemicrania, idiopathic stabbing headache, benign cough headache, benign exertional headache, and benign sexual headache. Chronic headache evoked by organic disorders such as intracranial tumors or inflammations, and posttraumatic intracranial lesions must always be ruled out. Chronic daily headache (CDH) is designated as a headache which lasts more than 15 days per month. Although the International Headache Society (IHS) classification does not contain the idea of CDH, 4–5% of the population are said to suffer from this type of headache. Primary CDH includes chronic migraine, chronic tension-type headache, new daily persistent headache, and hemicrania continua, and it should be born in mind that CDH is often induced by overuse of anti-migraine drugs and analgesics. Chronic headache is important in clinical practice because it is one of the major causes to lower QOL of the people and can usually be saved by correct diagnosis and treatments.

Key words: Chronic headache; International Headache Society classification; Chronic daily headache

Introduction

Chronic headache is not defined formally by the International Headache Society (IHS) classification (1988).[1)] However, it is commonly used as the headache which occurs repeatedly or persistently for a long period, including migraine, tension-type headache and cluster headache as major disorders. It involves many people and lowers their quality of life (QOL), thus implicating an important disease in daily clinical practice. In this article, classification of chronic headache and essential points for the diagnosis are presented.

The Disorders with Chronic Headache in the IHS Classification

In the IHS classification, headache is classified into primary headache which is functional

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and a secondary one which is of organic, metabolic or drug-induced origin.[1)] Primary chronic headache includes migraine, tension-type headache, and cluster headache, while secondary chronic headache consists of chronic posttraumatic headache, and chronic headache associated with substance use. The patients with primary headache outnumber those with secondary one. It is announced that the revised version of IHS classification will be presented at the XI Congress of IHS to be held in Rome in 2003,[2)] and that the number of major categories will increase from 13 in the first version to 15 in the revised. Although some modifications are predicted in the terminology of diseases, they are not clear at present. Therefore, in this article the name of headache disorders is expressed as in the first version.

In the IHS classification,[1)] the period implying "chronic" is not determined. However, "chronic tension-type headache" means the tension-type headache which occurs at least 15 days a month during 6 months. And, "chronic cluster headache" occurs for more than one year without remission or with remission lasting less than 14 days. It is thought, therefore, that "chronic" means a period of 6 to 12 months or more. In the literature, Lance classified headache into "acute", "subacute", and "chronic", describing under the title of chronic headache that "in the patient who has suffered from headache for a year or more, the prospect of a tumor or other serious disorder being the cause is more remote. If the patient's headache have been consistent in character for 5 years or more one may feel fairly confident that they are not caused by intracranial tumor".[3)] The disorders presenting with chronic headache are shown in Table 1, based on the IHS classification.

Major Disorders Presenting with Chronic Headache

1. "*1.1* Migraine without aura"

Typically, this type of headache has the characteristics of unilateral location and pulsating quality, aggravated by walking stairs or similar physical activity, which lasts 4 to 72 hours if untreated or unsuccessfully treated. It is of moderate or severe intensity, inhibiting or prohibiting daily activities. During attacks nausea, vomiting, photophobia, and phonophobia are frequent. The frequency of attacks differ from once in several years to several times every month. The liberation from mental stress as in the weekend, and particular foods such as cheese, chocolate, and red wine provoke the attacks, as well as menstruation in women. The prevalence of migraine without aura in women is two to three times that in men. Triptans are a specific remedy for the setback of the attacks.

2. "*1.2* Migraine with aura"

In this type of headache, migraine attacks follow auras, which are neurologic symptoms localizable to cerebral cortex or brain stem, consisting of unilateral scintillating scotoma, hemisensory disturbance, hemiplegia or aphasia. An aura lasts 5 to 20 minutes, usually less than 60 minutes, then shifting to headache phase. The nature, intensity, duration, frequency, and provoking factors of headache are almost the same as "*1.1* migraine without aura", as well as sex ratio in prevalence.

3. "*2.1* Episodic tension-type headache"

Headache attacks of this type occur repeatedly with duration of 30 minutes to several days. Typically, they are of pressing or tightening quality, bilateral location, especially in the occipital and/or temporal regions. The intensity is mild or moderate without an aggravation by walking stairs or similar routine physical activities, and also without prohibiting daily activities different from migraine. They are not accompanied by nausea or vomiting (anorexia may occur), as well as by photophobia and phonophobia, although only one of the latter two may be present. The prevalence in women is somewhat more frequent than in men, which is 1 to 1.5 times of that in men. It is subdivided

Table 1 Disorders Presenting with Chronic Headache

A. Primary headaches
- *1.* Migraine
  - *1.1* Migraine without aura
  - *1.2* Migraine with aura
    - *1.2.1* Migraine with typical aura
    - *1.2.2* Migraine with prolonged aura
    - *1.2.3* Familial hemiplegic migraine
    - *1.2.4* Basilar migraine
    - *1.2.6* Migraine with acute onset aura
  - *1.3* Ophthalmoplegic migraine
  - *1.4* Retinal migraine
  - *1.7* Migrainous disorder not fulfilling above criteria
- *2.* Tension-type headache
  - *2.1* Episodic tension-type headache
    - *2.1.1* Episodic tension-type headache associated with disorder of pericranial muscles
    - *2.1.2* Episodic tension-type headache unassociated with disorder of pericranial muscles
  - *2.2* Chronic tension-type headache
    - *2.2.1* Chronic tension-type headache associated with disorder of pericranial muscles
    - *2.2.2* Chronic tension-type headache unassociated with disorder of pericranial muscles
  - *2.3* headache of the tension-type not fulfilling above criteria
- *3.* Cluster headache and chronic paroxysmal hemicrania
  - *3.1* Cluster headache
    - *3.1.1* Cluster headache periodicity undetermined
    - *3.1.2* Episodic cluster headache
    - *3.1.3* Chronic cluster headache
  - *3.2* Chronic paroxysmal hemicrania
  - *3.3* Cluster headache-like disorder not fulfilling above criteria
- *4.* Miscellaneous headache unassociated with structural lesion
  (* Included in chronic headache when headache attacks occur repeatedly)
  - *4.1* Idiopathic stabbing headache
  - *4.2* External compression headache
  - *4.3* Cold stimulus headache
    - *4.3.1* External application of a cold stimulus
    - *4.3.2* Ingestion of a cold stimulus
  - *4.4* Benign cough headache
  - *4.5* Benign exertional headache
  - *4.6* Headache associated with sexual activity
    - *4.6.1* Dull type
    - *4.6.2* Explosive type
    - *4.6.3* Postural type

B. Secondary headaches
- *5.* Headache associated with head trauma
  - *5.2* Chronic post-traumatic headache
- *8.* Headache associated with substances or their withdrawal
  - *8.2* Headache induced by chronic substance use or exposure
    - *8.2.1* Ergotamine induced headache
    - *8.2.2* Analgesics abuse headache
    - *8.2.3* Other substances
- *10.* Headache associated with metabolic disorder
  (* Included in chronic headache when associated with chronic metabolic disorders)
- *11.* Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, mouth or other facial or cranial structures (* Included in chronic headache only when associated with chronic disorders)
- *12.* Cranial neuralgias, nerve trunk pain and deafferentation pain (* Included only when they are chronic)

Digits in italic show the code number in the IHS classification in 1988[1)]
* Comments by the author

into two types depending upon whether associated or not with disorders of pericranial muscles.

4. "*2.2* Chronic tension-type headache"

Headache attacks of this type occur for at least 15 days a month over more than 6 months. The nature, intensity, and location are the same as episodic tension-type headache, which may shift to chronic tension-type headache by an abuse of analgesics. Its subdivision also consists of the type associated or not with disorders of pericranial muscles.

5. "*3.1* Cluster headache"

Cluster headache implies the headache of severe unilateral excruciating or burning pain in the orbital, supraorbital or temporal regions. It lasts for 15 to 180 minutes, associated with conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead, and facial sweating, miosis, ptosis, and/or eyelid edema. Nausea is frequent, but vomiting is rare. Headache attacks occur almost at the identical time everyday, of which series lasts for weeks or months, and remits after an attack-free period of months or years. It is called chronic cluster headache when the series of cluster headache continues for more than a year without remission or with remission lasting less than 14 days. The prevalence of cluster headache in men is 2 to 5 times that in women. A subcutaneous injection of triptans or inhalation of 100% oxygen gives rise to an immediate improvement of headache in more than 80% of the patients.

6. "*3.2* Chronic paroxysmal hemicrania"

In this disorder the headache is a severe unilateral excruciating or burning pain in the orbital, supraorbital or temporal regions, quite similar to that of cluster headache, although the duration is 2 to 45 minutes and frequency is usually more than 5 times a day, with shorter duration and higher frequency than those of cluster headache. Nausea and vomiting are rare. It is more common in women, with the prevalence being 2 to 3 times that in men. Indomethacin prevents the attacks dramatically in contrast with the fact that it is ineffective for cluster headache.

Table 2 Proposed Classification of Chronic Daily Headache

Daily or near-daily headache lasting more than 4 hours for more than 15 days a month.
1.8 Chronic migraine (previously transformed migraine)
1.8.1 with medication overuse
1.8.2 without medication overuse
2.2 Chronic tension-type headache
2.2.1 with medication overuse
2.2.2 without medication overuse
4.7 New daily persistent headache
4.7.1 with medication overuse
4.7.2 without medication overuse
4.8 Hemicrania continua
4.8.1 with medication overuse
4.8.2 without medication overuse

Cited from Silverstein, S.D. *et al.*[4]

7. "*4.1* Idiopathic stabbing headache"

Transient stabbing pain occurs spontaneously in the distribution of the first division of the trigeminal nerve without the base of organic diseases. The pain lasts for a short time, with a single stab or series of stabs recurring at irregular intervals. It occurs more commonly in the people with migraine. Indomethacin prevents the attacks.

Chronic Daily Headache (CDH)

CDH means a headache which lasts more than 4 hours, occurring for more than 15 days a month, not related to a structural or systemic disease.[4] It is said that 4 to 5% of the general population suffer from this type of headache, and that 0.5% have severe headache everyday.[4] Although not included in the IHS classification, it is obviously important in daily clinical practice. Silberstein[4] proposed the classification of CDH, adding to and complementing the IHS classification (Table 2). Drug overuse (anti-migraine drugs, analgesics, etc.) frequently

causes CDH, and therefore, subdivision of CDH is based on the association with drug overuse or not.

