Recent advances in migraine

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ABSTRACT
This paper summarizes recent advances in migraine with reference to classification systems, epidemiological data, pathophysiology, the role of neuroimaging, treatment options and the relationship to thunderclap headache.

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Classification systems. For many years the definition of migraine proposed by Vahalquist was used for epidemiological purposes, even though the original definition had been developed for use in children. Migraine was defined as a paroxysmal headache with headache-free intervals, accompanied by two of the following: a) nausea, b) focal cerebral symptoms, c) unilaterality, d) positive family history involving at least one parent or sibling. Problems mainly arose when using this system in relationship to criterion d. Several studies have concluded that a family history of migraine is reported with both a poor sensitivity and specificity. Accordingly the International Headache Society (IHS) produced a more exact set of criteria which could define the condition more specifically.

Migraine without aura is thus defined as follows: a) at least five attacks fulfilling the following criteria, b) headache attacks lasting 4 to 72 hours, c) headache that has at least two of the following characteristics: 1. Unilateral location, 2. Pulsating quality, 3. Moderate or severe intensity (inhibits or prohibits daily activities), 4. Aggravated by walking, climbing stairs or similar routine physical activity, d. during headache at least one of the following: i. Nausea or vomiting, ii. Photophobia and phonophobia.

A separate definition has been produced for migraine with aura. The IHS criteria have found widespread acceptance and have been used to provide fresh epidemiological data on migraine.

Epidemiological data. An early study of migraine in the United States, using a modified form of Vahalquist’s criteria, serves as a useful comparison with recent data obtained using the IHS criteria. The early survey was of some interest, as it failed to confirm the commonly held notion that migraine was more common in the caucasian population and in the higher educated. In a recent study, utilizing a postal questionnaire, migraine prevalence was found to be lower in black males compared to white, though not in black females compared to white females. Some 20,000 subjects responded to the survey, producing a total of 17.6% females and 5.7% males between the ages of 12 and 80 who fulfilled the criteria for the definition of migraine. After adjusting for other covariates, attack frequency decreased as household income increased for both males and females. Furthermore, there was a consistent trend of higher prevalence in lower-income groups. In both sexes, peak prevalence rates were reached around the age of 40, with a decline thereafter. A recently published overview has brought together the data obtained from four studies including the one by Stewart et al.

Prevalence estimates for women ranged from 12.9 to 17.6 per cent and for men, 3.4 to 6.1 per cent. The female/male ratio lay between 2.5 and 3.8. The authors analyzed prevalence data from 57 population based surveys, though in the end only 24 studies fulfilled their criteria for inclusion. When comparison was made between studies using Vahalquist’s criteria, and those proposed by IHS, it was found that the former resulted in lower prevalence rates, and a lower female/male ratio. The authors concluded that further work on the IHS criteria might be necessary to improve reliability of diagnosis, quoting one study which had reported a good agreement between clinicians when studying videotaped interviews describing the major headache types, but with less satisfactory agreement when distinguishing subtypes of migraine and tension-type headache.

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Debate has continued as to whether migraine and tension-type headache are continuum, or separate entities. In an attempt to resolve the question, a Danish group interviewed 740 individuals drawn from a central registry. The analysis looked at both migraine with and migraine without aura, finding that women were significantly more likely to have migraine without aura than migraine with aura in comparison to men. In the previous year, 63 per cent of the sample had episodic tension-type headache and 3 per cent chronic tension-type headache. The sex ratio for the two conditions differed, with a female/male ratio of 3 to 1 for migraine but 5/4 for tension-type headache. The prevalence of tension headache in the migraine sufferers was no different from the prevalence in those not having migraine, and apart from occurring with greater frequency and severity in the migraine group, did not differ in its other characteristics from those occurring in individuals with pure tension-type headache. The authors concluded that the conditions were distinct, and not part of a continuum.

