Review

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2021, Vol. 41(4) 479–492

DOI: 10.1177/0333102421999045
journals.sagepub.com/home/cep

SAGE

Headache secondary to cerebrovascular disease

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Abstract

Objectives: To discuss headache secondary to cerebrovascular disease.
Background: Headache is an important symptom in cerebrovascular diseases. In some conditions, headache is the leading symptom. Migraine is associated with an increased risk of stroke.
Methods: The authors undertook a literature search for the terms "headache" and "cerebrovascular diseases".
Results: We report studies on headache in subarachnoidal hemorrhage, intracerebral hemorrhage, ischemic stroke, TIA, basilar artery thrombosis, cervical artery dissection, cerebellar stroke, arteritis and cerebral sinus venous thrombosis. In addition, we discuss migraine and stroke and thunderclap headache.
Conclusions: Headache is a leading symptom in many cerebrovascular diseases. Headache in combination with focal neurological deficits requires immediate diagnosis and treatment.

Keywords

Ischemic stroke, intracerebral hemorrhage, cervical artery dissection, arteritis, cerebral sinus venous thrombosis, treatment

Date received: 22 June 2020; revised: 15 December 2020; accepted: 2 February 2021

Introduction

The association between stroke and headache is complex, ranging from the non-specific, wherein headache is largely irrelevant, to the highly specific, wherein headache is a key component of diagnosis and management. Headache may accompany the acute stroke process, chronically complicate stroke or, as with migraine, in rare instances even serve a potentially causal role in generating stroke.

In terms of mechanism, there are two major types of stroke: Hemorrhagic and ischemic. Hemorrhagic stroke may be subdivided into two types according to the location of the vessel that ruptures: Intracerebral or subarachnoid. Ischemic stroke typically is due to embolism, thrombosis or vasospasm and may be subdivided further on the basis of the size of the vessel involved and whether that vessel is an artery or vein/sinus. Be it hemorrhagic or ischemic, each mechanistic subtype of stroke can be produced by a myriad of etiologies. Headache may acutely accompany or chronically complicate all stroke subtypes, and especially in the case of ischemic stroke the likelihood of acute headache is often highly dependent upon the specific stroke etiology (e.g. headache, facial pain or both occur much more frequently with internal carotid artery thrombosis from arterial wall dissection than from atherothrombosis).

In the sections that follow, we describe headache's place in the clinical presentation of each of the most common stroke types, the degree to which the International Headache Society's International Classification of Headache Disorders third edition (ICHD-3) criteria may assist in diagnosis of the respective stroke type and whether or not there exists for the headache associated with that stroke type a

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characteristic clinical phenotype (1). We conclude with a section that addresses such special circumstances and considerations as "thunderclap" headache, migraine's association with stroke, migrainous infarction, migraine treatment in patients with a history of cerebrovascular disease, stroke prevention in patients with migraine, and chronic headache complicating ischemic and hemorrhagic stroke. Table 1 outlines the individual components of this review and the sequence in which they are presented.

In many instances, the ICHD-3 criteria for diagnosis of headache secondary to cerebrovascular disease may appear self-evident and of limited clinical utility. For example, acute headache can be attributed to acute ischemic stroke (6.1.1.1) if acute ischemic stroke has been diagnosed, the accompanying headache developed in "very close" temporal association to the stroke and there is no other more plausible cause for the headache (1). As for clinical phenotype, there is nothing characteristic about the headache itself, and in regard to the headache's value in identifying an etiology for the acute ischemic stroke, there is only an accompanying comment that "headache is very rarely associated with lacunar infarcts" (1). Similarly, in regard to the treatment of acute ischemic stroke, the presence (or absence) of headache in a case of stroke due to, say, atherothrombotic occlusion of the left middle cerebral artery is unlikely to influence the decision whether or not to administer a thrombolytic agent or attempt mechanical clot extraction. The focal neurologic deficits are what drive diagnosis and management.

In contrast, there are four common stroke types frequently accompanied by acute headache wherein that headache may be the predominant or even sole symptom reported in the early stages of the clinical presentation, the stroke can be lethal and the process causing the stroke is treatable: Aneurysmal subarachnoid hemorrhage (SAH), basilar artery thrombosis, cerebellar stroke or hemorrhage and cerebral sinus thrombosis. We address each of these four stroke types in detail within its relevant section. In one case (aneurysmal SAH) the associated headache tends to possess characteristic features, and in all four early recognition that the headache is secondary and reflecting clinically significant vascular disease may assist in early diagnosis and a far more favorable outcome. As will be described in its specific section, aneurysmal SAH is best treated when a premonitory low volume bleed occurs and is recognized, not after a clinically devastating early rebleed. Similarly, patients with cerebral sinus thrombosis will enjoy a better outcome when they are diagnosed and treated prior to extensive clot propagation, venous infarctions, seizures and progressive neurologic deficit. Early diagnosis and potential intervention are no less crucial for patients with basilar artery thrombosis or cerebellar stroke/hemorrhage.

Table 1. Outline of review.

