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# Expert Opinion

## Headache at Onset of Acute Cerebral Ischemia

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**Key words: headache, transient ischemic attack, stroke, cerebral ischemia, cerebrovascular disease**

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In 1664, Willis first described the relationship between headache and vascular disease. Fisher provided the first detailed study of headache features and vascular disease in 1968.[1]

### CASE

Ten days previously, this 76-year-old woman suddenly developed a shadow over the left field of vision of both eyes associated with a right temporal pressure headache with an intensity of 9/10. The headache resolved in 3 days. There were no other associated neurological symptoms. When seen in consultation, the right temporal headache had recurred the evening before for about 20 minutes with an intensity of 8/10 without associated symptoms.

There was no prior history of headaches. There was a history of hypertension, type II diabetes, coronary artery disease post aortocoronary bypass, and cardiac arrhythmias requiring implantation of a permanent defibrillator-pacemaker. She was taking insulin, metoprolol, clonidine, and lasix.

On examination, the blood pressure in the left arm while sitting was 210/110. Neurological examination was normal except for a left homonymous hemianopsia. A computerized tomography (CT) scan of the brain was consistent with a subacute infarction of the medial right occipital lobe. A carotid ultrasound study was normal.

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**Questions:**

1. How often do headaches occur with transient ischemic attacks (TIAs) and ischemic strokes?
2. What are the features of the headaches?
3. What is the pathophysiology?

### EXPERT COMMENTARY

This patient presents with an ischemic stroke in the distribution of the right posterior cerebral artery. Ischemic strokes in the posterior cerebral artery territory are typically the result of either cardioembolism or embolism from a proximal arterial source, such as the aortic arch or the proximal vertebral or basilar arteries. In this case, the lack of additional diagnostic data does not allow definition of the ischemic stroke subtype. The headache occurs in close temporal proximity with the onset of the neurological deficit and can therefore be considered as part of the entire ischemic stroke syndrome, a true stroke-related or vascular headache.

Headache is an underemphasized symptom of cerebral ischemia, usually overshadowed by the other, more impressive clinical manifestations, such as aphasia, hemiplegia, hemianopsia, or neglect. The reported frequency of headache at onset of cerebral ischemia, also called onset headache, varies widely among studies. This variation is likely the result of

**Table 1.—Frequency of Headache in TIA**

| Study (reference) | Year | Headache frequency (%) |
|---|---|---|
| Medina et al[2] | 1975 | 21 |
| Edmeads[3] | 1979 | 24 |
| Portenoy et al[4] | 1985 | 36 |
| Loeb et al[5] | 1985 | 30 |
| Koudstaal et al[6] | 1991 | 16 |
| Arboix et al[7] | 1994 | 26 |
| Ferro et al[9] | 1995 | 29 |

TIA = transient ischemic attack.

several factors, such as study design (retrospective vs prospective but with retrospective recall of a headache complaint vs prospective with real-time recording of a headache complaint), population studied, type of ischemic event (TIA, minor or major stroke), and time interval elapsed between stroke onset and headache occurrence. Taking into account only the available prospective studies that distinguish between TIA and ischemic stroke by using the classic definitions (keeping in mind that these are subject to revisions in the very near future), the frequency of headache in patients with TIA appears to be about 16-36% (Table 1),[2-9] while in patients with ischemic stroke, headache occurs in approximately 8-34% (Table 2).[3,4,10-15] The frequency of onset headache is significantly lower in ischemic stroke compared with intraparenchymal hemorrhage.[4,7,10-15] It is also very likely that the frequency of onset headache in ischemic stroke is underestimated, as patients with language dysfunction, altered mental status, or other factors preventing reliable determination of a headache complaint are excluded from most studies.

The topography of the ischemic event apparently plays a major role in headache production, as onset headache is significantly more frequent with ischemic events in the posterior than in the anterior circulation (15-65% vs 8-46%).[3,6,7,10,11,14,16,17] With cortical involvement of indeterminate vascular territory, onset headache occurs with intermediate, between anterior and posterior circulation, frequency, while its frequency is the lowest in subcortical infarction.[10]

Defining the frequency of headache according to ischemic stroke etiology or subtype is a very challenging task, because the continuous evolution of neuroimaging and other diagnostic techniques allows for better classification of ischemic stroke, and ischemic strokes previously classified as of undetermined cause or of a specific determined cause, may often be reclassified. In addition, none of the available studies has used a systematic, simple, and reproducible classification scheme, such as the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification,[18] and this makes analysis of the available data difficult and often unreliable.

