Recent advances in migraine with reference to classification systems, epidemiological data, neuroimaging, treatment options and the relationship to thunderclap headache.

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Dr. G.D. Perkin, FRCP

Abstract
This paper summarizes recent advances in migraine pathophysiology, the role of neuroimaging, treatment options and the relationship to thunderclap headache. For many years, the definition of migraine proposed by Vahliquist was used for epidemiological purposes, even though it had been developed for use in clinical settings. However, a recent study utilizing a postal questionnaire revealed that migraine prevalence was lower in black males compared to white males, 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 45 and 65. A new classification system has been proposed to better reflect the current understanding of migraine.

Keywords: Migraine, 5HT receptor, neuroimaging

Classification system

The new classification system for migraine defines the condition based on the presence of several key features, including: a) nausea, b) focal unilateral headache, c) photophobia and phonophobia, and d) positive family history. This system is designed to improve the accuracy of diagnosis and treatment.

Recent advances in migraine

Recent advances in migraine have led to improved understanding of its pathophysiology and treatment options. These advances include new classification systems, improved neuroimaging techniques, and the development of effective treatment options.

Epidemiological data

Epidemiological data on migraine has revealed significant differences between different populations. For example, migraine prevalence is higher in females than in males, and prevalence is highest in the young adult population. In some populations, migraine prevalence is higher in black males compared to white males, though not in black females compared to white females.

Neuroimaging

Neuroimaging techniques, such as magnetic resonance imaging (MRI), have been used to study the brain in patients with migraine. These studies have revealed changes in brain structure and function in migraineurs, including alterations in brain morphology and changes in blood flow.

Treatment options

Recent advances in migraine treatment have led to the development of new drugs with improved efficacy and safety profiles. These include oral and intranasal sumatriptan, as well as new formulations of other drugs commonly used to treat migraine.

Relationship to thunderclap headache

The relationship between migraine and thunderclap headache has been a topic of recent research. Thunderclap headache is a severe, sudden-onset headache that can be associated with subarachnoid hemorrhage. Studies have shown that migraine and thunderclap headache may share some pathophysiological mechanisms.
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 nosological 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 pain phases 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%), aphasic (18%) and motor (6%) aura almost always occurred in association with visual aura. Though visual aura occurred in virtually every attack the other auras 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 pathophysiologic 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 trigeminovascular 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 trigeminovascular primary afferents, perhaps via release of noxious substances from the cortex. Specific agents that are effective in migraine control appear to act largely through 5-HT1 receptors, particularly of the 5-HT1D 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 repeated use. Recurrence of headache and other symptoms within 24 hours of initial response is a recognised feature in patients receiving sumatriptan³ 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.³ 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
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 migrainous 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