Headache associated with ischemic cerebrovascular disease

By Hans-Christoph Diener MD (Dr. Diener of the University of Essen received honorariums from Addex Pharmaceuticals, Allergan, Almirall, AstraZeneca, Bayer Vital, Boehringer Ingelheim, Bristol-Myers Squibb, Colucid, Coherex, Menerini, GlaxoSmithKline, Minster, Lilly, MSD, Novartis, Neuroscore, Johnson & Johnson, Pfizer, Sanofi-Aventis, Weber & Weber, and Medtronic for service as an advisor or speaker; financial support from Allergan, Almirall, AstraZeneca, Bayer Vital, GlaxoSmithKline, MSD, and Pfizer for research projects; and honorariums from Amgen as an advisor.)

Originally released July 17, 1995; last updated October 11, 2016; expires October 11, 2019

Introduction

Overview

Headache often accompanies acute ischemic stroke. Observational studies indicate that 15% to 40% of patients with acute ischemic stroke report headache in close temporal relation to the event. The onset headache is more often seen in posterior circulation strokes than in strokes in other vascular territories. The pathophysiology of headache associated with acute ischemic stroke includes edema, hemorrhagic transformation, and changes in the trigeminovascular system.

Key points

• Headache is the leading symptom in subarachnoidal hemorrhage
• Headache is more frequent in ischemic stroke in the posterior circulation than in the anterior circulation
• Acute severe headache with neurologic signs requires cerebral imaging, or lumbar puncture, or both

Historical note and terminology

The first description of a relationship between headache and cerebral vessel occlusive disease dates back to 1664, when Thomas Willis described the neurovascular autopsy findings of a patient with asymptomatic right carotid occlusion. This patient, who died from unrelated causes and never suffered a stroke, had reported head pain on the side opposite the occlusion. At autopsy, Willis found the left carotid and the vertebral arteries dilated up to 3 times the normal size. He hypothesized that this compensatory dilation and increase of blood flow might have been the cause of the patient’s head pain:

For indeed, nature had substituted a sufficient remedy against that danger of an apoplexy; to wit, the vertebral artery on the same side, in which the carotidick was wanting, the bulk of the pipe being enlarged, became thrice as big as both its pipes on the other side: because, the blood being excluded the carotidick, adding it self to the wonted provision of the vertebral artery, and flowing with a double flood into the same belly, had so diluted the channel of that artery above measure. This gentleman, about the beginning of his sickness, was tormented with a cruel pain of the head towards the left side. The cause whereof cannot be more probably assigned, than that the blood excluded from the right carotidick artery, when at first it rushed more impetuously in the left, had distended the membrane... (Willis 1664).

Fisher reported the first extensive study of clinical, arteriographic, and pathologic information as well as detailed descriptions of the headache characteristics in occlusive disease of various cerebral vessels (Fisher 1968). A number of authors subsequently provided detailed, but often conflicting, information on the frequency, features, and pathogenesis of headache in ischemic cerebrovascular disease (Welch and Bousser 2000).

Classifications include the following:

Headache associated with ischemic stroke. The International Headache Society classifies headache associated with ischemic cerebrovascular disease as headache associated with ischemic stroke, usually with acute onset and associated with focal neurologic signs (Headache Classification Committee of the International Headache Society 2013). Diagnostic criteria are as follows: (1) any new headache fulfilling criterion 3, (2) acute ischemic stroke has been diagnosed, (3) evidence of causation demonstrated by at least 1 of the following: (a) headache has developed in very close temporal relation to other symptoms and/or clinical signs of ischemic stroke, or has led to the diagnosis of
ischemic stroke, (b) headache has significantly improved in parallel with stabilization or improvement of other symptoms or clinical or radiological signs of ischemic stroke, (4) not better accounted for by another ICHD-3 diagnosis.

When a new headache occurs for the first time in close temporal relation to a vascular disorder, it is coded as a secondary headache attributed to the vascular disorder. This is also true if the headache has the characteristics of migraine, tension-type, or cluster headache. When a preexisting primary headache is made worse in close temporal relation to a vascular disorder, there are 2 possibilities, and judgment is required. The patient can either be given only the diagnosis of the preexisting primary headache, or can be given both this diagnosis and the diagnosis of headache attributed to the vascular disorder. Factors that support adding the latter diagnosis are as follows: (1) a close temporal relation to the vascular disorder, (2) a marked worsening of the preexisting headache, (3) good evidence that the vascular disorder can aggravate the primary headache, and (4) improvement of the headache after the acute phase of the vascular disorder.

Headache attributed to ischemic stroke (cerebral infarction, IHS 6.1.1) is described as a new headache developing simultaneously with or in close temporal relationship to signs or other evidence of ischemic stroke associated with neuroimaging confirmation of ischemic infarction.

In many cases, the patient has previously fulfilled criteria for migraine with neurologic aura, and the present attack is typical of previous attacks. However, neurologic deficits are not completely reversible within 7 days, and other causes of infarction are ruled out by appropriate investigations.

Migraine-induced stroke. The diagnostic criteria are as follows: (1) the present attack in a patient with 1.2 migraine with aura is typical of previous attacks except that 1 or more aura symptoms persist for longer than 60 minutes; (2) neuroimaging demonstrates ischemic infarction in a relevant area; and (3) symptoms are not attributed to another disorder.

Ischemic stroke in a migraine sufferer may be categorized as a cerebral infarction of another cause coexisting with migraine, a cerebral infarction of another cause presenting with symptoms resembling migraine with aura, or a cerebral infarction occurring during the course of a typical migraine with aura attack. Only the last fulfills criteria for 1.5.4 migrainous infarction.