1. Chronic migraine

Chronic migraine was previously called transformed migraine. Migrainous headache may become less intense as time passes, and its associated symptoms such as photophobia, phonophobia, nausea, and vomiting may be obscure, while the frequency of headache attacks may increase. It may look like chronic tension-type headache. However, its pulsating quality, an augmentation in menstrual period, and precipitating factors of attacks are remaining. Triptans are also effective for the abortion of headache.

2. Chronic tension-type headache

This is the same as "*2.2* chronic tension-type headache" in the IHS classification, which is often transformed to from "*2.1* episodic tension-type headache".

3. New daily persistent headache[5]

This is designated as headache of relatively abrupt onset of a constant unremitting CDH, not related to an evolution from migraine or tension-type headache. This daily headache develops abruptly during less than 3 days, fluctuating in intensity but lasting persistently. The nature of the headache such as intensity, and pulsating or pressing quality is not defined. The constancy of location is not always present. It may mimic chronic tension-type headache (CTTH), and, therefore, must be differentiated from CTTH from the negative history of tension-type headache. It may occur after viral infections, though often developing without obvious causes.

4. Hemicrania continua

This headache is not included in the IHS classification. It is a continuous, moderately severe, unilateral headache that varies in intensity, waxing and waning, often associated with jabs and jolts, and without disappearing completely.[6] It is frequently associated with such autonomic disturbances as ptosis, miosis, conjunctival injection, tearing, and sweating as seen in cluster headache. Indomethacin brings a dramatic relief of the pain.

Conclusion

Chronic headache in the general population largely belongs to primary headache. However, secondary headache must always be ruled out. Particularly, "*8.2* headache induced by chronic substance use or exposure" is important, of which diagnosis is obtained only by an elaborate history-taking and the actual withdrawal of causative substances (anti-migraine agents, analgesics, etc.). In chronic daily headache, a scrutiny into daily use of drugs is essential.

Differential diagnosis of the disorders of primary headache is based merely on symptomatology in the IHS classification. However, similarities exist among cluster headache, chronic paroxysmal hemicrania, and hemicrania continua in association with autonomic signs of the eye, nose, and face. Therefore, adjunctive diagnostic procedures using various clinical markers, biochemical, electrophysiological or of neuroimagings, should be developed in the future.

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Differential Diagnosis of Chronic Headache

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Abstract: Headache is one of the most frequent problems in daily general medical practice. New drugs effective for migraine, including triptan, have been released one after another, but it is beyond dispute that the first step to treatment requires primarily an accurate diagnosis. When headache is regarded to be a pain in the head, doctors often casually diagnose functional headache due to a lack of sense of seriousness or urgency. However, it must not be forgotten that serious sequelae, even death, can result if the correct diagnosis of an organic headache is not made. Furthermore, even with this in mind, diagnosing a chronic headache is not simple, and even diagnosing a migraine may sometimes be difficult. An accurate differential diagnosis of chronic headache, which may seem easy but actually is rather difficult, benefits patients' quality of life without question, and is very important.

Key words: Migraine; Tension-type headache; Cluster headache; Headache diagnosis

Introduction

Headache is such a common symptom that almost everyone experiences it now and then, and it is one of the most frequently encountered problems in daily general medical practice. The need for accurate diagnosis and proper treatment of an organic headache, which takes an acute course, is beyond dispute, but also in the case of a chronic headache like migraine and tension-type headache, which in the past has not necessarily been treated as a disorder because it is so common, the need for appropriate treatment has been advocated in recent years. However, an accurate diagnosis in patients with headache seems easy but is actually difficult.

Even when trying to make a diagnosis according to the classification[1)] of the International Headache Society (IHS), which can be called the bible of headache diagnosis, there are very many headaches that are difficult to be diagnosed. When we actually treat patients with headache after having studied headache to some extent, we encounter incredibly many cases which are puzzling.

In recent years, however, various useful drugs have become available, and the differential diagnosis of chronic headache, which seems easy but actually is difficult, benefits patients' lives without question, and is important.

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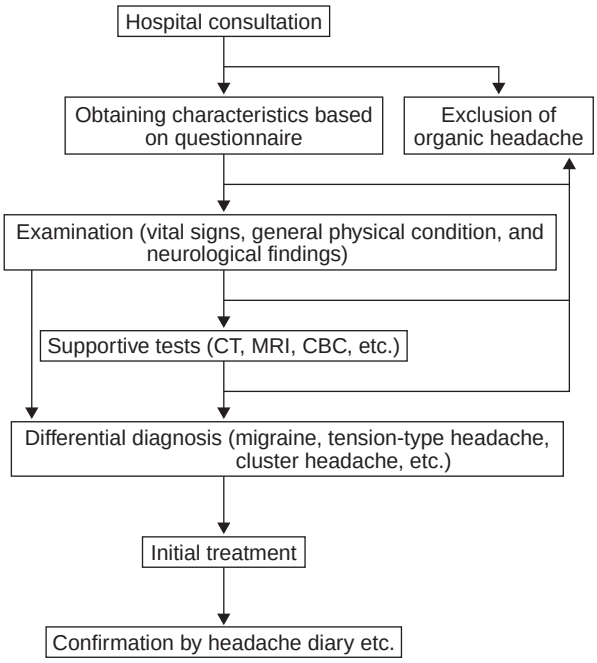

Fig. 1 Algorithm of Chronic Headache Diagnosis[2)]

When Consulted by a Patient with Chronic Headache

It is a well known fact that the causes of headaches are diverse. If the headache that the patient is seeking treatment for is clearly chronic and recurrent, there is probably nothing to worry about; however, the existence of serious diseases that would affect vital prognosis if diagnosis and treatment are delayed, such as subarachnoid hemorrhage, brain tumor, and cerebral meningitis, should be noticed.

In the case of acute/subacute headaches, a physical examination and laboratory tests should be performed quickly; however, it should be noted that organic headaches may be latent among chronic headaches. Therefore, if the patient's symptoms are completely different in character from past headaches, caution is needed. The entire flow-chart of the diagnosis of headache, centering on migraine, is shown in Fig. 1,[2)] but diagnosis, of course, does not always follow an established algorithm like this.

The IHS diagnostic criteria[1)] are considered useful to diagnose headache. The IHS classification was established in 1988 and revised in 2004,[3)] improving the old classification of headache, which was announced in 1962 by an Ad Hoc committee at the NIH in the U.S. Already over 10 years have passed since the announcement of this IHS classification in 1988, and today it is widely accepted internationally as the headache classification.

In addition to the diagnostic criteria, it is important to carefully collect information on the past history and present medical records, and especially concerning migraine, these are much more important than such supportive examinations as brain CT and MRI.[4–7)] Many cases can be diagnosed by careful history-taking alone.

We use a headache questionnaire[6)] prepared by ourselves, to help in making a diagnosis (Table 1). Excluding cases with acute or serious conditions, this form is completed while the patient is waiting, and can give easy and systematic general information on the age when the headache started, family history, past history, medication, character of the headache, aura, general condition including mental condition, and episodes related to the evoking for the headache. Various kinds of questionnaires are prepared at the respective institutions, but in recent years, Iwata *et al.* have been trying to standardize the questionnaires on chronic headache for use by primary care physicians (ADITUS Japan).

Based on these questionnaires, general physical and neurological findings are obtained, including blood pressure and various other vital signs. It is important even for physicians skilled in quickly and accurately obtaining neurological findings to pay attention to the mild consciousness disturbance, neck stiffness, minimal neurological signs, and temporal artery dilatation in temporal arteritis, and it is also essential to confirm the presence of a choked disc on funduscopic examination.

At our outpatient department, we also conduct such general examinations as blood cell count, biochemistry profile, and urinalysis, and

Table 1 Headache Questionnaire[6)]

• Please write (or circle the appropriate items) concerning your headache.
At what age did the headaches start?
Age: _____years old
Does anyone in your family (blood relatives) have headaches?
a) Yes (Who?: _____) b) No
What kind of headache is it?
a) Pulsating (throbbing pain, as if associated with the heartbeat and pulse)
b) Dull pain, a sense of pressure on the head (heavy feeling)
c) Sharp, stabbing-like pain
Please check any diseases you have experienced in the past.
Head injury Hypertension Epilepsy Diseases of the ear/nose, eye, and teeth, etc.
Do you take a medicine regularly for the headaches?
a) Yes (name of the medicine: _____) b) No
How does a headache occur?
a) Paroxysmal (occurs suddenly; How long does it last? About (__) hours)
b) Persistent (constantly)
How often does it occur?
a) Once a month to once in several months
b) Several times a month
c) Persistent, almost every day
In which part of the head do you have the headache?
a) Entire head b) One side c) Front part d) Around the eye(s) or deep behind eye(s)
e) Back of the head to neck
When do the headaches tend to occur?
a) Early morning b) Evening c) Night, during sleep
Do you have an aura (flickering, or blind spot/area in the visual field)?
a) Yes b) No
• About general physical and mental conditions
Do you have a fever?
a) Yes b) No
Do you have clear consciousness?
a) Yes b) No
Do you experience any abnormal vision?
a) Yes b) No
Do you experience nausea or vomiting?
a) Yes b) No
Do you experience stiffness of the shoulders?
a) Yes b) No
Do your eyes have excessive tears and/or is your nose runny?
a) Yes b) No
Do you feel depressed, such as feeling unwell all the time?
a) Yes b) No
Circle the items that are associated with your headache.
Fatigue Lack of sleep Hunger Light Noise Coldness Bathing Menstruation Mental stress
Relaxation after tension Foods (chocolate, cheese, hot dogs, nuts, wine, Chinese dishes) Alcohol
Change in position—such as standing and sitting Aggravated by climbing up or down stairs
Yawning

if a diagnosis cannot be made by observing the course, we order X ray imaging of the skull and cervical spine and brain CT/MRI examination, if there is no estimated risk from exposure to radiation and magnetism. Diagnosis of migraine does not necessarily require brain CT/MRI examination, but they are conducted to find rare brain tumors, subarachnoid hemorrhage,

