Chapter 108

Ischemic Stroke and Spontaneous Intracerebral Hematoma

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HEADACHE IN ISCHEMIC STROKE AND SPONTANEOUS INTRACEREBRAL HEMATOMA

Definitions

International Headache Society (IHS) codes and diagnoses (23):

6.1.1 Headache attributed to ischemic stroke (cerebral infarction)

A. Any acute headache fulfilling criterion C.
B. Neurological signs and/or neuroimaging evidence of a recent ischemic stroke.
C. Headache develops simultaneously with or in very close temporal relation to signs or other evidence of ischemic stroke.

6.1.2 Headache attributed to transient ischemic attack (TIA)

A. Any acute headache fulfilling criteria C and D.
B. Focal neurologic deficit of ischemic origin lasting <24 hours.
C. Headache develops simultaneously with onset of focal deficit.
D. Headache resolves within 24 hours.

6.2.1 Headache attributed to spontaneous intracerebral hematoma

A. Any acute headache fulfilling criterion C.
B. Neurologic signs or neuroimaging evidence of a recent nontraumatic intracerebral hemorrhage.
C. Headache develops simultaneously with or in very close temporal relation to intracerebral hemorrhage.

WHO code and diagnosis: 44.81. Headache associated with other vascular disorders

Headache is one of the primary features of acute focal cerebrovascular disease. A well-known accompaniment of hemorrhagic stroke, especially subarachnoid hemorrhage, headache is an underemphasized symptom of ischemic stroke, because it is usually overshadowed by other more dramatic clinical manifestations, such as aphasia, hemiplegia, hemianopsia, or neglect.

Thomas Willis (1664) first recognized the relationship between headache and cerebrovascular disease in a patient with asymptomatic carotid artery (CA) occlusion who experienced severe headache ipsilateral to the patent CA (63). Extreme dilation in the patent CA circulation, secondary to collateral blood flow, was the postulated cause of headache (63). Three centuries later, Fisher reported the first comprehensive study of headaches associated with ischemic and hemorrhagic cerebrovascular disease (18). Several authors subsequently provided detailed, but often conflicting, data on the frequency, features, pathogenesis, and prognostic value of headache in acute cerebrovascular disease (6,14,16,17,21,27,30,32,36,40,42,45,51,52,60).

ISCHEMIC STROKE AND TRANSIENT ISCHEMIC ATTACKS

Epidemiology

There is wide variability in the reported frequency of headache at onset of ischemic stroke or TIA among studies, due to a variety of factors, including study design (retrospective vs. prospective), population studied (community vs. referral hospitals), type of ischemic event (TIA, minor or major stroke), and time interval from stroke onset to headache occurrence.

Prospective studies on the occurrence of headache in patients with TIA reveal an overall headache frequency of 16 to 36% (6,14,16,17,30,36,40,51) (Table 108-1), while in populations of patients with ischemic stroke, headache occurs in approximately 8 to 34% (6,14,17,21,27,30,32,45, 51,52,60) (Table 108-2). Overall, the frequency of headache at onset of ischemic stroke is significantly lower to

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TABLE 108-1 Frequency of Headache in Transient Ischemic Attacks: Prospective Studies

Study	Year	Headache Frequency (%)
Medina et al. (40)	1975	21
Edmeads (14)	1979	24
Portenoy et al. (51)	1984	36
Loeb et al. (36)	1985	30
Koudstaal et al. (30)	1991	16
Arboix et al. (6)	1994	26
Ferro et al. (16)	1995	29

that associated with intraparenchymal hemorrhage (Table 108-3). However, headache frequency in patients with ischemic stroke may be underestimated when patients with language dysfunction, altered mental status, or other factors preventing reliable determination of a headache complaint are excluded. Also, most patients with severe sensory loss, memory loss, or pain asymbolia as part of the acute stroke syndrome may not report headache (18).