Coexisting stroke and migraine. A clearly defined clinical stroke syndrome must occur remotely in time from a typical attack of migraine. Stroke in the young is rare, and migraine is common. Clearly, the 2 conditions can coexist without migraine being a contributive factor to stroke. When the 2 conditions coexist in the young, the true pathogenesis of stroke may be difficult to elucidate. A comorbidity of stroke risk in migraine sufferers seems apparent from the case-controlled series (reviewed later in this article), wherein none of the strokes were induced by the migraine attack. This increases the clinical significance of coincident stroke and should serve to raise clinical consciousness to the need for stroke risk factor awareness in all migraine sufferers (Bousser and Welch 2005). A Scandinavian study found a prevalence of migraine of 20.6% in 175 stroke patients. Stroke patients with migraine were younger, had more frequently a patent foramen ovale, and less frequently had atrial fibrillation (Lantz et al 2015). A study from Belgium found a migraine prevalence of 11.2% in 323 stroke patients (Taheri et al 2015).

Stroke with clinical features of migraine. A structural lesion unrelated to migraine pathogenesis presents with clinical features typical of migraine. In symptomatic cases, established structural lesions of the central nervous system or cerebral vessels episodically cause symptoms typical of migraine with neurologic aura. Such cases should be termed symptomatic migraine (Olesen et al 1993). Cerebral arteriovenous malformations frequently masquerade as migraine with aura (Silvestrini et al 1992). Migraine attacks associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) also may be symptomatic of the membrane dysfunction associated with this disorder (Chabriat et al 1995; Davous 1998). Subarachnoid hemorrhage, venous-sinus thrombosis, and viral meningitis can mimic migraine attacks with or without aura in patients who suffer from migraine or who have a family history of migraine.

SMART syndrome. Stroke-like migraine attacks after radiation therapy involve complex migraine attacks with focal neurologic symptoms in patients who undergo cranial irradiation for the treatment of CNS malignancies (Kerklaan et al 2011). Neurologic symptoms can last for days and may include visual loss, weakness, aphasia, confusion, sensory loss, or seizures (Armstrong et al 2014).
Clinical manifestations

Presentation and course

In contrast to the headache of subarachnoid hemorrhage, which is usually explosive and of abrupt onset, the quality of pain in ischemic cerebrovascular disease varies widely. Fisher reported that most patients who had headache related to internal carotid artery disease had pain that was so minor or equivocal that it scarcely warranted mention (Fisher 1968). In contrast, a large proportion of patients with lateral medullary infarction reported severe, nonthrombogenic headache, which in some patients was aggravated by coughing and head-shaking. Patients with vertebrobasilar insufficiency usually reported throbbing or “bursting” frequently occipital headaches accentuated by stooping and straining (Williams and Wilson 1962).

The headache of ischemic cerebrovascular disease is equally likely to be abrupt or gradual in onset (Portenoy et al 1984). It is usually unilateral, focal, and of mild to moderate severity (Gorelick et al 1986; Vestergaard et al 1993; Arboix et al 1994); however, a significant proportion of patients (25% to 46%) may have incapacitating pain (Arboix et al 1994). Some patients present with thunderclap headache (Lopes Azevedo et al 2011). The majority of patients stated that the headache had a nonspecific character and described it as either throbbing (17% to 54%) or continuous and nonthrombogenic (14% to 94%) (Portenoy et al 1984; Vestergaard et al 1993; Arboix et al 1994). Rarely, it may be felt as stabbing, pulsating, or having clinical features similar to intracranial hypertension (Arboix et al 1994). It is frequently associated with nausea (44%), vomiting (23%), and photophobia and phonophobia (25%). One study investigated headache as a symptom at stroke onset in 4431 patients with ischemic stroke <55 years (Kropp et al 2013). Headache at stroke onset was more common during ischemic stroke in females, younger patients, with greater size of the acute lesion, and if the posterior cerebral artery or vertebrobasilar system were affected.

The headache is usually worsened by bending, straining, or jarring the head. Transient worsening can also occur with the use of sublingual nitroglycerin. Digital compression of the superficial temporal artery on the side of the headache temporarily eases the discomfort.

The headache often accompanies the ischemic event, and this juxtaposition strongly suggests a relationship between the 2 events. However, in addition to the so-called onset headache, defined as temporally surrounding the neurologic deficit, several authors have suggested that the headache can either precede or follow the ischemic event by days to years (sentinel and late-onset headache, respectively) and still be related to the pathogenesis of cerebral ischemia.

Fisher indicated that the majority of patients have headache onset that coincides with the symptoms of ischemia in either the anterior or the posterior circulation (Fisher 1968). Subsequent reports estimate the frequency of onset headache to be between 8% and 34% (mean 26%) (Medina et al 1975; Ferro et al 1995a; Ferro et al 1995b; Mitsias and Jensen 2005; Evans and Mitsias 2009), but studies indicate differences of timing between headache onset and onset of neurologic deficit. Headache is rarely the initial symptom of transient carotid ischemia but commonly begins either in association with other neurologic symptoms or after the attack resolves (Grindal and Toole 1974). It is a constant feature in only one third of patients who experience more than 1 carotid transient ischemic attack; it is present in the majority of patients with recurrent vertebrobasilar ischemia (Grindal and Toole 1974). Patients with larger artery thrombosis develop onset headache more frequently than patients with embolic or lacunar infarcts (Mohr et al 1978). The duration of the headache is longest in cardioembolic and thrombotic infarcts, shortest in transient ischemic attacks, and of medium duration in lacunar infarction (Arboix et al 1994; Rothrock 2014).

