Headache and Acute Stroke

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Abstract Disorders associated with prominent headaches, such as migraine with aura and cerebral arterial and venous diseases, increase the risk of ischemic and hemorrhagic stroke. Central nervous system vasculitis, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, and cerebral venous thrombosis are all disorders associated with severe or persistent headache in which the risk for ischemic and hemorrhagic stroke is increased. Hemorrhagic strokes, more frequently than ischemic strokes, present with distinct headaches, usually accompanied by focal neurological symptoms. Pregnancy, and especially the postpartum period, is a time of overlap between new-onset headache and stroke risk.

Keywords Acute stroke · Headache · Migraine · Venous diseases · Hemorrhagic stroke

Introduction

The interaction between headache and acute stroke is complex and multidimensional. Headaches are such a universal

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experience that some coincidental overlap is to be expected between a common symptom and a widespread neurological disorder. However, some cerebrovascular disorders that cause acute or chronic headaches are noted in the International Classification of Headache Disorders, 3rd edition (beta version) of the International Headache Society (IHS) as "headache attributed to cranial or cervical vascular disorder." [1] Headache may be the sole or predominant symptom of multiple different types of acute stroke [2, 3•] Acute stroke is further differentiated as acute ischemic stroke due to thrombotic or embolic arterial disease and the less common acute hemorrhagic stroke such as subarachnoid hemorrhage (SAH) or intracerebral (intraparenchymal) hemorrhage (ICH). Cerebral venous thrombosis (CVT) is an uncommon and often clinically obscure cause of headache, which may be the only symptom of the disorder. Disorders of cerebral arterial vessels, both inflammatory and non-inflammatory, can be a cause of headache, including multiple types of arteritis, reversible cerebral vasoconstriction syndrome (RCVS), and posterior reversible encephalopathy syndrome (PRES). Headache is a prominent symptom in cerebrovascular disorders involving disruption of the arterial wall, such as arterial dissection, aneurysmal rupture, and arterial leakage, causing intracranial hemorrhage. In the case of arterial thromboembolic disease, focal neurological symptoms, with accompanying neurological deficits on examination, generally overshadow complaints of headache.

Disorders in which headache is a prominent symptom may increase the risk of ischemic or hemorrhagic stroke. Primary headache disorders are not usually associated with increased stroke risk, with the notable exception of migraine with aura [4]. Multiple secondary headache disorders may be associated with increased risk of stroke. Giant-cell arteritis (GCA) is a cause of headache in the elderly that increases the risk of hemispheric and retinal infarcts [5]. Patients with stroke-related hereditary conditions such as CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts

and leukoencephalopathy), MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke), and hereditary hemorrhagic telangiectasia are predisposed to migraine headache as well as to ischemic and hemorrhagic stroke.

Headache as a Risk Factor for Acute Stroke

The presence of a headache disorder may indicate a risk of acute ischemic or hemorrhagic stroke such as ICH. Migraine with aura is the most common headache type with ischemic and, to a much lesser extent, hemorrhagic stroke. Migraine without aura is not considered a risk factor for acute stroke [6].

Migraine and Risk of Acute Stroke

The correlation between migraine with aura and acute ischemic stroke is complex, with some infarcts occurring as a prolongation of the usual migraine aura (migrainous infarction). These migrainous infarcts generally occur in younger women and in the posterior circulation territory [1]. Migraine with aura is an independent risk factor for ischemic stroke both during and remote from the migraine headache [4, 7]. Combined (estrogen and progestin) oral contraceptives, cigarettes, and uncontrolled hypertension magnify the stroke risk associated with migraine with aura. While the correlation between migraine with aura and acute ischemic stroke is usually associated with stroke in a younger population, it has also been noted with older patients who have large-vessel atherosclerotic and cardiac disease [8]. The cause of the epidemiologically noted association between stroke and migraine with aura is unclear, and is likely multifactorial. Abnormalities of the arterial vasculature (e. g., vasospasm, dissection, small-vessel arteriopathy), the blood (e. g., elevated von Willebrand factor, platelet activation, antiphospholipid antibodies), and the heart (e. g., patent foramen ovale, atrial septal aneurysm) are thought to be mechanisms for ischemic stroke.

