Pathophysiology of headaches with a prominent vascular component

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Vascular changes, whether preliminary or secondary, seem to accompany most headaches. The literature concerning pathophysiological mechanisms in headaches where vascular phenomena are a major, integral part, i.e., migraine and cluster headache syndrome, is reviewed and the most common forms of headache associated with cerebrovascular disease are discussed. Emphasis is placed on the vascular phenomena and on the abundant hypotheses and theories regarding headache mechanisms. This review also presents alternative explanatory models, and compares the available anatomical, physiological and biochemical results.

Key Words: Chronic paroxysmal hemicrania, Cluster headache, Headache, Migraine, Review, Subarachnoid hemorrhage

Vascular changes, whether preliminary or secondary, seem to accompany most headaches. The impact of vascular changes in the pathogenesis of any special type of headache is important. Another key aspect is how specific the vascular changes are in each particular type of headache.

Migraine and cluster headache (CH) have been classified as ‘vascular’ headaches (1), suggesting that prominent, vascular changes affecting intra- or extracranial vessels not only accompany the attack, but also are of primary importance in the pathogenesis of both types of headache. These vascular abnormalities may be specific for migraine and CH, regarding both the distribution of the vascular changes and the nature of each type. However, because etiology and pathogenesis are largely unknown in these types of headaches, one must be cautious delineating both the origin and the significance of the vascular phenomena. It may be more appropriate to classify them as ‘primary headaches’ without introducing a prejudgement of possible vascular origin, despite the relative prominence of vascular features in both types of headaches. The International Headache Society (IHS) classification of headache (2) does not employ the term ‘vascular headaches’ for migraine and CH.

Cerebral vessels are not known to show any evidence of a stationary, organic disorder in these headaches. Appropriate investigations should rule out such a possibility in solitary cases showing slightly deviating traits; as a minimum, computed tomography scan should be used, as well as magnetic resonance imaging.
Vascular phenomena

Studies from the '70s and '80s (8-11) demonstrated that regional cerebral bloodflow (rCBF) decreased in the supposedly affected hemisphere of the aura during a migraine attack. This local hypoperfusion usually started in the occipital region and subsequently seemed to spread anteriorly at a certain rate, but the extension of the oligemia had no relationship with any specific vascular territory. These findings, combined with the fact that the cerebral hypoperfusion did not seem to reach the ischemic range, were arguments that at least partly favoured the theory of neuronal dysfunction as the first event of the migraine attack. Primary neuronal involvement might lead to a reduced demand for oxygen, merely because of the state of the neurons. Neuronal dysfunction might produce the aura symptoms and, secondarily, the hypoperfusion.

The similarity of the progression of the oligemia to that of the neuronal cortical spreading depression (CSD) described by Leão (12) in animal experiments is particularly interesting. The latter phenomenon may be triggered by, for example, physical and chemical stimuli, and starts with a short-lasting 'electrical storm', in the wake of which is a neuronal 'silence'. The neuronal inactivation is transient and is followed by repolarization which fully restores function. The neuronal depolarization spreads at a rate of 2 to 3 mm/min. The rate of visual aura progression corresponds to the velocity of expansion of the process in the occipital cortex of around 3 mm/min (13). Thus, there seem to be spatial and temporal similarities between CSD, and visual aura progression and spreading oligemia.

Furthermore, it was demonstrated that at pain onset rCBF was still decreased in the corresponding cerebral area. The fact that the oligemia is persistent argues, to some extent, against the concept of arterial dilation as a cause of the pain. However, the possibility still existed at that stage that vasodilation started intracranially but outside the brain, or even started extracranially. Later, however, Skyhøj Olsen and Lassen (14) demonstrated that the hypoperfusion during the aura phase was more marked than previously conjectured, the oligemia appearing to reach the ischemia range. Results obtained with the technique they used (rCBF with intracarotid $^{133}$Xe) may have been influenced by the Compton scatter effect (15,16), which overestimates rCBF. It is therefore possible that the cerebral hypoperfusion had been underestimated (17). There is also evidence suggesting that the regional hypoperfusion during the aura phase of migraine is not secondary to reduced cerebral metabolic activity (18).

In theory, therefore, the focal symptoms during the aura may be due to neuronal ischemia. The spreading oligemia may be interpreted as an artefact caused by the Compton scatter effect.
(17). The gradual decrease of the rCBF in a cerebral territory not changing in size can give the impression of spreading when the intracarotid $^{133}$Xe technique is used. Fast oscillations in rCBF may produce a false impression of spreading, and variations in cerebral perfusion probably reflect vascular instability of the ischemic area (19).

The characteristic aura ‘marche’ may be due to the different sensitivity of various neuronal areas to the ischemia. The sensitivity to hypoxia may vary in different cerebral regions (20). In different individuals, there may even be variation in sensitivity over time.

Together those new findings somewhat revived the vascular theory of migraine and the old concept of arterial spasm leading to ischemia during the aura. However, CSD has never convincingly been demonstrated in the neocortex of humans in vivo. A process such as CSD, nevertheless, may provide a good explanation for the aura symptoms and especially for the characteristic marche.

The aura appears during focal oligemia (21), and the focal neurological symptoms seem to correlate with the side of the hypoperfusion in both adults and children (22). After headache onset, the rCBF gradually increases to the hyperperfusion range. Hyperemia may be a reaction to the previous oligemia and be produced by metabolic products (23), or it may be related to the repolarization phase of CSD or even the pathophysiological mechanisms of pain (24). In about 24 h the attack-induced rCBF abnormalities grossly disappear.

Both neurophysiological and neuroimaging studies have been employed to demonstrate persistent neuronal damage (25-31). There is evidence that some migraineurs may have brain lesions that are probably ischemic in nature. MRI studies have demonstrated an increase in small, hyperintense signals in T2 series in migraine sufferers. These small lesions may represent microinfarcts (30,31), but whether they were related to migraine has not been demonstrated because they were also found in headache-free control individuals.

Magnetic resonance spectroscopy studies have shown that during attacks there is no change in intracellular pH (32), which argues against an ischemic origin of aura. Moreover, magnetic resonance spectroscopy studies are consistent with a neuronal (and, to some extent, extraneuronal) disorder in oxidative energy metabolism in migraine sufferers that has been attributed to a mitochondrial metabolic defect (33,34). There is evidence for a systemic and brain magnesium deficiency (35), which may result in abnormal mitochondrial phosphorylation. Taking all these things into consideration, Welch et al (36) have proposed the theory that there is neuronal hyperexcitability in migraine due to abnormal mitochondrial metabolic function and magnesium deficiency. This can create a predisposition to CSD, either spontaneously or triggered by a migraine process. Magnetoencephalographic findings during migraine attacks have been claimed to indicate CSD (37), again supporting the neuronal theory.

