The pathogenesis of migraine

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For half a century, the generally held views on the pathogenesis of migraine were based on the work of Harold Wolff, Professor of Neurology in New York, who began its modern scientific study. He explained the visual aura on the basis of intracerebral vasoconstriction supported by the evidence that the progress of the visual aura could be arrested by inhalation of a vasodilator, viz amylnitrate. This has been repeated by others since, but these findings could not be replicated[1].

Wolff's explanation that migraine headache was due to extracerebral vasodilatation had more firm foundations. Firstly, the headache is often throbbing and synchronous with the pulse; secondly, the headache can be relieved by pressure on the carotid and superficial temporal arteries, and finally, but most convincingly, plethysmography showed that arterial pulsation diminished with parenteral administration of ergotamine, a well-known vasoconstrictor, which also relieved the headache. Ergotamine has a fascinating history, not least because of the part it has played in theories regarding migraine. It is a polar substance with a large molecule which does not easily pass the blood-brain barrier. Given intravenously, it blocks neuronal responses from blood vessels but not when applied locally. Ergotamine was considered to work by constricting arteries whereas dihydro-ergotamine (DHE), introduced to give less side-effects, was supposed to constrict capacitance vessels; it is now known that both substances suppress the neuronal discharge of pain afferents from cerebral vessels.

Wolff's views have been challenged by the advent of more accurate techniques for estimating cerebral blood flow[2,3]. Using radioactive xenon, given either by inhalation or angiographically, blood flow to the brain can be estimated by collimators over the scalp recording the amounts of isotope in different regions of the brain. Olesen and others in Copenhagen[4,5] have reported finding spreading oligaemia during the migraine visual aura, but no increased flow during the headache phase. These views have been challenged on methodological grounds by others, largely because of the phenomenon of Compton scatter[5].

Any theory regarding pathogenesis should explain all the variable manifestations of the migraine syndrome. These include such clinical features as age, sex, premonitory symptoms, aura, headache with its predominantly unilateral and throbbing character, gastroenterological features, heightened sensitivity and characteristic periodicity as well as the mechanism of its many trigger factors[6]. Premonitory symptoms are distinct from the aura and usually occur 3 h, but up to 24 h before the aura. They occur in from one-third to one-half of patients but have to be sought both by patients and doctor. The commonest is mood change, often euphoria and hyperactivity, but also irritability. Increased appetite with food cravings, especially sweet foods, is well recognized and may explain why chocolate is often considered a trigger, its consumption being the result, not the cause, of the attack. These premonitory symptoms are considered to be hypothalamic in origin.

If migraine is not primarily vascular, the chief alternative is that the process is initiated in the brain. An important piece of evidence comes from the visual aura. Because patients are anxious regarding their vision and threatened headache, they rarely give an accurate account of this phenomenon but many scientists and doctors have recorded and timed the exact sequence of the visual aura. Beginning with blurred vision, accurate charting of the visual fields shows that this is a bilateral homonymous paracentral scotoma. Within a minute or two this begins to expand in a semicircular fashion - the edge is jagged like a tooth-saw which was likened to a mediaeval fort as seen from above - hence the terms fortification spectrum and teichopsia, from the Greek teichos, meaning a wall. Following this enlarging jagged scintillating (flashing) outline, the vision is scotomatous. As the semicircle enlarges, the saw-tooth edge becomes wider angled and more irregular and the scintillations become more obvious. The whole moves to one side and disappears - the right side being the most common. The visual aura is succeeded by a headache, not necessarily unilateral. When unilateral, it is not always on the opposite side of the hemianopia[7]. Particularly in the older age groups, the visual aura may not be followed by headache - acephalgic migraine. When asked how long the visual aura lasts, patients vary considerably in their responses from a few minutes to over an hour. When actually timed, it is in fact 20 minutes.

What is the possible explanation of this unique phenomenon, quite different from the unilateral amaurosis fugax of a transient ischaemic attack with its curtain-like onset and disappearance due to carotid insufficiency or retinal emboli? It is inordinately difficult to explain on a primary vascular cause and the reasons are as follows. There is only one part of the brain where a homonymous paracentral scotoma can start and that is one occipital pole. There is no alternative to the view that the process is spreading forward across the visual cortex, first in the occipital lobe, the blood supply of which is the posterior cerebral artery (from the vertebro-basilar system) and then to the parietal lobe, the blood supply of which is the middle cerebral artery, a branch of the internal

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carotid artery (from the anterior circulation). What possible vascular mechanism could cross these different arterial distributions? Could an axonal reflex shut down adjacent capillaries or arterioles and spread over the cortex? A more satisfying, but far from conclusive, answer comes from the speed at which the process travels. Since the visual cortex is about 60 mm in length and since the visual aura lasts 20 min, the process - whatever its nature - is travelling at a rate of 3 mm/min.