Recent data has emerged on the epidemiological comparison of migraine with and without aura, and on the nosographic analysis of the aura. To analyse possible differences between migraine with aura (MA) and migraine without aura (MO) a population study was performed which allowed analysis of 740 patients. Patients with MA had less severe and shorter-lasting headache than patients with MO. About a fifth of the patients who had migraine with aura also had attacks without aura. The authors concluded that the symptoms of MA and MO were likely to have a shared pathophysiology. A larger group (4000) from the same population survey, all aged 40, has been surveyed to analyze migraine aura. One hundred and sixty three individuals suffered from migraine with aura and were personally interviewed. Nearly all the patients had visual aura, which was the only focal symptom that occurred in isolation. Sensory (31%), aphantic (18%) and motor (6%) aura almost always occurred in association with visual aura. Though visual aura occurred in virtually every attack the other aura were present in only a small percentage of the individual’s total number of attacks. Few of the patients had visual aura lasting beyond an hour. A typical sensory aura started in the hand, then progressed through the arm into the face and tongue, the progression taking up to 30 minutes and the duration up to one hour. Twenty per cent however, had a more prolonged sensory aura. Motor aura was more protracted (over 60 minutes in two-thirds) and always unilateral. In terms of the relationship of the headache to the aura, the former followed the latter in over 90 per cent of cases. Analysis of the characteristics of the aura, in terms of its evolution, led the authors to support the notion of cortical spreading depression as the most likely pathophysiological mechanism.

Pathophysiology. Regional cerebral blood flow studies have established that a unilateral reduction in flow takes place prior to the aura symptoms in migraine subjects, at least with reference to attacks induced by arteriography. In the early headache phase, regional flow remains depressed in the majority, though later headache tends to coexist with hyperperfusion. Not infrequently, however, hyperperfusion outlasts the headache. Previous studies have failed to demonstrate changes in extracranial blood flow during migraine attacks. Clearly neither intracerebral nor extracerebral vasodilation is a satisfactory explanation for migraine pain. It is now clear that the trigeminal system is closely associated with the pathophysiological processes occurring in migraine. The trigemino-vascular system consists of the cranial vessels and their trigeminal innervation. Relevant to the causation of the pain are the pain-sensitive intracranial structures, including the venous sinuses and the dura mater. The majority of the fibers from the dura, the large cerebral arteries and the superior sagittal sinus are found in the first division of the trigeminal nerve. Expression of c-Fos-like immunoreactivity has been used to map the cell bodies in the medulla and upper cervical spinal cord activated by stimulation of the superior sagittal sinus (SSS). Activation was found in the superficial laminae of the trigeminal nucleus caudalis and the contiguous dorsal horn of the cervical spinal cord (C1-C3). Neurons in the region are known to project to thalamic, midbrain and medullary reticular areas involved in the processing of noxious stimuli. The trigeminal system therefore is involved in vascular pain transmission. In addition, activation of the trigeminal ganglion increases blood flow via a reflex (vascular reflex) that traverses the brainstem, the efferent pathway being in the facial nerve. The transmitter for this effect is probably vasoactive intestinal peptide (VIP). Direct stimulation of the ganglion increases cerebral and extra cerebral blood flow in the experimental animal and in humans, with a concomitant increase in the local cranial release of neuropeptides, particularly calcitonin gene-related peptide (CGRP) and substance P. Release of CGRP has been detected in the external jugular vein in humans during attacks of migraine headache. These changes in blood flow and peptide release are antagonised by sumatriptan and dihydroergotamine. A link between cortical spreading depression (CSD) and subsequent headache is suggested by the fact that CSD can induce c-Fos-like immunoreactivity within the trigeminal nucleus caudalis, presumably by activating trigemino-vascular primary afferents, perhaps via release of nociceptive substances from the cortex. Specific agents that are effective in migraine control appear to act largely through 5-HT, receptors, particularly of the 5-HT, class. These receptors are
found both on pre-synaptic fibres (where they can influence release of neuropeptides from nerve terminals) and post-synaptically in cerebral vessels, though in the latter case, the type of receptor varies according to the vessel site.

**The role of neuroimaging.** Recently published studies have addressed both the need to image headache patients who have a normal neurological examination, and the yield of CT scanning in patients with chronic headache. An extensive analysis of the literature on CT or MRI scanning in patients with headache was published in 1994. Of 897 scans in patients with migraine, 4 detected potentially treatable conditions (3 tumor and 1 arteriovenous malformation). Of 1,825 scans in non-specific headache, 43 revealed potentially treatable conditions. A large study of migraine subjects deserves mention. In 435 patients with classical migraine (as it was then defined), only one abnormal scan was detected-despite removal of that patient’s choroid plexus papilloma, the migraine attacks continued. It has been concluded that adults with migraine who have experienced no recent change in headache pattern, who have no history of seizures, and no other neurological symptoms or focal signs do not warrant imaging.