There is some clinical evidence that migraine with and without aura are facets of the same disease (see, for example, 38). If so, the underlying mechanism would be the same, but the vascular process can be more intense in migraine with aura (20). In this connection, moderate rCBF changes would not be detected by the current techniques that require a decrease in rCBF of at least 20% with the inherent sensitivity of the procedure. Alternatively, migraine without aura could start in a different ‘silent’ area.

**Vasospasm and complicated migraine**

In most cases, cerebral hypoperfusion during migraine aura is brief and apparently well tolerated. On rare occasions, aura is long lasting (39-41); cerebral infarcts may follow (42,43). This may be due to particularly intense and/or long lasting hypoperfusion.

A sustained vasospasm is a possible mechanism that can underlie complicated migraine. Other putative factors, including platelet hyperaggregability (44), antiphospholipid antibodies and lupus anticoagulant (45,46), arterial dissection (47) and mitral valve prolapse (48), have also been reported as main or additional factors in production of the migrainous infarct (42,43). Even a relationship between migraine and arteriopathy (arteritis, atherosclerosis, intimal hyperplasia) has been conjectured (49-51).

None of the disorders or factors mentioned above has been proven to be directly responsible for migrainous stroke (52-54), but it is possible that a combination of intense cerebral hypoperfusion and some of the disorders mentioned (eg, platelet hyperaggregation) is necessary.

In some patients a transcranial Doppler study (55) or an angiography were carried out during ‘complicated’ and ‘noncomplicated’ migraine attacks. Studies of this type have claimed to show a narrowing of one or more intracranial arteries during episodes of complicated migraine (41,51,56,57). Furthermore, the observed segmentary narrowing seemed to be related to an arterial vasospasm because serial angiograms demonstrated the reversibility of the arterial stenosis. The possibility nevertheless exists that the decrease in arterial lumen is not due to vasospasm (56).

In migraine, vasospasm may be the cause of the cerebral hypoperfusion during the aura, and eventually a single, but long lasting and severe episode of vasospasm may cause or contribute to the ischemic complications of migraine. It is also possible that repetitive episodes of vasospasm of long duration may result in damage of the cerebral vessels, making them more susceptible to factors that may produce cerebral infarct in young people.

Sustained vasospasm is also associated with subarachnoid hemorrhage (SAH), but this will be dealt with more fully in a later section. It is now clear, however, that SAH and migraine have several neurobiological changes in common. Elevated plasma levels of endothelin-1, the strong vasoconstricting peptide produced by endothelial cells (58), are found in patients with SAH (59), ischemic cerebrovascular disease (60) and migraineurs (61), both during and outside attacks (62). Additionally, experiments in vitro have shown that vasoconstriction induced by subarachnoid blood appears to activate the trigeminovascular system (63). Increased release of calcitonin gene-related peptide (CGRP) has been demonstrated following SAH (64,65), and brain vessels taken from patients who had died following SAH had barely detectable levels of CGRP compared with vessels from patients dying of other causes (66,67). Such results suggest that the trigeminovascular system may be in-
The trigeminovascular system has long been suspected to play a role in headache pathophysiology (68). Such a theory is supported by results showing increased levels of CGRP-like immunoreactivity in extracranial blood samples from migraine patients during attacks (69), and by the observation that peptide levels return to normal in patients who obtain relief from sumatriptan or dihydroergotamine (70).

May migraine-related vasospasm produce the same vascular lesions as SAH? Any sufficiently intense, long lasting or repetitive arterial spasm may lead to a vascular lesion (56). However, it seems unlikely that the migraine vasospasm may be of the nature and intensity of the spasm associated with SAH.

**Pain mechanisms**

The pain of the migraine attack can originate from activation of intracranial sensory nerves because a major fraction of the cranial vessels are subserved by sensory fibres from the trigeminal nerve (71). This trigeminovascular system furnishes fibres to the anterior, middle and posterior cerebral arteries, and to the meningeal arteries. These vessels are innervated by the ipsilateral trigeminal branches, but the anterior cerebral artery and the longitudinal sinus receive bilateral innervation. The basilar and vertebral arteries are innervated by the upper cervical segments.

Autonomic vasodilator innervation for vessel smooth muscle is also provided by parasympathetic fibres from the facial nerve, whereas vasoconstrictor fibres stem from sympathetic nerves. The parasympathetic part of the facial nerve originates in the superior salivary nuclei that project to the sphenopalatine and otic ganglia. Superficial petrosal nerves furnish the fibres that end in the arterial smooth muscle. Activation of these fibres causes relaxation, and the main vasoactive substances implicated are acetylcholine and vasoactive intestinal peptide (VIP). Autonomic vasoconstrictor pathways stem from the first thoracic spinal segments via the superior cervical ganglion. The important transmitters are noradrenaline and neuropeptide Y (71).

Sensory stimuli travel via the trigeminovascular system to the Gasserian ganglion which, in turn, makes central synapsis with the trigeminal subnucleus caudalis, dorsolateral horn grey matter (at the level C3) and neurons of the dorsolateral white matter (level C2) (72). These cellular groups are part of the trigemino-vascular sensory endings. After synapsing, they cross the midline and project rostrally via ascending fibre systems (trigeminothalamic tract). Finally, from the thalamus, the sensory stimuli reach the cerebral cortex.

Trigeminovascular fibres are nonmyelinated, C type fibres. They contain vesicles with sensory neuropeptides, including CGRP, substance P (SP) and neurokinin A. These peptides may be released locally in an antidromic way in response to excitation of the neurons via local axonic reflexes (73,74).

Change in arterial width produces geometric alteration in the adventitia. This may be a factor that is necessary for triggering depolarization of the trigeminovascular sensory endings, although a combination of factors may be necessary for such triggering. Ischemic and/or other neuronal alterations, as with CSD, can be contributory factors for the activation of the trigeminovascular system.

Cellular damage, for instance arising from ischemia, produces the release of excitatory amino acid neurotransmitters, notably glutamate and aspartate (75), which stimulate neurons with subsequent disturbance of calcium homeostasis, resulting in an excess influx of calcium ions to the cell (76).

Concomitantly, the reduced availability of energy sources results in a reduction of ATP-driven metabolism, including the Ca

\(^{2+}\)-ATPase pump and Na\(^{+}\)-Ca

\(^{2+}\) antipporter which are primarily responsible for removing excess calcium from the cell. An uncontrolled high intracellular level of calcium carries a danger of overstimulation of calcium-mediated processes, including activation of proteases and lipases, and the generation of free radicals. This can lead to further damage of cellular membranes (76). In addition, excitatory amino acids may activate agonist-operated ion channels, leading to osmolytic damage (77).