A. Introduction
B. Headache as a symptom accompanying acute stroke
  1. Headache attributed to non-traumatic intracranial hemorrhage
    a) primary subarachnoid hemorrhage
    b) unruptured cerebral aneurysms
    c) primary intracerebral hemorrhage
  2. Headache associated with ischemic stroke
    a) ischemic stroke and TIA/general considerations
    b) basilar artery thrombosis
    c) cerebellar stroke
    d) transient ischemic attack
    e) cervical arterial dissection
    f) arteritis
    g) cerebral sinus thrombosis,s, persistent headache following stroke
C. Special circumstances and considerations
  1. Thunderclap headache
  2. Genetic vasculopathies
D. Migraine and stroke
  1. Migraine as a cause of stroke
  2. Treatment of migraine attacks in patients with transient ischemic attack or stroke
  3. Sroke prevention in patients with migraine
E. Persistent headache following stroke
  1. Persistent headache attributed to past ischemic stroke
  2. Persistent headache attributed to past non-traumatic intracranial hemorrhage

Headache as a symptom accompanying acute stroke

Headache attributed to non-traumatic intracranial hemorrhage (6.2)

Subarachnoid hemorrhage (6.2.2). The most common cause of spontaneous, non-traumatic subarachnoid hemorrhage (SAH) is rupture of a saccular ("berry") aneurysm located in or near the circle of Willis, and the hallmark of aneurysmal SAH is sudden, severe headache that often occurs during physical exertion (see subsequent Thunderclap headache section) (2). Because of the aneurysm's location within the subarachnoid space, and in contrast to the clinical presentation typically associated with intracerebral hemorrhage and most ischemic strokes, focal neurologic deficits acutely accompany the headache only if there is extension of the SAH into the brain parenchyma.

A significant proportion of high volume and clinically devastating aneurysmal SAH is preceded by a so-called "sentinel" headache that is analogous to the transient ischemic attack (TIA) of ischemic stroke. These sentinel headaches reflect relatively low volume SAH that usually is manifested clinically by sudden, severe headache only, without any alteration of consciousness or other neurologic signs (3,4). The importance of identifying aneurysmal SAH at the time of this "sentinel" presentation cannot be overemphasized. Sentinel SAH headache may herald an imminent high-volume re-bleed. The risk of re-bleed is highest during the 72 h following sentinel headache, and re-bleeds characteristically convey a very poor clinical prognosis.

The classic exertional thunderclap headache of aneurysmal SAH may be associated with primary headache disorders that possess a far more benign prognosis (e.g. primary headache associated with sexual activity, cough headache), but in those disorders headache duration is typically far shorter (< 2 h for primary cough headache vs. weeks or more for SAH) (5). Also contrasting with spontaneous SAH, in these typically benign headache disorders multiple and relatively stereotyped episodes occur over a more extended period of time.

The sensitivity of non-contrasted brain CT performed within the first 6 h following aneurysmal SAH approaches 100%, representing one of the few neurologic situations where CT is superior to MRI. That high sensitivity progressively declines over the ensuing 18 h. In cases of "thunderclap" headache wherein the suspicion of SAH remains high despite negative brain imaging, lumbar puncture should always be performed. As is the case for many of the cerebrovascular disorders listed in the ICHD-3, the notes accompanying the diagnostic criteria for non-traumatic SAH (6.2.2) appear to be of more clinical utility than the criteria themselves. Those notes emphasize the high diagnostic sensitivity of non-contrasted brain CT but go on to advise that "lumbar puncture is essential" when CT results are non-diagnostic (1).

Unruptured cerebral aneurysms (6.3.1). On occasion, a sudden and severe headache may develop in a patient with an unruptured cerebral aneurysm, in the absence of SAH. Authors have theorized that the relevant headache is indicative of acute expansion of the aneurysm and an imminent risk of rupture, while others have suggested that the headache reflects thrombosis occurring within a "giant" aneurysm (6).

More commonly, clinicians will encounter patients whose diagnostic evaluation for another disorder (e.g. migraine) has demonstrated an unruptured, incidental and asymptomatic aneurysm. How to best manage such aneurysms remains an area of some controversy, but generally speaking the size and location of the aneurysm(s) influence the risk of rupture. Small (< 6 mm) aneurysms are less likely to rupture than larger (> 5 mm) aneurysms, and aneurysms in the anterior circulation are 2–3 times more likely to rupture than those within the posterior circulation (7).

The ICHD-3 criteria for headache due to an unruptured saccular aneurysm (6.3.1) confirm the observation that the headache may be "thunderclap" in character, and the comments accompanying the criteria emphasize that before headache is attributed to an unruptured saccular aneurysm, intracranial hemorrhage and reversible cerebral vasoconstriction syndrome should be excluded.

Headache attributed to non-traumatic intracerebral hemorrhage (6.2.1). Spontaneous, non-traumatic intracerebral hemorrhage (ICH) is often accompanied by acute headache, but the association is hardly invariable. About half of patients with ICH who are capable of providing a coherent history report acute headache (7). Although this is far lower than the incidence of headache in aneurysmal SAH, the combination of headache and vomiting is at least three times greater in ICH than in ischemic stroke (7). Although the absence of these symptoms does not exclude ICH, their presence, especially when combined with acute hypertension, focal neurologic deficits, a depressed level of consciousness and an early clinical course characterized by smoothly progressive neurologic deterioration, should encourage strong consideration of the diagnosis.

Headache is more common with lobar hemorrhage than with deep ICH, and in the latter headache occurs more often with putaminal hemorrhage than with hemorrhage involving the caudate nucleus or thalamus (8–

10). Headache is of little value in localizing ICH, but, in general, lobar occipital bleeds tend to produce ipsilateral orbital/periorbital pain, with more anteriorly situated hemorrhages causing headache that may be periauricular, temporal or frontal (11).