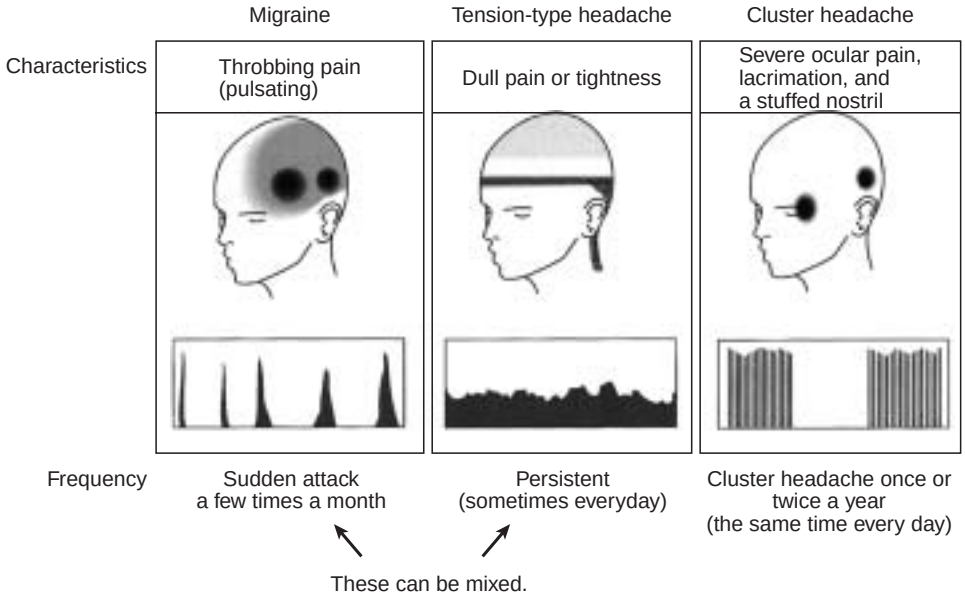

Fig. 2 Three types of chronic headaches

chronic subdural hematomas, etc., which do not take an acute course or have clear neurological signs. Electroencephalography is sometimes useful to diagnose basilar migraine in addition to the differentiation of organic headache.[8)]

When the migraine can clearly be diagnosed by the first examination, this may not be necessary, but diagnosis is occasionally very difficult in transitional, or intermediate, or mixed cases of both tension-type headache and migraine. In these cases, a "headache diary" or "headache notebook" is given to the patient to obtain longitudinal information for treatment.[4)]

Knowledge Necessary for the Differential Diagnosis

The main chronic headaches are migraine, tension-type headache, and cluster headache, which are primary headaches (Fig. 2), but it is necessary to know about the existence of headaches due to glaucoma, trigeminal neuralgia, and intracranial hypotension, and very rare functional headaches such as benign exertional headache and primary headache associated with sexual activities.

1. Migraine

Migraine is characterized by the following: hemicrania or, occasionally, bilateral pulsatile headache; a headache has a paroxysmal onset at an interval of several days or weeks, but lasts only a few days; there is also nausea, vomiting, and hypersensitivity to light and sound during attacks; and a pain is caused by release from stress, hunger, crowdedness, excessive sleep, being in direct hot sunlight, drinking, exercise, etc.

Further, a headache begin by age 30 at the latest, and almost always similar headaches are experienced by some blood relatives of the patient, such as parents, siblings, and children. If the pain is severe, the patient prefers to lie down in a quiet, darkened room and tries to sleep.[4)]

Migraine is further classified according to the IHS diagnostic criteria,[1)] as shown below.

(1) **Migraine without aura**

This corresponds to the former common migraine, and this most common migraine accounts for 80% of all migraines. There is no aura like scintillating scotoma, but other associated symptoms, such as nausea, vomiting, and

hypersensitivity to light and sound, occur. A pulsating or non-pulsating headache occurs on one side of the head or the entire head, and it lasts for 4 to 72 hours. As there is no characteristic symptom that can be identified as an aura, diagnosis is sometimes difficult particularly differentiation from episodic tension-type headache.

(2) **Migraine with aura**

This corresponds to the former classic migraine, and is relatively uncommon, accounting for approximately 10 to 30% of all migraines. The characteristic sign is the aura preceding the onset of the headache. The most frequent aura is scintillating scotoma, where a small blind spot in the visual field gradually expands over approximately 20 minutes and ends within 60 minutes. The border shines zigzag and the blind spot in the visual field remains inside.

In general, a headache appears in the opposite temporal region of the side on which the scintillating scotoma is seen after the aura disappears. The headache pain is usually pulsating. Migraine with a typical aura, usually a visual aura, is further classified as "migraine with typical aura", and this is characterized by hypoesthesia of one side of the body or hemiplegia.

Though rare, we also find familial hemiplegic migraine, which has an attack of familial migraine with hemiplegia during the aura; basilar migraine, which has symptoms of ischemia in the vertebrobasilar artery region, such as consciousness disorder and brain stem symptom, during the aura; and migraine with only aura without headache itself. These may require different treatment policies, and caution is needed.

2. Tension-type headache

Tension-type headache is the most frequent chronic headache, and it is said that it is experienced by 20 to 30% of Japanese people. Tension-type headache is relatively clearly classified by diagnostic criteria. In actual clinical practice, however, it is sometimes difficult to differentiate between and classify episodic tension-type headache (ETTH) and chronic tension-type headache (CTTH), the latter of which lasts longer than 15 days a month. Tension-type headache is bilateral, and often located in the occipital region, and the pain feels like being pressed or tightened up. The headache is not paroxysmal but persistent, accompanied by stiff shoulders and a sense of dizziness, but without vomiting or hypersensitivity to light and sound; and it is characterized by being induced by a posture of looking down,[9] stress, and overfatigue.[4]

This headache represents a trash box-like diagnostic concept that includes former psychogenic headache and headache due to dysfunction of the mouth and jaw, and it is sometimes difficult to make a diagnosis. It is often difficult to differentiate between chronic migraine and tension-type headache, especially CTTH. Some patients are judged to have transitional, or intermediate, or mixed types of tension-type headache and migraine, like the former mixed-type headache. Differentiation from CTTH is difficult, and in addition, transformed migraine and chronic daily headache (CDH), which are related to drug overuse and have characteristics of both migraine and tension-type headache, are also found.[10,11]

Chronic daily headache is also referred to as chronic habitual headache, but this name is not found in the IHS classification. Presently, most cases with chronic daily headache are considered to have an aberrant type of migraine. In other words, it is considered that this type of headache has an initial migraine-like phase, and that its main pathology is migraine which gradually progresses to chronic daily headache in many cases.

Headache caused by drug overuse, as mentioned earlier, is also called drug-induced headache, and it is caused by the excessive administration and chronic use of ergotamine and analgesics, which are originally used for treatment, or sometimes triptan. In fact, a considerable number of patients have drug-induced

headache.

3. Cluster headache

Cluster headaches are so called because they occur in clusters, daily, almost at a set time, for one to two months, in many cases. The cluster period, in which a severe headache behind the eyes is accompanied by lacrimation from the eyes and a stuffed nostril, can occur once or twice a year, or once in several years, but after the period passes, no headaches occur. The severe headache lasts for one to two hours, and then resolves on its own.

Less than 0.1% of people have cluster headaches, and we don't see patients with this type of headache very often in clinical practice. Cluster headache is accompanied by relatively characteristic symptoms, so making a diagnosis is not very difficult. It is one of the most excruciating pains people experience, similar to trigeminal neuralgia, and its existence should be known.

Conclusion

As mentioned at the beginning, diagnosing chronic headache seems to be easy but actually difficult. An accurate diagnosis of functional headache should only be made after excluding organic headache. Toward this end, it should be reconfirmed that the most important is to have knowledge of the accurate diagnostic criteria and accurate medical history-taking based on the patient's understanding and cooperation.

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Migraine

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Abstract: Migraine is a very common disorder. In Japan, an estimated 8.4% of the population experience migraine, but many go undiagnosed and undertreated. Even though the pathophysiology of migraine is unclear, we have three theories for the mechanism of migraine. The first one is the vascular theory, according to which, the dilatation of cerebral blood vessels causes the headache. The second one is the neuronal theory, according to which a spreading depression is the origin of the migraine. The third one is the trigeminovascular theory, according to which the trigeminal nerve surrounding the cerebral vessels is the origin of migraine. Recent advances in basic and applied clinical neuroscience have led to the development of a new class of selective serotonin (5-hydroxytryptamine (5-HT)) receptor agonists that activate 5-$HT_{1B/1D}$ receptors. These are known as triptans. They have three main mechanisms of action: cranial vasoconstriction, peripheral trigeminal inhibition, and inhibition of the transmission through second order neurons of the trigeminocervical complex. Even in our country, we can now use three kinds of triptans, which are very effective drugs for acute migraine, with a well-developed scientific rationale. Despite the higher price, triptans are preferred over ergots in most patients.

Key words: Migraine; Trigeminal nerve; Serotonin; Triptan

Introduction

In Japan it is estimated that about 8.4% of the population experiences migraine.[1)] As treatment drugs, ergotamine agents and analgesic drugs have been employed for a long time for headache attacks. Studies of the pathophysiology of migraine, on the other hand, have reported transmitters such as serotonin, catecholamine, and neuropeptides play an important role in migraine. Especially the use of sumatriptan, a serotonin (5-hydroxytrytamine ($5\text{-}HT_{1B/1D}$)) receptor agonist developed by Humphrey *et al.*,[2)] started approximately 10 years ago in overseas countries. The drug is effective in 50 to 70% of migraine patients during the headache phase. Because of these facts, the relationship between serotonin and migraine has regained attention. Ever since various drugs that have a similar chemical