Primary stimulating agents such as hormones and neurotransmitters exert their effects by binding to specific receptors, their chemical information being mediated to key effector enzymes in the membrane, such as adenylyl cyclase (78), phospholipase A

\(_2\) (79), or phospholipase C (80), and then through second messengers. Activation of phospholipase C may also lead to an increase in intracellular calcium (81,82). Other intracellular events initiated may include the release of other transmitter substances, and there is clearly an intricate system of activation and inhibition of these systems by each other (83). The relationship between putative excitotoxic mechanisms and trigeminovascular activation has still to be determined (84).

Receptor-mediated activation of phospholipase A

\(_2\) will result in hydrolysis of membrane phospholipids and release of arachidonic acid (81), which is the main precursor for a number of other active substances such as prostaglandins, thromboxanes and leukotrienes (85). Arachidonic acid has been found in high concentrations in brain during ischemia (86) and may be involved as a direct messenger in pathological processes, releasing sequestered calcium to the cytoplasm (87).

Tissue damage, subendothelial collagen or both activate the local and intravascular production of algogenic/noicceptive substances such as bradykinin (from alpha-2-macroglobulin), histamine (from mast cells), serotonin (from blood platelets) and metabolites of arachidonic acid. A prostaglandin such as PGE

\(_1\), which has been shown to cause migraine-like attacks in healthy volunteers (88), may sensitize sensory nerve endings, thereby decreasing the pain threshold and enhancing the algogenic action of other factors (89).

Irrespective of the route of trigeminovascular activation, the excitation of Gasserian neurons will produce antidromic release of vasodilatory peptides such as SP, neurokinin A and CGRP. SP in particular is believed to contribute to both painful dilation of cranial vessels and plasma extravasation, typical of neurogenic inflammation (90). SP may also trigger the release of other factors, such as histamine (91) and serotonin. SP has now been shown to be released from endothelial cells (92), so it is not clear whether the two sources play different roles in pathophysiological situations.

Neurogenic inflammation mostly affects the vessels of the cerebral cortex and the dural venous system (Figure 1). As a result, the functional integrity of the blood-brain barrier (BBB)
may be transiently compromised in the affected areas. Some of the neuronal effects of the substances released by the platelets (eg, serotonin or thromboxane A₂) or damaged tissues (eg, glutamate) may be enhanced in this way. These substances may be important in producing a local, transient neuronal dysfunction (perhaps CSD-like) (76,90).

Glutamate, and especially the glutamate agonist N-methyl-D-aspartate (NMDA), (93,94) may trigger CSD which, in turn, may be blocked by NMDA receptor antagonists (95). Glutamate levels have been reported to be raised in plasma (96) and CSF (97) during migraine attacks, although different profiles of excitatory amino acid metabolism in migraine with or without aura have recently been found (98).

NMDA receptor activation is important in stimulating the synthesis of nitric oxide (NO) (99), which is not only an important vasodilator, but also a nonsynaptic, diffusible neurotransmitter (100). In endothelial cells, NO is the endothelium-derived relaxing factor released in response to transmitters such as acetylcholine (101). Indeed, several substances putatively involved in neurogenic inflammation and migraine pain, such as SP and possibly bradykinin, only induce vasodilation if an intact endothelium is present (102,103) because they stimulate release of NO or prostacyclin.

Recently, both NO and CGRP have been implicated in the initial dilation associated with CSD (104). The CSD theory of migraine may therefore provide a reasonable explanation not only for the aura symptoms, but also for the triggering of pain mediators and vascular phenomena. Theoretically, decreased rCBF observed in migraine may be related to transient neuronal inactivation. Whether CSD activates the trigeminovascular system is unknown.

Interestingly, drugs that are effective in the treatment of migraine, such as ergotamine or sumatriptan, have been found to block the neurogenic inflammation caused by the release of vasoactive substances after stimulation of Gasserian cells in experimental animals (105,106). As mentioned earlier, sumatriptan and dihydroergotamine reduce CGRP release to normal levels in migraineurs responsive to the drugs (70). The release of a factor such as NO in affected cranial arteries during neurogenic inflammation may enhance the inflammation (90), but may also reduce local thrombogenesis through anti-aggregation of platelets (107).

Through the trigeminospinal nuclei, connections with many other cranial nerves may be activated. Trigeminal nerve stimulation may cause ipsilateral, intracranial vasodilation, possibly through the parasympathetic part of the facial nerve by co-activation of the superior salivary nuclei.

There may rarely be an association between intracerebral
hemorrhage and migraine (108-111). It has been suggested that ischemic tissue damage can co-exist with endothelial damage as independent phenomena, resulting in fragile vascular walls. Cerebral bloodflow can be enhanced by trigeminovascular activation in such migraine patients. The vessel wall may then be resistant enough to bear the extra load, and hemorrhage may ensue.

In this context the coincidental occurrence of cerebral hemorrhage following trigeminal stimulation in connection with dental removal or trigeminal decompression procedures for tic douloureux treatment (112,113) is thought-provoking. It seems that mechanical trigeminal stimulation during surgical procedures may produce intense intracranial vasodilation. This response may be mediated through the connections of this nerve with the parasympathetic part of the facial nerve, and partly through antidromic release of vasoactive substances. If the dilation phase of a migraine attack takes place in a vascular bed with pre-existing neurogenic inflammation, then this combination may explain some of the cryptogenic, intracerebral hemorrhages.

The pain of the migraine attack is frequently ipsilateral to the cerebral hemisphere with the actual neurovascular events, in agreement with ipsilateral trigeminal innervation. However, some patients report bilateral pain. That the trigeminovascular system provides bilateral innervation to the anterior cerebral arteries and superior longitudinal sinus (71) is interesting in that a migrainous process affecting these vascular territories may be perceived as bilateral pain.

There is evidence to suggest an intracranial origin of pain in migraine. However, some patients get relief by pressure towards the superficial temporal artery and superior longitudinal sinus (71) in the periphery may be factors such as sympathetic fibers leading to the dorum sellae (114) in the periphery may be factors such as sympathetic fibers leading to the pain relief by pressure towards this vessel, strongly suggest a local contribution to the pain pathways of other origin (56).

CGRP blood levels have been found to be increased in the external jugular vein on the symptomatic side during migraine attacks (69). One possible interpretation of the release of vasoactive substances in extracerebral vascular territories is that it stems from an extracranial extension of the neurogenic inflammation and an autonically induced vascular dilation. Convergence of extracephalic and viscerocopal stimuli at the trigeminal nuclear complex can also explain the referred pain to the superficial region of the head in a way similar to the visceral pain of other origin (56).

