Examining the Essence of Migraine—Is it the Blood Vessel or the Brain? A Debate

Abstract

A debate is presented that examines whether it is the blood vessel or the brain that determines the essence of migraine.

INTRODUCTION

In this, like any debate, it is vital to define the issue. The title would have us debate whether it is the blood vessel or the brain that determines the essence of migraine. I am going to assume that the essence of migraine is that which disables our patients, keeps our waiting rooms crowded and waiting lists long, defines our treatments as “migraine-specific,” and has driven drug discovery for more than 50 years – the essence of migraine is the headache. Nevertheless, I will also entertain even the possibility that cortical spreading depression, the putative substrate of the migraine aura, may have a vascular mechanism.

While the primacy of the blood vessel in the pathogenesis of migraine headache endured 4 centuries, from Willis to Wolff, contemporary thought leaders have successfully moved the fundamental biology of migraine headache away from the trigeminovascular junction and along peripheral and central trigeminal pathways. While it has even been proposed that migraine headache can be generated and maintained within the central nervous system – without ever leaving the brain – most still consider the disorder to be neurovascular– a term which maintains but relegates the vascular changes of migraine headache to an epiphenomenon or downstream effect of metabolic changes within the brain.

One thing is for certain – given the dense sensory innervation of the cerebral vasculature, the ability to provoke migraine-like headache by a purely vascular mechanism, the changes in blood vessel caliber and blood flow that are evident during migraine headache, the comorbidity between migraine and other systemic and cerebrovascular disorders, and the vascular action of all migraine-specific drugs – there is no doubt that the blood vessel is important.

DO VASCULAR HEADACHES EXIST?

There should be no argument that diseases or disorders that are exclusively confined to the cerebral vasculature can and do produce headache as the predominant or solitary feature, often with a clinical phenotype resembling a migraine headache. Headache is a prominent feature of patients with cervicocephalic arterial dissection, cerebral venous sinus thrombosis, reversible cerebral vasoconstriction syndromes, central nervous system vasculitis, and unruptured cerebral aneurysms. These clinical examples of purely vascular headache are supported by experimental evidence that stimulation of intracranial arterial and venous structures alone can elicit headache. The classic experimental studies of Wolff and his colleagues demonstrated that manipulation, stimulation or distention of intracranial and extracranial blood vessels and dural venous sinuses in awake patients
resulted in reproducible patterns of headache referred to specific regions of the head, depending of the vessel being stimulated. In addition, balloon inflation of the distal internal carotid artery and middle cerebral artery produces reproducible patterns of headache in the ipsilateral temporal, frontal, and/or retro-orbital region. Headache is the most common symptom in patients undergoing percutaneous angioplasty of carotid or vertebral arteries during balloon inflation. The headache usually disappears within seconds after balloon deflation. These experimental and clinical observations reflect the dense sensory innervation of the cervicocephalic and intracranial blood vessels and confirm without a doubt that headache can be precipitated by a purely vascular mechanism.

MIGRAINE AND THE BLOOD VESSEL

Vasodilators Trigger and Vasoconstrictors Relieve Migraine Headache.— It is well established that drugs that lead to vascular dilation may be potent triggers for migraine in predisposed individuals, while compounds that cause vasoconstriction may provide rapid relief of migraine headache. Alcohol, nitroglycerine, phosphodiesterase inhibitors such as dipyridamole and sildafenil, and systemic antihypertensives that cause profound vasodilation such as nifedipine and hydralazine are well known to provoke typical (International Classification of Headache Disorders) migraine in migraineurs and throbbing migraine-like headache in nonmigraineurs. Wolff proposed that migraine was a vascular disease because he was able to measure pulsations in the superficial temporal artery that correlated temporally with the headache, while pulsations subsided as headache resolved after the administration of ergotamine tartrate. Serotonin and noradrenaline, both potent systemic vasoconstrictors, have also been demonstrated to provide rapid relief of migraine headache.

The discovery of sumatriptan and the subsequent revolution in acute migraine treatment was based on the observation that serotonin (5HT) and methysergide, both potent antimigraine agents, were both potent constrictors of extracranial cerebral arteries. Though the triptans have been subsequently shown to inhibit neuropeptide release from trigeminal sensory fibers though binding to 5HT1D receptors on trigeminal nerve terminals, selective 5HT1D receptor agonists failed to show efficacy for the acute relief of migraine headache, suggesting that the agonist activity at the vascular 5HT1B receptor, and therefore the blood vessel, is necessary for the acute relief of migraine.