Sentinel headache, which usually occurs prior to subarachnoid hemorrhage, is also not an uncommon symptom of cerebral ischemia. The reported interval between the headache and the ischemic event varies widely, ranging from a few hours to years; however, when the latter is the case, the headache is conceivably unrelated to the ischemic event. The headache is usually unilateral and focal and lasts more than 24 hours (Gorelick et al 1986). The side and duration do not differ significantly among stroke subtypes. Sentinel headache occurs in 10% to 43% of patients with ischemic stroke (Gorelick et al 1986). It is more frequent in cardioembolic infarcts (22%) than in transient ischemic attacks, lacunar infarcts, or thrombotic infarcts. In embolic infarctions, in particular, sentinel headache is mostly unilateral, of sudden onset, and can precede the onset of the neurologic deficit by 24 to 72 hours (Fisher and Pearlman 1967).

Late-onset vascular headaches associated with ischemic cerebrovascular disease are ill-defined. According to Medina and colleagues, these are observed frequently in patients with transient ischemic attacks (52%); they begin a few days to a year after the ischemic event, and a significant proportion of them (39%) are throbbing (Medina et al 1975). Some
of these headaches may be given undeserved significance, as their association with ischemia is unclear. It is possible that the transient neurologic symptoms are due to migraine aura rather than to transient ischemic attacks, or even that ischemia activates a preexisting migraine tendency.

Headache is more frequent when ischemic events involve the posterior circulation (29% to 75%) than when they involve the anterior circulation, where headache occurs in 14% to 59% of patients (Grindal and Toole 1974; Medina et al 1975; Koudstaal et al 1991; Mitsias and Ramadan 1992; Vestergaard et al 1993; Jorgensen et al 1994; Kumral et al 1995; Mitsias and Jensen 2005). Headache occurs with an intermediate frequency when the vascular topography is indeterminate (33%). Headache is also more common when there is cortical involvement (56%) than when there are subcortical infarctions (26%) (Arboix et al 1994). Arboix and colleagues recorded headache in 484 patients with lacunar strokes; 9.3% presented headache within a 72-hour interval of stroke onset. Intensity of headache was mild in severity and poorly localized (Arboix et al 2005).

Jorgensen reported that headache was lateralized in 46% of patients, being ipsilateral to the stroke in 68% of these patients and contralateral in 32% (Jorgensen et al 1994).

Headache occurs in 10% to 31% of patients with symptomatic atherothrombotic disease of the internal carotid artery (Silverstein and Hollin 1965). However, most patients experience no pain regardless of the severity and duration of the neurologic symptoms. The headache is usually frontal and lateralized, but frontal nonlateralized, fronto-occipital, and cervico-occipital pain has also been reported. Discomfort over the carotid area in the neck may occur but is rare (Fisher 1968).

The typical pain of middle cerebral artery stem thrombosis is located behind, in, and above the corresponding eye. It is usually steady and may precede, accompany, or develop during ischemia (Fisher 1968). In contrast, middle cerebral artery embolism is more likely to produce headache on the side of the head above the temple (Fisher 1968). Headache occurs in 10% to 39% of patients with middle cerebral artery occlusive disease (Silverstein and Hollin 1965) and is more common with thrombosis than with embolism (Fisher 1968).

In anterior cerebral artery occlusive disease, the incidence of headache ranges from 0% to 18% (Bogousslavsky and Regli 1990). The headache is usually severe and bifrontal, unilateral frontal, or even bioccipital.

Between 64% and 90% of patients with posterior cerebral artery distribution ischemia develop headache (Fisher 1968; Brandt et al 2000). It is more frequent with thrombosis than with embolism (Fisher 1968). The headache is usually frontal and lateralized, but less often is frontal nonlateralized, fronto-occipital lateralized or nonlateralized, occipital lateralized or nonlateralized, over the vertex, or in a hat-band distribution (Fisher 1968). Rarely, it may be throbbing and worsen with coughing or head shaking.

Reversible cerebral vasoconstriction syndrome is characterized by the association of severe headache with neurologic symptoms (John et al 2016). Focal neurologic deficits can last for hours, even days, and are fully reversible (Ducros et al 2007; Goddeau and Alhazzani 2013). Angiography shows “string and beads” sign of cerebral arteries. Reversible cerebral vasoconstriction syndrome is treated with nimodipine. This syndrome can also appear 1 to 2 weeks after delivery, and lead to severe headache and stroke (Fugate et al 2012).

The majority of patients (68%) with vertebral artery occlusion and lateral medullary syndrome report head discomfort (Fisher 1968). Two different types of pain are described. The first and less frequent, considered typical of the lateral medullary syndrome, is located in the eye, nose, and cheek and is probably related to ischemia of the nucleus of the descending root of the trigeminal nerve because it is usually succeeded by numbness. The second is probably of arterial origin and is usually suboccipital or occipital and lateralized in location; however, occipital nonlateralized, occipitofrontal, dull frontal, nuchal, or generalized locations have been recorded (Pessin et al 1987). Coughing and head shaking can worsen the pain. Neck ache, centered around the C5 level, is probably secondary to occlusion of the cervical portion of the vertebral artery. Brainstem ischemia can result in indomethacin responsive hemicrania continua (Valenca et al 2007).

Headache is a frequent accompaniment of symptomatic basilar artery occlusive disease. It occurs in 21% to 53% of patients with major or minor basilar syndromes (Williams and Wilson 1962). Most often, it is occipital and can be either lateralized or nonlateralized. Less frequently, it is localized to occipitofrontal or frontal distributions, lateralized or nonlateralized, and rarely, it is described as band-like. Occasionally, there is associated occipital tenderness and neck
stiffness. The pain is throbbing or banging, and it is aggravated by postural changes, stooping, and straining. Commonly, headache is related to the neurologic deficit, but it may persist longer than the other symptoms or even occur independently.

