Headache Platform

Functional neuroimaging evidence of the role of the vasculature in migraine

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Abstract

The pathogenesis of migraine pain has not yet been adequately explained and remains the subject of vigorous debate. Early studies on the extracranial terminal branches of the external carotid artery provided compelling evidence of their involvement in the evolution of migraine pain. Since 1958, however, since Milner proposed that the visual aura of migraine may be caused by the "spreading depression" of Leão, most migraine researchers have focused almost exclusively on changes in the intracranial arteries. In this article, the evidence provided by functional neuro-imaging is reviewed with respect to the vascular changes in migraine during a) the aura phase, and b) the headache phase.

Functional neuroimaging

Many functional neuroimaging techniques have been employed, with varying success, to study the vascular changes during migraine. Unfortunately the paroxysmal and unpredictable nature of migraine attacks, and the relatively short duration of the aura phase (typically less than one hour), have hampered attempts to conduct extensive studies on large samples. There have been some contradictory findings, but nevertheless, certain patterns have emerged that have been confirmed repeatedly using a variety of methods.

Aura phase

In approximately 15% of migraine sufferers, the pain is preceded by focal neurological symptoms that can be localised to the cerebral cortex. The most common aura symptoms include transient visual disturbances, unilateral paraesthesia and/or numbness or weakness in the face or arm that may be associated with speech disturbances (the digitolingual syndrome).[1]

In 1941 Lashley, himself a migraine sufferer, plotted the progress of his own visual aura. He noticed that his scotoma started as a small area, which enlarged progressively, moving toward the periphery of the visual field, and then disappeared. Anatomically, the steady enlargement of the scotoma could not be explained by progressive vasoconstriction of the arterial system, and he postulated that the visual aura was caused by a wave that moved across the surface of the cerebral cortex and a rate of 2-3mm per minute, like ripples spreading in concentric rings from an initial stimulus.[2]

Three years later, Leão described the phenomenon of "spreading depression". The application of weak faradic or mechanical stimulation to the exposed cerebral cortex in the rabbit elicited a characteristic response which he termed spreading depression. Shortly after the stimulus was applied, spontaneous electrical activity decreased markedly at the stimulated region. This depression then slowly spread in all directions, successively affecting adjacent areas. Recovery required 5-10 minutes in each region. The spontaneous activity at the stimulated region was often well recovered by the time the depression is just starting in distant parts. It appears though, that Leão was more interested in the role of spreading depression in epilepsy, and did not make the connection with migraine aura, as migraine aura was not mentioned in his paper.[3]

It was not until 14 years later when Milner suggested that "In view of the correspondence between these observations (of Lashley and Leão) there would seem to be a distinct possibility that migraine scotomas are manifestations of spreading depression triggered off in susceptible individuals. Other symptoms of migraine (tingling in the extremities, nausea, etc.) may be due to spread of depression in other areas of the cortex".[4]

Since the publication of Milner's article, Leão's paper was more and more frequently cited, and the postulate that spreading depression may be the initiating factor in migraine began to gain ground, even though most migraineurs never experience an aura of any kind. The general concensus among migraine researchers over the last few decades has been that spreading depression is related to a transient cerebral oligaemia, while the headache phase that follows is initiated by dilatation of the cerebral vessels.

Intracranial blood flow during the aura phase

The changes in intracranial haemodynamics during migraine with aura, demonstrated with functional imaging techniques such as [133]Xenon intra-arterial injection, single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI), are an initial brief hyperperfusion[5-7], followed by hypoperfusion.[5,7,8-14]

Xenon blood flow studies

Investigations, using intra-arterial ^{133}Xe blood flow techniques, into the haemodynamic changes during aura-like symptoms induced by carotid angiography, demonstrated reductions in cerebral blood flow (CBF) in the posterior regions of the brain.[5,10,15] Blood flow changes remained relatively static for 30-60 minutes, after which it returned to normal or was focally decreased.[7,11] In some studies, an anterior spread of oligaemia was noted, at a rate of 2-3mm per minute across neurovascular boundaries.[10] Others observed that there seemed to be a correlation between the severity and duration of blood flow decrease, and the severity and duration of the aura symptoms.[16] In several series, however, there has been no disturbance in CBF, in spite of the presence of aura symptoms.[10,11,16]

Hypoperfusion follows hyperperfusion in aura phase

Furthermore, estimated reduction in blood flow ranges from 17% to 35% - insufficient to cause ischaemia.[5,11] It is possible that the conflicting results may be partly due to differences in the time of measurement.[1]