The gender-specific association between migraine with aura and acute stroke reflects the female predominance of migraines. Data from the Women's Health Study confirmed that women with migraine with aura have a greater risk of cardiovascular as well as cerebrovascular disease [4]. Women with active migraine with aura had an increased risk of ischemic stroke, myocardial infarction, myocardial revascularization, angina, and vascular death, with increased risk noted after approximately six years of follow-up. Women with migraine without aura saw no increased risk of any vascular event [9]. The association between migraine with aura and ischemic stroke is less well defined in men, due in part to the decreased prevalence of migraine in men. In a prospective cohort study of participants in the Physicians' Health Study, men who reported migraine were at significantly increased risk of cardiovascular disease and myocardial infarction compared to men without a history of migraine [10]. There was an association between migraine and ischemic stroke (age-adjusted HR 1.84; 95 % CI, 1.10–3.08; P=.03) for migraineurs younger than 55 years of age compared to men without migraine.

The association between migraine and ICH is a controversial issue [11]. In a meta-analysis of eight studies (four case-control and four cohort studies) involving a total of 1,600 hemorrhagic strokes, researchers found the risk of hemorrhagic stroke was greater in females with any migraine (1.55; 95 % CI, 1.16–2.07; P=0.003) and female migraineurs younger than age 45 (1.57; 95 % CI, 1.10–2.24; P=0.012) compared with control subjects [12]. A population-based age- and sex-matched cohort study indicated that migraine was linked to an increased risk of hemorrhagic stroke [13].

Secondary Headache with Stroke Risk

Giant-cell arteritis (GCA), an inflammatory disorder of the medium-sized extracranial arteries, is a major cause of headache in the elderly. GCA is also associated with intracranial arteritis, systemic symptoms, and polymyalgia rheumatic. If untreated, GCA can cause ischemic optic neuropathy or ischemic stroke, which is often in the posterior circulation. The diagnosis of GCA is made when a superficial temporal artery biopsy shows vasculitis with mononuclear cell inflammatory infiltrates, often with giant cells. Biopsy-proven GCA is treated with steroids, generally high-dose prednisone [5]. Leukodystrophies may be associated with headache, either as an intrinsic part of the disease or related to ischemic or hemorrhagic stroke occurring as a complication of the disorder. NOTCH3 gene mutations within the first 24 exons result in the gain or loss of a cysteine amino acid, leading to CADASIL. Other exonic NOTCH3 variations may increase the risk of large- and small-vessel ischemic stroke [14]. The characteristic white matter lesions seen on FLAIR in CADASIL involving the anterior temporal lobes and the external capsule region are assumed to be ischemic in origin. However, CADASIL rarely can be linked to hemorrhagic stroke [15]. Diffuse leukoencephalopathy and intracerebral hemorrhage may also be found in COL4A1 and COL4A2 disorders, which can be differentiated clinically by other developmental and systemic findings [16].

Headache at Presentation of Acute Ischemic Stroke and Transient Ischemic Attack (TIA)

Headache as premonitory or presenting symptom is more frequently associated with hemorrhagic than ischemic stroke. The markedly different intracranial pressure shifts that occur with ischemic and hemorrhagic stroke prevent a unifying characteristic headache among all stroke types. In a study of patients with both ischemic and hemorrhagic stroke,

headaches generally started on the day of stroke. They were more often continuous, pressure-type, bilateral, and located in the anterior region, increased with movement and cough, and lasted for a mean of 3.8 days [17].

Headache is a common symptom of ischemic stroke and TIA that is often overlooked in the setting of other ischemic stroke symptoms and signs. Rapid diagnosis of acute ischemic stroke in patients presenting within hours of the onset of neurological symptoms can identify patients who are suitable for thrombolytic therapy or mechanical revascularization. While an emergent CT scan of the head can rule out acute hemorrhage, the lack of evident acute change on CT scan cannot distinguish between acute ischemic stroke and non-cerebrovascular causes of headache combined with acute neurological deficits. The presence of a prominent headache associated with focal ischemic stroke symptoms may delay diagnosis and appropriate treatment. Conversely, non-ischemic causes of headache with focal neurological deficits, such as migraine with aura or headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL), may be confused with acute ischemic stroke, leading to inappropriate thrombolytic treatment. Intravenous thrombolytic therapy may cause ICH in some cerebrovascular cases of headache with focal neurological symptoms such as PRES or CVT.

