Neuroimaging of Migraine

Shazia K. Afridi, MD and Peter J. Goadsby, MD

Corresponding author
Peter J. Goadsby, MD
Institute of Neurology, Queen Square, London.
WC1N 3BG, UK.
E-mail: peterg@ion.ucl.ac.uk

Current Pain and Headache Reports 2006, 10:221–224
Current Science Inc. ISSN 1531-3433
Copyright © 2006 by Current Science Inc.

Neuroimaging of migraine recently has provided us with further information regarding the pathophysiology of the disorder and posed important questions as to whether migraine is a progressive disorder. This article provides the background of imaging in migraine and discusses recent advances in the field.

Introduction

Neuroimaging has been used to improve our understanding of the pathophysiology of migraine and also to demonstrate the possible consequences and risks associated with migraine.

Functional imaging has provided important insights into migraine pathophysiology and has contributed to the argument that migraine is a neurovascular, as opposed to a vascular, headache—fundamentally, a disorder of brain function. It also has provided clear evidence linking cortical spreading depression and aura. Early imaging studies involved xenon flow imaging and single photon emission computerized tomography (SPECT). However, positron-emission tomography (PET) and functional MRI (fMRI) now have superseded the older methods, as they enable ictal imaging with greater temporal and spatial resolution.

Structural imaging has been used to assess the consequences of repeated migraine attacks and has triggered a debate as to whether migraine is a progressive disorder.

Episodic Migraine: Ictal Phase

Xenon SPECT

The earliest attempts at functional imaging in migraine tended to focus on the migraine aura. In the early 1970s, Xenon flow imaging showed a reduction in cerebral blood flow during aura and hyperperfusion during headache in migraine triggered by angiography [1,2]. In 1981, another Xenon flow study showed that the vascular theory, which proposed that aura was a result of intra-cerebral vasoconstriction and that the headache was due to reactive vasodilatation of the carotid artery, was not sufficient to explain migraine [3]. It showed that in three of six subjects, the unilateral, focal (occipitoparietal) oligemia during the aura was preceded by hyperemia. In five subjects, the oligemia spread anteriorly. What was particularly interesting was that in four subjects, severe headache was observed during the oligemic phase. This observation was replicated by SPECT studies [4–6]. The hyperemic phase also has been shown to persist beyond the headache phase [5,7]. Therefore, vasodilatation could not explain the headache component of migraine.

Functional magnetic resonance imaging (blood oxygen level-dependent)

A case report of a subject with migraine with aura scanned within 10 minutes of onset of his spontaneous aura (left, homonymous quadrantanopia) demonstrated an increase in T2-weighted contrast intensity bilaterally in the occipital cortex, the red nucleus, and the substantia nigra [8]. Following this, 26 migraineurs (23 with aura and three without aura) were scanned during repetitive visual stimulation, using a checkerboard stimulus, to trigger a migraine [9]. Fifteen subjects (13 with aura and two without) developed headache, aura, or both. In 75% of these patients, baseline T2-weighted magnetic resonance signal intensities increased in the red nucleus, substantia nigra, and occipital cortex. In seven of the subjects, signal increases also were detected in other brainstem structures, including the locus coeruleus, periaqueductal grey, pons, and central midbrain, although the time course, duration, and extent of activation in these structures is not documented. The same authors then studied the occipital cortex in greater detail using the same stimulus [10]. In five of 12 subjects, the onset of headache or visual change was preceded by suppression of initial activation. The suppression propagated into contiguous occipital cortex at a rate of 3 to 6 mm/minute and was accompanied by baseline contrast intensity increases that indicated vasodilation and hyper-oxygenation. Interestingly, one of these five subjects had a diagnosis of migraine without aura. No clear evidence of ischemia was noted in this study.

In a more detailed study of aura, BOLD-fMRI changes were recorded that suggested that cortical spreading depression was responsible for generating migraine aura [11•]. The study involved three subjects and five attacks of migraine with aura were studied, two induced by exercise
and three spontaneous. Initially, a focal increase in BOLD signal (thought to reflect vasodilatation) developed within the extrastriate visual cortex. This signal then propagated contiguously at a rate of $3.5 \pm 1.1$ mm/minute over the occipital cortex, congruent with the retinotopy of the visual percept. The BOLD signal then diminished, possibly reflecting vasoconstriction. The spreading phenomenon did not cross prominent sulci and were restricted to the hemisphere corresponding to the aura.