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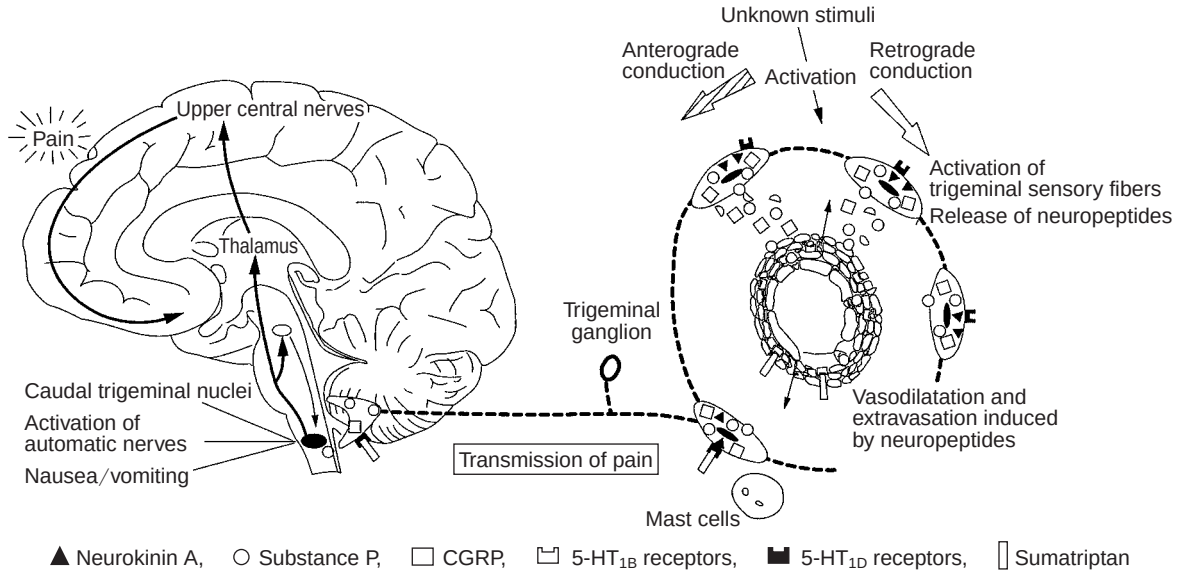

Fig. 1 Mechanism of the development of migraine via the trigeminovascular system

Some kind of stimulation acts on the axons in the trigeminal nerves, which are found around the dural vessels, and vasoactive neuropeptides (substance P (SP), neurokinin A (NKA), calcitonin gene-related peptide (CGRP), etc.) are released and cause neurogenic inflammation (vasodilatation, leakage of plasma protein, and mast cell degranulation). Because of this, both anterograde and retrograde conduction occur in the trigeminal nerves.

Anterograde conduction reaches the trigeminal nuclei, and is then transmitted to the thalamus and cerebral cortex. This message is felt as pain. Retrograde conduction, on the other hand, further activates a release of vasoactive neuropeptides on the periphery of the trigeminal nerves. It has been demonstrated that sumatriptan acts on 5-HT_{1B} receptors, which are found in the intracranial vascular smooth muscle, to constrict the vessels, and it also inhibits a release of neuropeptides by binding to 5-HT_{1D} receptors, which are found in the trigeminal nerves around the blood vessels.

(Figure modified from Moskowitz and Goadsby)

structure as sumatriptan, have been developed. They are getting attention as the second generation of triptans. The recent development of these treatment methods for headache and the pathophysiology of migraine are discussed.

Pathophysiology of Migraine

Regarding the pathophysiology of migraine,[3] traditionally the vascular theory, according to which vasoconstriction occurs during an aura whereafter dilatation leads to headache, has been widely believed. However, recently, two theories for the pathophysiology of migraine are suggested and have become the focus of attention. One is the neuronal theory,[4] according to which the excessive excitement of nerve cells in the cerebral cortex is the origin of migraine. The other is the trigeminovascular theory that focuses on the relationship between the trigeminal nerves and intracranial vessels.

Moskowitz[5] underscored the relationship between the trigeminal nerves and intracranial vessels, especially dural vessels, and indicated that unmyelinated C-fibers, which originate from the trigeminal ganglion, are distributed among the dural vessels. Furthermore, they revealed that neurogenic inflammation occurs in the dural vessels if the trigeminal nerves are electronically or chemically stimulated. Therefore they thought that neurogenic inflammation, which originates in the trigeminovascular system, could serve as a migraine model. Consequently the trigeminovascular theory was suggested. A summary of this theory is shown in Fig. 1.

In other words, some kind of stimulation acts on the axons in the trigeminal nerves, which are

found around the dural vessels, and vasoactive neuropeptides (substance P (SP), neurokinin A (NKA), calcitonin gene-related peptide (CGRP), etc.) are released. These in turn cause neurogenic inflammation (vasodilatation, leakage of plasma protein, and mast cell degranulation). This causes both anterograde and retrograde conduction in the trigeminal nerves.

According to this theory, anterograde conduction reaches the trigeminal nuclei, and is then transmitted to the thalamus and cerebral cortex. This message is felt as pain. Retrograde conduction, on the other hand, further activates a release of vasoactive neuropeptides on the periphery of the trigeminal nerves. In addition, it is demonstrated that sumatriptan acts on 5-HT_{1B} receptors in the intracranial vascular smooth muscle to constrict the vessels, and it also inhibits the release of neuropeptides by binding to 5-HT_{1D} receptors which are found in the trigeminal nerves around the blood vessels.

Furthermore, Moskowitz presented an article in which this unknown stimulation is considered as the cortical spreading depression found during an aura. This theory seems to be an organic combination of the traditional vascular and neuronal theories.

Relationship between Migraine and Serotonin

Since 1959 when Sicuteri *et al.* measured the serotonin metabolite 5HIAA in the urine of patients with migraine and discovered that its level is higher than that of healthy individuals, the relationship between migraine and serotonin has become a fascinating topic. When the level of platelet serotonin was measured in migraine patients, it was revealed that the level decreased to about 40% during a headache attack. In addition, when reserpine, which acts to release serotonin from platelets, is administered, a migraine-like headache is produced. It was proved that this headache is improved by the intravenous administration of serotonin. However, because serotonin also has systemic effects, various side effects are produced; and serotonin has therefore not come into practical use.

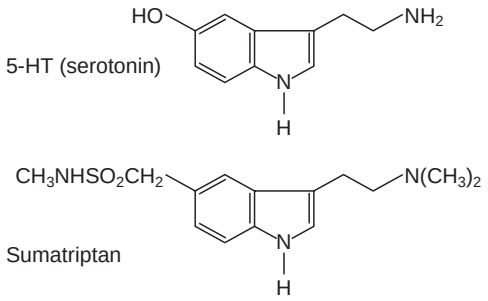

Fig. 2 Chemical structures of serotonin and sumatriptan

Table 1 Comparison of the Affinities to Each Kind of Receptor between Sumatriptan and Dihydroergotamine

Receptor	Dihydroergotamine	Sumatriptan
Serotonin (5-HT)		
1_A	###	+
1_B	###	##
1_D	###	##
1_E	##	−
1_F	+	##
$2_{A/C}$	+	−
3	−	−
Adrenaline		
$\alpha_{1a, b}$	##	−
$\alpha_{2a, b, c}$	##	−
$\beta_{1, 2, 3}$	−/−/+	−
Dopamine		
$D_{1, 5}$	−	−
$D_{2, 3, 4}$	##	−

Compared with dihydroergotamine, sumatriptan is characterized by a higher affinity to 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors, while it has almost no affinity to adrenaline and dopamine receptors.
(Cited from Goadsby, P.J.: *Prog Neurobiol* 2000; 62: 509–525.)

Thereafter serotonin agonists that selectively act on the cerebral blood vessels were developed. A serotonin 5-$HT_{1B/1D}$ receptor agonist, sumatriptan (Fig. 2), developed by Humphrey *et al.*[2] was effective in 50 to 70% of the migraine patients during the headache phase. It has been discovered that sumatriptan acts on

5-HT_{1B} receptors, which are found in the intracranial vascular smooth muscle, to constrict the vessels, and it also inhibits the release of neuropeptides by binding to 5-HT_{1D} receptors which are found in the trigeminal nerves around the blood vessels (Fig. 1). Furthermore, the possibility that sumatriptan acts on 5-HT_{1F} receptors, which are found in the trigeminal nerve cells, to inhibit a migraine attack has been considered.

Ergotamine agents, which have traditionally been used, also act on these serotonin receptors, and constrict the cerebral vessels. However, as shown in Table 1,[6] since these agents act not only on serotonin receptors but also on adrenaline and dopamine receptors, they cause various side effects.

Sumatriptan

Twenty placebo-controlled trials of the subcutaneous administration of sumatriptan,[7] a serotonin 5-$HT_{1B/1D}$ receptor agonist, have been performed. In all these trials sumatriptan manifested significantly superior effects on migraine to placebo. In other words, the remission rate of headache by subcutaneous injections of 6 mg of sumatriptan is 65 to 80% and of that of 3 mg subcutaneous injections is 57 to 75%; both showing a superior effect to that of placebo. The incidence of adverse reactions at that time was significantly higher in the subcutaneous sumatriptan group than in the placebo group. Injection site pain/redness and chest discomfort were recognized as adverse reactions. Furthermore, 20 placebo-controlled double-blind trials[8] of the effect of oral administration of sumatriptan were conducted. In all these trials the sumatriptan administration groups showed a significantly superior effect to the placebo groups.

In Japan, sumatriptan injection (3 mg) has been available since April 2000, while an oral agent (sumatriptan 50 mg tablet) has been available since August 2001. Also, a nasal spray will be approved in the future. Sumatriptan 6 mg injection, 25, 50, and 100 mg tablets, nasal spray and suppositories are utilized around the world.

With the injection the bioavailability is 96% and a therapeutic range is reached in 10 minutes, while with the tablet, the bioavailability is only 14% and a therapeutic range is reached after 30 to 90 minutes. The elimination half-life in the blood is approximately 2 hours.

In addition, it has been proven that sumatriptan is also effective against concomitant symptoms such as nausea, vomiting, and photophobia/phonophobia which accompany migraine attacks. However, administration of sumatriptan during the aura is not very effective. It is more effective to administer the drug during the headache phase. Nevertheless, in approximately 1/3 of the patients in whom sumatriptan was effective, there was a problem with recurrence of the headache 24 to 48 hours after administration.

Sumatriptan is contraindicated in patients with ischemic heart diseases and/or epilepsy, inadequately controlled hypertension or hepatic dysfunction, and in patients who had taken ergotamine agents within 24 hours, or who are taking monoamine oxidase (MAO) inhibitors.