The location and etiology of the stroke is a determining factor in the presence of headache, as the complaint is common with arterial dissection causing a large-vessel thromboembolic cortical infarct but rare with stroke due to small-vessel occlusion causing lacunar infarction. The frequency of headache at onset of ischemic stroke varies from 7.4–27 %, reflecting inconsistent patient sampling [18–21]. In many incidence studies, subjects with aphasia, confusion, or decreased level of consciousness were excluded, suggesting that the incidence of headache with acute ischemic stroke may be even higher than reported. In a study of 2,196 patients, approximately 27 % experienced headache at the onset of TIA or acute ischemic stroke. Headache at stroke onset was found to be associated with female sex, history of migraine, younger age, cerebellar stroke, and blood pressure values on admission of <120 mm Hg systolic and <70 mm Hg diastolic [21]. With TIA, the frequency of headache ranged from 16–36 % [20, 22]. While it was classically thought that headache at ischemic stroke onset was due to cardioembolism [23••, 24], more recent studies have shown that there is no statistically significant difference between the incidence of headache at the onset of cardioembolic versus large-vessel thrombotic stroke [21, 25]. The presence of headache is less common at the onset of lacunar stroke compared to non-lacunar stroke, ranging from 13–23 %, suggesting that this stroke subtype is actually a negative predictor of stroke-associated headache [20, 25–27]. Significantly more posterior circulation (vertebrobasilar arteries, posterior cerebral arteries) infarcts are associated with headache at onset than those in the anterior circulation (carotid arteries and its branches) [20, 21, 25, 28•]. Headache is also more common in cortical than subcortical infarcts [18, 25]. Acute stroke patients with a history of migraine note headache associated with stroke more often than acute stroke patients without migraine. Patients with migraine have been shown to be more likely to have a brainstem ischemic stroke, compared to anterior circulation strokes found in non-migraineurs [29].

There is a wide range of stroke-related headache descriptions. The onset of pain can be abrupt, such as a "thunderclap" headache, or it can be gradual [22, 30, 31]. The headache location can be holocephalic or focal. In the case of unilateral headache, the location is more often ipsilesional than contralesional, although headache location is not a reliable indicator of stroke location. [17, 21, 25, 27]. Headache quality can be dull, pressing, stabbing, throbbing, or continuous; rarely, headaches are burning or pulsatile [20, 25]. The mean duration of headache is 3.8±2.1 days, and when analyzed by stroke subtype, is longest in cardioembolic (mean 29.5± 28 hours) and thrombotic (mean 26.5±18 hours) infarcts [17, 25]. The severity of headache reported among studies is inconsistent, but it is rarely incapacitating [25, 27].Headache severity, however, has not been consistently shown to be associated with stroke severity, infarct size, or stroke localization [18, 27].

The mechanism of headache in ischemic stroke and TIA is not well understood. The sensory nerve fibers from the superficial temporal artery, superior sagittal sinus, and middle meningeal artery pass through both the trigeminal and rostral cervical spinal nerves, and terminate in the ventrolateral part of the C1–C3 dorsal horns and the caudal and interpolar divisions of the spinal trigeminal nucleus. Vascular projections into the brainstem and central regions appear to be involved in the central processing of noxious craniovascular signals [32]. Some of the demographic findings in stroke-associated headache can be explained within this trigeminovascular framework. Headache at stroke onset is more frequent in posterior circulation infarcts, which may be due to a more densely innervated vasculature in the posterior versus anterior circulation.[17, 33]. The higher frequency of headache at stroke onset in younger patients may be due to decreased atherosclerotic burden and thus increased vessel elasticity, allowing vessels to distend in ischemia and trigger the trigeminovascular system [3•, 23••].