Factors Related to the Occurrence, or Not, of Headache at Onset of Ischemic Stroke

Studies have shown consistently that headache is more frequent in patients with vertebrobasilar territory ischemia as compared to anterior circulation involvement (6,17,27,30,32,34,44,60) (Table 108-4). Individual reports reveal that the following factors may be operant in the onset of headache with cerebral ischemia: female gender (27,51), underlying migraine (17,32,44,51), younger age (6,17,27,44,60), nonsmoking status (17,21,60), absence of hypertension (44), underlying diabetes mellitus (32),

TABLE 108-2 Frequency of Onset Headache in Acute Ischemic Stroke: Prospective Studies

Study	Year	Headache Frequency (%)
Mohr et al. (45)	1978	8
Edmeads (14)	1979	25
Portenoy et al. (51)	1984	29
Gorelick et al. (21)	1986	17
Koudstaal et al. (30)	1991	19
Vestergaard et al. (60)	1993	23
Jorgensen et al. (27)	1994	28
Arboix et al. (6)	1994	31
Kumral et al. (32)	1995	16
Ferro et al. (17)	1995	34
Rathore et al. (52)	2002	22

TABLE 108-3 Headache Frequency in Ischemic Stroke vs. Intraparenchymal Hemorrhage

Study	Year	Ischemia (%)	Hemorrhage (%)	p value
Mohr et al. (45)	1978	3–12	33	
Portenoy et al. (51)	1984	29	57	<0.05
Gorelick et al. (21)	1986	17	55	0.0001
Vestergaard et al. (60)	1993	23	50	
Jorgensen et al. (27)	1994	25	49	0.002
Arboix et al. (6)	1994	32	65	<0.0001
Kumral et al. (32)	1995	16	36	<0.001
Rathore et al. (52)	2002	22	55	0.001

underlying ischemic heart disease (27,30,32), aCL immunoreactivity (44), and treatment with warfarin at the time of occurrence of the index stroke (44). It should be noted that these factors cannot be considered independent for the development of onset headache in ischemic stroke until multivariate confirmatory analyses are conducted.

Headache Characteristics

Intensity and Quality

The headache can be abrupt or gradual in onset (51). It is usually unilateral, focal, and of mild to moderate severity (6,21,60); rarely, it may be incapacitating (6,60). The character of the headache is nonspecific, described as either throbbing (17 to 54%) (6,51,60) or continuous and nonthrobbing (14 to 94%) (6,30,51). Stabbing or pulsating

TABLE 108-4 Headache Frequency in Posterior vs. Anterior Circulation Ischemic Stroke

Study	Year	Anterior (%)	Posterior (%)	p value
Koudstaal et al. (30)	1991	13	27	<0.00003
Vestergaard et al. (60)	1993	23	46	0.02
Jorgensen et al. (27)	1994	26	37	0.007
Arboix et al. (6)	1994	26	59	<0.0001
Kumral et al. (32)	1995	14	29	<0.001
Ferro et al. (17)	1995	35	65	0.0002
Libman et al. (34)	2001	8.7	15	0.013

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character have also been reported (6). Frequently, the headache is accompanied by nausea (44%), vomiting (23%), and photophobia and phonophobia (25%) (60).

Headache severity is not related to the size of infarction or stroke location (6,27,60), but in general it is more severe with posterior circulation infarcts (30,60), and worse when it is located occipitally rather than frontally (60). The headache is usually worsened by coughing, bending, straining, or jarring the head, or following sublingual nitroglycerin (14,18). In contrast, digital compression of the superficial temporal artery on the side of the headache temporarily eases the discomfort (14).

Location

It is debated whether the location of headache provides useful information about the vascular site and mechanism in ischemic cerebrovascular disease. Fisher indicated that the lateralized headache of CA occlusion is usually located in the ipsilateral frontal and orbital regions, while the pain of MCA thrombosis affects the orbital and supraorbital area and that of MCA embolism the ipsilateral temple (18). Others (51) found that headache location did not vary with the type of vascular event and did not predict the location of stroke. Overall, the headache location cannot accurately predict the location of the ischemic event or the affected vessel (6,14,27,32,60), and as Edmeads stated, attempts to localize the infarct or the occluded vessel based on headache location is an exercise fraught with error (14).

Timing and Duration

The headache often accompanies the ischemic event (onset headache), and this temporal connection underscores a relationship between the two events. Headache can also precede (sentinel or premonitory headache) or follow the ischemic event (late-onset headache) and still be related to the pathogenesis of cerebral ischemia.

Fisher (18) reported that in the majority of patients, headache onset coincided with the ischemic symptoms in either the anterior or the posterior circulation. Subsequent reports estimated the frequency of onset headache as 8 to 34% (6,14,16,17,21,27,30,32,42,51,52,60). The mean duration of the headache is the longest in cardioembolic (29.5 hours) and atherothrombotic (26.5 hours) infarcts, shortest with TIAs (17 hours), and of medium duration in lacunar infarction (19.5 hours) (6).