Clinicians often consider that occurrence of headache at the onset of neurologic deficit in ischemic stroke indicates brain embolism, usually cardioembolism. This view, however, is challenged by the findings of large prospective studies. For example, in a large series and review of cerebral embolism,[19] onset headache was reported by only 18% of patients (mild in 10%, severe in 8%). In the Harvard Cooperative Stroke Registry, onset headache occurred in 9% and sentinel (premonitory) headache in 5% of patients with embolic infarctions (embolism here was defined as either cardioembolism or artery-to-artery embolism),[10] figures that are similar to those of atherothrombotic strokes. Similarly, others[11] found headache in 14% of patients with embolism (vs 26% in large vessel disease), or[7] in 39% of cardioembolic strokes (vs 41% in atherothrombotic ones). And a more recent large series found no association of headache with ischemic stroke etiology.[20] Thus, the fre-

**Table 2.—Frequency of Onset Headache in Acute Ischemic Stroke**

| Study (reference) | Year | Headache frequency (%) |
|---|---|---|
| Mohr et al[10] | 1978 | 8 |
| Edmeads[3] | 1979 | 25 |
| Portenoy et al[4] | 1985 | 29 |
| Gorelick et al[11] | 1986 | 17 |
| Koudstaal et al[6] | 1991 | 19 |
| Vestergaard et al[12] | 1993 | 23 |
| Jorgensen et al[13] | 1994 | 28 |
| Arboix et al[7] | 1994 | 31 |
| Kumral et al[14] | 1995 | 16 |
| Ferro et al[8] | 1995 | 34 |
| Rathore et al[15] | 2002 | 22 |

quency of headache in cardioembolic stroke is at least equal to, if not lower, that of in ischemia due to large vessel disease. Consequently, the presence of onset headache cannot be used as a diagnostic indicator of ischemic stroke subtype.

Onset headache is significantly less frequent in lacunar stroke, compared with nonlacunar stroke, with its frequency varying from 1-23%.[7,8,10-12,21,22] Otherwise stated, patients with headache at stroke onset are much less likely to a lacunar than a nonlacunar syndrome,[6] and a lacunar stroke mechanism is a negative predictor of stroke-associated headache.[8] Headache may be more frequent in pure sensory stroke compared with other lacunar syndromes,[7] or in deep brain gray matter or brainstem lacunar infarction than in supratentorial white matter infarction.[23] The above statements are made with the reservation that in most studies, with some exceptions,[22,23] it is uncertain whether diagnostic investigations were performed to accurately define the ischemic stroke subtype. In addition, a history of hypertension is significantly less common among patients with lacunar stroke and headache, the duration of hypertension is longer among subjects without headache, and leukoaraiosis on CT scan is more frequent and severe among patients without headache.[22]

## WHAT ARE THE FEATURES OF THE HEADACHES?

The characteristics of headache of cerebral ischemia vary widely among patients and clinical studies. Older descriptive reports indicate that patients with symptomatic internal carotid artery disease experience only minor or equivocal pain, while patients with lateral medullary infarction typically report severe, nonthrobbing headache, aggravated by coughing and head shaking,[1,3] and those with basilar territory ischemia often have severe, throbbing or "bursting" occipital headache, aggravated by stooping and straining.[1,24,25] Recent systematic prospective studies, however, suggest that in the majority of patients onset headache has nonspecific features.[7,12,13,26]

The headache is equally likely to be abrupt or gradual in onset.[4,26] Most reports suggest that it is lateralized, experienced as unilateral or focal,[7,11,12] although others suggest that bilateral cranial involvement, with more frequent frontal localization, is a more common pattern.[26] Along the same lines, most reports suggest that the severity of onset headache is mild to moderate,[7,11,12] and may rarely become incapacitating,[7,12] while others indicate that the headache is much more likely to be severe (45%) or moderate (39%).[26] In most patients, the character of the headache is rather nonspecific, described most often as either continuous, pressure-like, nonthrobbing (14-94%) or throbbing (17-54%).[4,6,7,26] Other qualities, such as stabbing, burning, wet, "wind" or cold-like, pulsating, or those of intracranial hypertension have also been reported.[7,26]