**Diffusion-weighted imaging/perfusion-weighted imaging**

Perfusion-weighted imaging (PWI) abnormalities have been demonstrated in migraine with aura [12]. During aura, relative cerebral blood flow was found to be decreased (27%) in the contralateral occipital cortex. Regional cerebral blood volume was decreased (15%) and mean transit time increased (32%), persisting up to 2.5 hours into the headache phase. No changes in diffusion-weighted imaging (DWI) have been observed in migraine with aura [13].

The level of blood flow reduction that occurs during aura is now clearer due to the advent of PET and MRI. Evidence from these imaging studies suggests that ischemia does not account for aura, nor does it seem that significant ischemia (> 50% decrease in perfusion) generally is provoked by aura [14].

No abnormalities have been recorded in PWI or DWI in migraine without aura.

**Positron-emission tomography**

Bednarczyk et al. [15] studied nine subjects within 13 hours of onset of migraine without aura. They observed a 9.9% decrease in global cerebral blood flow and a 5.2% decrease in cerebral blood volume persisting for at least 6 hours. Oxygen metabolism and oxygen extraction remained unchanged.

Woods et al. [16] reported a case report of a subject with migraine with no previous aura who unexpectedly developed a migraine during her participation in a visual activation paradigm while lying on a PET scanner. The subject described some visual blurring during one of the scans, but did not clearly describe any other features of typical aura. The migraine was associated with bilateral hypoperfusion starting in the occipital lobes and spreading anteriorly into the temporal and parietal lobes. The contiguous spread covered areas in the territories of the posterior and middle cerebral artery. More recently, a further PET study of spontaneous migraine also has reported bilateral posterior circulation hypoperfusion in migraine without aura [17]. However, it must be noted that the analysis in this study did not involve correction for multiple comparisons and, consequently, these findings need to be reproduced using more rigorous statistical procedures. These changes may represent hypoperfusion associated with cortical spreading depression [18], albeit without any clinical manifestations. Alternatively, they may represent a neurogenically mediated oligemia, which may be seen in experimental animals with activation of the nucleus locus coeruleus [19] and is typically dominant in the posterior cortical structures [20].

Moving away from aura, the first PET study detailing regional activation during migraine was the study of Weiller et al. [21]. They investigated nine subjects with migraine without aura. The subjects presented with right-sided spontaneous headaches and were scanned within 6 hours of onset of migraine, prior to having taken any medication. They were scanned during spontaneous migraine attacks and following an injection of sumatriptan. Interestingly, three of the subjects were taking migraine preventives (β-blockers). The study revealed brainstem activation during the migraine, which persisted after sumatriptan administration had relieved the pain. The resolution of the PET camera used was not high enough to identify specific nuclei, but the foci of maximum increase were around the dorsal midbrain, which contains the dorsal raphe nucleus and periaqueductal grey matter, and the dorsolateral pons, which contains the locus coeruleus. Activation also was seen in the anterior cingulate and in the visual and auditory association cortices. A case of a glyceryl trinitrate (GTN)-triggered migraine also revealed brainstem activation in the dorsolateral pons, which again persisted following abortion of the migraine [22].

In a more recent study involving migraine with and without aura, five patients were imaged in ictal and interictal states and the differences were analyzed using statistical parametric mapping [23]. Two patients had a typical migrainous aura prior to the onset of the headache. All of the attacks studied fulfilled standard diagnostic criteria for migraine [24]. Comparing the migraine scans with interictal scans, there was significant activation in the dorsal pons. Activation also was seen in the right anterior cingulate, posterior cingulate, cerebellum, thalamus, insula, prefrontal cortex, and temporal lobes. Similar findings in the brainstem have been reported in a further study of spontaneous migraine [25]. In this study, hypothalamic activation also was noted during migraine. This is an interesting observation considering that many of the premonitory symptoms of migraine are thought to have hypothalamic features.

The largest PET study to date involved 24 migraineurs (with and without aura) and eight healthy control subjects [26••]. The migraineurs were divided into three groups according to the site of their headache: right, left, bilateral. In each group, a migraine was induced using a GTN infusion. The subjects were scanned at various points (pre-infusion, during GTN, during migraine, and after migraine). Significant brainstem activation was seen in the dorsal pons during the migraine state versus the pain-free state when comparing migraineurs with control subjects. When each group was analyzed separately to investigate laterality, it was found that the dorsal pontine