Between 50% and 66% of patients with subclavian steal syndrome complain of pain located either in the cervico-occipital or mastoid regions. It is usually throbbing and precipitated by strenuous exercise and not associated with neurologic deficit (Hennerici et al 1988).

**Prognosis and complications**

The prognosis depends on the primary cerebrovascular condition that caused the headache. Jorgensen and colleagues found that headache has no independent relationship to neurologic outcome and does not alter the overall outcome of ischemic stroke (Jorgensen et al 1994). In contrast, the Taiwan Stroke Registry reported that 7.4% of 11,523 patients with first ever stroke reported new headache (Chen et al 2013). Compared with patients without onset headache, those with onset headache had a lower frequency of stroke in evolution (4.5% vs. 6.7%; adjusted relative risk, 0.64; 95% confidence interval, 0.52-0.79), greater improvement in National Institutes of Health Stroke Scale score on discharge (0.08 vs. -0.20; P=0.02), higher mean Barthel index scores (86.5+/−20.0 vs. 83.9+/−23.3; adjusted difference, 1.43; 95% confidence interval, 0.28-2.89), and a lower frequency of modified Rankin scale higher than 2 (27.6% vs. 31.5%; adjusted relative risk, 0.85; 95% confidence interval, 0.72-0.95) at 1-month follow-up. There was also a trend for better functional outcome in 3- and 6-month follow-up. In a study of 1411 acute stroke patients, the Dijon Stroke Registry found increased early mortality associated with headache at stroke onset only in patients with cerebral hemorrhage, but not in patients with ischemic stroke (Abadie et al 2014).

**Clinical vignette**

A 35-year-old woman was admitted to the emergency room with complaints of unilateral throbbing headache accompanied by nausea, photophobia, and phonophobia. She also reported visual disturbances in the left visual hemifield and left-sided disturbances of sensation. Her history revealed that she had suffered from migraine with aura since the age of 18 years, with 3 to 5 attacks per year. The attending emergency physician suspected a migraine aura and treated the headache with aspirin. The neurologist recorded the history again and learned that in contrast to the past, during this event the neurologic deficits did not develop slowly, within 20 minutes, but were fully developed within a minute. The MRI including diffusion-weighted imaging showed a right posterior circulation stroke. The time interval between onset of symptoms and the correct diagnosis was longer than 3 hours. Therefore, systemic thrombolysis could not be performed. The history further revealed the existence of several vascular risk factors such as smoking, oral contraceptives, obesity, and lack of exercise.

This case shows that the development of aura symptoms usually is slow and not abrupt as in a case of posterior circulation infarct. The headache might be that same as that seen in a typical migraine attack and does not help to differentiate migraine aura, ischemic stroke, or even cerebral hemorrhage.

**Biological basis**

**Etiology and pathogenesis**

The headache of ischemic cerebrovascular disease is classified as a secondary headache because there is a clear underlying etiology: ischemic stroke or transient ischemic attack. Therefore, only its frequency will be analyzed with respect to the etiology of the underlying cerebral ischemia. In many patients, headache in the acute phase of stroke seems to be a reactivation of preexisting primary headache (Verdelho et al 2008). Seifert and colleagues assessed patients with acute ischemic stroke (n = 100) by brain MRI at 3 T including diffusion weighted imaging (Seifert et al 2016). Fifty patients with stroke and headache as well as 50 patients with stroke but no headache symptoms were included. Infarcts were manually outlined and images were transformed into standard stereotaxic space using nonlinear warping. Voxel-wise overlap and subtraction analyses of lesions as well as nonparametric statistics were conducted. Between the headache group as well as the nonheadache group there was no difference in infarct volumes, in the distribution of affected vascular beds, or in the clinical severity of strokes. The headache phenotype was tension-type-like in most cases. Subtraction analysis revealed that in headache sufferers infarctions were more often distributed in 2 well-known areas of the central pain matrix: the insula and the somatosensory cortex. The insular cortex is a well-established region in pain processing. The results suggest that, at least in a subgroup of patients,
acute stroke-related headache might be centrally driven.

**Atherothrombotic cerebral ischemia.** Headaches are frequently associated with atherothrombotic cerebrovascular disease. Gorelick and colleagues reported no statistically significant difference in the frequency of onset headache among patients with disease of the extracranial carotid artery, the carotid siphon, the middle cerebral artery, or the carotid siphon and middle cerebral artery in tandem (Gorelick et al 1986). In the Harvard Cooperative Stroke Registry, onset headache occurred in 12% of patients with large artery thrombotic infarctions, whereas sentinel and late-onset headaches were reported in 10% and 9%, respectively (Mohr et al 1978). Fisher reported headache in 31% of patients with internal carotid artery stenosis or occlusion and in 21% of patients with middle cerebral artery thrombosis (Fisher 1968).

**Cerebral embolism.** It is a common belief that headache is more frequent in embolic infarcts or that headache at the onset of neurologic deficit in ischemic cerebrovascular disease indicates embolism. In a large series of cases of cerebral embolism, McDowell reported onset headache in 18% of patients (McDowell 1972). It was mild in 10% and severe in 8%. In the Harvard Cooperative Stroke Registry, onset headache occurred in 9% of the embolic infarctions, whereas sentinel and late-onset headache occurred in 5% and 11% of the patients, respectively (Mohr et al 1978). These figures are similar to those associated with atherothrombotic stroke. Fisher reported that only 14% of patients with middle cerebral artery artery embolism had headache, in contrast to 21% of those with middle cerebral artery thrombosis (Mohr et al 1978). Posterior cerebral artery thrombotic infarcts also were more likely to cause headache than embolic posterior cerebral artery occlusion. Thus, these data indicate that, in embolic infarcts, headache is equally or perhaps even less frequent compared with atherothrombotic.