Serotonin

Serotonin is a constituent of various nuclei and pathways in the brain. Most 'peripheral' serotonin is found in platelets and the enterochromaffin (argentaffin) cells in the crypts of Lieberkühn. During the initial phase of the migraine attack, serotonin is released from platelets. 5-Hydroxyindolacetic acid, the main catabolite of serotonin, increases in the urine, indicating that serotonin metabolism is accelerated (115,116). The platelets of migraine sufferers seem to show an increased tendency to adhesion and aggregation.

Reserpine may trigger a headache attack (117) that is similar in many ways to migraine (7), probably due to the amine releasing properties of the drug (serotonin and other vasoactive substances). Interestingly, serotontin injected intravenously during a migraine attack usually stops the attack (118).

Because serotonin generally does not cross the BBB, its beneficial effect is thought to be due to its vascular constrictive action on cranial vessels. This is particularly interesting in connection with sumatriptan, which has the ability to stimulate serotonin 1-like receptors selectively. While serotonin per se gives rise to many unwanted side effects because it also stimulates other subclasses of serotonin receptors in the body, sumatriptan should have only selective 'serotonin effects' on certain blood vessels to the head (119,120). Because sumatriptan lacks analgesic properties, its efficacy appears to be achieved through vasoconstriction of the intracranial vessels. Such a model for aborting migraine attacks may be valid if migrainous pain were caused by vasodilation-activating sensory nerves of the trigeminovascular system. Plasma extravasation (as in sterile neurogenic inflammation) and secretion of sensory neuropeptides may stop upon vessel vasoconstriction. Alternatively, or perhaps simultaneously, sumatriptan may act on the serotonin-1 presynaptic receptors of the trigeminal sensory terminals within dural blood vessels, inhibiting the release of sensory neuropeptides and, therefore, the neurogenic inflammation (84) — this is a possibility because dura mater lacks the BBB, which sumatriptan cannot cross under normal circumstances.

Some prophylactic migraine drugs are serotonin-2 antagonists that probably act by modifying neurovascular control and counteracting the platelet release reaction, which is also mediated in part by serotonin-2 receptors. Other drugs, such as ace­tylsalicylic acid, are probably effective in migraine, not only because of their inhibition of platelet aggregation, but also possibly because of their effect on the arachidonic acid cascade or neurogenic inflammation (121).

In some migraine patients there is a periodic defect in monoamine oxidase (MAO) activity. Because this enzyme plays a role in the catabolism of catecholamines and serotonin, normal MAO activity may be crucial in avoiding attacks triggered by dietetic substances such as tyramine and phenylethylamine, which are not properly metabolized in the absence of MAO activity (122).

Apart from its direct effects on vascular tone, serotonin also plays an important role in central pain control systems (serotonin-1 and -3 receptors) (123). Central depletion of serotonin may be an important factor in the pathogenesis of migraine (124) because the transmission of central pain stimuli may be facilitated in the relative absence of serotonin (125). A possible, beneficial effect of serotonin precursors such as 5-hydroxytryptophan (126) is believed to be due to a 'central' repletion of serotonin.

It is highly unlikely — but still possible — that the effect of serotonin in discontinuing the migraine attack is partly due to the correction of a central serotonergic deficit. If neurogenic inflam­
mation creates leakage through the BBB, it can permit central uptake of serotonin. The local effect of serotonin as a mediator of pain and inflammation may also be an important part of migraine pathogenesis.

Central mechanisms
The individual susceptibility for migraine is genetically determined, but the nature of the underlying, basic pathophysiological disposition is unknown, as are the details of the process that leads to the full migraine attack.

The attack starts either 'spontaneously' or after exposure to one or more of several possible precipitating factors. It is well known that, for example, cerebral arteriography especially with the old and more toxic contrast media (127), may precipitate an attack with migraine-like qualities (7). Vasodilator agents may do the same, an effect believed to be due to direct action of these factors on the vessel wall. Alternatively, vascular afferents can be activated. Such triggering mechanisms point to a primary vascular origin of the solitary attack. Nevertheless, the natural precipitants for the migraine attack, such as stress, bright light, hunger and sleep, seem to work through the central nervous system (128) and not through the vessels.

The periodicity of spontaneous attacks and their frequent association with physiological cycles (e.g., menstruation) suggest a chronobiological dysregulation. This is consistent with a prime role of the hypothalamus in migraine pathophysiology. It is well known that the hypothalamus has important regulatory, autonomic and endocrinological functions. Indeed, the chronobiological pacemaker that determines the timing of physiological events is located in the anterior part of the hypothalamus (supra-chiasmatic nuclei). Changes in hypothalamic activity may explain the periodicity, the prodromic symptoms (sleepiness, craving for sweets, mood changes, etc) and even some of the autonomic features that characterize the attack.

The hypothalamus is connected with the periaqueductal grey matter and with other brainstem structures, such as locus coeruleus (LC) and the dorsal raphe nuclei. The periaqueductal grey matter plays an important role in pain modulation, and LC and the dorsal raphe nuclei are thought to have vasoactive effects on cerebral arteries (129,130).

All the aforementioned structures have direct or indirect connections with the trigeminovascular system. Thus, a morphological basis for a primary central origin of the pain of migraine attacks may exist.

According to Lance (130), LC stimulation produces ipsilateral intracranial vasoconstriction and extracranial vasodilation, while the dorsal raphe nucleus and trigeminal nerve stimulations produce intracranial vasodilation. Therefore, changes in the activity of these brainstem structures may reproduce the vascular events that characterize migraine attacks (131). Substrates for a possible neuronal origin of attacks putatively exist. Again, similarity is not the same as identity.

Vascular activity due to dorsal raphe nucleus stimulation may be mediated through a noradrenergic pathway, while responses to LC stimulation may be mediated via the direct noradrenergic supply to the intracranial vessels. Connections with the parasympathetic fibres of the facial nerve can represent the dilatory pathway. This latter mechanism may also create vasodilation upon trigeminal nerve stimulation.

Activation of these brainstem structures may be mediated via descendent fibres from the hypothalamus, cerebral cortex and thalamus. These fibres may transmit either the cyclic excitation of the chronobiological pacemaker and neuroendocrine changes, or the central effect of the external stimuli that triggers a migraine attack. Connections between LC and the intermediolateral column of the spinal cord may facilitate the release of noradrenaline. These connections, or perhaps a serotonin-releasing factor, may stimulate platelet liberation and aggregation.

