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Occasional review

Migraine pathogenesis: the neural hypothesis reexamined

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SUMMARY The hypothesis that migraine is a primary neurological disturbance with secondary vascular manifestations is tested by analysing the five phases of migraine attacks and the eight groups of recognised precipitating factors. Accessory evidence from cerebral blood flow and EEG recordings taken during attacks is also considered. The evidence supports the concept that the sensory cortex and hypothalamus could be initiating sites for migraine attacks, and indicates that a neurological mechanism, suggested by Liveing and Gowers 100 years ago, remains viable and needs to be considered in future research.

A vascular cause for migraine has been accepted for several decades, on the assumption that extracranial vasodilatation produced the characteristic throbbing headache.[1] The extracranial hypothesis was challenged because facial pallor is common during migraine episodes and because patients with temporal arteritis do not vomit or have photophobia.[2] Subsequent observations revealed that in 49/50 patients examined during migraine attacks, some pain arose from the meninges.[3] This site would account for the cardinal symptoms of migraine, headache, vomiting and photophobia, akin to the symptomatology of meningitis.

No one questions that blood vessels are involved in the migraine process, but the hypothesis proposed here is that the vasomotor features are secondary to neural stimulation. That migraine is a neurogenic disorder is not novel, being favoured 100 years ago by Liveing and supported by Gowers[4] who wrote: "Two chief theories have been held regarding the origin of attacks. One is based upon the alteration in the state of the vessels that is so conspicuous in the aspect of the patient. The pallor of the surface must be due to contraction of the arteries, and the flushing of the skin due to their dilatation, and it is assumed that a corresponding condition of the vessels of the brain is the cause of the derangement of functions. . . . According to the other and alternative explanation of the disease, the primary derangement is of nerve-cells of the brain. Their function from time to time is disturbed in a peculiar manner, and the visible vaso-motor disturbance is secondary in origin".

More recently clinicians supporting a neurological cause include Appenzeller,[5] Bruyn,[6] Johnson,[7] Pearce,[8] Sjaastad,[9] and Ziegler.[10]

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Hypothesis

Migraine is a primary neurological disturbance with secondary vasomotor changes.

EXAMINATION OF HYPOTHESIS

The hypothesis is tested by analysing the five stages of migraine attacks, the eight groups of recognised precipitants that induce attacks and evidence from electroencephalography (EEG) and cerebral blood flow (CBF) studies carried out during the headache phase of migraine attacks.

The five phases of migraine attacks

Prodromal symptoms The separation of prodromes from the aura[11] led me to favour a neurologi-

cal basis for migraine having previously supported a vasomotor theory.[2] None of the prodromes is explicable on a vascular basis; they are all in the mind or arise from the brain. Prodromal symptoms occur 1–24 hours before the advent of an aura or headache and consist of altered behaviour, mood changes, food craving, particularly for carbohydrate, yawning, altered bowel frequency, feeling unduly tired or inappropriately cold.

A major differential between migraine and other headaches is the concomitant alimentary disturbance; craving before, nausea and vomiting during, and restricted food tolerance after the headache. Hence the conclusion in a recent review[12] that "the integration of the impulses causing appetite regulation takes place mainly in the hypothalamus" is relevant. Further, altered intestinal sympathetic and parasympathetic activity results from experimental destruction of the hypothalamus, whose nuclei have serotonergic, dopaminergic and glucose receptors and even respond to iontophoretic application of free fatty acids; each of these chemicals has been implicated in migraine precipitation. The recent successful trial of a peripheral dopamine antagonist, Motilium, in aborting migraine during the prodromal phase[13] is relevant, so is the efficacy of metoclopramide, a central dopamine antagonist, taken early during the headache phase.[14]

Feeling cold when hungry and warm after a meal is a common physiological experience. Impaired temperature control is also closely linked with appetite in hypothalamic damaged animals.[12] It may therefore be significant that many migraineurs complain of feeling cold before and during a migraine: they attempt to get warm and managing to do so heralds or accompanies the end of an attack.

The classic aura Most of us have accepted for many years that at least the aura of migraine must be vascular in origin. Surprisingly Miller Fisher,[15] one of the world's authorities on cerebro-vascular disease, has presented compelling arguments why *the aura cannot be explained on a vascular basis:*

(1) The gradual spread of the visual or other sensory aura taking 10–30 minutes from beginning to end does not occur, in his experience, in cerebrovascular disease—a most telling point bearing in mind Miller Fisher's many original contributions and his 30 years' experience in this field.