Treatment of ICH is directed towards prevention of hematoma expansion, management of increased intracranial pressure and prevention of medical complications such as deep vein thrombosis and pulmonary embolism. In regard to the first, whether aggressive management of systemic hypertension reduces early expansion of the hematoma and improves clinical outcome remains controversial; current guidelines recommend that systolic blood pressure be maintained between 140 to 160 mmHg in patients with ICH whose systolic pressure exceeds 150 mmHg at the time of presentation (12,13). Despite years of clinical investigation, we still lack any therapy of clearly established value for direct treatment of the ICH itself. Although hematoma evacuation is considered acceptable management for patients with supratentorial ICH and incipient herniation despite best medical management, there is little evidence to support such intervention. The best treatment for ICH remains prevention, involving careful surveillance for and treatment of its leading cause, hypertension. The usefulness of the ICHD-3 criteria for spontaneous ICH (6.2.1) is limited, especially so in cases where the patient presents with no history of trauma, focal neurologic deficit and imaging evidence of parenchymal hemorrhage. Comments accompanying the listed criteria include the observations that, infrequently, headache may be the "presenting and prominent feature" of primary ICH, that ICH headache "occasionally" is thunderclap in character, and, interestingly, that in ICH as opposed to ischemic stroke, headache at onset is associated with a higher risk of early mortality (1).

Finally, these accompanying comments emphasize the important points that in contrast to intra*cerebral* hemorrhage, with intra*cerebellar* hemorrhage headache is more commonly the prominent initial clinical feature, and that patients with intracerebellar hemorrhage may require emergent surgical decompression.

Headache associated with ischemic stroke

Ischemic stroke and TIA/general considerations

The ICHD-3 diagnostic criteria for "acute headache attributed to ischemic stroke (cerebral infarction)" (6.1.1.1) require *a priori* diagnosis of acute ischemic stroke, headache onset in close temporal association with stroke signs and other symptoms and significant improvement in headache occurring with stabilization or improvement of other manifestations of the stroke; also included is the caveat commonly employed in the classification system: Not better accounted for by another ICHD-3 diagnosis (1).

As has been reported from a recent meta-analysis of 20 studies involving 33,231 patients, between 6% and 44% reported headache at the onset of neurological deficits in ischemic stroke; the pooled prevalence rate was 14% (14). The onset of headache is sudden in the majority of patients but may be delayed in 10–15%. Most patients experience non-specific head pain resembling tension-type headache, but accompanying symptoms may include nausea, vomiting, photophobia or phonophobia (14,15). Predictors of headache associated with an ischemic stroke are female gender, younger age, major infarctions and ischemia in the posterior circulation (14,15). The reported frequency of headache with ischemia in the posterior circulation ranges between 30% and 75% and in the anterior circulation between 15% and 60% (17–19). Headache is more common with cortical infarction than with subcortical, and correspondingly, headache is more frequently reported after cardio-embolic and large vessel stroke than after small vessel or lacunar stroke (20,21). In lacunar infarctions, headache is reported in less than 10% of patients (22). Ischemia in the territory of the middle cerebral artery typically causes additional pain in the eye region, whereas ischemia in the distribution of the anterior cerebral artery produces headache that is usually bifrontal. With ischemia in the posterior circulation, headaches are usually diffuse but may also be localized to the occipital area.

Basilar artery thrombosis. Although headache commonly accompanies acute, symptomatic basilar artery thrombosis (BAT), occurring in 20% to 53% of patients with the various syndromes, it does not possess a specific place in the ICHD-3 classification system (23). In acute BAT the headache can resemble that characteristic of subarachnoid hemorrhage (24). Although the headache is typically occipital and can be either lateralized or non-lateralized, in some cases the pain is localized to the occipitofrontal or frontal areas. The headache can be associated with occipital tenderness, neck stiffness and neck pain. The pain is often described as throbbing and may be aggravated by postural change. The headache usually occurs in parallel with the onset of BA-associated neurologic deficits but may persist longer than the other BAT symptoms/signs or even occur independently.

Because when left to itself symptomatic BAT so often may be fatal or inflict permanent neurologic disability, and because thrombolytic therapy, mechanical clot retrieval or both may positively impact clinical outcome, clinicians encountering patients with acute symptoms and signs referable to the pons – with or without associated headache – should proceed with

alacrity to confirm or exclude the diagnosis (25,26). This is especially true in situations when the patient is experiencing progressive neurologic worsening referable to the posterior circulation, with that progession most often stepwise in character. This stepwise progressive early clinical course is presumed to reflect thrombus propagation within the basilar artery and occlusion of the ostia of the parent vessel's pontine perforators.

Take home message:

- BAT's initial presentation may be non-specific or seemingly innocuous, involving headache only or minor focal neurologic deficit.
- Headache often accompanies BAT but is far from invariably present.
- Left undiagnosed or untreated, symptomatic BAT may cause significant and irreversible neurologic deficit or death.
- Stepwise neurologic worsening referable to the posterior circulation requires emergent diagnostic testing (angiography, specifically) to confirm or exclude BAT.

Cerebellar stroke. The typical symptoms of a patient presenting to an emergency department with acute ischemic stroke involving the cerebellum may be non-specific: Headache, "dizziness", nausea and vomiting. The character and location of any associated headache conveys no diagnostic value; despite the posterior location of the stroke, head pain may be referred to the frontal area (26).

Even when a large portion of the cerebellar hemisphere undergoes acute ischemic infarction, consequent neurologic deficit may not be apparent until the patient is examined while sitting or standing. Appendicular ataxia may not be present, especially if the exam is conducted with the patient supine and thus with gravitational assistance for heel-to-shin testing, and truncal ataxia cannot be adequately assessed in such circumstances. With sitting or standing, however, the truncal ataxia becomes obvious, as the patient will sway or fall consistently toward the side of the affected cerebellar hemisphere.