Migraine as a Systemic Vasculopathy.— Migraine with aura is an inherent feature of a diverse array of both acquired and genetic vasculopathies. To date, many retrospective, prospective, cross-sectional studies, and some studies using data from stroke registries have demonstrated an increased risk of ischemic stroke among women less than 45 years of age who reported a history of migraine with aura with risk estimates ranging from 3.8 to 8.4.7-9 Two additional case–control studies found increased risk for migraineurs with aura among both genders.10,11 Recent evidence from the Women's Health Study also confirmed an increased risk of ischemic stroke among apparently healthy women aged >45 years who reported migraine with aura when compared to women without migraine.12 Furthermore, migraine with aura has been shown to be associated with a 14-fold increased risk of silent posterior
circulation (cerebellar) infarctions and a 4-fold increased risk of white matter hyperintensities, which are microvascular in origin.13

The Women’s Health Study also demonstrated that among 27,840 apparently healthy women, migraine with aura was associated with a significantly increased risk of major cardiovascular disease (nonfatal myocardial infarction, nonfatal ischemic stroke, ischemic cardiovascular disease death), myocardial infarction, coronary revascularizations, angina, and cardiovascular disease death, when compared to women with migraine without aura and women with no history of migraine.12 With regard to men, recent data from the Physicians' Health Study, in which 20,084 apparently healthy US male physicians were followed for a mean of 15.7 years, indicate an association between overall migraine and major cardiovascular disease, which was driven by a significant increase in the risk of myocardial infarction.14

Migraine may itself represent and/or result from an underlying arteriopathy. The increased prevalence of arterial dissection in migraineurs suggests that migraine is associated with abnormalities within the extracellular matrix of the vessel wall. In a hospital-based case–control study, migraine was present in 49.1% (23/47) of patients with cervical artery dissection and in 21% (11/52) of patients hospitalized for a cerebral ischemic event not related to a cervical artery dissection (adjusted odds ratio 3.6).15 That migraine, especially with aura, may be the consequence of an underlying arteriopathy is illustrated by the common occurrence of migraine with aura in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL is a systemic vasculopathy characterized by lacunar infarctions, subcortical dementia, and psychiatric manifestations. Migraine with aura is present in one-third of patients with CADASIL. Cerebral blood flow studies in patients with CADASIL have demonstrated widespread reductions in cerebral blood flow. This comorbidity suggests that alterations in cerebral blood flow, and cerebral ischemia, which is well known to trigger cortical spreading depression in animal models, may account for the frequent aura seen in migraineurs with CADASIL. The association of aura in patients with CADASIL also raises the possibility that the aura and headache in these patients may be precipitated by a purely vascular mechanism. In addition to CADASIL, migraine is also highly associated with other genetic vasculopathies including hereditary vascular retinopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke, autosomal dominant cerebroretinal vasculopathy, and Raynauds phenomenon.16-20

The mechanism by which genetic and acquired vasculopathies give rise to migraine is unclear. However, endothelial dysfunction has been proposed as a possible underlying mechanistic factor for both migraine, cardiovascular and cerebrovascular disease. Endothelial dysfunction results in decreased vascular reactivity, hyper-coagulability and vascular inflammation. Evidence of endothelial dysfunction is supported by findings of altered cerebral and systemic vasomotor reactivity, increased peripheral vascular tone, increased peripheral and central vascular pressure, and increased aortic augmentation index, in migraineurs during headache-free intervals.21,22 Livedo reticularis and elevated von Willebrand factor in migraineurs, especially with aura, is supportive clinical evidence of the potential role of endothelial dysfunction in migraineurs.23,24 In addition, the MTHFR C677T and angiotensin-converting enzyme gene deletion polymorphisms have both been associated with endothelial dysfunction, migraine with and without aura, and ischemic stroke.25,26
THE NEUROVASCULAR HYPOTHESIS

The preceding discussion has provided support that headache may be generated by a purely vascular mechanism, and that migraine headache is at least associated with, if not in some cases the cause and consequence of, genetic and acquired vasculopathies. While the mechanism(s) that underlie these associations are unclear, endothelial dysfunction may be one potential mechanism. The frequent occurrence of aura in some of these vasculopathies, particularly CADASIL, also suggests that this neuronal phenomena may be triggered by a vascular mechanism.