The periaqueductal grey matter forms part of the pain modulation system. Patients with painful disease who have been treated by electrode implants in the periaqueductal grey matter develop chronic headaches with migrainous elements. These headaches have a strict, temporal relationship with the therapeutic procedure (132). Thus, the periaqueductal grey matter may be an important structure for the genesis of head and facial pain. The region is connected with the midline raphe nuclei. The midline raphe nuclei inhibit, by a serotonergic descending projection, the transmission of pain impulses at the level of the spinal interneuron. This interneuron has connections with the posterior spinal horn cells (trigeminospinal column at the superior cervical levels). The transfer of impulses is mediated by endorphins. LC may also modulate pain perception by a noradrenergic descendent pathway that reaches the spinal endorphinergic neuron.

All these connections suggest an interaction between the chronobiological pacemaker and the trigeminovascular and pain control systems. One hypothesis (131) is that brainstem structures may give rise to the neurovascular process of migraine – on the one hand the characteristic vascular events may be produced, but on the other hand the pain originating in the cranial arteries may be modulated.

Endorphins exert neurochemical control (modulation) of the central pain transmission. It is probable that both pain tolerance and pain threshold depend on the activity of these endogenous opioids. Patients suffering from migraine have low endorphin levels (133). In the particular case of menstrual migraine, the endogenous opioid tone decreases during the luteal phase (134). The response to pain and the effectiveness of analgesic treatment with morphine are strongly related to the day/night cycle and melatonin plasma levels (135,136). Melatonin is synthesized in the pineal body and is released particularly during the night.

Interestingly, the analgesic response to morphine is at its maximum during the night and correlates with the melatonin plasma levels. Thus, pain tolerance is better at night, possibly due to the rise in endogenous opioid tone and melatonin levels. Moreover, melatonin inhibits prostaglandin E2 synthesis (137), thereby possibly reducing pain modulation.

Melatonin derives from serotonin, and its synthesis is regulated via, for example, sympathetic fibres from the pineal gland. In migraineurs, melatonin levels are low (138,139), which may be due to a chronobiological dysfunction or a sympathetic hypofunction.

There are anatomical connections between hypothalamus and brainstem structures that control both neurovascular tone and
pain transmission. These pathways may be crucial to the mediation of impulses from centres determining the chronobiological timing of migraine attacks and determining the subjective perception of, and tolerance to, pain.

The autonomic nervous system seems to have a protective function regarding cerebral vessels; the constrictor tone of smooth arterial muscle increases when bloodflow becomes excessive. This reflexogenic sympathetic constriction permits adaptation of vessel calibre to changes of intravascular blood volume (140), which avoids excessive vasodilation and penetration/rupture of the BBB in the more peripheral arterial branches. Finally, this sympathetic effect may also be important in order to minimize the distant effects of an eventual cerebral artery thrombosis.

The sympathetic trophic effect provides modulation of the vascular response to locally released vasoactive agents, making the vascular response less intense and reducing the effects of the axon reflexes. Thus, a putative unilateral sympathetic deficit can contribute to lateralization of a migraine attack to the more vulnerable side. However, sympathetic deficit may be an epiphenomenon of the migraine process instead of a mechanism that contributes to the attack.

**CLUSTER HEADACHE SYNDROME**

CH predominantly occurs in males. It is characterized by the appearance of unilateral, relatively short-lasting pain attacks localized in or around the orbit. The pain is severe and is typically accompanied by prominent, ipsilateral autonomic signs, such as lacrimation, conjunctival injection and rhinorrhea (for reviews see 141,142).

The periodicity of the attacks is a striking feature of this headache. Symptomatic periods may last for one to three months or more; during this time patients have daily or almost daily pain attacks with a relative night predominance. Remission periods may be lacking, either from the very beginning of the disease or after some time with an episodic pattern. In such cases, CH is to be classified as chronic (2).

Chronic paroxysmal hemicrania (CPH), described by Sjaastad and Dale (143) in 1974, has provisionally been categorized as a subtype of the CH syndrome (2). It is a headache mainly affecting females, and patients typically have multiple, brief, unilateral attacks, exruciating in intensity (144). The attacks are shorter and more frequent compared with ordinary CH. Indomethacin has an absolute effect in CPH but has little or no effect in ordinary CH. Although most CPH patients show a chronic pattern, there may also be a remitting stage, which may or may not precede the chronic stage (141). Both the chronic (unremitting) and the remitting stages are thus subtypes of CPH.

Despite the clinical differences between CH and CPH, both share fundamental characteristics and have been classified as parts of the CH syndrome; the pathophysiology of the CH syndrome in this report thus considers the two headaches together.

**Vascular mechanisms**

Clinical and supplementary test data suggest a craniovascular involvement in CH pathogenesis. During the symptomatic period, attacks may be triggered by administration of vasodilating substances such as alcohol, histamine or nitroglycerin (145,146), but only after a delay. Subsequent treatment with vasoconstrictive agents, such as 100% oxygen or ergotamine, may curb the attack. Compression of the superficial temporal artery may, to some extent, decrease the pain intensity, although patients sometimes report that the orbital pain increases, while temporal pain improves with this manoeuvre (147). Orbital pain may decrease following ipsilateral carotid compression. Such observations indicate that ipsilateral vascular abnormalities are present during attacks.

As far as rCBF is concerned, studies during attacks have shown inconsistent results (24,148-151). Studies by Horven et al (152), Horven and Sjaastad (153) and Sjaastad (154,155) demonstrated an ipsilateral increase in intracocular pressure (IOP) and corneal indentation pulse amplitudes during attacks in both CH and CPH.

Doppler and thermographic studies during attacks have shown results consistent with an increase in bloodflow through the ipsilateral opthalmic artery (156). In a patient in whom an arteriography was performed during a CH attack, the internal carotid artery was dilated in its intracavernous portion, and narrowed distal to its exit from the carotid canal (157). The narrowing was believed to be due to a swelling of the arterial wall produced by local inflammation. It should be emphasized that the pulse synchronous changes in arterial diameter were not compensated for in these observations. Corneal temperature was increased on the painful side during symptomatic periods (153,155). Systemic blood pressure does not seem to increase systematically (141). These findings suggest that vascular abnormalities are not only present during the cluster period, but also are probably localized to some extent. Their origin may be between the intracavernous segment of the internal carotid artery and the posterior part of the orbit of the ipsilateral eye (‘midline theory’) (141).

A ‘venous vasculitis’ has been claimed to be present in some cases during symptomatic periods of CH (158), either in ophtalmic veins or in the cavernous sinus. It is unknown whether this putative vasculitis represents a neurogenic inflammation, a recurrent infection process or even a pseudonormal phenomenon. The localization of the pain is consistent with the experimental findings of pain projection mainly to the orbit after stimulation of the cavernous portion of the carotid artery (3).