Second Generation Agents of the Triptan Family

Since the success of sumatriptan, various triptan agents have been developed by improving the weak points of sumatriptan (the elimination half-life in the blood is short, crossing of the blood-brain barrier is weak, and the metabolites do not have an inhibiting action on migraine.). From 1997 to 1998, zolmitriptan, naratriptan and rizatriptan were approved in various countries. Thereafter, almotriptan, eletriptan, and frovatriptan have been developed (Fig. 3). Compared with sumatriptan, in these second generation agents of the triptan family, the bioavailability is higher (45 to 75%), the time it takes for the blood concentration to reach the therapeutic range is short (30 to 60 minutes), the elimination half-life in the blood is longer, and because of their high liposolu-

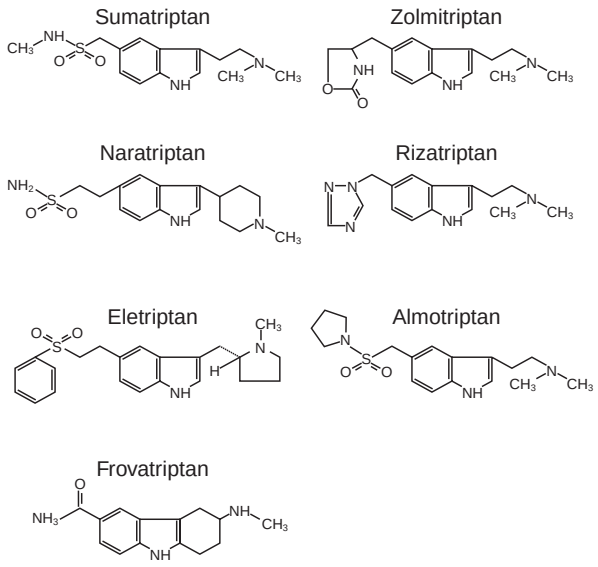

Fig. 3 Chemical structures of sumatriptan and the second generation agents of the triptan family

bility, they can cross the blood-brain barrier to act on the central nerves.

Recently it was reported that naratriptan was effective in over 40% of the migraine patients in whom sumatriptan treatment failed. The efficacy of zolmitriptan was 73% and that of rizatriptan was 81% in migraine patients in whom sumatriptan was not effective. As a result, it was revealed that even if one agent of the triptan family is not effective, it is worthwhile to try other triptan agents.

In 2001 Ferrari *et al.*[9] carried out a meta-analysis of 53 clinical trials on seven triptans involving 24,089 patients and presented the following results: the mean improvement rate of headache at two hours after taking 100 mg of sumatriptan is 59%. By using this data as the standard, the improvement rate of each triptan agent was examined. As a result, compared with 100 mg sumatriptan, 10 mg rizatriptan and 80 mg eletriptan showed significantly higher efficacy on improving headache.

Furthermore, in 2000, an expert group from Europe reviewed the pre-clinical and clinical data on ergotamine as it relates to the treatment of migraine. They agreed on the following points: from the perspective of effect and adverse reactions, triptan agents are superior in most of the migraine patients. Ergotamine agents, on the other hand, would be used only when migraine attacks are infrequent or the duration of headache is long.

Prophylactic Therapy for Migraine

Prophylactic therapy for migraine should be considered when the frequency of migraine is high, when treatment of the acute phase is insufficient, when treatment during the acute phase is contraindicated or is impossible due to adverse reactions, or when abuse of the acute phase treatment is observed. Traditionally propranolol, a β-adrenergic blocking agent, and amitriptyline, an antidepressant, were considered effective prophylactic agents and they have thus been employed.

Flunarizine, an effective calcium channel blocker, was employed lately, but it has been taken off the market in Japan due to adverse reactions. Thereafter, lomerizine was developed in Japan. In a placebo-controlled double-blind development study[11] it was revealed that, compared with placebo, lomerizine significantly reduces the frequency and degree of headaches. Currently, it is widely utilized on the clinical scene.

Conclusion

Since the development of sumatriptan in Europe and the United Sates the treatment of migraine has changed. In the guidelines for migraine headache set out in the Report of the Quality Standards Subcommittee of the American Academy of Neurology in 2000,[12] triptan agents are also regarded as the first choice drugs for migraine.

Since April 2000 the subcutaneous sumatriptan injection has been available in Japan. From August 2001 orally administered sumatriptan and zolmitriptan have also been available, and eletriptan was approved in July 2002.

Consequently, the treatment of migraine has drastically changed in Japan. In the guidelines for treatment of chronic headache, the Japanese Society of Neurology (http://www.neurology-jp.org/guideline/headache/index.html) also placed triptan agents as the most effective drugs for the treatment of migraine and cluster headache, also from an EBM perspective.

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Tension-Type Headache
—Its mechanism and treatment—

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Abstract: Tension-type headache, often accompanied with dull pains originating from the occipital area, shoulder stiffness etc., is the headache caused by ischemic muscle contraction, which must be distinguished from those having psychological or depression-type pathogenesis. Headaches in patients with tension-type headache begin often in bending down posture or during a night sleep with a high or hard pillow. Those patients have the tendency of having a slender and long neck and problems with cervical angulation or cervical instability. It is important to strengthen the neck muscles by exercising the abdominal and back muscles and also to try to maintain the correct, straight posture in daily life. Medical treatment is necessary for those with hypotension or anemia, and neuroleptics are effective for headache caused by stress.

Key words: Tension-type headache; Muscle contraction headache; Psychological headache; Depression

Introduction

Tension-type headaches make up 2/3 of all chronic headaches. This fact is important when considering the treatment of headache. Actually, muscle contraction headache, psychological headache and masked depression are often confused with each other.

In psychological headache, headache is the chief complaint, and its intensity (complaint) is often strong. The condition of the headache, however, varies, and it always has concomitant symptoms such as sleeplessness, dizziness, numbness of the four extremities, and irritability. Although the patients with psychological headache strongly complain of their headache, they have a relatively normal daily life and do not seem to worry much about their headache. On the other hand, when the headache disappears, the patients suffer sleeplessness or other concomitant symptoms, which then become the center of their attention. In other words, the patients with a psychological headache are living comfortably as if they are protected by a surrounding wall called headache; thus, in reality, it will become a problem if the head-

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ache is cured. A large number of intractable headaches are psychological headaches. Psychological headaches cause drug dependence, and most of them also progress into chronic daily headaches.

The headache of patients with depression, is often an ache that should be called a dull headache. The complaints are described as "always feeling dull," "wearing an iron pot on the head," and "a feeling of dullness radiating primarily from the forehead." It is not so that the patients wake up because of, or cannot tolerate, the pain. The headache often occurs with more than 4 concomitant symptoms such as numbness of the hands, sleeplessness, loss of appetite, stomach discomfort and constipation. There is no point of tenderness in the occipital area. In most cases, the purpose of the patients' visits is that they are concerned about a possible big underlying disease, rather than wishing to cure the headache.

The psychological headache and headache caused by depression, which fall in the domain of psychiatry, and the tension-type headache (muscle contraction headache), which falls in the field of neurology under internal medicine, must be clearly distinguished. Tension-type headache, which is dealt with by neurology under internal medicine, has the following characteristics: 1) the chief complaint is headache, 2) a dull ache, tightness and pressure are felt in the occipital area, and 3) occipital muscle contraction is evident when the patient demonstrates how he or she begins to feel the headache.

The Pathophysiology of Tension-Type Headache

When making a diagnosis of tension-type headache, the following factors are particularly important: the pain is a dull pain that radiates from the occipital area, occasionally is accompanied by shoulder stiffness, causes nausea but not vomiting, and has no concomitant symptoms of migraine such as scintillating scotoma, hemiplegia or sensitivity to light or noise.

1. The pain mechanism

If the muscles continue to contract for a long time despite a decreased blood supply (called ischemic muscle contraction), pain substances such as lactate, pyruvic acid etc. are released. Pain occurs when these substances stimulate the nerves. Then a sensation of pain occurs at the sites of muscle attachment and ligaments where peripheral nerves are densely distributed.

This pain is characterized by a dull ache. With tension-type headache, the pain occurs at the insertion of the posterior neck muscles in the occipital area. At the same time, the pain radiates across the sides of the head or the retroorbital areas; thus, the pain is also felt around these areas. This is the pain mechanism of tension-type headache. On the other hand, in the belly of muscles where the nerves are loosely distributed, a duller and localized, vague feeling of so-called "stiffness" is felt in the belly of muscles.

2. Why does tension-type headache occur?

By thorough observation of patients with tension-type headache, it is found that the headache begins when they are bending their heads down. They are in the so-called bending down posture.

As a result, the posterior neck muscles become very tense. If the abdominal muscles are actually touched, they are hard. In those cases where the patients wake up early in the morning due to a headache, it happens because they use high or hard pillows, which consequently increase the tension in the posterior neck muscles.

The patients first feel "tension" or "stiffness" in the posterior neck area. Here "tension" refers to the muscles that are tensed while "stiffness" means the beginning of a dull ache that results from the tension. The pain then radiates across the sides of the head and further to the retroorbital area.

When giving infiltration anesthesia with

Xylocaine at the tender point, which is located in the posterior neck, the entire expanded headache immediately disappears. Therefore, it shows that the headache is a referred pain that radiates from this tender point.

EMG activity of the posterior neck muscles in a sitting posture reveals that the changes in EMG, indicating the degree of the muscle contraction, is higher in patients with headache than in control subjects without headache. If a headache occurs, the posterior neck muscle contraction only disappears when the head is kept straight in an upright postition. Therefore, this intense muscle contraction is not a result of the pain.

3. The body structure of patients with headache

An adult head weighs approximately 4 kg. This corresponds to 3 full bottles of wine or one watermelon. If one holds either of these in one's hands and extends the arms, pain immediately spreads throughout the arms and "stiffness" remains. We are almost never aware of the heaviness of the head, but the neck is constantly supporting such a heavy object.

Upon examining the frame of patients with headache, it is revealed that the neck is usually slender and long compared to the weight of the head. Head weight moment index (headache index) shows such a frame. It is calculated as follows: head circumference$^3 \times$(the torus occipitalis — the 7th cervical spine)/neck circumference$^2 \times 1000$. This indicates the head weight moment over the neck per unit dimension. Female control subjects and headache patients are 2.4 ± 0.4 and 2.9 ± 0.4, respectively, while male control subjects and headache patients are 2.0 ± 0.4 and 2.4 ± 0.4, respectively. It is significantly larger in the headache patients than in the control subjects, and also larger in the female than the male. In other words, this indicates that the neck is slender and long compared to the head weight. Most of the patients suffering from headache are females with long necks. One cannot change one's frame, however, strengthening of the neck muscles by exercising the abdominal and back muscles is important.

4. Problems with the cervical spine

Cervical stability means that the cervical spine supports the head in a stable way. The cervical vertebrae usually form a slight curve to support the head securely. If there is no cervical spine, it would be impossible to support the head only with muscles. Nonetheless, patients with headache have problems with this cervical stability. When the cervical spine is bent forward, it is called angulation. In such a case, the weight of the head cannot be supported.

In addition, when the spine is shifted forward in a bending down posture, it is called instability. This also significantly prevents the cervical spine from supporting the weight of the head.