Sentinel or prodromal headache, a well-known feature of subarachnoid hemorrhage, is also described in 10 to 43% of ischemic stroke patients (6,21,60). The interval between the headache and the ischemic event varies widely, ranging from a few hours to days. The sentinel headache is most often unilateral and focal and lasts more than 24 hours (21). The side and duration do not differ among stroke subtypes (21).

It is doubtful that late-onset headache associated with ischemic cerebrovascular disease truly exists. In one report, this form of headache was observed in 52% of patients with TIA, beginning within a few days to 1 year after the ischemic event, and in 39% of patients the headache was throbbing (41). These headaches were likely given undeserved significance and their association with cerebral ischemia is unclear.

Vascular Topography

Headache is significantly more frequent after ischemic events in the posterior than in the anterior circulation (15 to 65% vs. 8.7 to 46% of patients, respectively) (6,14,21, 30,32,45).The frequency is intermediate when the vascular topography is indeterminate cortical involvement and the lowest in subcortical infarction (6) (Table 108-5).

Ischemic Stroke Subtype

Defining the frequency of headache according to ischemic stroke subtype is a challenging task because of the continuous evolution of neuroimaging and other diagnostic techniques leading to reclassification of many ischemic strokes. In addition, none of the available studies has used a systematic, simple, and reproducible classification scheme, such as the TOAST classification (1), and this makes analysis of the available data particularly difficult. With these limitations in mind, the frequency and other features of headache in patients with specific ischemic stroke subtypes are as follows:

Large artery occlusive disease related ischemic stroke: headache accompanies large vessel atheroocclusive stroke with the same, or even perhaps higher,

TABLE 108-5 Headache and Vascular Topography (43)

Affected Vessel	*Headache Frequency (%)*	*Usual Headache Location*
Internal carotid artery	10–31	Ipsilateral frontal
Middle cerebral artery	10–39	Ipsilateral orbital/temporal
Anterior cerebral artery	0–18	Bilateral frontal
Posterior cerebral artery	64–70	Ipsilateral frontal
Vertebral artery	68	Ipsilateral occipital/suboccipital
Basilar artery	21–53	Bilateral/ipsilateral occipital
Amaurosis fugax	0–16	Ipsilateral frontal/orbital

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frequency than other subtypes of ischemic stroke. In large prospective studies, this frequency varies from 12 to 41%. In the Harvard Cooperative Stroke Registry (45), onset headache occurred in 12% of patients with "large artery thrombotic infarctions," while sentinel and late-onset headache were reported in 10% and 9%, respectively. Arboix et al. found that stroke-related headache occurred in 41% of patients with atherothrombotic infarcts (6).

Cardioembolic stroke: Headache at the onset of neurologic deficit in ischemic stroke was thought to be due to brain embolism, usually cardioembolism, but large prospective studies have challenged this belief. For example, in a large series and review of cerebral embolism (39), onset headache was reported by 18% of patients (mild in 10%, severe in 8%). In the Harvard Cooperative Stroke Registry, onset headache occurred in 9%, sentinel headache in 5%, and late-onset headache in 11% of patients with embolic infarctions (45); these figures are similar to those of atherothrombotic stroke. Similarly, Arboix et al. reported headache in 39% of cardioembolic vs. 41% of atherothrombotic infarcts (6).

Lacunar stroke: The frequency of headache is significantly lower in lacunar than nonlacunar strokes. In large series, the headache frequency may vary from 1.3 to 23% (17,21,32,37,45,55,60). Patients with headache at stroke onset less often have a lacunar (OR: 0.55, CI, 0.45–0.66) than a nonlacunar syndrome (30), and a lacunar stroke mechanism is a negative predictor of stroke-associated headache (OR: 0.06, 0.7–0.01) (17). Headache in lacunar stroke cannot be predicted by the clinical characteristics of the stroke (55); however, pure sensory stroke may be more often, and pure motor stroke less often, associated with onset headache (6). Preexisting hypertension is less common among patients with lacunar stroke and headache, and the duration of hypertension is longer among subjects without headache (55). Leukoariosis on computed tomography scan is more frequent and severe among patients without headache (55).

Biologic Basis

The mechanisms of headache in ischemic cerebrovascular disease are poorly understood. The atherosclerotic process and intraplaque hemorrhage are painless processes (18). The cerebral and cerebellar parenchyma and intraparenchymal vessels are insensitive to all forms of stimulation (53). Massive hemorrhage or severe edema complicating ischemic infarction can cause headache by displacing and stretching pain-sensitive intracranial structures, but many ischemic infarcts are of small or moderate size and uncomplicated by hemorrhage or edema, and yet are accompanied by headache. Also, the occurrence of headache and its severity do not correlate with the size of the cerebral infarction (27,60).

