Familial Hemiplegic Migraine

Familial hemiplegic migraine (FHM) is an autosomal dominant disorder characterized by episodes of recurrent hemiplegia during the aura phase of migraine headache. The gene for FHM has been mapped to chromosome 19p13. Recently missense mutations of the P/Q-type Ca^{2+} channel alpha1 subunit gene, CACNL1A4 were identified (1).

According to the diagnostic criteria by the International Headache Society (IHS), FHM is classified in a subcategory of migraine with aura (2). This criteria requires the following: 1) fulfill criteria for migraine with aura; 2) the aura includes some degree of hemiparesis and may be prolonged; 3) at least one first degree relative has identical attacks. Details of clinical features of FHM varies among families. In some families, ocular nystagmus and cerebellar atrophy are often present (3); in others, seizure or consciousness disturbance are present. It is noteworthy that angiographic study, except for MR-angiography, is hazardous for patients with FHM. Regarding FHS, the IHS classification committee stated "This disorder probably has the same pathophysiology as migraine with typical aura. The reason for still keeping it separate is that families have been described where attacks are strikingly identical and sometimes long lasting." Actually, the region containing the 19p13 FHM locus was shown to also be involved in the more common form of migraine (4). FHM is hypothetically regarded as a part of the migraine spectrum involving similar genetic factors and biological mechanisms.

See also p 166.

In this issue of Internal Medicine, Hayashi et al (5) report a case of FHM with irreversible brain damage. Their patient showed a prolonged hemiplegia and consciousness disturbance with evidence of hyperperfusion of the cerebral cortex. The vascular theory of migraine claims that vasoconstriction causes local ischemia of the brain, which is responsible for aura symptoms, such as hemiplegia. The following vasodilatation causes throbbing headaches. Single photon emission computed tomographic studies support this hypothesis (6). Regional cerebral blood flow (rCBF) studies do not always consistently demonstrate this patterns, however, most rCBF studies agree that abnormal change of cerebral circulation occurs during aura and headache phases of migraine attack. Abnormal platelet serotonin metabolism plays a crucial role in the alteration of vascular tone in migraine headaches (7). The released serotonin from one platelet stimulates other platelets to release serotonin. The chain reaction of serotonin release causes high serotonin levels in the blood and vasoconstriction. Afterwards, the serotonin in the blood is metabolized into 5-hydroxyindole acetic acid (5-HIAA). 5-HIAA is secreted into the urine and blood and the platelet serotonin level decreases, which causes vasodilatation and throbbing headaches.

On the other hand, the neural theory of migraine headache claims that metabolic changes of neurons are primary event which cause a change in vascular tone. Hyperexcitability of the central nervous system causes aura symptoms and cortical spreading depression, with subsequent vascular throbbing headaches (8). The trigemino-vascular theory claims that some neurochemical noxious trigger stimulates the trigeminal nerve and causes hyperactivity of trigeminal nerves (9). Substance P and other neurotransmitters are released from small-diameter trigeminal sensory afferents around the meningeal and dural blood vessels, initiating vasodilatation, plasma extravasation, and release of histamine from mast cells and serotonin from platelets. Serotonin causes vasoconstriction and local ischemia of the brain. Interestingly, a severe episode in patients with FHM can be triggered by minor head trauma and cerebral angiography.

Impact of discovery that mutations of brain-specific Ca^{2+} channel cause FHM would provide a new hypothesis that migraine headache is a channelopathy. Vascular, neural, serotonergic, and trigeminovascular hypothesis therefore should be reorganized with the concept of channelopathy. At present, there have been no clear positive reports of CANCL1A4 mutation in Japanese families with migraine headache. Most families link to chromosome 19p13 bearing cerebellar atrophy. The Japanese case reported in this issue (5), does not have cerebellar atrophy, however, the deteriorating course and severe brain edema may suggest some abnormality in the ion-channels of brain cell membrane. The new concept that migraine is a channelopathy will open a new avenue for therapeutic strategy of migraine headaches. Accumulation of Japanese cases with a detailed clinical description and genetic survey are deemed important. Genetic studies of calcium and other ion-channel, receptors of neurotransmitters, and transporters are a promising field in headache research.

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