In contrast to brain CT, brain MRI is extremely effective in demonstrating even very early acute ischemic stroke involving the cerebellum. The diffusion-weighted and FLAIR sequences are of particular value in this regard.

As a delay in diagnosis may lead to severe clinical consequences from edematous swelling of the infarcted tissue, with obstructive hydrocephalus and tonsillar herniation, clinicians must maintain a high index of suspicion for the diagnosis of cerebellar stroke. When the concern for that diagnosis appears justified, an adequate diagnostic evaluation should be performed.

Take home message:

- If the patient's history suggests acute ischemic stroke of the cerebellum, examine the patient while sitting/standing.
- In confirming suspected acute cerebellar ischemic stroke, brain MRI is more sensitive than CT.

Transient ischemic attack. Transient ischemic attacks (TIAs) are often the harbingers of imminent stroke, and as with all subtypes of acute ischemic stroke, TIAs may be accompanied by headache. In one analysis of over 2000 patients with acute ischemic stroke or TIA, 27% experienced headache at event onset, and headache was equally common in patients with no persistent neurologic deficit (27). The presence of acute headache correlated with younger age and with a prior history of migraine, underscoring the potential hazard of attributing acute TIA or minor stroke to "complicated" or "complex" migraine, each a diagnosis absent from the existing ICHD criteria and correspondingly lacking in specificity or clinical utility.

Another factor complicating diagnosis is cortical spreading depression (CSD), the neurophysiologic event considered to be the source of typical migraine aura and, perhaps, the biologic "headwaters" of headache and other migrainous phenomena as well (28,29). While spreading waves of neuronal depolarization/hyperpolarization nicely explain the positive, negative, and dynamic features of the most common aura types, CSD is not unique to migraine. Along with trauma, ischemia may trigger CSD (or its equivalent in the retina), and sources of cortical ischemia as diverse as carotid dissection or cardioembolism from mechanical prosthetic valves may produce paroxysmal visual or sensory symptoms identical to those of migraine aura (30).

The ICHD-3 criteria for "headache attributed to transient ischemic attack (TIA)" (6.1.2) mirror those provided for acute ischemic stroke save for the stipulation that the associated headache must resolve within 24 h (1). A recent study examining the diagnostic specificity of the current ICHD-3 criteria relative to the pre-existing beta version of those criteria found that the current criteria are significantly more specific for diagnosing aura and distinguishing aura from TIA in patients presenting with the first episode of probable migraine with aura (31). Even so, the notes accompanying the current criteria rightfully emphasize that distinguishing between TIA with headache and migraine with aura may be "particularly difficult". The "positive" features often present with aura and aura's tendency to evolve rather than occurring as a "suddenly here/suddenly gone" phenomenon can help, but are neither entirely sensitive nor specific for

diagnostic purposes. The notes also advise that an otherwise typical TIA accompanied by *severe* headache should raise concern for TIA/stroke etiologies, which more commonly generate prominent, high intensity headache (e.g. arterial dissection) (1).

Take home message:

- Even with utilization of the ICHD-3 criteria for migraine with aura, it remains common for TIA to be misdiagnosed as aura.
- Be wary of diagnosing migraine with aura in patients presenting with aura symptoms but lacking an established history of migraine.
- Especially with older patients or any patient with risk factors for vascular disease, be wary of diagnosing new onset aura even when the patient reports an established history of migraine without aura.

Cervical arterial dissection. Cervical artery dissection (CAD) involving either the internal carotid or vertebral artery is a common cause of stroke in people younger than 50 years of age. Headache occurs in up to 90% of patients and may precede the development of cerebrovascular symptoms in half of CAD patients (32).

In the Cervical Artery Dissection Ischemic Stroke Patients Group study of 982 consecutive patients, headache was more frequent in internal carotid artery dissection than in vertebral artery dissection (OR = 1.36; 95% CI 1.01–1.84) (33). Headache can be the only symptom in arterial dissection (34). In carotid dissection, the pain is localized in the anterior neck and face and radiates to temporal and frontal regions (35–37). Vertebral artery dissection can lead to isolated neck pain (35). Pain in cervical artery dissection is ipsilateral to the dissection and tends to be severe and throbbing in character (38). The headache associated with vertebral artery dissection is more variable and can even mimic cluster headache (39). Migraine increases the risk of CAD (40).

The clinical presentation of CAD ranges from incidental discovery in a patient who is entirely asymptomatic to disabling or even fatal stroke. Cervical artery dissection may be "spontaneous" bruising or occur as a consequence of trivial (e.g. with sneezing) or major trauma. When TIA or stroke complicates CAD, the interval between the anatomical onset of dissection and the development of cerebrovascular symptoms may extend up to days.

Not surprising for a vascular disorder with such a variable clinical presentation, the ICHD-3 diagnostic criteria for "acute headache...attributed to cervical carotid or vertebral artery dissection" (6.5.1.1) are of limited utility due to their lack of specificity and perhaps to some degree diagnostically insensitive plan for past displacements his breakfast on exam lunch insensitive. For example, although those criteria appear to imply that the headache of CAD is usually abrupt and often "thunderclap" in character, a more gradual onset is at least as common. Suffice it to say that the development of uncharacteristic headache accompanied by TIA or stroke in a younger patient with no other compelling etiology for TIA/stroke or lateral medullary (Wallenberg) stroke occurring in a younger patient should raise concern for extracranial internal carotid or vertebral artery dissection.

Although for years anticoagulant therapy had been considered by many the preferred treatment for CAD involving the carotid artery, a recent randomized, prospective study demonstrated no benefit of acute and subacute anticoagulation over antiplatelet therapy for patients with cervical carotid or vertebral dissection (41).