Data are conflicting with regard to the prognostic significance of headache at stroke onset. An older study found headache to be an independent factor associated with early neurological deterioration in patients with first-ever acute ischemic stroke [34]. However, recent studies suggest that patients who experience headache in association with TIA or minor ischemic stroke appear to have a better vascular prognosis, with a lower risk of vascular death, than those without concomitant headache. In patients who developed headache at

the onset of TIA or minor ischemic stroke, there was a lower risk of death from vascular events as well as lower frequency of neurologic deterioration during hospitalization and improved National Institutes of Health Stroke Scale scores on discharge compared to patients who did not have onset headache [26, 28•].

Central Nervous System Vasculitis

Primary CNS vasculitis, also known as primary angiitis of the CNS (PACNS), as well as systemic vasculitides with secondary CNS involvement, often occur with headache as the initial symptom. The neurological manifestations of primary CNS vasculitis are diverse, but generally consist of headache, alteration in consciousness, focal weakness, seizures, or stroke, either hemorrhagic or ischemic. White matter lesions seen on MRI may be non-specific, and four-vessel catheter angiography can be non-diagnostic. Perivascular inflammation found on biopsy of leptomeningeal and cortical tissue is diagnostic in the appropriate clinical setting. PACNS is an inflammation of blood vessels of any caliber or location in the brain and spinal cord, producing a wide spectrum of CNS involvement. Men and women are affected at approximately the same rate. Average age of diagnosis in adults is 50 years [35], although vasculitis can affect adults and children of all ages [36, 37].

One of the most common presenting symptoms of PACNS, headache can be due to the arterial changes that occur as a result of the vasculitis or to the hemorrhagic and ischemic complications of the disorder [38]. Headache can result from involvement of the blood vessels supplying brain, meninges, and venous draining structures. The cytokine release (calcitonin gene-related peptide, substance P) within structures innervated by the trigeminal nerve produces a sensation of pain that is consequently transmitted to the cerebral cortex and limbic system through the brainstem and thalamus, resulting in headache. Headache presentation varies from localized to generalized, without any specific characteristics. Severity can vary during the course of the disease. It can be mild and slowly progressive at presentation, and then spontaneously remit [39].

Secondary headache associated with vasculitis can result from direct complications of vasculitis such as ICH or ischemic stroke [38]. In their analysis of 101 patients, Salvarani et al. found that stroke and persistent neurological deficit was the second-most common feature on presentation after headache, noting a total of 40 strokes and 28 TIAs [40]. Cerebral infarction and large-vessel involvement at onset have been associated with higher mortality and morbidity in patients with PACNS [35]. Intracranial hemorrhage with CNS vasculitis, both primary and secondary, is less common and is seen in 11–12 % of patients [41]. Intracranial and intraspinal hemorrhage is predominantly seen in patients with necrotizing vasculitis [42]. Parenchymal hemorrhage is more common than SAH, which is rarely found in patients with primary CNS vasculitis, although it has been noted in secondary vasculitis, including lupus and Churg-Strauss syndrome [43, 44]. Early recognition of CNS vasculitis is important, as treatment with corticosteroids, with or without cytotoxic drugs, can often prevent ischemic and hemorrhagic complications. The differential diagnosis of CNS vasculitis includes reversible cerebral vasoconstriction syndrome as well as other less common multifocal ischemic disorders such as intravascular lymphoma.

Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is a collective term used for reversible angiopathies that presents acutely with a sudden severe "thunderclap" headache and multifocal arterial vasoconstriction [45, 46]. RCVS was proposed as a unifying term for multiple vasoconstrictive syndromes of different etiologies, such as Call-Fleming syndrome, postpartum angiopathy, drug-induced cerebral vasculopathy, and benign angiopathy of the CNS. About 60 % of patients develop the syndrome in the postpartum period or after exposure to vasoactive substances [46]. RCVS is more common in women, with an average age at presentation of 45 years.