Particularly in CPH, the sudden and marked rise in IOP during attacks suggests intracranial vasodilatation and a local release of vasoactive substances (141). Intraocular release of prostaglandins, SP or CGRP can explain the pain and miosis, as well as the raised IOP. Indeed, the dramatic effect of indomethacin treatment is consistent with the former possibility because this drug is a potent prostaglandin inhibitor. There may, however, be other explanations for the salutary effect of indomethacin in CPH (141,155). There is little to suggest that increased IOP causes the pain of attack.

**Pain mechanisms**

It is widely believed that a local irritative process affects the sensory endings of the trigeminovascular system in CH (71, 159,160). Orthodromic activation of C fibres likely produces the
pain. Antidromic stimulation can produce a neurogenic inflammation and vasodilation, as may occur in migraine (71), and antidromic release of peptides can contribute to the pain. Brainstem connections or axonal reflexes may, in turn, activate the facial parasympathetic fibres, producing the parasympathetic features.

In CH sufferers, CGRP and VIP were found to be increased in blood samples taken from the ipsilateral external jugular vein during attacks. The difference was significant compared with controls. Successful treatment of attacks with either oxygen or sumatriptan normalized the CGRP and VIP levels (161). The raised VIP level found during CH attacks indicates parasympathetic activation, which can be related to trigeminovascular activation by central brainstem connections.

For many years the sympathetic pericarotid plexus has been thought to be compressed between a swollen arterial wall and the bony carotid canal (162). Local compression may explain the sympathetic defect observed during, and partly between, attacks (Homer-like syndrome).

MRI studies have failed to show any abnormality in the cavernous sinus or surrounding area in CH (163). However, these studies were not made during attacks, and suspicion regarding the cavernous sinus area is still strong.

Single photon emission computed tomography studies performed with $^{67}$Ga have shown increased activity in the parassellar region during CH attacks in 50% of the patients studied (164). Since $^{67}$Ga is concentrated in the tissues affected by inflammatory processes, it has been assumed that an intracavernous neurogenic inflammation could exist.

**Autonomic features**

Generally, attacks are accompanied by bilateral autonomic signs, clearly most prominent on the painful side. A relative parasympathetic overactivity during CH attacks may possibly explain the ipsilateral eye redness, lacrimation and nostril block or rhinorhoea. The high values for IOP and corneal indentation pulse in the symptomatic eye are most likely secondary to intracocular vasodilatation. Activation of the trigeminovascular system may produce an axon reflex between the proximal part of the Gasserian ganglion neurons and the sphenopalatine ganglion neurons that are connected with the spinal trigeminal nuclei. Finally, the parasympathetic target organs may be stimulated. Other features, such as the reduced salivation during attacks, are hard to explain on the basis of parasympathetic stimulation (165).

Miosis is largely present also outside attacks, and pupillary asymmetry tends to increase during attack. These features can be caused by diminished sympathetic activity. Pupilometry in CH indicates a Horner (166)–or, preferably, ‘Homer-like’ syndrome (167) (the dysfunction underlying the Horner-like picture does not seem to be purely sympathetic and thus the term ‘Homer-like’ is preferred)– with a sympathetic deficit of the first or (even more likely) third neuron. Additional studies with evaporimetry (168) have shown that spontaneous and heat-induced sweating is reduced over the medial part of the ipsilateral forehead. Pilocarpine stimulation induces a more marked sweating on the symptomatic versus the nonsymptomatic side. Pupilometric and evaporimetric abnormalities were observed in a clear majority of patients, but not in all. The reason some patients do not exhibit any putative sympathetic deficiency (not even a latent one) is not understood. It may be due to a lesser total impact of the component of the attack (lesser severity, shorter duration or both), for example, that gives rise to the Homer-like picture.

If the deficit were purely sympathetic, it might be due to local compression of the pericarotid sympathetic fibres between a swollen artery and the bony part in the carotid canal (162), or to involvement of the sympathetic fibres by a local, neurogenic inflammation. However, whether this putative sympathetic deficit is a central or peripheral dysfunction is controversial (165,169).

A sympathetic deficit in the anterior part of the hypothalamus may provide an explanation for the sympathetic dysfunction in CH (170). Most likely the defect is peripheral in nature.

There are clear differences between CH and CPH regarding the autonomic pattern. Pupilometry and evaporimetry studies have failed to show a clear and invariable sympathetic defect in CPH. These autonomic differences increase the likelihood that CH and CPH are independent nosological entities, despite being currently grouped in the same category of CH syndrome.

**Role of nociceptive substances and SP theory**

Some changes in biogenic amines reportedly may be of possible pathogenetic importance in CH. Thus, serotonin and histamine levels (or their metabolites in blood (171) and occasionally in urine (172)) have been reported to be modestly altered during the symptomatic phase of CH (171). If anything, these substances may be more important as local algogenic mediators than as important humeral attack triggers in CH.

Sicuteri and co-workers (173) proposed that CH symptoms may be mediated by antidromic release of SP from activated trigeminal neurons. There is little doubt about the prime effect of SP along with bradykinin and probably serotonin in inducing local pain. In CH, the activation of sensory fibres may be located somewhere along the sensory pathway that carries the stimuli from the ipsilateral eye to the cortex.

Antidromic release of SP can produce miosis and a rise in the IOP (174), both of which appear to be part of CH symptomatology. Capsaicin, a derivative of homovanillic acid found in hot pepper, causes release of neuropeptides, including SP from primary sensory neurons (175). Repetitive, local, intranasal application of capsaicin depletes stores of SP, and reduces lacrimation, nasal obstruction and rhinorrhoea (176). More recent studies have pursued the possibility of capsaicin use as a novel treatment for CH (177,178).

**Chronobiological considerations**

CH is a striking example of a disorder with a circannual and circadian periodicity. Headache cycles tend to occur once or twice a year (cluster periods or bouts). During the active phase, patients usually have one to three attacks daily, with a nocturnal preponderance. Even more striking is that in some patients, attacks tend to start at the same hour of the day (179). There even seems to be a moderately expressed ultradian rhythm if we consider the relationship of some of the nocturnal attacks with the rapid eye movement (REM) sleep stage (180). The tendency
effect of the chronobiological structures determining the timing essentially different mechanisms.