The migraine aura has long been the subject of fascination and intensive investigation. Over the past 30 years, increasingly sophisticated imaging techniques have shown consistent changes in cerebral blood flow during both spontaneous and provoked migraine aura. Using 133Xe blood flow techniques to investigate the changes that occurred during aura-like symptoms induced during carotid angiography, Olesen and colleagues demonstrated temporary (1 hour) reductions (17% to 35%) in regional cerebral blood flow (rCBF) in posterior regions of the brain,27,28 though areas of hypoperfusion in the frontal cortex were also seen sometimes with and sometimes without simultaneous reductions in posterior parietal or occipital blood flow. Since that time, studies involving perfusion-weighted magnetic resonance imaging (P-MRI), blood oxygen level dependent (BOLD) MRI, 15O–labelled H2O positron emission tomography, and single photon emission tomography have shown similar changes in cerebral blood flow during aura.29-32 In all studies, blood flow values within the areas of hypoperfusion were not low enough to cause ischemia, and hence, the term oligemia has been introduced to described the blood flow changes seen during aura. Another consistent feature of these imaging studies is that oligemia invariably begins in the visual association cortex and spreads anteriorly without obeying vascular anatomical boundaries. In addition, BOLD imaging studies in patients with triggered and spontaneous aura have demonstrated suppression of visual activation that spreads across the occipital lobe at a slow rate of 3.5 mm per minute) which corresponds to the rate of cortical spreading depression in animal models.30,33 Indeed, migraine visual aura and cortical spreading depression (CSD) share several characteristic fMRI findings including that both are associated with an initial hyperemia lasting 3 to 4.5 minutes which is followed by mild hypoperfusion lasting 60 to 120 minutes. The hyperemia/hypoperfusion spreads across the cortex at a slow rate of 2 to 5 mm per minute; evoked visual responses during aura and CSD are suppressed and take about 15 minutes to recover; and the first affected area is the first to recover normal evoked responses.30

These imaging data have supported the current prevailing hypothesis that the migraine aura is due to a CSD-like event characterized by depolarization of neuronal and glial membranes and the changes in cerebral blood flow that are seen are simply a passive phenomena that reflect the coupling between metabolism and blood flow (metabolic-flow coupling). Depolarization of neuroglial membranes during CSD is associated with a marked but brief increase in CBF while the subsequent hyperpolarization and suppression of neuroglial membranes are associated with a commensurate and appropriate reduction in CBF. That the headache which follows the migraine aura has been shown to occur while CBF is still reduced, has been considered proof that rebound vasodilation, as the classic vascular hypothesis held, has nothing to do with the headache phase. Instead, the headache that often follows the aura is considered to be a result of activation of trigeminal nociceptor and parasympathetic fibers by
nociceptive substances (e.g., hydrogen ions, potassium ions, glutamate, nitric oxide) released during CSD. These findings, together with the theory of neurogenic inflammation, served as the major sources of evidence that led to the displacement of the vascular hypothesis and to the emergence of the neurovascular hypothesis, a term which reflects the primacy of the neuron as the site where migraine is initiated, while the changes in vascular caliber or cerebral blood flow have been relegated to an epiphenomena and indicative of nothing more than a passive downstream effect of neuronal activity.

**THE VASCULONEURONAL HYPOTHESIS**

Central and obligatory to the neurovascular theory of migraine is that the event which initiates the cascade of events that result in the aura and migraine headache occurs at the level of the neuron. Data from animal studies clearly show that neuronal activation induces spreading depression, but recent studies raise the possibility that a vascular event may also triggering spreading depression. This would and should not be altogether surprising. The clinical observation that arteriovenous malformations and small angiomas may cause migraine with aura suggests that vascular anomalies and alterations in cerebral blood flow have the potential to trigger CSD and migraine headache. Cortical spreading depression has been shown in both animals and humans in the setting of cerebral ischemia, brain trauma, spasm of extraparenchymal cerebral blood vessels. CSD is considered to raise the ischemic threshold of neurons in the face of an ischemic and/or hypoxic brain insult, but it is also known to lead to expansion of infarct size and volume. It is important to note that CSD has never been directly demonstrated during the migraine aura—it has been inferred from functional neuroimaging studies.