**Lacunar infarcts.** There are conflicting reports regarding the incidence of headache in patients with lacunar infarcts. Fisher reported headache in only 4 of 70 patients with pure motor hemiplegia and in only 1 of 36 patients with pure sensory stroke (Fisher 1968). Atkinson and Appenzeller suggested that small intracerebral arterioles are not innervated, and, therefore, disease of these vessels would not be expected to cause headache (Atkinson and Appenzeller 1975). Several studies indicated that headache is an infrequent accompaniment of lacunar infarction, occurring in 3% to 6% of patients (Mohr et al 1978). Other studies indicated that headache is not such an uncommon occurrence in lacunar infarction, because 10% to 23% of their patients reported onset headache (Portenoy et al 1984; Salgado and Ferro 1995). Notably, 27% of the patients with headache accompanying small deep infarcts also reported symptoms suggestive of cortical dysfunction, such as aphasia or visual field deficits (Koudstaal et al 1991). Thus, the difference in the frequency of headache with lacunar infarction in the above-mentioned series could be related, at least in part, to different definitions of this condition. In a cohort of 387 patients with neuroimaging-proven acute lacunar infarction collected from a prospective, hospital-based stroke registry over a 12-year period, 43 patients (11.1%) presented with headache within a 72-hour interval of stroke onset (Arboix et al 2006). Headache was more common in deep brain gray matter or brainstem lacunar infarction than in supratentorial white matter lacunar infarction (14.9% vs. 8%, P < .033), but lacunar infarctions in the supratentorial white matter less frequently had absence of limitation at discharge (15.1% vs. 25.1%, P < .013). In deep brain gray matter or brainstem lacunar infarction, early neurologic recovery decreased from 26.2% to 19.2% when headache was present at stroke onset. In the multivariate analysis, dysarthria-clumsy hand and absence of headache in deep brain gray matter or brainstem lacunar infarction were independent predictors of favorable outcome.

Headache after stroke can be induced by drug treatment. Nitrous oxide donors frequently cause headache. Dipyridamole given in combination with acetylsalicylic acid can cause headache in the first days of use (Diener et al 1996).

The mechanism of headache in ischemic cerebrovascular disease is poorly understood. The basic atherosclerotic process, regardless of its site, is always or almost always painless (Fisher 1968). The entire parenchyma of the cerebrum and cerebellum, including the intraparenchymal vessels, is insensitive to all forms of stimulation (Ray and Wolff 1940). Massive hemorrhage or severe edema complicating an ischemic infarct can cause head pain by displacing and stretching pain-sensitive intracranial structures. Many ischemic infarcts are not massive, however, and are not complicated by hemorrhage or severe edema but are accompanied by headache.

The headache associated with ischemic cerebrovascular disease is presumably vascular in origin, arising from either the intracranial or the extracranial vessels. By applying direct mechanical or electrical stimulation intraoperatively, Ray and Wolff mapped the pain-sensitive intracranial structures (Ray and Wolff 1940). The following arteries were pain-sensitive:
• the main trunks of all the dural arteries (pain localized fairly accurately to the area of stimulation)
• the intracranial segment of the internal carotid artery (pain behind the eye and low in the temple ipsilaterally)
• the middle cerebral artery along its proximal 1 to 2 cm (pain in and behind the eye)
• the anterior cerebral artery from its point of origin to a point 1 cm beyond the genu of the corpus callosum (pain rather poorly localized behind and above the ipsilateral eye)
• 1 of the principal pontine arteries (pain behind the homolateral eye)
• the posterior inferior cerebellar artery in the proximal 1 to 2 cm of its course
• the vertebral artery (pain in a rather diffuse area in the homolateral occiput and subocciput)

The pial arteries over the superior and lateral convexities of the cerebrum and the cerebellum were insensitive to pain.

Another possible mechanism is increased blood pressure in the acute phase of stroke. Hong and colleagues found that elevated systolic blood pressure correlated with headache within the first 24 hours after stroke onset (Hong et al 2003).

Moskowitz and colleagues pointed out that the circumscribed unilateral headache and pain referred to the cutaneous receptive field of the first trigeminal division indicated an important role for the trigeminal nerve in pain transmission and possibly blood flow control (Moskowitz 1984; Moskowitz 1986). Moskowitz and his coworkers demonstrated that the pial nerve fibers were of trigeminal origin and that the perivascular nerve fibers contained vasoactive neuropeptides (eg, calcitonin gene-related peptide, substance P), which, on release into the vessel wall, increase blood flow and vascular permeability. The origin and distribution of the perivascular afferent fibers explain several unique features of vascular headache. For example, the predominantly ipsilateral distribution of trigeminal fibers explains the strictly ipsilateral distribution in many vascular headaches. In addition, the bilateral innervation of certain vessels (eg, anterior cerebral artery) explains the bilateral or even contralateral location of the headache in diseases affecting these vessels. Moreover, the dual innervation of the superior cerebellar artery and the rostral basilar artery (ie, from the upper cervical roots and the trigeminal fibers) provides an anatomical explanation for the coexistence of occipital and frontal headaches. Finally, the observation that some dural and pial arteries receive divergent axon collaterals from single trigeminal neurons may account for the difficulty in distinguishing the source of pain in vascular headache. The same sensory ganglia would discharge with appropriate stimulation in both circulations.