Rect, the hypothalamus may be a crucial anatomical structure in CPH (135). Indeed, CPH is included in the group of sleep disorders known as parasomnias (181). This suggests that in CH syndrome there is alteration of the biological clock or a prime effect of the chronobiological structures determining the timing of the symptomatic periods and individual attacks, produced by essentially different mechanisms. If these assumptions are correct, the hypothalamus may be a crucial anatomical structure in the pathogenesis of CH (182). This applies to the ‘preparatory’ stage. Once an attack has started, ‘peripheral’ mechanisms seem to predominate. Hypothalamic connections with brainstem structures that regulate pain transmission or craniovascular tone have been discussed earlier.

Periodic reactivation of a chronic infection has been proposed as a mechanism that can trigger cluster periods (183,184). Herpes simplex virus has a well known neurotrophic profile and is periodically activated. This virus may produce a ganglionitis affecting the Gasserian and/or sphenopalatine ganglia, and this process may be cyclically reactivated. A relationship between CH and lymphogranulomatous meningitis (185) or aseptic meningitis (186) has even been proposed.

There are several common examples of the relationship between the neuroendocrine system and immunology. The menstrual herpes virus reactivation is one of the best known. In fact, immunological activity also has circannual and circamenstrual waxing and waning cycles for macrophage and lymphocyte functions. A remote possibility is that a neuroimmunological system dysfunction plays a role in determining the timing of CH bouts (159). Whether, and to what extent, a direct hypothalamic stimulus or an infection reactivation triggers the bout is unknown.

Hypoventilation during REM sleep, sleep apnea or both may play a role for the sleep-related attacks. An increased incidence of sleep apnea and a tendency for CH patients to suffer attacks at high altitude have been reported (187), although the present authors are not aware of any comprehensive study concerning high altitude and an increased attack tendency. However, oxygen inhalation is frequently effective as a treatment for single attacks, and Kudrow (188) has hypothesized that CH pathogenesis is intimately linked with respiratory dysregulation by sympathetic inhibition and parasympathetic disinhibition of carotid body autonomic tone.

Chemoreceptors located in the carotid body physiologically respond to variations in blood oxygen, carbon dioxide and pH, and influence the brainstem respiratory regulatory system. This regulatory system then adjusts ventilation to maintain normal blood gas levels. In CH, hypoxia during sleep may induce a hyperactivation (possibly denervation supersensitivity) of the chemoreceptors and consequently a stimulation of the respiratory centre with ensuing ventilatory drive. However, because the hypothalamus is the major autonomic centre, the primary dysfunction may still be located in that area.

During REM sleep, respiration is under the direct influence of the forebrain, the chemoreceptors playing only a secondary role restricted to the brief periods of REM phasic events. Hypoxia is a poor stimulus for activation of chemoreceptors during sleep, at which time the main stimulus for the ventilatory drive seems to be carbon dioxide.

More recent studies have demonstrated that daytime hypoxia does not seem to produce CH attacks (189,190). Sleep-related hypoxia may act as a contributory factor to REM-related CH attacks rather than being the sole trigger. The most current study results emphasize that hypoxia is of little or no significance for the generation of solitary attacks.

HEADACHE ASSOCIATED WITH VASCULAR DISORDERS

Generally, headaches may occur in patients with clinical and supplementary test evidence indicating a vascular disorder.

According to the IHS classification (2), a new form of headache (including migraine, tension-type headache and CH) that develops in close temporal relation with a vascular disorder is to be classified in one of the latter groups, although a causal relationship is not necessarily implied. If the vascular disease only produces a worsening pre-existing headache, the headache should still be classified according to its previous form.

Cerebrovascular disease, in particular bleeding, is frequently accompanied by headache or facial pain (Table 2).

| TABLE 2  | Headache associated with vascular disorders |
|----------|------------------------------------------|
| Acute ischemic cerebrovascular disease |
| Transient ischemic attack |
| Thromboembolic attack |
| Intracranial hematoma |
| Intracerebral hematoma |
| Subdural hematoma |
| Epidural hematoma |
| Subarachnoid hemorrhage |
| Unruptured vascular malformation |
| Arteriovenous malformation |
| Saccular aneurysm |
| Arteritis |
| Giant cell arteritis |
| Other systemic arteritides |
| Primary intracranial arteritis |
| Carotid or vertebral artery pain |
| Carotid or vertebral dissection |
| Carotidynia |
| Postendarterectomy headache |
| Venous thrombosis |
| Arterial hypertension |
| Acute pressor response to exogenous agent |
| Pheochromocytoma |
| Malignant hypertension |
| Pre-eclampsia and eclampsia |

Adapted from reference 2
Headache associated with ischemic cerebrovascular disease

Approximately 30% of patients having ischemic cerebrovascular episodes of various types report headache among the initial symptoms (191-198). Headache is more frequent with infarcts in the cortical versus in the deep layers (199), and is only rarely associated with lacunar infarcts. Thrombosis and transient ischemic attacks produce headache more frequently than embolism. Generally, the headache of an ischemic episode is ipsilateral to the lesion, although basilar artery ischemia may produce bilateral headache. With carotid artery ischemic events, the headache (193) is generally reported in the anterior regions, while in vertebrobasilar ischemia, the pain is located posteriorly. Most headaches associated with cerebral ischemia are of moderate intensity and the pain is throbbing or steady (193).

Information concerning the pathophysiology of these ischemic headaches is scarce. The temporal relationship with the ischemic episode and the unilaterality of the pain suggest a local origin of the pain in the vessel(s) affected or the area perfused. The hypoxia or the metabolic products released by ischemic tissues may be of importance for activation of sensory fibres. It is also feasible that these fibres are stimulated in a mechanical way by the thrombotic or embolic arterial occlusion. Intracerebral arterial arterioles (penetrators) are not innervated and are thus insensitive to pain (200). In the rare cases of headache associated with lacunar infarcts, pain may arise from occlusion of the stem of a major cerebral artery, resulting in downstream ischemia and distal deep infarct. It has been proposed (193) that serotonin and prostaglandins are released by platelets, act on the vascular wall and contribute to the pain. The ischemic process and platelet activation occur in all patients, but only 30% of them report headache; perhaps headache associated with cerebral ischemia is characterized by vascular pain susceptibility so that the pain process is easily activated by hypoxia.

Can such a predisposition be part of a ‘migrainous diathesis’? Migraineurs may exceptionally present a cerebral infarction as a complication of a migraine attack. In such cases, cerebral hypoperfusion might have been intense enough to produce ischemic lesions. Alternatively, an additional factor may be necessary to produce the infarct.

It is important to note that migraine does not produce cerebral infarct via production of atherosclerotic lesions and that atherosclerosis does not produce headache.

Migraine and cerebrovascular ischemic disease are frequent disorders. Cerebral ischemia may trigger mechanisms supposedly typical of migraine, but this does not imply that headache associated with cerebral ischemia is a migraine-like process. These headaches and others probably use the trigeminovascular system as a final common pathway of pain expression, the differences being the causative factors and the ‘neural constitution’.