The value of scanning for patients with more chronic headache has also been examined. Over a five year period, patients attending a chronic headache clinic who had developed an increase in severity of headache, resistance to therapy, a change in the pattern of headache or family history of intracranial structural lesions were scanned. Three hundred and seventy-three patients received 402 CT scans. Of the patients, about three quarters had migraine. The scanned group represented about 10% of the clinic population. Of the 402 scans, 14 revealed minor findings that did not alter patient management, while 4 showed what the authors described as significant lesions (osteoma (2), low-grade glioma (1) and aneurysm (1)). Only the aneurysm was treated. The overall cost of scanning to find one treatable vascular lesion was $74,243. Clearly scanning chronic headache patients on the basis of the above criteria is not justified.

**Treatment options.** Considerable literature has accumulated on the use of sumatriptan in migraine. Response rates reported after a single injection reached 86%, and 75% after a single 100mg oral dose. Sumatriptan is a highly selective agonist at the 5-HT1 receptor site, without effect on 5-HT, 5-HY, or 5-HT receptors. Sumatriptan can constrict dilated isolated human basilar arteries, may inhibit peptide release via a neurogenic action and inhibits plasma protein extravasation induced by antidromic stimulation of the trigeminal nerve. To date, longer term studies have not shown any tendency for the drug to lose its efficacy with repeated use. Recurrence of headache and other symptoms within 24 hours of initial response is a recognised feature in patients receiving sumatriptan and occurs after an oral dose in 25 to 33 per cent of patients. A second dose two hours after the first does not enhance the effect of the first dose nor does it influence headache recurrence. Headache recurrence (which in this study occurred at a mean time of around 16 hours) responded successfully (in three-quarters) to a further oral 100 mg dose. Taking up to 3, 100 mg, tablets within a 24 hour period was well tolerated. Adverse effects of sumatriptan include the development of chest pain, reported in 7.9% of patients in one survey. Both iv and sc sumatriptan are capable of causing a reduction in coronary artery diameter particularly in the presence of coronary artery disease. In many patients who experience chest pain with sumatriptan, however, the pain is probably esophageal in origin.

The effect of sumatriptan when administered during the aura phase has been studied. Neither did the drug have a significant effect upon the nature or duration of the aura, nor did it prevent or significantly influence the severity of the subsequent headache. Developments have also taken place in preventative migraine therapy. Established, effective prophylactic agents include the β-blockers, some of the calcium channel blockers (particularly flunarizine) and certain antidepressants, including amitriptyline. Many of the nonsteroidal anti-inflammatory drugs exert a prophylactic effect. Sodium valproate has now joined the list. In a study of 43 patients, sodium valproate, in a dose of either 1000 or 1500 mg/day (adjusted according to serum levels) was compared to placebo. There was a significant reduction in attack number during valproate therapy, though attacks that still occurred were of unchanged severity and duration. The drug effect appeared to increase throughout the 12 weeks of therapy. The mode of action of valproate in stemming migraine attacks is unclear, though the drug can reduce firing rates of serotonergic neurones.

**Thunderclap headache.** Thunderclap headache is a term used for patients with a sudden onset of severe, excruciating generalized headache, mimicking subarachnoid hemorrhage but without CT or CSF evidence to support that diagnosis. In a follow-up study of 71 such patients, over a mean of 3.3 years, none had had a subsequent subarachnoid hemorrhage, though a sixth had had further, similar headaches, while nearly a half had developed either tension headache or migraine without aura. A similar, follow-up study of thunderclap headache was reported in 1991. None of the sixteen patients developed evidence of subarachnoid hemorrhage during a mean follow-up of 20 months. The aetiology of the condition remains uncertain. Day and Raskin reported one such patient, with normal CSF, in whom angiography revealed an unruptured...
internal carotid aneurysm associated with diffuse vasospasm. Others, however, have suggested that finding unruptured aneurysms in these patients is a chance occurrence, and that vasospasm in such cases might be migrainean in origin. Certainly migraine probably accounts for some of these cases, as does sudden exertion, including sexual intercourse. In the remainder, follow-up has established that seldom, if ever, is the presentation due to an unruptured aneurysm.

References