Mitsias and colleagues analyzed prospectively collected data relevant to headache occurring at ischemic stroke onset in consecutive patients included in the Henry Ford Hospital Stroke Data Bank (Mitsias et al 2006). Three hundred and seventy-five patients had complete headache and clinical data sets and were included in the analysis (headache, n=118; no headache n=257). Multivariate analysis revealed that the independent predictors of headache were: infarct in the distribution of the posterior circulation (P=0.0076, odds ratio 2.15), absence of history of hypertension (P=0.0106, odds ratio 0.48), and treatment with warfarin at the time of the index stroke (P=0.0135, odds ratio 4.89). The occurrence of headache at onset of ischemic stroke was determined by posterior circulation distribution of the ischemic event, absence of a history of hypertension, and treatment with warfarin at the time of the index stroke. These results suggest that preserved elasticity and maintenance of the intracranial vasculature in a relaxed state, in combination with coagulation system derangements, and activation of dense perivascular afferent nerves play a role in the pathogenesis of onset headache.

These discoveries indicate that headache in cerebrovascular disorders is mostly related to electrochemical or mechanical stimulation of the trigeminovascular afferent system. The evidence that posterior circulation ischemic events are more often associated with headache and the suggestion that the posterior circulation is more densely innervated by the trigeminovascular system support the above theory. What triggers the trigeminovascular system in ischemic stroke remains to be determined.

Other possible triggers could originate intravascularly. Circulating hormones, biogenic amines, and antiphospholipid antibodies have all been considered in the pathogenesis of headache in ischemic stroke, but their precise role has yet to be determined. Platelet aggregation, the products of the "release reaction" including serotonin and prostaglandins, and the primary and secondary effects of these products on pain-sensitive vessels also have been incriminated in
migraine. A similar mechanism may operate in ischemic cerebrovascular disease, where platelets play a more significant and prominent role.

Castillo and colleagues reported that elevated plasma and CSF glutamate levels and decreased plasma and CSF taurine levels were found in patients with headache during the acute phase of ischemic cerebrovascular disease (Castillo et al 1995). These findings suggest that during cerebral ischemia the release of excitatory amino acids in combination with the decrease of taurine (which may carry postsynaptic inhibitory effects) may lead to excessive spontaneous depolarization and a state of neuronal hyperexcitability, possibly promoting pain mechanisms. The excessive release of glutamate may also modify the cerebral circulation by intermediate mechanisms, acting as a major stimulus for the production of nitric oxide and resulting in local increases in cerebral blood flow and arteriolar vasodilation.

None of the above mechanisms can explain the occurrence of headache in lacunar strokes, as the intracerebral arterioles are not innervated, and disease of such vessels would not be expected to cause headache. Nevertheless, Koudstaal and colleagues found that 27% of patients with headache accompanying small deep infarcts also reported symptoms suggestive of cortical ischemia. This suggests that the infarct was probably caused by occlusion of the stem of 1 major cerebral artery, resulting in ischemia of the territory of the deep perforators so that the headache occurred because the large vessel was involved (Koudstaal et al 1991).

Epidemiology"

**Transient ischemic attack and minor stroke.** Headache has been reported in 16% to 65% of patients with transient ischemic attack and minor stroke (Grindal and Toole 1974; Medina et al 1975; Ferro et al 1995a; Ferro et al 1995b). In a retrospective analysis, Grindal and Toole reported headache in 25% of patients with transient ischemic attacks (Grindal and Toole 1974). The authors considered this figure to be an underestimate because of the retrospective nature of the study and because only 21% of the patients gave a definite negative history of headache. In contrast, Medina and colleagues reported headaches in 65% of 34 prospectively evaluated patients with transient ischemic attacks (59% in the anterior and 75% in the posterior circulation) (Medina et al 1975). Onset headache occurred in only 44%, however. In a prospective study, Edmeads found headache in 26% of patients with carotid transient ischemic attack and in 17% of patients with vertebrobasilar transient ischemic attack (Edmeads 1979). Portenoy and colleagues reported headache in 10 of 28 (36%) prospectively evaluated patients with transient ischemic attack (Portenoy et al 1984). In the study by Loeb and colleagues, headache occurred in 30% of transient ischemic attack patients; there was no difference between headache and nonheadache patients with regard to gender and age (Loeb et al 1985). The headache prevailed in patients with vertebrobasilar transient ischemic attack. In the Dutch transient ischemic attack prospective trial, headache occurred in 18% of 3126 patients with acute cerebral and retinal ischemia and was equally common among patients with minor stroke (19%), reversible ischemic neurologic deficit (18%), and transient ischemic attacks (16%) (Koudstaal et al 1991). Arboix and colleagues found headache in 39% of 31 patients with transient ischemic attack (Arboix et al 1994). The mean age of this study population was 66±13.5 years.