Take home message:

- Cervical arterial dissection (CAD) may occur spontaneously or as a result of trauma, trivial or otherwise.
- The clinical manifestations of CAD are quite variable, ranging from asymptomatic to clinically devastating ischemic stroke.
- Headache ipsilateral to the affected artery commonly accompanies acute CAD and may precede the onset of ischemic symptoms and signs.
- CAD involving the carotid may produce anterior neck and facial pain as well.
- CAD is an infrequent cause of stroke in the general population but is disproportionately common in stroke patients under age 50.

Arteritis. Giant cell arteritis (GCA), commonly known as "temporal arteritis", produces anterior ischemic optic neuropathy and acute blindness much more often than cerebral infarction, but carotid and vertebrobasilar distribution strokes can occur. When they do, it is usually within the first few weeks of active disease and at times may occur even in patients with a normal erythrocyte sedimentation rate, a normal temporal artery biopsy and despite concomitant treatment with a corticosteroid (42,43). Although stroke generated by GCA typically involves the extracranial portions of the carotid and vertebrobasilar systems, intracranial arteritis may occur (44).

Patients with GCA are usually over 65 years of age but may be as young as 50. There is roughly a 3:1 female-to-male preponderance. There is almost always associated headache, and the headache either is an unprecedented symptom for the patient or is described as "different" from the patient's usual headaches. The pain typically is constant and most often

temporal with radiation to the scalp, face, jaw, or occiput. It may be pulsatile. More than half of patients with GCA have accompanying polymyalgia rheumatica (PMR), and slightly less than half of patients with PMR develop GCA.

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level typically are elevated in patients with GCA. Unfortunately, abnormalities of each are notoriously non-specific, and in at least 5% of biopsy-proven cases the ESR may be normal or only modestly elevated.

In regard to clinical phenotype, the ICHD-3 criteria for diagnosis of "headache attributed to giant cell arteritis" (6.4.1) are that scalp tenderness, jaw claudication or both are characteristic but not absolutely required. Tautologically, the criteria do require an established diagnosis of GCA. Typically, the ICHD-3 has applied headache secondary to several vascular diseases, therefore the comments accompanying the diagnostic criteria may have more clinical utility than the criteria themselves. Those comments related to GCA advised that because of the variability of the clinical features associated with that disorder, the diagnosis should be considered in any adult over the age of 60 with the recent onset of persisting headache.

A less common inflammatory vascular disorder wherein headache is a near-invariable and prominent symptom is primary angiitis of the central nervous system (PACNS) (45,46). Unusual for being restricted to the central nervous system, PACNS may afflict adult patients of any age. The typical symptom complex involves chronic, non-specific headache with progressive cognitive decline and recurrent episodes of TIA or stroke. Blood markers of inflammation, routine analyses of cerebrospinal fluid, cerebral arteriography and even brain/meningeal biopsy are not always sufficient to establish the diagnosis even in cases where PACNS seems highly likely. Given that PACNS may be treated effectively with chronic steroid therapy in combination with cyclophosphamide, but there are risks inherent in such treatment, accurate diagnosis is critical.

As with GCA, the ICHD-3 criteria for diagnosis of headache attributed to primary angiitis of the central nervous system (6.4.2) require an established diagnosis of PACNS. The comments accompanying the criteria emphasize that while headache is a common feature of PACNS, the headache lacks any specific characteristics and is "therefore of little diagnostic value" until other signs such as focal deficits, seizures, impaired cognition, or disordered consciousness are present (1).

Take home message:

- GCA afflicts individuals 50 years of age or older (typically over 60).
- ESR and CRP levels and GCA are usually but not invariably elevated.
- Adults over 60 with recent onset persisting headache: Consider GCA.

Cerebral sinus thrombosis. Thrombosis of a cerebral vein or sinus may occur at any age and can be caused by a wide variety of disorders. The clinical presentation is similarly variable, but headache is often prominent.

Headache is the most common symptom of cerebral sinus thrombosis (CST), occurring in about 90% of cases and more often in females and younger patients (47,48). It is the presenting symptom in three-quarters of cases, and it may occur in isolation or herald the development of other neurologic signs and symptoms (49,50). The headache's location varies widely from case to case and is of little or no diagnostic value. The head pain is typically persistent, and although in the majority of cases its intensity builds gradually, in about 10% the onset is sudden and severe ("thunderclap") (51).

Propagation of thrombus may result in progressive neurologic deterioration, permanent neurologic disability and even death (47,51). Systemic anticoagulation with intravenous unfractionated heparin or subcutaneously administered low molecular weight heparin is considered first-line therapy for acute CST even when venous infarction and associated hemorrhage are demonstrated by brain imaging (grade 2C level of evidence) (52,53). Although endovascular intervention involving intra-sinus thrombolysis, mechanical thrombectomy or both may be considered for patients who do not respond to anticoagulant therapy, in the TO-ACT trial, patients with clinically severe CST randomized to endovascular therapy experienced no better outcome than those randomized to intravenous heparin (54).

In many cases the increased venous pressure resulting from CST produces intracranial hypertension that results in a chronic headache disorder indistinguishable from idiopathic intracranial hypertension (IIH). As with IIH, afflicted patients are at risk for progressive visual loss and blindness.