(2) Miller Fisher's own dissection showed that as the middle cerebral artery ascends the Rolandic fissure it sends branches anteriorly to the motor cortex and posteriorly to the sensory cortex. Unilateral paraesthesiae without motor involvement beginning in the fingers, spreading slowly up the arm and then down the leg, are well recognised as a sensory aura in migraine. The slow progression of sensory symptoms would therefore require spasm sequentially of successive branches on the posterior aspect of the middle cerebral artery without altering the blood supply anteriorly. "How the arrangement could subserve a slow gradual extremely orderly spread of an ischaemic process staggers the imagination".[15] We are forced to agree with Miller Fisher that this notion is untenable.

(3) Lashley[16] charted his own migrating teichopsiae more than 100 times, the slowly enlarging scintillating arc that "drifts across the visual field" leaving normal vision behind. He calculated that this process would transgress the calcarine cortex at a rate of 3 mm per minute. However, vasospasm or ischaemia could not explain this classic phenomenon according to Miller Fisher, who suggested that only a "neuro-electric" disturbance comparable with Leão's[17] spreading depression could provide a possible explanation.

(4) Finally, Miller Fisher found the arteriographic evidence obtained during migraine attacks conflicting.

Headache Phase Patients carefully questioned say their headache is throbbing for *some of the time,* but it is a steady ache for the remainder of the headache phase. But, even a throbbing pain need not be primarily vascular: a toothache, throbbing or aching, is not a primary vascular disorder, but a vascular response to local inflammation.

Neurological symptoms during the headache phase include photophobia, phonophobia, general irritability, hypersensitivity to vibration and smells, lack of concentration, sleepiness, yawning, temperature lability and occasionally patients mention increased libido in spite of pain. Clearly more than extracranial vasodilatation is involved but there is no way of determining at present whether these neural disturbances during the headache phase are primary or secondary to cerebro-vascular derangements, hence further consideration of these symptoms cannot help our analysis. Nevertheless, as discussed later, experimentally, vascular changes *follow* within milliseconds of metabolic changes in the cerebral cortex.[18]

Sleep Resolution The fact that sleep, a neurological event, is the most common way that migraine attacks resolve[19] does not necessarily mean that the underlying migraine process is neurological. However, looking at the attack as a whole, tiredness and yawning begin as prodromes before the headache starts, continue during and persist after the headache phase, indicating a neurological substratum to the whole attack. If we add that sleep could have a cerebral and mental restorative function,[20] and that mental stress or insufficient sleep can induce attacks (see next section) then sleep resolu-