Headache associated with ischemic cerebrovascular disease likely arises from the intracranial or extracranial vessels. The main trunks of the dural arteries, the intracranial segment of the internal CA, the proximal MCA and anterior cerebral artery, and the superior cerebellar, proximal posterior inferior cerebellar, basilar, and vertebral arteries are pain-sensitive structures; the pial arteries over the superior and lateral convexities are insensitive to pain (46–48,53). 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, the vagus, and the trigeminal nerves (29,46–48,53). 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 many features of stroke-related headache (46–48). Thus, headache in cerebrovascular disorders is mostly related to electrochemical or mechanical stimulation of the trigeminovascular system. That posterior circulation distribution of the ischemic stroke is an independent factor determining headache at ischemic stroke onset supports this hypothesis. Furthermore, the posterior circulation extracranial and intracranial vessels are more densely innervated by the trigeminal system (29), and ischemia of the trigeminal nucleus leading to dysfunction and activation of the trigeminovascular system may result in headache (2).

Blood flow disturbances or dilation of pain-sensitive collaterals was thought to trigger the trigeminovascular system, but lack of association between headache and angiographically demonstrated collateral circulation or perinfarct hyperperfusion (14), and lack of (positive or negative) association between cerebral blood flow reduction in stroke and headache (38) speak against these hypotheses. Depolarization of the trigeminal system with afferent discharge perceived as pain and release of vasoactive neuropeptides producing subsequent vasodilation is an alternative explanation (47,48). That patients with onset headache are less likely to have preexisting hypertension, shorter duration of hypertension, and less periventricular leukoariosis compared to those without headache suggests that a relatively preserved elasticity and ability of the large cerebral vessels to dilate is a significant factor in its development. These qualities are related partially to mechanical factors (concentric intimal thickening, disrupted internal elastic lamina) (24) and hypertension-induced endothelial dysfunction that results in inhibition of endothelial nitric oxide (NO) synthase (25,31). Intravascularly originating triggers (circulating hormones, biogenic amines, antiphospholipid antibodies) are potential, albeit controversial, contributors in the production of stroke-onset headache (11,15,44). Antiphospholipid antibodies in particular may

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cause a complex activation of endothelial cells, resulting in NO and nitric superoxide production (5,57) and enhanced thrombosis (50).

In summary, onset headache in ischemic stroke likely involves activation of the trigeminovascular system, especially in densely innervated vessels. 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.

INTRACEREBRAL HEMATOMA

Epidemiology

Recent studies, which were performed after the availability of modern neuroimaging techniques, paint a rather different picture from the previously held belief that most patients with intracerebral hemorrhage (ICH) have headache. For example, in the Harvard Cooperative Stroke Registry (45), headache at onset of the deficit was reported by only 33% of patients sufficiently alert to be interviewed. Subsequent reports on unselected patients with ICH indicate that 33 to 65% of patients with intraparenchymal hemorrhage have headache in close temporal association with the ictus (6,21,27,32,42,51,52,60). It is plausible that the frequency of headache in ICH is underestimated because of the exclusion of patients who are insufficiently alert for interview. Studies that included populations with both ischemic and hemorrhagic stroke indicate that the frequency of headache is significantly higher in patients with hemorrhage than in those with ischemia (6,14,18,21,23,27,30,32,36,40,45,51,52,60,63) (Table 108-6).

Melo et al. indicated that the predictors of headache at onset of ICH were meningeal signs, cerebellar or lobar location of the hematoma, transtentorial herniation, and female gender (42). Hematoma volume is not an independent predictor of headache (42) (Table 108-7).

TABLE 108-6 Frequency of Onset Headache in Intracerebral Hematoma: Prospective Studies

Study (reference)	*Year*	*Headache Frequency (%)*
Mohr et al. (45)	1978	33
Gorelick et al. (21)	1986	55
Vestergaard et al. (60)	1993	50
Jorgensen et al. (27)	1994	49
Arboix et al. (6)	1994	65
Kumral et al. (32)	1995	36
Melo et al. (42)	1996	57
Rathore et al. (52)	2002	56

TABLE 108-7 Predictors of Headache in Intracerebral Hematoma* (42)

Meningeal signs
Cerebellar or lobar hematoma localization
Transtentorial herniation
Female gender
Age <70 yr

*Determined by logistic regression analysis.