The severity of the headache is the highest on the first day of stroke and gradually lessens afterwards.[26] Headaches that start after the first day are typically less severe than those starting on day 1.[26] The headache severity is not related to infarct size, stroke localization, arterial blood pressure levels, underlying vascular risk factors, or nitrate or calcium antagonist intake,[7,12,13,26] but in general it is more severe with posterior circulation infarcts,[6,12] and worse when it is located occipitally rather than frontally.[12] If the character of onset headache is classified according to the IHS criteria, it more often has qualities of tension-type headache (43-49%), and less often those of migraine (28-42%).[12,26] The longer the headache persists after the onset of the neurological deficit, the more likely it is to acquire qualities of tension-type headache.[26] Nausea (44%), vomiting (23-40%), photophobia and phonophobia (25%) are frequent accompaniments.[12,26]

The headache often worsens by bending, straining, coughing or jarring the head,[3,26] or with the use of sublingual nitroglycerin,[3] while digital compression of the superficial temporal artery on the side of the headache temporarily eases the discomfort.[3]

It is debated whether the location of headache provides useful information about the vascular site and mechanism in ischemic cerebrovascular disease. While early reports noted specific headache locations with occlusions of specific vessels,[1] such as ipsilateral frontal headache with carotid occlusion or ipsilateral temporal headache with middle cerebral artery thrombosis, subsequent analytical work indicates

that the headache location cannot accurately predict the location of the ischemic event or the affected vessel.[3,4,7,12-14,26] Attempts to localize the infarct or the occluded vessel based on headache location is an exercise fraught with error.[3]

The headache often accompanies the ischemic event (onset headache), and this temporal connection underscores a relationship between the 2 events. Headache can also precede (sentinel headache) or follow the ischemic event by days to years (late-onset headache) and still be related to the pathogenesis of cerebral ischemia. Attention was drawn to the fact that sentinel headache, usually occurring prior to subarachnoid hemorrhage, is not uncommon in cerebral ischemia, occurring in 10-43% of patients.[7,11,12] The reported interval between the headache and the ischemic event may vary widely, ranging from hours to years; in the latter case the headache is probably unrelated to the ischemic event.

The stroke-related headache usually lasts for longer than 1 day. A recent study utilizing daily interviews of stroke patients developing headache recorded a mean duration of 3.8 days.[26] The duration of the headache seems to be the longest in cardioembolic and atherothrombotic infarcts,[7] the shortest in TIAs, and intermediate in lacunar infarcs.[7]

## WHAT IS THE PATHOPHYSIOLOGY?

The mechanisms by which an acute ischemic stroke results in headache are poorly understood. The atherosclerotic process and hemorrhage into atherosclerotic plaques are apparently painless processes.[1] The entire parenchyma of the cerebrum and cerebellum and the intraparenchymal vessels are insensitive to all forms of stimulation.[27] Massive hemorrhage or severe edema complicating an ischemic infarct can cause headache by displacing and stretching pain-sensitive intracranial structures, but the majority of ischemic infarcts are small or moderate in size and uncomplicated by hemorrhage or severe edema, and yet are accompanied by headache. In addition, it has been shown that the occurrence or not of headache and its severity do not correlate with the size of the cerebral infarction.[12,13,26]

The headache associated with ischemic cerebrovascular disease is likely vascular and arises from either the intracranial or the extracranial vessels. The main trunks of the dural arteries, the intracranial segment of the internal carotid artery, the proximal middle cerebral artery, the anterior cerebral artery from its origin to slightly beyond the genu of the corpus callosum, the superior cerebellar artery, the proximal posterior inferior cerebellar artery, the basilar artery, and the vertebral artery were shown to be pain-sensitive,[27-31] while the pial arteries over the superior and lateral convexities of the cerebrum and the cerebellum are insensitive to pain.[27-31] The trigeminal nerve serves as the major afferent pathway transmitting pain messages from the vessels of the circle of Willis and the supratentorial dura matter, whereas the vascular structures of the posterior fossa are supplied by the upper cervical nerves, as well as the vagus and the trigeminal nerve.[27-31] The perivascular nerve fibers contain vasoactive neuropeptides which upon release into the vessel wall increase blood flow and vascular permeability. The origin and distribution of the perivascular afferent fibers explain several of the features of stroke-related headache.[28-30]