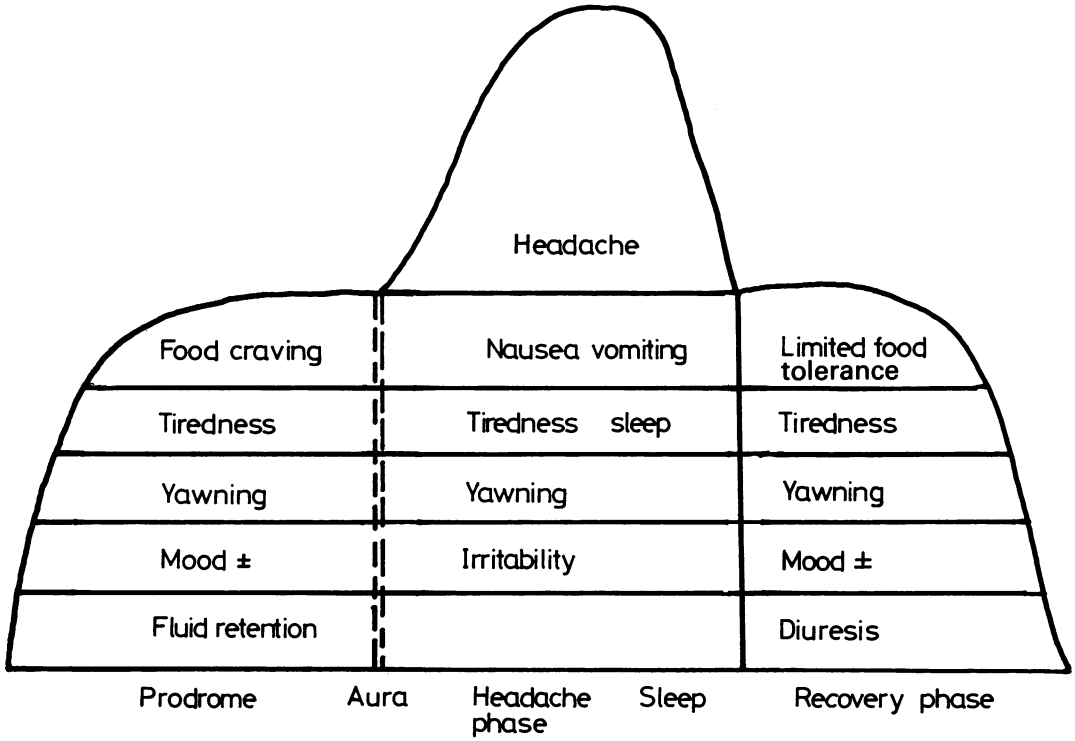

Fig *Phases and symptoms during complete migraine attacks.*

tion assumes greater significance.

Recovery Symptoms Forty-seven out of fifty patients continued with symptoms for about a day after the headache had disappeared:[19] mood and mental changes, yawning and tiredness were most frequent, but food intolerance and fluid imbalance also featured. Because symptoms persist when the headache has resolved and because they are explicable on a neurological basis, these continuing symptoms support a neurological hypothesis and enable a new view of migraine, illustrated in the figure.

If correct then the headache of migraine is like the roof of a house and we have been neglecting the main building, let alone its foundations.

Precipitating factors of individual migraine attacks

Psychological Stress. Even the most ardent protagonist of the platelet theory of migraine, Dr Edda Hanington,[21] has stated that "stress is the most common precipitant of migraine". If, as we believe, the mind is inside the brain, then neural stimulation operates in psychological stress.

Hunger or delaying meals does not affect blood vessels directly but does act on the brain as a whole: witness the irritability of children waiting for a meal.

Cheese or chocolate via tyramine or phenylethylamine probably activate blood vessels although tyramine induces EEG changes;[22] furthermore, it has been suggested recently that there are specific receptors for phenylethylamine in the rat hypothalamus.[23] *Alcohol* acts both on neurons and blood vessels. However, the migraine that follows alcohol intake does not begin at the time of mental, behavioural or vascular effects, but on waking the following morning after a night's sleep: deep sleep is therefore a possible cause. Another possible mechanism is that ethanol induces hypoglycaemia which began in fasting subjects four hours after and continued for seven hours or longer after intravenous injection.[24]

Sleep. Too much or too little sleep provokes headaches in 5% of the normal population and in a proportion of migraineurs. Admittedly vascular changes accompany sleep which nevertheless is primarily neurologically controlled and mentally influenced.

Hormonal variation in menstruating women. A proportion of women have their migraine attacks strictly related to their menstrual cycle (Blau and Ratcliffe, unpublished observations). Menstruation is controlled by the hypothalamic-pituitary-ovarian axis, and most women know from personal experi-

ence that a menstrual period can be brought on early or missed as a result of emotional stress. Furthermore, the contraceptive pill, which can accentuate migraine, provokes depression in some, but affects blood vessels in others.

Environmental stimuli. Environmental triggers are transmitted directly to the central nervous system by the special senses: *light, sound, smells,* the first being a more common precipitant than the others. *Travelling,* stimulating the nervous system through the eyes and labyrinth, also provokes attacks. In this context, aeroplane journeys induce migraines possibly via mild anoxia, cabins are pressurised only to 6000 ft, or via stress.

Local pains in the head and neck can precipitate migraine. These nociceptive stimuli are clearly neural.

Allergy. If current claims are substantiated, then this stimulus is more likely to be vascularly mediated.

Exercise produces vascular and glucose changes, but exercise-induced migraine usually begins *after* the game is finished, and not during vasodilation. Footballers' migraine,[25] caused by heading the ball, directly affects the brain by jolting. Competitive sport in general is a great psychic stimulus.

Consideration of precipitating factors show that some stimulate the nervous system directly, others affect blood vessels, and some both.

Direct evidence of brain involvement before and during headache phase

Two migraineurs each had a craniotomy for a benign condition leaving a skull defect, and were studied in subsequent migraine attacks. In Goltman's[26] case there is published photographic evidence; Dr Macdonald Critchley had a similar patient, a doctor in 1928, but the observations were not published.

Photographs from the first patient[26] show an unduly slack skull decompression some hours before the attack. As the headache developed, the decompression became tense and later, when the headache and vomiting were at their height, bulged outwards. After the attack the decompression returned to its normal slackness.