On X-ray, angulation and neck instability were found in 50% of patients with tension-type headache.

Cervical stability impairment of the ligaments that are attached to the cervical vertebrae results. In other words, bending the head down for a long time or using a high and/or hard pillow extends the ligaments.

5. Hypotension and anemia

Poor oxygen supply to the muscles also triggers ischemic contraction. So, when does the oxygen supply become insufficient?

Firstly, hypotension is one of its causes. When a person with hypotension bends down, the muscles become tightly contracted, and the blood flow stops due to the low pressure in the blood vessels.

In the case of anemia, the basic problem is that the blood cannot supply sufficient oxygen, therefore oxygen deficiency occurs easily even though the vascular flow is maintained.

6. Stress

Stress and depression do not trigger headache immediately.

When stress, such as a mental arithmetic load

is given under the electromyogram and vascular flow tests, changes in muscle contraction are not observed. However, blood circulation sometimes drops to 50%.

Therefore, if a strong stress load is given when the muscles of the head are continuously contracted for some reason, muscle contraction with oxygen deficiency occurs immediately, and pain substances are released. Then headache begins.

7. Differences between voluntary bending down posture and involuntary bending down posture

Athletes never feel "stiffness" during matches. On the other hand, if the same posture must be maintained, "stiffness" occurs easily.

Upon examining the EMG activity and the blood flow volume, it was revealed that when involuntarily passive muscle contraction occurs, the blood flow in the muscles decrease and the decreased state continues as long as it is contracted. On the other hand, even though muscle contraction has the same intensity, when muscle contraction is initiated voluntarily, the blood flow recovers in about 20 to 30 seconds as a reflex reaction.

In fact, headache is easily induced when the neck and shoulders are relaxed, and the head is loosely bent downward.

8. Problems with pillow

The higher the pillow, the stronger the tension in the posterior neck muscles. This fact can actually be confirmed by surface EMG.

Treatment for Tension-Type Headache

1. Do not bend down

In most cases, tension-type headache can disappear by only correcting the posture.

When correcting the posture, take the following steps: first, actually touch the posterior neck muscles with the hands to check their firmness. Bend over, looking above the knees. Gradually look up. The muscle tension diminishes as the visual line approaches the horizontal level. A straight posture with a book on the head is indeed the best posture. Try to maintain this posture in daily life. Also, it is effective to develop the habit of immediately looking up and relaxing for about 5 minutes when tension or a dull pain emerges in the posterior neck area.

Re-checking the environment to establish the origin of daily headaches is also necessary. For example, if headaches occur easily while working at a desk, ideas such as lowering the chair, tilting the writing board or tilting the keyboard need to be practiced.

2. Muscle training

Nonetheless, the posture can be taken involuntarily, and cannot be corrected easily if the muscle strength is not sufficient. For instance, it is reported that 40% of amyotrophic lateral sclerosis carriers and many Duchenne Muscle Dystrophy carriers complain of tension-type headaches. It is advisable to exercise the abdominal and back muscles in the morning and evening, even if it is only for 1 to 2 minutes.

Concerning the present-day body structure of women, the abdominal and back muscles are often poorly developed. The body structure appears to be fairly solid from the front view, but when looking at it from the side, the body does not have thickness and the "queen of playing cards" body frame is noticeable. With this body frame, one easily becomes humpbacked, consequently promoting a bending down posture.

3. Treatment of hypotension and anemia

When a person with hypotension bends down, the muscles become tightly contracted, and the blood flow stops due to the low pressure in the blood vessels. In the case of anemia, the basic problem is that the blood cannot supply sufficient oxygen, therefore oxygen deficiency occurs easily even though the vascular flow is maintained. Treatment therefore is necessary by way of diet or medication.

4. Treatment for stress

Neuroleptics show certain effects.

Conclusion

Tension-type headache is a distinctive biophysical phenomenon. Treatment demands that a good posture is taught from childhood.

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Chronic Headache and the Pain Clinic

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Abstract: Nerve block is the mainstay of therapy at pain clinics in Japan. The results of nerve blocks, namely the blocking of sensory pain pathways, vicious cycles of pain, sympathetic neural functions, and motor nerves are very useful in treating pain. If the same effects are to be obtained by drug administration, the concomitant use of many drugs with different actions is necessary, but even so, the effects would not be as good as those of nerve blocks. The headaches that are dealt with at pain clinics are mostly chronic, recurrent headaches such as migraines, cluster headaches, tension-type headaches, and posttraumatic symptomatic headaches. Headaches that originate in the cervical spine, although they are acute in nature, also respond well to nerve blocks. Stellate ganglion block, gasserian ganglion block, trigeminal nerve branch block, and occipital nerve block are the major nerve blocks that are used for the treatment of headaches. The concomitant use of general drugs as well as oriental therapies is also common.

Key words: Chronic headache; Pain clinic; Nerve block

Introduction

The idea of a pain clinic as a separate medical division is not yet sufficiently understood by the people at large. However, pain clinics already have a history of nearly 40 years as a clinical division, performing their activities aimed at relieving patients' pain.

The institute where the author works has started its activities as a pain clinic in September 1966 as part of the Department of Anesthesia. On July 1, 2001, it became independent as Japan's first Department of Pain Medicine at a University School of Medicine, and treatment and research of pain are conducted there.

The significance of nerve blocks, the treatment of choice at pain clinics, as well as the control of chronic headache, as we conduct it, are introduced from the perspective of a pain clinic physician whose objective is to treat pain.

What is a nerve block?

Modern pain clinics proactively adapt and employ various methods, such as drugs, surgery, psychophysiological therapy, and oriental therapies, which may be helpful in the treatment of pain. However, the present medical division has a history of being the first to treat patients' pain with nerve blocks; and nerve

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Fig. 1 Gasserian ganglion block
A block needle is passed through the oval foramen and inserted into the trigeminal ganglion. Blocking of trigeminal nerve branches, e.g. supraorbital/infraorbital nerves, maxillary nerves, or auriculotemporal nerves are also conducted as necessary.

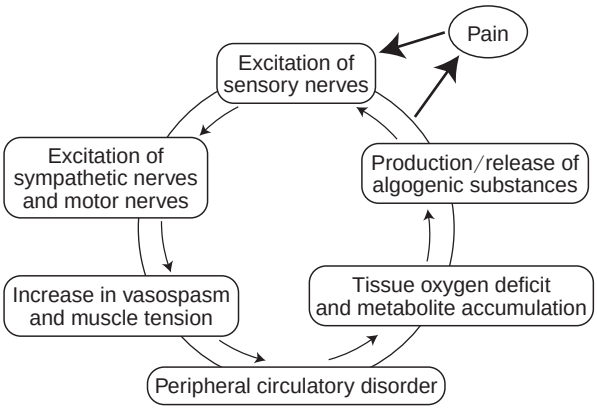

Fig. 2 Formation of a vicious cycle of pain
If the pain is not controlled sufficiently, the body releases irrational factors one after another. This not only causes an increase in the pain, but also physiological changes in the nerve functions.

blocks are therefore the mainstay of its treatment methods.

A nerve block is defined as follows: "a procedure that temporally or permanently blocks the functions of nervous transmissions by inserting a block needle along the cerebrospinal nerves, the cerebrospinal ganglion or the sympathetic ganglion and nerve plexuses that form these, and injecting a local anesthetic or neurolytic agent directly into or near the target."

The effects of nerve blocks in the body are very important in the treatment of such chronic pains as headaches.

1. Blocking the sensory pain pathways

Eliminating patients' pain greatly contributes to the improvement in their quality of life (QOL), although it is not a radical treatment. The ability to eliminate pains that result from modern medicine's inability to prevent such pains, e.g. cancer pain, is highly valuable.

In addition, in the case of trigeminal and glossopharyngeal neuralgia, where the only symptom is that of excrutiating pain, a reliable nerve block can completely stop a long-lasting crisis for a period of a few months to several years (Fig. 1).

2. Blocking vicious cycles of pain

Noxious stimuli are transmitted to the central nervous system from the peripheral nerves via the spinal cord, and they simultaneously excite the sympathetic and motor nerves along the spinal reflex pathways. As a result vasospasm and muscle tension occur in the affected area and its surroundings. A decrease in the local blood flow and oxygen deficiency then accelerate abnormal metabolism, the production and release of algogenic substances are promoted in the local area, and the sensitivity of nociceptors increase. A vicious cycle consequently develops (Fig. 2). The best procedure to interrupt this vicious cycle is a nerve block.

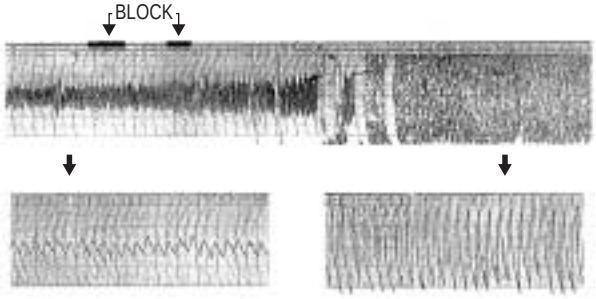

Fig. 3 Blood flow changes with a sympathetic nerve block

A significant increase in the blood flow is observed after conducting a nerve block. This effect of increased blood flow occurs locally, but cannot be obtained by vasodilators that act systemically.

3. Blocking sympathetic neural functions

When sympathetic neural functions are blocked by a nerve block, the local blood flow increases, sweating is suppressed, and the sympathetic sensory nerve branches are blocked. Ischemic pain usually requires an increase in the local blood flow (Fig. 3).

4. Prevention of pain development

If an intercostal nerve block is used concomitantly with open chest surgery, development of the so-called post-thoracotomy pain syndrome can be prevented. In the case surgery for intra-abdominal tumors are concluded with an exploratory laparotomy, the possibility of preventing the development of post-operative pain is higher if a block of the celiac plexus or the inferior mesenteric plexus is conducted during the open surgery. Similarly, sufficient analgesia by means of a nerve block during the acute stage of herpes zoster is expected to prevent the development of postherpetic neuralgia.

5. Blocking motor nerves

Reducing muscle tension with a motor nerve block is indispensable when treating pain.

Headaches Treated at Pain Clinics

When considering the kinds of headache treated at pain clinics (i.e. with nerve blocks), it is good to distinguish between "acute" and "chronic" headache: the pain of the former starts abruptly, while the pain crisis repeats itself or persists for years with the latter.