Clinical Manifestations

Headache Features

Twenty to 70% of patients with ICH-related headache report severe headache (6,21). In 70% it is unilateral (21), and in 48 to 93% it is focal (6,21). Focal headaches, as well as headaches with features of intracranial hypertension, are frequent and incapacitating (27). The headache quality is variably described as either steady or throbbing. The onset headache of ICH is often accompanied by vomiting, experienced by 38% of patients (vs. 6.5% in ischemic stroke) (6). In the vast majority of patients, the headache lasts more than 24 hours (6,21).

Timing

In the majority of patients with headache related to ICH, the headache occurs at the onset of the ictus, in close temporal connection with the onset of the neurologic deficit. This onset headache occurs in 33 to 65% of patients (6,21,32,42,45,52,60).

A smaller proportion of patients with ICH may develop a sentinel headache in the days to weeks before the onset of the neurologic deficit. Sentinel headache occurs in 7 to 16% of patients (6,21,42), is almost always focal (21), lasts for more than 24 hours (6,21), and is significantly more frequent with ICH (lobar more than deep cerebellar [42] than with ischemic stroke [6,21]).

Location of Headache

The headache is less frequently diffuse (23 to 52%) (6,42) than localized (48 to 93%) (6,21,42). Headache location depends primarily on the location of the hematoma (10,18–28,35,51,54,56,58), but also on other factors such as the development of increased intracranial pressure or tissue shifts and herniation (42). The location also may change as time passes, depending on the presence or absence of

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TABLE 108-8 Headache and Hematoma Location

Hematoma Location	*Headache Frequency (%)*	*Usual Headache Location*
Putamen (18,51)	13–67	Ipsilateral frontotemporal
Lobar (3,28)	68–76	Location dependent
Frontal		Bifrontal
Parietal		Anterior temporal
Temporal		Auricular
Occipital		Periorbital
Thalamus (54)	32	Frontal, occipital
Caudate (10)	90	Diffuse
Pons (58)	35	Variable
Cerebellum (18,19,56)	50–73	Occipital, frontal, diffuse
Primary intraventricular (35)	100	Diffuse

mass effect, especially on the surface of the brain, or the draining of the blood into the ventricular system or the subarachnoid space.

Headache is more frequent on the side of the hematoma (21,42). Two thirds of patients with putaminal bleeds have ipsilateral frontal headache (21,42), and occipital headache is mainly associated with cerebellar or occipital hematomas (42). The specific headache location according to hematoma locations is described in Table 108-8.

Biologic Basis

Contributors to ICH-related headache may include (1) mass effect–induced distortion and traction of the overlying meninges, pial vessels, and other pain-sensitive structures; and (2) generalized increase in the intracranial pressure. Release of blood into the ventricles or cerebrospinal fluid (CSF) on the surface of the brain has been a suggested mechanism of ICH headache, but Fisher reported that grossly bloody CSF fails to produce headache in most instances, even if under moderately increased pressure (18). He speculated that the predominance of occipital pain suggests that blood in or distending the posterior fossa cisterns may be a source of pain (18).

Melo et al. identified that hematoma location, the presence of meningeal signs, and female gender are better predictors of headache than the volume of the hematoma (42). These findings indicate that the headache of ICH is often related to activation of an anatomically distributed system, such as the trigeminovascular system, in headache-prone individuals. Also, the diffuse nature of the headache in some patients may be related to the release of irritating blood products in the subarachnoid space rather than to intracranial hypertension.

DIFFERENTIAL DIAGNOSIS

The major differential diagnosis of headache and focal neurologic deficit is ischemic stroke and hemorrhagic stroke, either in the form of ICH or subarachnoid hemorrhage (Table 108-9).

Expanding aneurysms, cerebral arteriovenous malformations, and cerebral neoplasia may also present with localized headache and neurologic deficit.

Migraine-induced stroke enters the differential diagnosis of headache with focal neurologic deficits in cases where the deficit is prolonged. In these cases, the patient has previously fulfilled criteria for migraine with aura, the attack is typical of previous attacks but the 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.