There is therefore no doubt that there can be intracranial involvement hours *before* the onset of headache. Brain swelling or increased cerebrospinal fluid (CSF) production during the headache means that extractional vasodilatation is not solely responsible for the symptoms. Clearly there must be a vascular or an oedematous element but no evidence whether the initial disturbance of function is of vascular or neural origin. However, cerebral oedema can be produced by centrally released vasopressin and noradrenalin,[27] by opening tight junctions in cerebral capillaries.[28] Similar considerations could apply to an increase in the total amount of CSF.

Electroencephalography (EEG)

EEG abnormalities in migraineurs between attacks range from 20–55% in different series.[29] More importantly, EEG disturbances during attacks outlast the headache by several days.[30] Also prolongation of the P_2 wave in visual evoked potentials in migraine subjects has been ascribed to either "ischaemic or synaptic damage due to a neurotransmitter derangement".[31] The fact that EEG and evoked potentials abnormalities can be detected between migraine attacks, when there is no headache and no apparent vasomotor changes, lends support to a neurological substratum.

Experimental observations

Cerebral metabolic studies. Modern dynamic studies still support Roy and Sherrington's[32] hypothesis that altered cerebral metabolism *causes* calibre variation in cerebral vessels, and not vice versa: using carbon labelled deoxyglucose, Sokoloff[18] showed that focal metabolic alterations occurred first and were followed by vascular reactions within seconds; hypoxia hypoglyaemia and/or amphetamine, each increased cerebral blood flow;[33] physiological stimulation of the cortex with evoked potentials resulted in regional microflow increase within 1–2 seconds of stimulation.[34]

Leão's spreading depression and cerebral blood flow Although Leão's[17] experiments have been criticised for being unphysiological, such as touching the cortex or using tetanising currents, he also reported his spreading cortical silence after intermittent retinal stimulation in rabbits with flashing lights, highly relevant to precipitation of migraine. It is therefore of great interest that Olesen *et al*[35] in classic migraine reported variation in cerebral blood flow transgressing the cortex at a rate similar to that demonstrated by Leão, concluding that their observations were not compatible with cortical vascular changes.

SUMMARY OF ARGUMENT

The points supporting a neurological pathogenesis for migraine are:

(1) Attacks can be precipitated by stimuli from inside the nervous system (stress or sleep) or direct excitation of neural pathways from the environment (light) or pain in the head, without the intervention of blood vessels.

(2) Neurological prodromes occur hours before the headache or aura: yawning, tiredness or food cravings, symptoms that implicate the hypothalamus.

(3) The classic sensory aura, explicable only on a

neurological and not on a vascular basis, is not seen in cerebrovascular disease.
(4) Neurological symptoms persist throughout the headache phase; yawning, tiredness, irritability and lack of concentration.
(5) Sleep resolves attacks.
(6) Neurological symptoms persist for hours after the headache has resolved: mood changes, mental tiredness and yawning.
(7) Altered cerebral metabolism *causes* calibre variation in cerebral vessels—the Roy and Sherrington hypothesis, is maintained by modern isotope studies. Cerebral blood flow variations during classical migraine attacks are *not* explicable on a vascular basis.
(8) EEG changes can occur before, during and after the headache phase.

I conclude from this analysis of the sequential stages of migraine attacks and their precipitants, as well as from cerebral blood flow and EEG observations, that a neurological mechanism could be responsible.

Discussion

What is the site of the lesion? If the hypothesis is correct, we ought to attempt to answer the classical neurological question, "Which site(s) could be responsible?" Visual or auditory stimuli causing attacks will first be transmitted to their respective areas of cortex. Hunger or lack of sleep are presumed to be monitored in the hypothalamus. Stress, a mental response, is more difficult to localise: the whole brain could be involved; alternatively we know that stress influences the hypothalamus. Hence I propose that specific sensory areas of the cortex and the hypothalamus can act as sites where migraine attacks may be initiated.
What is the nature of the lesion? This, the second classical question of the neurologist, has to be modified to, "What is the nature of the disturbances of function?" Because anoxia, hypoglycaemia or alcohol can induce migraine as well as a similar symptom-complex in non-migrainous subjects (headache, behavioural changes, hunger and nausea) I propose that we are dealing with a disturbance in the oxidative pathway of the neuronal metabolism, suggested by Amery,[36] and suspect that a number of neurotransmitters may be involved.

Conclusion

We ought not to throw out the vascular hypothesis because blood vessels *are* involved, although, if the hypothesis is correct, secondarily to neural stimulation. Hence studying the autonomic control of the affected blood vessels could lead to a deeper understanding of altered neural transmission. However, looking at the migraine process as a whole, the brain, and particularly the hypothalamus, would seem sites worthy of attention.

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