It appears therefore that the headache in ischemic stroke is related to some form of stimulation, perhaps electrochemical or mechanical, of the trigeminovascular afferent system. The so far presented epidemiological data also support this concept. It has been extensively and repeatedly documented that patients with headache at the onset of stroke are more likely to have infarcts in the distribution of the posterior rather than the anterior circulation,[16] or, otherwise stated, posterior circulation ischemic events are more often accompanied by headache (Table 3).[6-8,12-14,17] The reasons for this special predilection of posterior circulation ischemic strokes to be accompanied by headache still remain incompletely understood. A denser perivascular innervation of the extracranial and intracranial vessels of the posterior circulation,[30] ischemia of the trigeminal nucleus leading to dysfunction and activation of the trigeminovascular system,[32] ischemia and dysfunction of the serotoninergic nuclei of the brainstem,[33] or even ischemia of the dura (a pain-sensitive structure), which may be partially supplied by the posterior cerebral artery,[34] have been hypothesized to participate in headache production. Unfortunately,

**Table 3.—Headache Frequency in Posterior vs Anterior Circulation Ischemic Stroke**

| Study (reference) | Year | Anterior | Posterior | *P* value |
|---|---|---|---|---|
| Koudstaal et al[6] | 1991 | 13 | 27 | <.00003 |
| Vestergaard et al[12] | 1993 | 46 | 23 | .02 |
| Jorgensen et al[13] | 1994 | 26 | 37 | .007 |
| Arboix et al[7] | 1994 | 26 | 59 | <.0001 |
| Kumral et al[14] | 1995 | 14 | 29 | <.001 |
| Ferro et al[8] | 1995 | 35 | 65 | .0002 |
| Libman et al[16] | 2001 | 8.7 | 15 | .013 |
| Mitsias et al[17] | 2006 | 23.7 | 44.3 | .0001 |

no study has used modern functional or anatomical neuroimaging techniques to support any of these hypotheses and allow correlation of headache production with specific locations or activation patterns of the ischemic lesions.

What triggers the trigeminovascular system in ischemic stroke remains to be defined. Disturbance in blood flow or dilation of pain-sensitive collateral vasculature has been considered, but lack of association between headache and angiographically demonstrated collateral circulation or peri-infarct hyperperfusion,[3] and lack of a positive or negative association between onset headache and cerebral blood flow reduction in stroke,[35] suggests that the headache of ischemic cerebrovascular disease is not secondary to simple intracranial vasodilation and increased flow through collateral channels. Depolarization of the trigeminal system with afferent discharge perceived as pain and release of vasoactive neuropeptides producing subsequent vasodilatation is reasonable explanation.[29,30]

Patients with headache at stroke onset are less likely to have history of hypertension,[16] or had lesser duration of hypertension and less periventricular leukoaraiosis,[22] suggestive of a less severe burden of hypertension on the cerebral vasculature, compared with those without headache. These findings suggest that relatively preserved elasticity and ability of the large cerebral vessels to dilate is a significant factor leading to the development of onset headache. These qualities are related in part to mechanical factors, such as concentric intimal thickening and disrupted internal elastic lamina,[36] and in part to hypertension-induced endothelial dysfunction. The latter may result in inhibition of endothelial nitric oxide synthase (eNOS) causing further vasoconstriction and hypertension.[37,38] Nitric oxide (NO) generation from the endothelium is important to maintain the vasculature in a relaxed state,[36] and eNOS activity in the endothelium causes NO production and smooth muscle relaxation by direct activation of the NO-cyclic guanosine monophosphate pathway, and may be involved in the initial NO-related headache response.[39]

Intravascularly originating triggers, such as circulating hormones, biogenic amines and antiphospholipid antibodies, are potential, albeit controversial, contributors in the production of onset headache in stroke.[40,41] As an example, anticardiolipin antibodies (aCL), especially the IgG isotype, are more frequently found in patients with onset headache.[17] The mechanisms by which aCL contribute to the development of headache are unclear. Most likely this involves a complex activation of endothelial cells resulting in NO and nitric superoxide production[42,43] and enhanced thrombosis.[44]

In summary, onset headache in ischemic stroke likely involves activation of the trigeminovascular system, especially in vessels where it provides denser innervation. Preexisting susceptibility of this system to excitation, perhaps through specific biomechanical properties of the vessels and NO-mediated vascular smooth muscle relaxation, in combination with intravascularly originating triggers are essential for the production of onset headache in ischemic stroke.

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