**Transient ischemic attack and completed ischemic stroke.** In a large series including patients with both transient ischemic attacks and cerebral infarcts, Fisher found that 31% of patients with internal carotid stenosis or occlusion (proven by pathologic or arteriographic examination), had headache, independent of whether they had transient ischemic attacks, a minor stroke, or a major neurologic deficit (Fisher 1968). Headache was reported by 44% and 35% of patients with basilar territory infarcts or transient ischemic attacks, respectively. In the Harvard Cooperative Stroke Registry, headache occurred at the onset of the ictus in 9% of patients with cerebral embolism, in 12% of those with large artery thrombosis, and in 3% of patients with lacunar infarcts (Mohr et al 1978). Headache preceding the ischemic event occurred in 10% of patients with large artery thrombosis, in 5% with embolic infarcts, and in 6% with lacunar infarcts, whereas the figures for headache following the event were 9%, 11%, and 2%, respectively. Edmeads found headache in 25% of prospectively evaluated patients with either transient ischemic attacks or ischemic infarcts admitted to the stroke unit of a university medical center (Edmeads 1979). Patients with aphasia or other factors that prevented reliable determination of whether headache occurred were excluded. Portenoy and colleagues reported headache in 29% of consecutive patients with ischemic infarcts and in 36% with transient ischemic attacks who were evaluated prospectively at 2 teaching hospitals in New York (Portenoy et al 1984). After analysis of data derived from a stroke registry at 2 inner-city referral hospitals in Chicago, Gorelick and colleagues reported onset headache in 17% of patients with ischemic stroke (Gorelick et al 1986). Patients with vertebrobasilar
occlusive or embolic disease and nonatherosclerotic strokes were excluded. Vestergaard and colleagues reported headache in 26% of 214 patients with cerebral infarction (Vestergaard et al 1993), whereas Arboix and colleagues found headache in 32% of 195 patients with ischemic stroke (Arboix et al 1994). Hansen and colleagues followed 299 consecutive stroke patients for 6 months and observed new headaches in 13.1% (Hansen et al 2012). In a large prospective study including 867 patients with ischemic and hemorrhagic stroke, Jorgensen and colleagues indicated that headache occurred in 25% of the patients with ischemic stroke (Jørgensen et al 1994). It was more frequent when the vertebrabasilar circulation was involved (37%), whereas fewer patients (26%) with carotid territory ischemia experienced headache. Women developed headache more frequently than men (31% vs. 25%). Patients with headache and ischemic stroke tended to be younger than patients without headache (71.4 ±12 years vs. 74.1 ±11 years). In a community study, 27.4% of 402 patients with ischemic stroke complained of headache (Rathore et al 2002). In a study of 2196 patients with transient ischemic attack or ischemic stroke, headache occurred in 27% of the patients (Tentschert et al 2005). In a multivariate analysis, headache at stroke onset was correlated with female gender, a history of migraine, younger age, and lower blood pressure at admission.

Hansen and colleagues followed 256 patients 3 years after a stroke for persistent novel headache following stroke (Hansen et al 2015). Twelve percent (26/222) of patients reported new persistent headache. The headache was tension-type-like in 50%, migraine-like in 31%, and fulfilled criteria for medication overuse in 6%.

The difference in the frequency of headache among the quoted studies is related to several factors, such as the study population, stroke subtype, nature of the study (prospective vs. retrospective), method of data collection, and inclusion criteria. With the exception of those studies that included only patients with transient ischemic attack, the frequency of headache in patients with ischemic cerebrovascular disease appears to be underestimated. Patients with language dysfunction, altered mental status, or other factors preventing reliable determination of a headache complaint were excluded from most studies. In addition, patients with severe sensory loss, preventing or modifying the headache; memory loss; and pain asymbolia as part of the acute stroke syndrome may negate the complaint of the headache, and this results in an overall lower frequency of headache. On the other hand, pre-CT scanning studies used clinical criteria alone to differentiate ischemia from hemorrhage; therefore, some hemorrhagic strokes could have been included in the ischemic category, thus, increasing the estimated frequency of headache in that group.

**Prevention**

Prevention of ischemic cerebrovascular disease, with antiplatelet drugs and anticoagulants, depending on the mechanism and vascular structures involved, would be expected to decrease the occurrence of this type of headache. Whether pretreatment with antiplatelet agents or antimigrainous medications (such as beta-blockers, calcium antagonists, or anticonvulsants) alters the frequency of headache at the onset of stroke remains to be determined.

**Differential diagnosis**

The differential diagnosis includes migraine with aura (especially hemiplegic migraine) and the major differential diagnoses of headache related to transient ischemic attacks. A subgroup of migraine patients with unilateral motor symptoms and migraine will present with motor weakness outside of migraine attacks. About 40% of these patients are diagnosed with stroke (Young et al 2007). The mode of evolution of the neurologic deficit and the accompanying headache, the history of prior similar attacks, the possible family history of a similar problem, and frequently the negative diagnostic workup will point toward that diagnosis. Migraine-induced stroke enters the differential diagnosis in cases where the neurologic deficit is long-lasting. In these cases, the patient has previously fulfilled criteria for migraine with neurologic aura, and the present attack is typical of previous attacks. However, neurologic deficits are not completely reversible within 7 days, neuroimaging demonstrates ischemic infarction in the relevant area, and other causes of infarction are ruled out by appropriate investigations (Welch and Levine 1990).

Headache with neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL) can present with stroke-like manifestations before the diagnosis is verified by lumbar puncture (Aries et al 2008). The condition has a good prognosis with full recovery from neurologic symptoms, and neuroimaging shows normal results. Perfusion CT might help to differentiate HaNDL from acute ischemic stroke (Pettersen et al 2008).

Drugs used in the acute phase of stroke and for secondary stroke prevention can cause headache. This is true for nitrates used for angina pectoris and dipyridamole used for secondary prevention (Diener et al 1996; Lindgren et al 2004). In a randomized trial, transdermal glyceryl trinitrate resulted in headache in 15% of patients with acute stroke
Compared to 0% with placebo (Rashid et al 2003). Headache due to dipyridamole use is more frequent in patients suffering from migraine (Kruuse et al 2006) and can be prevented in part by an initial dose reduction and titration (Chang et al 2006; Diener and Davidai 2007; Douen et al 2008). The female sex, transient ischemic attack, absence of hypertension, and nonsmoking are predictors of headache from aspirin plus dipyridamole (Halkes et al 2009; Lokk 2009). However, a randomized open study with 114 patients failed to show that slower than standard dose escalation reduces drug-induced headache frequency (de Vos-Koppelhaar et al 2014). Interestingly, stroke patients who develop dipyridamole-induced headache have a better long-term prognosis for recurrent stroke, indicating preserved cerebrovascular function (Davidai et al 2014).