Acute pain occurs suddenly and lasts only temporarily. In most cases it heals naturally; however, acute pain is often cured by taking commercially available analgesic medications two to three times. Nevertheless, the causes of acute pain also include fatal subarachnoid hemorrhage and glaucoma, which may lead to blindness.

Special attention should be paid to an intense headache that has never been experienced before, a headache that gradually worsens, or a headache with concomitant symptoms such as abnormal vision, fever, vomiting, or movement disorders of the four extremities. A headache that develops after the head was knocked is also a reason for concern. Such headaches may not become the subjects of nerve blocks.

In other words, the headaches for which nerve blocks can be applied are chronic headaches that persist for years or repeat a cycle of crisis and abatement; therefore, acute headaches with the characteristics described above, are not considered treatable by nerve block. Functional headaches such as migraine, cluster headache, and tension-type headache are considered treatable by nerve block. In addition, symptomatic headaches, in which pain persists after the injury or disease has been stabilized, and neuralgia are also treatable by nerve blocks.

Although a headache that originates in the cervical spine is acute, nerve block is an excellent therapeutic method for this type of headache.

Treatment of Headaches at Pain Clinics

1. Drug therapy

Concerning the basic drug therapies available for functional headaches, e.g. vasodilators, vasoconstrictors, and muscle relaxants, the ma-

jority of doctors who treat headaches on a daily basis use the same regime. However, it is common that most patients with chronic headache who are referred to pain clinics have already received basic drug therapy for a long period of time. The patients often turn to pain clinics because the drug therapy did not have satisfactory results.

The characteristics of the drug therapy at pain clinics are that antiepileptic drugs and antidepressants are often employed, not only for the treatment of the headache as such, but also of so-called chronic pains. In addition, Chinese herbal medicines are frequently used.

Antiepileptic drugs are effective for sharp pain that is described as a running, electric, lightning, stabbing, or cutting sensation. Antidepressants, on the other hand, are effective for dull pain that is described as a numbing, squeezing, aching or squashing sensation. Moreover, many patients with chronic headache are in a "depressive state," because they have suffered headaches for years. In such a case, antidepressants give even better results.

The use of Chinese herbal medicines is based on experience and is not directly, theoretically linked to the mechanisms of headache. However, if the patient's condition and the selected drug are well matched, dramatic effects are produced. The following Chinese herbal medicines are frequently employed: goshuyu-to, kamishyouyou-san, choutou-san, gorei-san, oren-gedoku-to, and kakkon-to.

2. Nerve blocks

Nerve Blocks become helpful when pain cannot be controlled with the typical drug therapy for chronic headache (Table 1).

Table 1 Main Nerve Blocks Used for Functional Headaches

Migraine
Stellate ganglion block
Gasserian ganglion block
Auriculotemporal nerve block
Cluster headache
Stellate ganglion block
Gasserian ganglion block
Supraorbital/infraorbital nerve block
Maxillary nerve block
Sphenopalatine ganglion block
Total spinal block
Tension-type headache
Stellate ganglion block
Trigger point block
Greater/lesser occipital nerve block
Cervical nerve root block

The following nerve blocks are mainly employed for chronic headache:

(1) Stellate ganglion block

When the stellate ganglion is blocked, blood flow to the head, face, neck, upper extremities, and upper chest increases, and these areas become warm. As a result, it gives a good feeling and in some cases, leads to sleepiness. Sympathetic nerves are activated when a person becomes extremely excited and tense. The advantage of this kind of block is that it opposes the sympathetic nerves, creating a calm situation. It is suggested that, in the case of headaches that are caused by the dilation of blood vessels (migraine and cluster headache), repeated employment of this block stabilizes the activity of the blood vessels, and a crisis consequently occurs seldom.

Stellate ganglion blocks are used for the treatment of migraines, cluster headaches, symptomatic trigeminal neuralgia, and atypical facial pain.

(2) Blocking of the gasserian ganglion and trigeminal nerve branches

Since the trigeminal nerves control all sensation of the head (excluding the occipital area), the face, and the cranium, a headache inevitably means excitement of these nerves. If these nerves are blocked, all sensation of the head and face disappear, and it is obvious that the headache is no longer present, either.

Theoretically, a headache cannot be felt when the trigeminal nerves are blocked. If a patient still experiences pain under such circumstances, it is not exaggerated to assume that the pain is caused by other factors, e.g.

psychologic problems.

Blocking of the gasserian ganglion and the trigeminal nerve branches are most effective for the treatment of idiopathic trigeminal neuralgia, but is also applied to migraines, cluster headaches, symptomatic trigeminal neuralgia, and atypical facial pain.

(3) Occipital nerve block

Since the second and third cervical nerves control the area from the posterior region of the neck to the parietal region, pain in this area can be treated by blocking the greater occipital nerves, arising from the second or third cervical nerves, while blocking of the lesser occipital nerve is used for pain that occurs in the occipital area.

Depending on the type of pain, root blocks of the second and third cervical nerves are often used.

Occipital nerve blocks are employed for idiopathic occipital neuralgia and cervical headaches.

Conclusion

I hope you can see that the treatment of chronic headaches at pain clinics does not only consist of a combination of general drug therapy and nerve blocks, but in order to decrease patients' pain, other methods are also proactively incorporated if necessary to alleviate other pains.

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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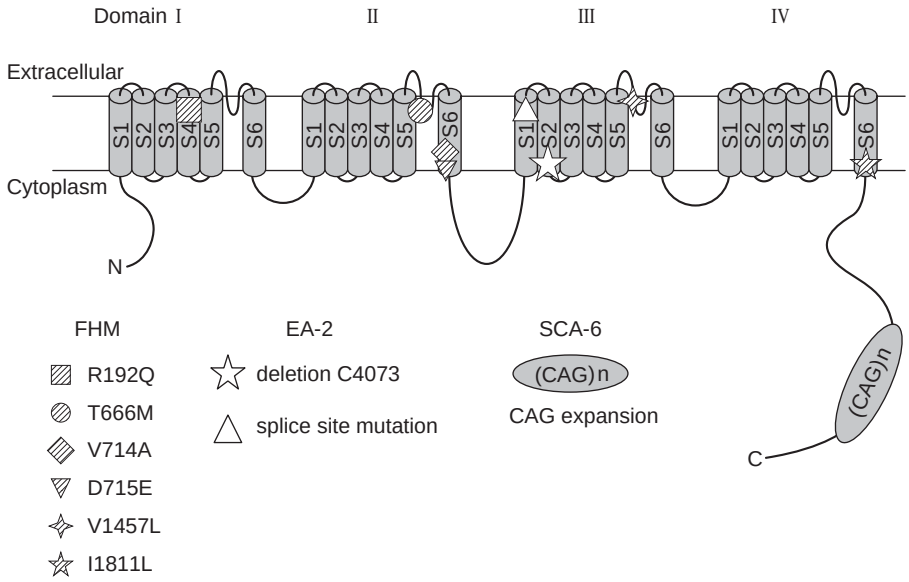

Fig. 1 Structure of the P/Q type Ca^{+2} channel α1 subunit (CACNA1A) and the FHM mutation site

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

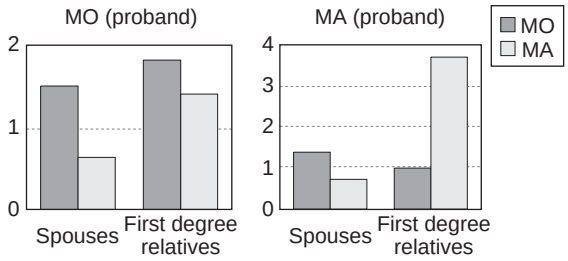

Fig. 2 Relative risk for migraine among spouses and first degree relatives
MA: Migraine with aura, MO: Migraine without aura
(Partly adapted from Russell, M.B. *et al.*: *Cephalalgia* 1996; 16: 305–309)

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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Treatment of Varicose Veins

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Abstract: Varicose vein is a condition that was first described about 1550 BC. The mechanism of varicose vein formation is reflux of blood into the superficial venous system through the perforating veins, including both saphenous veins. Although very common, the etiology of this reflux remains unclarified. The disease progresses slowly from mild swelling of the leg to lipodermatosclerosis and venous ulcer formation around the ankle joint. The mainstay of conservative treatment is compression applied by elastic stocking. Although sclerotherapy has become popular in Japan, its usefulness in the presence of saphenous reflux is questionable. While many patients seek treatment for cosmetic reasons, the absolute indication for operative intervention is changes in the skin. Stripping of the saphenous veins accompanied with varicectomy is a time-honored treatment, and the introduction of segmental stripping has eliminated the once-common complication of saphenous neuralgia. In the presence of dermal sclerosis or venous ulcers, the major drawback of the classical Linton's operation was a high rate of wound dehiscence and infection. The recent innovation of endoscopic subfascial division of incompetent perforators and removal of saphenous veins (SEPS) has eradicated the complications and helped to promote patient comfort.

Key words: Varicose vein; Stripping; Sclerotherapy; SEPS

Introduction

Varicose veins of the lower limbs have a long recorded history. The oldest known description of this condition is found in Ebers Papyrus, which has been dated to approximately 1550 BC. In addition, legs with bulging varicose veins appeared on a lithograph from the Acropolis of Athens in the fourth century BC. This historical lithograph is often used in brochures of academic meetings related to veins.[1)]

A 1992 survey carried out in London of people aged 35–70 years revealed that 17% of men and 31% of women had varicose veins.[2)] In Japan, varicose veins occur less frequently, but the condition is fairly common and it is not rare to find people who exhibit it on the street. Varicose veins are more common in women,

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particularly in the early stage of pregnancy, suggesting the involvement of progesterone. According to a previous survey by the Conjoint Meeting on Vascular Surgery, the male:female ratio of patients with varicose veins in Japan was about 1:3, and patients aged 30 years or older accounted for 96% of cases.[3)]

Anatomy and Physiology

The muscles of the lower limbs are covered by the fascia lata and the fascia cruris. Veins lying shallower and deeper than these fascias are called, respectively, superficial veins and deep veins. The main superficial veins include the greater and lesser saphenous veins, both of which have many branches. The greater saphenous vein flows into the femoral vein at the fossa ovalis in the upper part of the thigh, whereas the lesser saphenous vein flows into the popliteal vein at the popliteal fossa. In addition, many communications, known as perforators, exist between the superficial and deep venous systems. Venous valves in the perforators are arranged in the direction of blood flow from the superficial to deep veins. The greater and lesser saphenous veins can be regarded as perforators in view of their function.