As with giant cell arteritis, the ICHD-3 diagnostic criteria for "headache attributed to cerebral venous thrombosis" (6.6.1) require *a priori* that the diagnosis of CST has been made, do not stipulate specific features other than either worsening of headache in association with signs of thrombus extension, improvement or resolution after thrombosis has resolved, or both. Comments accompanying the criteria indicate that CST-related headache lacks any specific characteristics but "most often is diffuse, progressive and severe" (1). The comments also emphasize that the headache of CST may mimic that of a variety of other primary

and secondary headache disorders, including migraine, hemicrania continua, cluster, primary thunderclap headache, non-traumatic subarachnoid hemorrhage, and intracranial hypotension. Perhaps most helpful is the comment that given this absence of characteristic headache features, persisting headache of recent onset "should raise suspicion" for the diagnosis of CST "especially in the presence of an underlying prothrombotic condition" (e.g. puerperium, presence of prothrombin gene mutation) (1).

Take home message:

- While headache typically is present with CST and may represent the sole clinical manifestation of the disorder, CST-related headache lacks any distinguishing characteristic.
- Persisting headache of recent onset should raise concern for the diagnosis of CST, especially in the presence of an underlying prothrombotic condition.
- Systemic anticoagulation with intravenous unfractionated heparin or subcutaneously administered low molecular weight heparin is considered first-line therapy for acute CST.

Special circumstances and considerations

Thunderclap headache (4.4)

The phrase "the worst headache of my life" traditionally has been considered a diagnostic red flag but coming from a patient with an established history of recurrent headache this frequently means that he or she is simply experiencing a particularly severe episode of migraine. More concerning is a "thunderclap" headache, implying the sudden onset of severe head pain that rapidly reaches its maximum intensity (55).

What is perhaps the most clinically worrisome cause of thunderclap headache has been described previously. So-called "sentinel" headache is the TIA of aneurysmal subarachnoid hemorrhage, auguring a high risk of imminent re-bleed. Other causes of thunderclap headache, both primary and secondary, are listed in Table 2.

Reversible cerebral vasoconstriction syndrome (RCVS; 6.7.3) is, as the relevant ICHD-3 comments indicate, a "poorly understood condition". In its most specific clinical form, RCVS presents as recurrent episodes of thunderclap headache, often triggered by sexual activity or other behavior involving physical exertion or Valsalva maneuver, with angiographic evidence of transient segmental cerebral arterial narrowing and adjacent dilatation ("string of beads") (1). The majority of RCVS patients present with headache only, but a sizeable minority may exhibit fluctuating focal neurologic deficits, seizure activity, or both. The disorder is self-limited, with cessation of headache episodes and resolution of any angiographic findings within 3 months. The clinical presentation and arteriographic findings characteristic of RCVS may occur secondary to a variety of causes as diverse as post-partum eclampsia, use of sympathomimetic drugs (e.g. methamphetamine, bromocriptine) and other primary etiologies associated with acute hypertension wherein it is not easily distinguished from so-called posterior reversible encephalopathy syndrome (PRES). As such, RCVS is best regarded not as a diagnosis unto itself but rather as a unifying term intended to catalyze diagnosis and management of the underlying symptomatic disorder (56).

Table 2. Causes of "thunderclap" headache.

Secondary
• Aneurysmal subarachnoid hemorrhage
• Reversible cerebral vasoconstriction syndrome
• Cerebral arterial dissection
• Acute intracranial hypotension
• Cerebral sinus thrombosis
• Posterior reversible leukoencephalopathy syndrome
• Acute hypertensive crisis
• Pituitary "apoplexy"
• Colloid cyst of IIIrd ventricle
• Chiari malformation
Primary
• Primary headache associated with sexual activity
• Primary exercise headache "idiopathic recurrent thunderclap headache"
• Primary cough headache
• Primary thunderclap headache
• "Crash" migraine

Although migraine headache typically builds over hours to its maximum intensity, in instances of "crash" migraine the pain may reach maximum intensity quite rapidly. In addition, clinicians may infrequently encounter patients who experience "idiopathic" recurrent thunderclap headache in the absence of any history of established migraine and without documented acute, transient cerebral vasospasm. Especially with its initial occurrence, and as is the case for any first episode of thunderclap headache, primary thunderclap headache (4.4) is, as emphasized in comments accompanying the ICHD-3 criteria, a diagnosis of exclusion.

To underscore the absolute necessity of excluding aneurysmal subarachnoid hemorrhage in this clinical setting, the ICHD-3 criteria define primary thunderclap headache (4.4) as severe head pain of abrupt onset, reaching maximum intensity within 1 min, lasting at least 5 min, and *mimicking the headache of a ruptured cerebral aneurysm] but occurring in the absence of any intracranial pathology* (authors' italics) (1). Supplementing the criteria are notes cautioning that primary thunderclap headache should be considered a

"diagnosis of last resort" and that "the search for an underlying cause should be both expedited and exhaustive" (1).

Take home message:

- Although thunderclap headache has a wide variety of causes, exclusion of aneurysmal SAH is paramount.
- For virtually all patients presenting with thunderclap headache, and especially in the absence of any prior history of such headache or if the headache is exertional, non-contrasted brain CT should be performed; if the CT is negative, a lumbar puncture should be performed; if the lumbar puncture is negative, angiography should be considered.
- Primary (idiopathic) thunderclap headache should be considered a diagnosis of last resort.

Headache attributed to genetic vasculopathy (6.8)

Distinct from migrainous infarction (1.4.3) are genetic disorders clinically characterized by episodic headache and stroke or stroke-like episodes. The two prototypic disorders of this type, CADASIL and MELAS, are briefly described here.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; 6.8.1) is a disease that involves the smooth muscle of the arterial media and typically results from a mutation of the NOTCH-3 gene. The headache episodes of CADASIL resemble those of migraine with aura, and per the ICHD-3 criteria there is "an unusual frequency of prolonged aura" (1). Along with the characteristic white matter abnormalities demonstrated by MRI, the ICHD-3 criteria specifically require a history of aura for the diagnosis of CADASIL. The aura episodes may precede the development of other clinical manifestations of the disorder and subsequently decline or even cease when those manifestations come to fore.

MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; 6.8.2) is a heterogeneous mitochondrial genetic disorder. According to the ICHD- 3 criteria, the clinical phenotype of MELAS is characterized by attacks of migraine headache with or without aura, with headaches preceding or occurring concomitant with stroke-like episodes conveying focal neurologic deficit.

Take home message:

- CADASIL and MELAS are genetic vasculopathies that mimic migraine but involve stroke-like episode that may cause transient or permanent focal neurologic deficit.
- Diagnosis of CADASIL may be confirmed by genetic analysis or skin biopsy.

Migraine and stroke

Overview. While results from many epidemiologic studies have differed in regard to what specific subpopulations of migraineurs may or may not be at risk for stroke, the evidence available clearly demonstrates an association between migraine and stroke. This association is most prominent in younger females of age 45 or less who have migraine with aura (57–59). When ischemic stroke occurs in an individual with a history of migraine, the stroke may result either from another condition coexisting with migraine and independent of a migraine episode or as a complication of an episode of acute migraine.

In females who have migraine with aura, use of an estrogen-containing oral contraceptive conveys approximately a seven-fold increase in stroke risk. While even with this substantial increase in relative risk the absolute risk of stroke remains small consequent to the low stroke incidence in younger individuals, in the absence of any compelling need to continue such use a switch to an alternative means of contraception is recommended (e.g. a progesterone-based preparation; hormone-secreting or non-hormone-secreting intrauterine device) (60).

When it is the coexisting disorder and not migraine itself that is responsible for producing ischemic stroke, a preponderance of that coexisting disorder in the migraine population relative to the age and gender-matched population free of migraine could account for at least a portion of the migraine:stroke association. For example, some investigators have found evidence of a bidirectional relationship between patent foramen ovale (PFO) and migraine, and in a study of patients with cryptogenic stroke and a history of migraine, just under 80% had evidence of a PFO with right-to-left shunting (61). In the study by West et al., the prevalence of PFO in patients with cryptogenic stroke and migraine with frequent aura was 93% (62). Although catheter-based PFO closure reduces risk of recurrent stroke after "cryptogenic" stroke, whether closure performed for migraine prevention may serve to reduce migraine burden remains an issue of some controversy (63,64).

Take home message:

- Migraine conveys roughly a two-fold increase in stroke risk.
- Most of that risk appears to reside in the subpopulation of young females who have migraine with aura.
- Use of an estrogen-based oral contraceptive increases the relative risk of migraine-associated stroke, but the absolute risk is low.

- The specific reason(s) accounting for the increased risk of stroke in the migraine population remains unclear.

Migraine as a cause of stroke. Although the majority of strokes occurring in migraineurs do not occur during an acute migraine episode, at times acute migraine is complicated by brain infarction. The ICHD-3 criteria for a diagnosis of "migrainous infarction" (1.4.3) require an established history of migraine with aura, acute aura symptoms typical of previous migraine episodes, persistence of those symptoms beyond 1 h and neuroimaging evidence of infarction involving an area relevant to the symptoms (1). If migrainous infarction can occur in individuals without a history of aura or involve deficits that do not mimic previous aura symptoms, these criteria may be diagnostically insensitive (26).

How migraine directly causes stroke remains unclear. Cerebral angiography performed at the time of migrainous infarction or shortly thereafter has demonstrated findings consistent with arterial vasospasm, but such abnormalities have been reported in only a relative handful of cases (65,66). Migraine-induced arterial dissection, thrombosis resulting from a migraine-associated chronic arteriopathy and cerebral oligemia related to the migraine process itself all have been proposed as potential sources of migrainous infarction, but it is as yet unknown whether migrainous infarction is the result of a single biologic process or can occur consequent to a variety of independent mechanisms.

Comments accompanying the ICHD-3 criteria for migrainous infarction reinforce the point that although migraine appears to convey a two-fold increase in stroke risk, the majority of strokes occurring in the migraine population are not migrainous infarctions. That this migraine-associated increase in stroke risk does not appear to extend to the population of migraineurs without any history of aura may help explain why the criteria for migrainous infarction require that the patient have an established history of migraine.

Take home message:

- Ischemic stroke is an acknowledged but rare complication of acute migraine.
- According to current ICHD- 3 criteria, the diagnosis of migrainous infarction requires an established history of migraine with aura.
- The specific cause(s) of migrainous infarction have not been clearly established.

Treatment of migraine attacks in patients with transient ischemic attack or stroke. According to their labels, triptans are contraindicated for the treatment of migraine attacks in patients with TIA or stroke and in patients with multiple uncontrolled vascular risk factors. Triptans have mild vasoconstrictive properties, and theoretically a triptan could decrease cerebral blood flow already decreased during aura. The degree of vasoconstriction observed in humans, however, would not be expected to decrease cerebral blood flow to a level sufficient to cause tissue ischemia (67). Ergots are contraindicated for the same theoretical reason (67). Small molecule calcitonin-gene-related peptide (CGRP) antagonists (gepants) and ditans (e.g. lasmiditan, a 5-HT1F-agonist) have no vasoconstrictive properties and consequently are considered to be safe for treating migraine attacks in patients with clinically controlled vascular risk factors or stable vascular disease (69–72).