Migraine with aura, and especially hemiplegic migraine or basilar migraine, is the major differential diagnosis of headache associated with TIAs. 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 the often negative diagnostic workup point toward that diagnosis. Transient focal neurologic events and headache can also be associated with the antiphospholipid syndrome (59); whether the antibody induces episodes of transient cerebral ischemia or symptomatic migraine with aura remains to be determined. Early in its course, cerebral neoplasia and chronic subdural hematoma may present with localized headache and transient neurologic deficit. Partial seizures, particularly those associated with focal neurologic deficit (Todd paralysis), must be considered in the differential diagnosis. Rare familial disorders, such as the mitochondrial encephalomyopathies (MELAS and its variants), present with focal neurologic deficits, headache, and seizures. In these instances, muscle biopsy or brain and muscle magnetic resonance spectroscopy may confirm the diagnosis.

TABLE 108-9 Differential Diagnosis

Ischemic stroke or transient ischemic attack
Intracerebral hemorrhage
Aneurysmal subarachnoid hemorrhage or large unruptured aneurysm
Cerebral arteriovenous malformation
Migraine with aura or migraine-induced stroke
Cerebral neoplasm
Chronic subdural hematoma
Antiphospholipid syndrome
Partial seizures with ictal headache and postictal paralysis
Mitochondrial encephalomyopathies
CADASIL

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PREDICTIVE AND PROGNOSTIC VALUE

Predictive and prognostic values of stroke-related headache are addressed as follows:

1. *Does the presence of headache at stroke onset predict the stroke type (ischemia vs. hemorrhage)?* Onset headache in association with younger age and vomiting favors the diagnosis of subarachnoid hemorrhage. Onset headache in association with higher systolic and diastolic blood pressure favors the diagnosis of intracerebral hematoma. In contrast, the absence of onset headache, absence of vomiting, and older age favor the diagnosis of ischemic stroke (21).
2. *Does the presence or the severity of headache at stroke onset predict the size of the ischemic infarct or the hematoma?* Few studies have specifically addressed this issue. Jorgensen et al. found that infarct size had no independent influence on the presence of headache (27), while Vestergaard et al. indicated that the ischemic infarct size did not correlate with headache severity (60). Two reports (27,42) also indicated that the occurrence of headache at onset of intracerebral hematoma was not dependent on hematoma size.
3. *Does headache location predict the affected vessel or the location of the hematoma?* Systematic evaluation of this question in several large studies indicates that neither the location of the headache nor its characteristics are predictive of either location of the ischemic infarct or the involved artery (17,27,60) or the location of the hematoma (18,42).
4. *Does onset headache predict ischemic stroke subtype?* Consistently among reports, the absence of headache at stroke onset favors the lacunar subtype of ischemic stroke (17,30,60). Aside from the distinction between lacunar and nonlacunar ischemic stroke, the presence of headache at stroke onset has little value in predicting the ischemic stroke subtype.
5. *Does onset headache predict the early course of ischemic stroke?* Neurologic deterioration in the first few days after stroke is a frequent phenomenon. Several factors, including initial stroke severity, early neurologic improvement, brain edema, large initial diffusion-weighted imaging lesion, proximal CA or MCA occlusion, uncontrolled hypertension or hyperglycemia, overzealous blood pressure control, no prior treatment with antithrombotic medications, elevated acute phase reactants, and excitotoxicity, have been considered responsible (7–9,13,22,26,33,61). Leira et al. (33) found that headache at the onset of ischemic stroke is an independent predictor of neurologic worsening (sensitivity 56%, specificity 99%, positive predictive value 98%). The good correlation between elevated levels of glutamate, interleukin-6, and NO metabolites and headache and stroke progression indicates that onset headache is a surrogate marker of the molecular mechanisms involved in neurologic worsening after acute stroke.
6. *Does the presence or absence of headache at stroke onset predict stroke outcome?* The presence of headache has no independent relationship to neurologic outcome or stroke mortality and does not alter the overall outcome of ischemic stroke (27,55). Further studies are needed to better answer this question.

MANAGEMENT

There has been no attempt to systematically study specific treatments and their effects in patients with headache at stroke onset. Often, this form of headache, because of its rather mild intensity, will be overshadowed by the stormy neurologic picture and will not require specific treatment. When needed, the headache may respond to treatment with simple analgesics, and sometimes narcotic analgesics. The latter class of medications may obscure the clinical picture and have adverse effects, such as hypotension, respiratory depression, and increased CSF pressure, and ideally should be avoided. Anecdotal experience indicates that a single high dose of corticosteroids may be sufficient to control severe headache at stroke onset. Obviously, agents with antiplatelet action should be avoided in patients with intracerebral hematomas because of the potential risk of promoting further hemorrhage.

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