SPECT

SPECT has been used to semiquantitatively assess regional cerebral blood flow (rCBF). Studies in patients with aura demonstrated areas of hypoperfusion (reduced cerebral blood flow consistent with vasoconstriction) in most cases. This hypoperfusion usually (but not always) corresponded with the topography of the reported symptoms.[13,14]

PET

PET allows quantitative measurement of CBF, unlike SPECT, with which only semiquantitative measurements can be obtained. Because of technical difficulties, PET is more useful in studying migraine without aura, but hypoperfusion during the aura phase has been demonstrated.[17,18]

fMRI

The advantages of fMRI that make it attractive for the study of transient phenomena such as migraine are fast acquisition times and the fact that isotopes are unnecessary.

Using perfusion-weighted imaging, three parameters can be measured: relative CBF, relative cerebral blood volume (rCBV), and mean transit time (MTT). Findings in 13 patients with aura consistently showed decreases in CBF, decreases in rCBF, and increased MTT.[1,19]

Headache phase
Intracranial blood flow

If dilated cerebral vessels are the source of pain in migraine, then it should be possible to demonstrate arterial dilation and hyperperfusion during the headache phase. Although it has been shown that there is indeed a prolonged period of cerebral hyperperfusion, there is no consistent temporal relationship between the pain and the hyperperfusion.

O'Brien investigated the cerebral cortex perfusion rates using the [133]Xenon inhalation technique in 18 migraineurs. There was a small increase in cortical perfusion rates, which he interpreted as being reactive hyperaemia.[8] Olesen et al measured the rCBF in 57 patients during the headache phase (of migraine with aura). In the early headache phase, rCBF was focally reduced in 34 patients, normal in 7, and increased in 2. During the later stages of the attack, hyperperfusion and headache coexisted in several patients, but hyperperfusion was also observed in 14 patients at a time when there was no headache. In 2 patients, hyperperfusion occurred before the headache, and in 11 it outlasted the headache. In 1, the headache outlasted the hyperperfusion.[6] Andersen et al measured rCBF by means of SPECT in 7 patients during attacks of migraine with aura. All their subjects developed headache while focal hypoperfusion was still present. Usually the shift from hypoperfusion to hyperperfusion occurred at the time when patients described their headaches as regressing. In most cases the hyperaemia occurred while the headache was slight and regressing.[12] This study confirmed earlier findings [6,11] that hypoperfusion persists well into the headache phase, and that the throbbing headache often disappears even though the rCBF hyperaemia persists. The hyperaemia has also been observed to persist for days after the headache has subsided.[20,21]

Extracranial blood flow

A positive correlation between the amplitude of pulsation of the branches of the external carotid artery and the intensity of the migraine headache was first demonstrated by Graham and Wolff.[22] The mean pulse-amplitude of the frontal branch of the superficial temporal artery was twice that of normal controls.[23]

It was also shown that the temporal pulse diminished in amplitude by 12% to 84% in migraineurs as they stood up from lying down, while only minor changes (9% to 13%) took place in normal subjects.[24] Following exercise, the temporal artery on the affected side in migraineurs dilated more than on the headache-free side.[25] The luminal diameter of the frontal branch of the superficial temporal artery, measured with high resolution ultrasound, is significantly larger on the symptomatic side than on the non-symptomatic side, during but not between headaches.[26]

The frontotemporal area is supplied by the frontal branch of the superficial temporal artery. In studies on migraineurs that were carried out using the tissue clearance method of the isotope Na^{24} to measure frontotemporal blood flow, asymptomatic patients exhibited blood flows similar to those of normal control subjects, but during the headache phase, there was increased blood flow. Scalp blood flows were increased on both sides of the head in an attack of unilateral migraine compared to those of the same subjects when asymptomatic; but the increase was greater on the side of the headache than on the contralateral side.[27]

Sakai and Meyer, using the ^{133}Xe-inhalation method to measure extracranial blood flow found it to be increased during migraine headache, subsiding rapidly just as the headache subsides.[21,28]

Conclusion

Functional neuroimaging studies confirm the correlation between the spreading depression of migraine aura and cerebral hypoperfusion. To date it has not been possible to demonstrate that the pain of migraine bears any relationship to the limited cerebral hyperperfusion found during the headache phase of migraine. There is, however, compelling evidence of a strong correlation between the headache phase of migraine and dilatation of the extracranial branches of the external carotid artery.

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