Headache associated with spontaneous dissection of intra- and extracranial arteries

The dissection of intra- and extracranial arteries causes approximately 2% of all ischemic cerebrovascular episodes and up to 5% of the infarcts in young people. Headache is a frequent symptom in this disorder and typically precedes the onset of the ischemic event. Awareness of the important clinical characteristics of this disorder may lead to alertness regarding the insidious onset of cerebral ischemia, so that the damage can be minimized.

Headache starts abruptly and is always ipsilateral to the dissection. Pain is referred to the anterior region of the head when the affected artery is the internal carotid artery or some of its principal branches. Dissection of the vertebral artery produces occipital and neck pain. The headache is moderate to severe and is frequently steady in character, although it is sometimes perceived as throbbing (201,202). Dissection frequently takes place after traumatic events, but it may also be spontaneous. In some incidents, it reportedly is caused by arteriopathy with a predisposition to spontaneous dissection (203). The occurrence of this disorder among migraineurs (202-207), combined with the observed improvement of the pain with treatment also effective in migraine (methysergide, prednisone), suggests—but does not prove—that both share some pathophysiological mechanisms (201).

When dissection is extracranial, pain precedes the ischemic event by hours or days. The ischemic event in these cases may be embolic. In intracranial dissection, headache is severe and more immediately before the ischemia (202).

The localization and temporal relationship of headache and arterial dissection suggest a local origin of the pain. The dissecting hematoma produces a distension of the vessel wall and may lead to a traumatic stimulation of arterial wall sensory endings. Pain in these cases, therefore, is believed to be mechanically triggered. The onset of headache antedating the cerebral ischemia seems to rule out any cerebral, biochemical mediation of the pain.

Carotidynia

Pain in the face, neck, ocular area or head triggered by pressure over the internal carotid artery is called carotidynia. The artery may be dilated in addition to being tender. Carotidynia may be a sign accompanying the migraine attack, or it may be an independent syndrome (208,209). In its usual form, carotidynia seems to be a self-limiting disorder with one, single, short pain period (mean duration is 12 days according to Roseman [210]).

The clinical manifestation of primary carotidynia is a unilateral, protracted pain over the neck, inferior part of the face or the head (210,211). An episodic variety has also been described with a more intense and pulsatile pain, with a duration of minutes to hours (209). During the symptomatic periods, the internal carotid artery is particularly sensitive to local pressure. This manoeuvre evokes the characteristic pain that is referred to neck and face.

Primary carotidynia responds to the same treatment as migraine. However, it may be necessary to add corticosteroids at the beginning of a treatment course to obtain successful prophylactic treatment with antimigraine drugs. The frequent association between migraine and carotidynia and the pharmacological response to migraine drugs may point to some common mechanisms of pain.

Headache associated with cerebral hemorrhagic disease and hypertension

Headache may be a symptom of cerebral hemorrhagic episodes. Almost all SAH patients and more than half the patients with parenchymal hemorrhage report headache as an initial symptom.
In many cases the head pain precedes the clinical bleeding. SAH produces a severe, holocranial headache with abrupt onset in most cases. Usually the headache is accompanied by nausea, vomiting and neck stiffness. The pathophysiology of the pain is meningeal irritation from the bleeding or possibly intracranial hypertension produced by a sudden increase in intracranial volume (212).

Rupture of an aneurysm or an arteriovenous malformation (AVM) is the usual cause of SAH (213). In aneurysmal rupture, about 50% of patients have had headache days or even weeks before rupture (212, 214). The headache may even be caused by a minor leakage. In some cases with localized headache (212), the underlying mechanism may be the focal, vascular pain produced by the local irritation of the leakage. 'Thunderclap headache' (215, 216) is an acute, severe episode of head pain that at times is produced by an unruptured aneurysm. In such cases, the mechanism of pain may be related to intramural bleeding, intrasaccular thrombosis or aneurysmal expansion (217). If large enough, the aneurysm may, on rare occasions, produce chronic headache by a mass effect on the adjacent structures (217).

Vasospasm associated with SAH may produce vascular damage, affecting the three layers of the vessel wall. Such changes are smooth muscle necrosis, vascular degeneration with intimal swelling, cell desquamation and fibrosis of the endothelium, and edema of the adventitia (56, 218). Under such conditions, a thrombus can build up because loss of the endothelial cells leaves the subendothelial collagen uncovered. Collagen is a potent mechanism of pain which may be related to thrombosis or aneurysmal expansion (217). If large enough, the aneurysm may, on rare occasions, produce chronic headache by a mass effect on the adjacent structures (217).

Arteriovenous malformations may produce headache without rupture in about 20% of cases (220). These headaches are sometimes episodic and clinically similar to migraine. In most cases, the migraine-like headache steadily recurs on the side of the AVM (221), and sometimes the aura symptoms correlate with AVM topography. Thus, an interdependence of both disorders has been claimed (222). However, it has not been convincingly demonstrated that there is any type of causal relationship between AVM and migraine. A coexistence of both disorders can even occur by chance (223).

Parenchymal hemorrhage is usually due to vessel wall abnormalities generated by hypertension. Deep artery wall degeneration causes the formation of microaneurysms that may eventually rupture. Parenchymal hemorrhage causes headache that is insidious in onset, is frequently unilateral (192) and may eventually become severe. The mechanism of pain production is probably a distension and compression of sensitive intracranial structures caused by the accumulation of blood.

Classically, chronic hypertension has been thought to produce headache. However, several studies have failed to provide proof (224-227). Most patients with chronic hypertension report headache only when their blood pressure reaches high levels, such as occurs in patients with hypertensive encephalopathy and, occasionally, pheochromocytoma. Headache occurs in 75% of the cases of hypertensive encephalopathy. The underlying mechanisms may be intracranial hypertension secondary to the vasodilation and an increase in vascular permeability, with edema tendency. This may be the sequence of events when vascular autoregulation is lost as a result of dramatically increased blood pressure levels (228, 229).

About 80% of pheochromocytoma patients report headache during exacerbations of the disease (230, 231). In these cases, headache is rapid in onset, severe, throbbing (230) and holocranial. Typically, the pain episodes are short-lasting (less than 1 h) in most patients. The mechanism underlying these headaches is probably the abrupt increase in blood pressure due to the pressor effect of noradrenaline and adrenaline (231).

Although our understanding of the mechanisms underlying vascular pain is increasing there are still many obscure aspects. Knowledge within this field is expected to increase enormously in the foreseeable future.
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