Fig. 1 Lipodermatosclerosis accompanied with brown pigmentation
Sites of perforators are marked.

Fig. 2 Venous ulcers
Ulcers occur predominantly on the medial side of the leg above the ankle.

Etiology and Pathophysiology

Dilated tortuous veins are called varicose veins regardless of their size. Secondary varicose veins include superficial veins dilated as collateral pathways owing to deep venous thrombosis, those associated with arteriovenous fistula, and those resulting from congenital vascular anomaly. Varicose veins not caused by these conditions are called primary varicose veins. Most of the commonly observed varicose veins are primary.

Although primary varicose veins are frequent, the pathogenesis is controversial and has not been well established. The development of varicose veins formerly was explained by a mechanism through which the hydrostatic pressure of blood disabled the valves of the greater saphenous vein serially in a descending manner. If this hypothesis were true, varicosity of the greater saphenous vein should precede tributary vein varicosity. In actuality, however, some cases do not present dilatation of the greater saphenous vein. Moreover, it is apparent that varicosity of the main stem of the greater saphenous vein begins with dilatation of the vein just beneath a valve rather than above a valve, creating another inconsistency in the above hypothesis. In addition, the greater

saphenous vein is often used as an arterial bypass conduit. It is known that no varicose dilatation occurs in normal greater saphenous vein grafts that have been under arterial pressure for years. Other suggested mechanisms include arteriovenous fistula, metabolic disorder of the venous wall, and incompetence of perforator veins. In addition, adhesion and activation of leukocytes and enzyme abnormalities have been cited recently as possible mechanisms. In any case, the venous wall itself is considered to be vulnerable in patients with varicose veins.

Clinically, varicose veins occur more frequently in women, particularly in early pregnancy, as mentioned previously. In relation to occupation, the condition is common in jobs associated with prolonged standing, for example, among those who work in restaurants, factories, and the like. Familial occurrence of varicose veins is also observed.

Venous varicosities range widely, from simple types to those accompanied with edema, eczematoid changes, pigmentation, lipodermatosclerosis (hardening of the skin and subcutaneous tissue), or venous ulcers (Figs. 1 and 2). Patients may perceive no symptoms, or may complain of heaviness, fatigue, itching, or pain. Female patients often notice the severest symptoms on the first day of their menstrual period, suggesting hormonal involvement.

It is important to note that no correlation exists between the apparent severity of varicosities and subjective symptoms. Some patients who have prominent varicosities may report hardly any symptoms, whereas others who have modest varicosities may have severe dermal changes and experience severe pain. The latter patients are considered to have tensed varicose veins even if they are mildly tortuous, resulting in a state of venous hypertension. The presence of varicosities may not be detected visually or by palpation when dermal sclerosis is severe. In such cases, ultrasonic tomography using a high-frequency probe reveals varicose veins subcutaneously at the site of skin pigmentation.

Skin lesions occur frequently on the medial side of the leg just above the ankle joint (gaiter area). This locational feature is in contrast to the location of ischemic ulcers resulting from insufficiency of arterial blood flow, which frequently occur in toe tips and heels. Venous ulcers do not reach the crural fascia, another characteristic feature. Unlike ischemic ulcers, venous ulcers are often painless, and thus may be left untreated for a long period of time.

Treatment

1. Indications

As mentioned previously, the subjective symptoms of varicose veins are not well correlated with the apparent severity of varicosities. Furthermore, patients may seek medical consultation for cosmetic reasons ("unsightly", "show when wearing a skirt"), even if they have no pain or other symptoms. In our opinion, the treatment of varicose veins should be indicated for the following conditions.

First, dermal changes including eczematoid changes, pigmentation, skin sclerosis, and ulcers are absolute indications for treatment, particularly surgical treatment, because they progress to intractable ulcers if left untreated. In addition, surgery is recommended for cases of bleeding from ruptured varicosities, past history of thrombophlebitis, and varicosities measuring 2 cm or more in diameter and thus at risk for developing thrombosis. Otherwise, treatment is implemented only when the patient requests it. Patients who complain of pain or fatigue often experience relief of symptoms after treatment. However, patients who request treatment for cosmetic reasons should clearly understand that surgical treatment causes scarring and that sclerotherapy is frequently associated with recurrence.

2. Conservative treatment

The basis of conservative treatment is compression therapy. Elastic compression stockings designed for patients with varicose veins are currently in widespread use. These stock-

ings provide graded pressure, with the greatest pressure at the ankle and less pressure in the upper parts. These types of stockings were first developed by Conrad Jobst in the 1950s. Jobst, who himself suffered from varicose veins, realized that his symptoms were improved by standing in a swimming pool, and he subsequently developed the elastic stockings.[4] Compression therapy is worth trying as the initial treatment in patients who have relatively mild varicosities not accompanied with dermal changes. Weariness and heavy sensation of the legs may be improved to a great extent. If the patient's compliance with the elastic stockings is favorable, he or she may be followed without any other treatment. The use of stockings also aids in preoperatively predicting the efficacy of surgical treatment (surgical procedures will be discussed later). Specifically, if the patient's symptoms are improved by the stockings, the symptoms are very likely attributable to varicose veins, and thus surgery is expected to be effective.

Various types of elastic stockings are available. Long stockings covering the thigh are used for patients who have large varicosities in the femoral region, as in Klippel-Trenaunay syndrome. However, such long stockings are apt to slide down and can be inconvenient. Therefore, for the treatment of general varicose veins, below-knee stockings are practical, are associated with minimal sliding, and provide adequate efficacy even when some varicosities are present in the thigh as well. Stockings that provide 40 mmHg of pressure at the ankle are generally used. Among medical elastic stockings, moderate compression stockings are recommended.

One drawback of compression stockings is their price, generally 8,000–10,000 yen per pair. Since the stockings are not covered by health insurance in Japan, the patient must assume the entire cost. However, below-knee stockings that offer about 30 mmHg of compression have recently been marketed at prices less than 2,000 yen. These seem to be effective for mild cases. Patients are instructed to remove compression stockings at bedtime and sleep with the lower limbs elevated.

3. Sclerotherapy

Sclerotherapy has a relatively long history. It was introduced in the late 1920s, because the technique of greater saphenous vein extraction, which was introduced at the beginning of the 20th century, was initially associated with frequent complications. However, sclerotherapy showed a recurrence rate as high as 60% at 5 years, even when combined with high ligation of the greater saphenous vein, and therefore was out of favor for some time.[5] In recent years, sclerotherapy is again being practiced mainly in Europe, because of the advent of new sclerosing agents and the desire to preserve the greater saphenous vein for possible future bypass surgery. In Japan as well, sclerotherapy is becoming better known, and a number of patients visit medical institutions to request "treatment with injection". However, randomized controlled studies carried out in 1974 and 1993 showed high recurrence rates similar to those obtained previously.[6,7] In particular, the presence of reflux of the greater saphenous vein appears to lead to poor outcome.

Currently, we are limiting the application of sclerotherapy to the following conditions: 1) spider angioma; 2) varicosities measuring 1–3 mm without apparent reflux owing to saphenous vein incompetence; and 3) varicosities remaining or occurring after surgery. As sclerosing agents, we use polidocanol or hypertonic saline. It has become apparent that foam sclerosing agents are more effective, and some institutions have begun to use such agents on a trial basis. In the practice of sclerotherapy, it is important to employ the sclerosing agent at the minimum necessary concentration and amount, and to apply compression securely.

4. Stripping

Extraction of the greater and lesser saphenous veins with resection of varices constitutes the current most common surgery for

varicose veins, i.e., stripping surgery. This is a relatively simple operation, and some modifications have recently been made for this procedure.

First, the lower limbs of the patient are subjected to ultrasound examination for mapping varicose veins and incompetent perforators. Previously, incompetent perforators were located by milking or palpation of the fascia, but these procedures seldom enabled us to confirm the location of incompetent perforators. Duplex ultrasonography accurately reveals the location of perforators and permits a reliable diagnosis of the presence/absence of saphenous vein reflux.

Second, stripping of the greater saphenous vein is restricted to as far as the knee level. This is because anatomically there is no perforating vein that directly enters the greater saphenous vein distal to the perforator from the popliteal vein (Boyd's perforator), thus precluding further extraction of the vein as a rule. Lack of extraction of the below-knee greater saphenous vein decreases the frequency of injuries to the saphenous nerve, thereby preventing postoperative paraesthesia in the instep of the foot. Some institutions in the US have recently begun to use catheterization into the greater saphenous vein to carry out thermal coagulation of the vein.[8)]

5. Linton's operation

In many cases, the surgical treatment for varicose veins consists of stripping and resection of varices. However, varices are difficult to resect in patients with severe sclerosis of the skin or those with ulcers. Although varices with pigmentation or ulcers can exist below the skin, they are difficult to resect, and, even if they are resected, healing of the wound cannot be expected. For the treatment of such conditions, Linton proposed subfascial perforator ligation in 1938.[9)] In this technique, a long longitudinal skin incision is made on the medial side of the leg, and the fascia cruris is incised to ligate incompetent perforators subfascially. If the saphenous vein is incompetent, stripping of the vein is added. Although this method is effective, a major drawback is frequent dehiscence of the long skin incision. The causes of this complication include incision in morbid skin and high susceptibility to infection via ulcers.

Fig. 3 Laparoscopic surgical instruments used for SEPS
The two instruments on the left are balloon devices used to dissect the subfascial space.

6. SEPS

Subfascial endoscopic perforator surgery (SEPS) has recently been employed to overcome the drawbacks of Linton's operation. As mentioned previously, skin lesions caused by varicose veins occur frequently just above the ankle. Therefore, a small incision is made in the upper part of the leg, where dermal changes are not substantial, and a trocar is inserted from the incision to detach the subfascial tissue and cut off incompetent perforators under endoscopic observation. Finally, stripping of the greater saphenous vein is performed from the inguinal region to the site of trocar insertion. In our institution, this operation is carried out using apparatuses generally used for laparoscopic surgery, with the femoral region covered by pneumatic tourniquet and with carbon dioxide insufflation to areas under the fascia cruris (Fig. 3). It is both easy and convenient to use an ultrasonic coagulator (LCS) for cutting off perforators.[10)] According to our experience over the past 4 years, this is a useful method

and is associated with fewer complications of the surgical wound. It is expected that this technique will become more widespread in the future.

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