Cardiac evaluation with electrocardiography, Holter monitor, and transesophageal echocardiography may exclude or even conventional cerebral angiography should be considered, according to the clinical presentation. Vascular studies, including B-mode carotid and transcranial ultrasonography, magnetic resonance angiography, or cerebral angiography may exclude subarachnoid hemorrhage, central nervous system infection, or extent of the ischemic infarct. Cerebrospinal fluid analysis may exclude subarachnoid hemorrhage, central nervous system infection, or extent of the ischemic infarct. Neuroimaging studies (CT, MRI, MRA, or CTA) are necessary to evaluate the possibility of intracerebral hemorrhage, subarachnoid hemorrhage, aneurysm, or cerebral neoplasm and to evaluate the location, vascular distribution, and extent of the ischemic infarct. Cerebrospinal fluid analysis may exclude subarachnoid hemorrhage, central nervous system infection, or primary CNS angiitis.

Vascular studies, including B-mode carotid and transcranial ultrasonography, magnetic resonance angiography, or even conventional cerebral angiography should be considered, according to the clinical presentation. Cardiac evaluation with electrocardiography, Holter monitor, and transesophageal echocardiography may exclude or

---

**Diagnostic workup**

There is no specific diagnostic workup for the headache itself. The diagnostic evaluation should be directed toward identifying the location, vascular distribution, and mechanism of the ischemic cerebrovascular disease. This should include hematological testing, with particular attention to red cell count and hemoglobin as well as platelet function. If necessary, especially in young patients or patients with cryptogenic stroke, testing for anticardiolipin antibodies, lupus anticoagulant, antithrombin III, and protein C and S should be considered.

Neuroimaging studies (CT, MRI, MRA, or CTA) are necessary to evaluate the possibility of intracerebral hemorrhage, subarachnoid hemorrhage, aneurysm, or cerebral neoplasm and to evaluate the location, vascular distribution, and extent of the ischemic infarct.

Cerebrospinal fluid analysis may exclude subarachnoid hemorrhage, central nervous system infection, or primary CNS angiitis.

Vascular studies, including B-mode carotid and transcranial ultrasonography, magnetic resonance angiography, or even conventional cerebral angiography should be considered, according to the clinical presentation.

Cardiac evaluation with electrocardiography, Holter monitor, and transesophageal echocardiography may exclude or
confirm a cardiogenic or aortic source of cerebral embolism.

**Management**

No specific information is available concerning the specific treatment of headache associated with ischemic cerebrovascular disease. When hemorrhage is excluded, headache can be treated with acetylsalicylic acid or acetaminophen. **Triptans** are contraindicated. If antihypertensive treatment is indicated in stroke patients with a history of migraine, beta-blockers are preferred over calcium-channel blockers (Webb and Rothwell 2012).

**Special considerations**

**Anesthesia**

No specific anesthesia requirements have been reported. These depend on the primary cerebrovascular condition.

**References cited**


Bousser MG, Welch KM. Relation between migraine and stroke. Lancet Neurol 2005;4(9):533-42. PMID 16109360

82. PMID 10773642


Chang YJ, Ryu SJ, Lee TH. Dose titration to reduce dipyridamole-related headache. Cerebrovasc Dis 2006;22(4):258-62. PMID 16788299


Grindal AB, Toole JF. Headache and transient ischemic attacks. Stroke 1974;5:603-505. PMID 4413633


Kruuse C, Lassen LH, Iversen HK, Oestergaard S, Olesen J. Dipyridamole may induce migraine in patients with migraine without aura. Cephalalgia 2006;26(8):925-33. PMID 16886928


Stroke Cerebrovasc Dis 2003;12(3):143-51. PMID 17903919


Rist PM, Diener HC, Kurth T, Schurks M. Migraine, migraine aura, and cervical artery dissection: a systematic review and meta-analysis. Cephalalgia 2011;31(8):886-96. PMID 21511950


Runchev S, McGee S. Does this patient have a hemorrhagic stroke: clinical findings distinguishing hemorrhagic stroke from ischemic stroke. JAMA 2010;303(22):2280-6. PMID 20530782


Sibert PL, Mokri B, Schievink WI. Headache and neck pain in spontaneous internal carotid and vertebral artery dissections. Neurology 1995;45:1517-22. PMID 7644051


Welch K, Levine SR. Migraine-related stroke in the context of the International Headache Society classification of head

Williams D, Wilson TG. The diagnosis of the major and minor syndromes of basilar insufficiency. Brain 1962;85:741-74. PMID 14000840


**References especially recommended by the author or editor for general reading.

**Former authors
K Michael A Welch MD (original author) and Panayiotis Mitsias MD

**ICD and OMIM codes

**ICD codes

ICD-9:
Headache, unspecified: 784.0

ICD-10:
Headache: R51

**Profile

**Age range of presentation

02-05 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance

male=female

**Family history

none

**Heredity

none

**Population groups selectively affected

none selectively affected

**Occupation groups selectively affected

none selectively affected
Differential diagnosis list

migraine with aura
hemiplegic migraine
migraine-induced stroke
Headache with neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL)
headache due to nitrates use
headache due to dipyridamole use
carotid artery dissection
vertebral artery dissection
cluster headache
primary intracerebral hemorrhage
aneurysmal subarachnoid hemorrhage
cerebral arteriovenous malformation
cerebral neoplasia
partial seizures (Todd paralysis)
mitochondrial encephalomyopathies (MELAS and its variants)
MELAS

Other topics to consider

Acute headache: diagnosis
Cerebral embolism
Ischemic stroke
Lacunar infarction
Late-life migrainous accompaniments
Migraine
Migrainous infarction
Stroke associated with myocardial infarction
TIAs (carotid)
Vertebrobasilar transient ischemic attacks

Copyright© 2001-2017 MedLink Corporation. All rights reserved.