Take home message:

- A history of stroke should be regarded as at least a relative contraindication to the use of triptans or ergotamines stroke for acute migraine treatment.
- Gepants and ditans are considered safe and appropriate therapies for treatment of acute migraine headache.

Stroke prevention in patients with migraine. Most patients with non-cardioembolic TIA or ischemic stroke receive antiplatelet treatment. Aspirin lowers stroke risk and has a weak preventive action in migraine, and in some patients clopidogrel might improve migraine (73–75). The combination of aspirin plus slow-release dipyridamole is also used for secondary stroke prevention, and dipyridamole may lead to headache during the first few days of use. (76) In migraine patients with cardioembolic stroke, chronic treatment with warfarin or the non-vitamin-K oral anticoagulants is well-tolerated. In patients with significant carotid stenosis angiography, carotid endarterectomy or stenting with angioplasty can induce migraine attacks in patients with a history of migraine.

Patients with hypertension and migraine should typically be treated with beta-blockers with proven efficacy in migraine prevention, a group that includes propranolol, metoprolol, timolol, bisoprolol, and atenolol. (77) Alternatively, lisinopril, an angiotensin-converting enzyme inhibitor, and cadesartan, an angiotensin II receptor blocker, may be effective for migraine prophylaxis (78,79).

OnabotulinumtoxinA is effective in the prevention of chronic migraine and can be used safely in migraine patients with history of stroke or TIA (80). While valproic acid may occasionally induce thrombocytopenia, it is typically a safe therapy for migraine prophylaxis in stroke patients who are not at risk of pregnancy (81). The same may be said for topiramate.

Given that CGRP is a potent vasodilator, monoclonal antibodies directed against CGRP or its receptor pose a theoretical risk of provoking unopposed

vasoconstriction. Phase 3 clinical trials investigating the currently available anti-CGRP monoclonal antibodies included patients with a history of stroke, and a history of ischemic stroke or subarachnoid hemorrhage currently does not represent a contraindication to the use of any anti-CGRP therapies in patients with migraine.

Take home message:

- Low-dose daily aspirin or clopidogrel may serve the dual purpose of preventing recurrent vascular events and reducing migraine burden.
- Antihypertensive therapy with certain of the beta-blockers, lisinopril and candesartan may also serve as prophylactic therapy for episodic migraine.
- For many patients with a history of stroke or TIA, both valproic acid and topiramate are reasonable choices for migraine prophylaxis.
- Despite the theoretical risk of vascular complications related to unopposed vasoconstriction, the anti-CGRP monoclonal antibodies currently are considered appropriate therapy for migraine prophylaxis in the patient population with a remote history of clinically evident cerebrovascular disease.

Persistent headache following stroke

Persistent headache attributed to past ischaemic stroke (6.1.1.2). According to the ICHD-3 classification system, the criteria for this diagnosis simply require a history of "acute headache attributed to ischemic stroke" (6.1.1.1), clinical stabilization of the index stroke and persistence of headache for greater than 3 months following stabilization (1). Similar to the situation for persistent post-traumatic headache (5.2), the pathophysiology producing headache as a chronic complication of stroke is unknown, and evidence-based treatment is lacking.

According to a recent meta-analysis, the reported prevalence of headache chronically complicating ischemic stroke has varied widely, ranging from 1% to 23% (82). In one cohort included in that analysis, approximately 2% of patients reported daily headache 3 years following stroke (83).

New-onset headache presenting at the time of acute ischemic stroke is a predictor of persistent headache 6 months following the stroke (84). Whether a pre-existing history of migraine increases the likelihood of a patient developing persistent headache following stroke is unknown. Extrapolating from what is known regarding variables predisposing to acute headache associated with ischemic stroke, one can hypothesize that posterior circulation stroke, cortical infarction, younger age, female gender and, perhaps, a cardioembolic etiology each may be associated with a greater risk of developing persistent headache following stroke (82). Similarly, extrapolating from short-term follow-up data, one would expect the clinical phenotype of a persistent headache to more often resemble chronic tension-type headache than migraine (81).

In the absence of any evidence-based guidelines for treatment of persistent headache following ischemic stroke, it would seem reasonable to match any therapy prescribed to the clinical phenotype of the relevant headache.

Persistent headache attributed to past non-traumatic intracranial hemorrhage (6.2.4). If anything, even less is known regarding the epidemiology, clinical characteristics and potential treatment for headache persisting after non-traumatic SAH or ICH. In one prospective single-center study, 41% of 93 patients surviving aneurysmal SAH reported "burdensome" headache at a mean follow-up of just under 3 years (85). Persistent headache correlated with younger mean age and, despite more favorable neurologic status, lower health-related quality of life scores relative to patients free of chronic headache.

In a study involving 90 survivors of non-traumatic ICH, 11% reported the new onset of persistent headache following the hemorrhage; there appeared to be an association with depression (86). Somewhat at odds with the ICHD-3 criteria for 6.2.4.1, the authors noted that "there was usually a delay of weeks or months between ICH and the first headache episode" (86). The new-onset headaches were primarily tension-type in character. Interestingly, 19% of their patients with a pre-existing history of recurrent headache experienced headache remission after ICH.

Clinical implications

- Persistent headache is not an uncommon complication of ischemic stroke or non-traumatic intracranial hemorrhage.
- At least for patients with ischemic stroke or SAH, development of persistent headache appears to correlate with younger age.
- At least for ischemic stroke and ICH, the clinical phenotype of headache reported by patients is more often that of chronic tension-type headache than migraine.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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DOI: 10.1177/0333102421999045
URN: urn:nbn:de:hbz:465-20230526-125645-0