The Brazilian neurophysiologist, Aristide Leào[8], has reported that stimulation of the cerebral cortex of a rabbit produced a wave of electrical negativity spreading at the rate of 3 mm/min. The stimulus could be either chemical, eg KCl, mechanical, eg touch or pinprick, or electrical. During this phenomenon, there are marked ionic changes as well as a loss in membrane resistance. There is evidence that the latter is not due to a breakdown in membrane integrity but to exitatory neurotransmitters such as glutamate and GABA activating ionic channels.

Spreading depression stops when the cyto-architecture changes and rarely spreads to the opposite hemisphere. It was said to be more readily elicited in lissencephalic species (where the cortex is smooth) than in gyrencephalic animals, but this has recently been challenged. Spreading depression is also dependent on brain maturation eg it is readily elicited in guineapigs soon after birth but not for several weeks in rats and rabbits. The spread is faster and easier in the more superficial layers of the cortex. It can be elicited in most parts of the brain, as well as the retina, but not in the spinal cord. One explanation for the predilection of the visual cortex to a migrainous aura is that the neurones here are packed more tightly than elsewhere. The scintillation has been described as a positive phenomenon and the succeeding scotoma as a negative one. The angular shape of the scintillations has invoked the X and Y neurones that are sensitive to the movement of straight lines[9].

Although it has been argued that the spreading oligaemia seen in the visual aura of migraine is associated with a spreading wave of electrical negativity (spreading depression of Leào)[10], glucose metabolism in the brain is unaltered or even increased. This uncoupling of flow and metabolism could be explained by the spreading depolarization involving neurones which serve resistance microvessels. Cerebral metabolism can remain unchanged with decreased flow if the oxygen extraction fraction is increased, as shown in the few cases of migraine investigated by Positron Emission Tomography.

The migrainous aura, although most commonly visual, can also be sensory, with tinglings in hand and cheek of one side, (cheiro-oral migraine) and not infrequently involves Broca's area to give a transient dysphasia. It has been suggested that the migrainous visual aura could be due to the spreading depression of Leào. This phenomenon has not conclusively been shown to occur in man, although recent work with magneto-encephalography is suggestive.

While many changes, biochemical, metabolic and neurophysiological, have been found during migraine attacks, there are some that are present between attacks and these could be of particular importance, giving clues as to why some individuals are prone to attacks whilst others are not.

Although variations in the EEG have been found, we showed that the visual evoked potential was different in migrainous patients when compared to normals, viz. that the difference in amplitude between the primary positive and negative waves was greater[11-13]. Others have confirmed this and shown that this difference is not related to duration or severity of migraine but reflects predisposition to migraine attacks.

No matter how fascinating and informative is the aura of migraine the fact remains that the majority of attacks are common migraine - migraine without aura, and the explanation for the headache is just as controversial as that for the aura. The site of the pain has been variously put as the cranial vessels or meninges but particularly the dural vessels. While much attention has rightly been focused on the intracranial circulation, the extracranial circulation was considered to be the basis for headache, not least because of its throbbing quality in time with the pulse. The original work by Wolff was done in only a limited sample (10 of 75) and the relationship found between headache severity and amplitude of pulsation has subsequently been found in only about one-third of patients, ie compression of the superficial temporal artery does not always relieve the pain.

One of the problems that has intrigued migraine researchers is the mechanism of painful headache following the painless aura. That the aura is cortical in origin is proven by blood flow studies; cortical vessels have little sensory innervation. The studies of Wolff 50 years ago indicated that the trigeminal nerve must be the sensory pathway for painful sensations from either the meninges or vessels of the anterior and middle cranial fossae. There is now considerable experimental evidence that the pain of vascular headaches is mediated by the trigemino-vascular system[14], extracranial vasodilation results from stimulation of the trigeminal nerve. If the Gasserian ganglion is stimulated, there is an increase in extracranial blood flow. If the trigeminal root is cut, most of that increase disappears and this supports the concept of the trigemino-vascular reflex. In cases of migraine with aura, the headache usually follows the end of the aura. One suggestion is that the spreading depression depolarizes the perivascular sensory fibres of the vessel which made up the trigemino-vascular system. If the sensory supply of the intraparenchymal vessels are depolarized, this could explain the swollen brain that occurs during an acute attack, as evidenced in a craniectomized patient, but this hypothesis does not explain findings of the pain being either ipsi or contra-lateral.

The relevant neurotransmitters (neuropeptides) are synthesized by ganglion cells and travel to small unmyelinated fibres around the vessels as well as the trigeminal nucleus[15]. The most important neuropeptide is probably CGRP, followed by substance P. The half-life for CGRP is 7 min and for substance P much less. Electrical stimulation of the trigeminal ganglion not only produces vasodilatation but enhances plasma protein permeability, probably due to release of substance P; similar changes occur with epileptic and hypertensive attacks, both of which provoke headaches. These changes are mediated, not centrally, but by local axonal reflexes[14].

The overall explanation of the mechanism of migraine still eludes us. Some questions are answered only to be replaced by further questions. In recent years, the increase in research in what is now

an exciting neuroscientific field gives ground for optimism that the whole explanation can not be too far away.

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