Evidence to support a vascular basis of CSD comes from recent data from Dreier et al. This group demonstrated that local application of endothelin-1 generates spreading depression activity mediated by the N-methyl-D-aspartate channel, with changes in extracellular potential and spreading oligemia being recorded at sites distinct from the site of application. As endothelin-1 had no spreading depression-inducing properties in vitro, the authors concluded that a vascular mechanism was the likely initiating factor. This article is the first to demonstrate that endothelial factors can precipitate spreading depression and led some to comment that these findings “raise an interesting compromise for the advocates of the vascular and neurogenic theories of migraine because both primary vascular and neuronal disturbances can precipitate this phenomenon. Therefore, both views could hold the correct answer for certain individuals or circumstances.”

The central tenet that changes in vascular caliber and cerebral blood flow occur passively in response to neuronal activity in migraine has recently also been challenged in a recent study from Brennan et al. This group demonstrated that dilatation of cortical surface arterioles propagated with a significantly greater intrinsic velocity than the parenchymal CSD wavefront as measured by optical intrinsic imaging and electrophysiological techniques. Moreover, dilatation traveled in a circuitous pattern along individual arterioles, indicating specific vascular conduction as opposed to concentric propagation of a parenchymal signal. In addition, arteriolar dilatation propagated into areas that extended beyond the margins of the spread of parenchymal CSD indicating a dissociation of metabolic demand and vascular
response. They also demonstrated that the cortical surface arteriolar changes associated with CSD appear to have independent, and possibly active mechanisms of propagation along endothelial or smooth muscle cells. Their conclusion was that changes in vascular caliber may be of primary importance in the pathogenesis of migraine headache and prompted Goadsby to question “How could this be? Do not changes in blood flow follow neuronal changes passively with flow-metabolism coupling? It seems the issue is not that simple. Their data suggest a mechanism that requires the vasculature and not the neuronal component. These data demand a complete reevaluation . . . and challenge the cerebrovascular physiology community to consider this remarkable new mechanism.”

SUMMARY

At first blush, accepting the task of arguing for what is now considered the antiquated and thoroughly disproven vascular hypothesis of migraine is unenviable at best, foolhardy at worst. One’s task in a debate is to make a convincing argument for the assigned position, even if at the time one is on the complete opposite side of the fence. However, as is frequently the case, reflecting upon and evaluating a seemingly untenable position often generates more questions and raises doubt about the veracity of previously held assumptions and central dogma. In this particular case, Socratic reasoning should hold that; the cerebral blood vessel are densely innervated by sensory nerves; manipulation, distention, compression or dilation of these nerves generates headache (often throbbing); vasodilators in migraineurs trigger migraine headache (even aura); vasoconstrictors in migraineurs relieve migraine headache; migraine is comorbid with a vast array of acquired and genetic vasculopathies; cerebral blood flow changes occur in migraine with and without aura; CSD, the presumed substrate of migraine aura, is a neuronal event that may be triggered by alterations in cerebral blood flow or by depolarization of smooth muscle or endothelial cells via propagated calcium waves along cerebral blood vessels. Therefore, migraine, both with and without aura, may have a vascular basis in at least some individuals. There is no disputing the role of the central nervous system in the susceptibility, modulation and expression of migraine headache and the associated affective, cognitive, sensory, and neurological symptoms and signs. However, to presume that migraine is always generated from within the central nervous system, based on the evidence available presented herein, is naïve at best and unscientific at worst. The emerging evidence would suggest that just as alterations in neuronal activity can lead to downstream effects on the cerebral blood vessel, so too can changes within endothelial cells or vascular smooth muscle lead to downstream alterations in neuronal activity. Therefore, there are likely patients, and/or at least attacks in certain patients, where vasculoneuronal mechanisms predominate.

As usual, John Edmeads’ words capture the essence in a way that none other can, and his comment on this ongoing debate almost 20 years ago are rather prophetic in light of recent data and the current state of the science:

If we swing between vascular and neurogenic views of migraine, it is probably because both vascular and neurogenic mechanisms for migraine exist and are important.

John Edmeads, 1989
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