Thunderclap headache is a presenting feature of RCVS, occurring in 95–100 % of cases [45]. Most patients describe these symptoms as multiple recurrent "thunderclap" headaches, which are severe and sudden in onset, reaching peak intensity in less than one minute. One of the defining features of RCVS is transient cerebral vasoconstriction that resolves within one to three months. The presence and subsequent resolution of vasospasm are confirmed by cerebral angiography, which has been considered the gold standard for diagnosis of RCVS [45]. CT angiography (CTA) and magnetic resonance angiography (MRA) are less invasive methods for identifying the arterial changes observed in RCVS and, importantly, ruling out the presence of a cerebral aneurysm and the diagnosis of aneurysmal subarachnoid hemorrhage. The typical angiographic pattern consists of alternating areas of arterial constriction and dilatation, often called "beading" or "sausage on a string," in multiple vascular beds (Fig. 1). There is no intrinsic inflammation of the blood vessels as seen in CNS vasculitis. However, RCVS may be associated with extracranial arterial dissection, further complicating the characteristics of the headaches, with a sudden acute headache and superimposed more chronic headaches [47]. Unlike in PACNS, SAH in RCVS is more common than ICH or ischemic stroke. The common characteristic feature of SAH in RCVS is the cortical location of the hemorrhage (Fig. 2), which is commonly small in volume. Complications of RCVS include cerebral infarction (4–40 %), ICH (6–20 %), SAH (22–34 %), and PRES (less than 10 %). Occasionally, complications of RCVS may prove fatal, with mortality rates as high as 2 % [46, 48, 49].
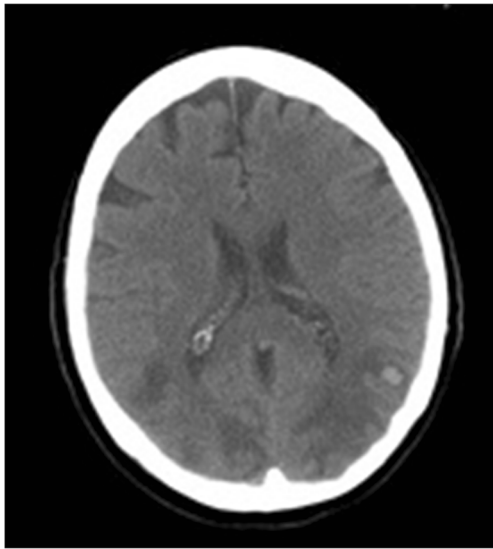
Fig. 1 A 69-year-old woman with post-infectious glomerulonephritis and uncontrolled hypertension developed a 10/10 headache. A CT scan of the head showed bilateral posterior hypodensity and a left parietal subcortical intraparenchymal hemorrhage, consistent with PRES with ICH

Distinguishing between PACNS and RCVS is crucial, as treatment for the inflammatory condition requires immunosuppressive therapy such as steroids and immunosuppressants, whereas RCVS tends to be a self-limiting condition that responds well to calcium channel blockers and usually has a more benign prognosis.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) is characterized clinically by headache, altered consciousness, visual disturbance, seizures, and less commonly, focal neurological deficits. PRES can be associated with many medical conditions, including acutely elevated blood pressure, pre-eclampsia/eclampsia, allogeneic bone marrow transplantation, solid organ transplantation, autoimmune diseases, chemotherapy, and electrolyte abnormalities. The development of vasogenic edema that is characteristic of PRES may be related to severe hypertension, leading to the breakdown of cerebral autoregulation, with hyperperfusion and then endothelial injury/vasogenic edema. Alternatively – or in addition – vasoconstriction and hypoperfusion can lead to brain ischemia and subsequent fluid leakage [50]. Clinical and radiographic findings indicate that hypertension is not always present in PRES. Marra et al. recently suggested a new model where activation of the immune system and consequent endothelial activation start a molecular cascade, ultimately resulting in the production of molecules that alter the normal homeostasis of the blood-brain barrier [51]. This alteration consists of a weakening of brain vessel tight junctions, which allows fluid leakage and edema. In this scenario, hypertension would be an epiphenomenon of the underlying mechanism and not the cause.

Along with clinical features, brain MRI plays a major role in the diagnosis of PRES [52–54]. Changes from PRES on MRI are found in the brain watershed zones, with variable involvement of the cortex and subcortical and deep white matter. Three hemispheric patterns, which can be found individually and in combination, include a holohemispheric watershed pattern, a superior frontal sulcal pattern, and primary parietal-occipital involvement. A central pattern with brainstem and basal ganglia as well as isolated brainstem involvement are described as well [55–57]. Focal areas of restricted diffusion, representing infarction or tissue injury with cytotoxic edema, are uncommon (11 %–26 %) and appear to be associated with an adverse outcome [54].
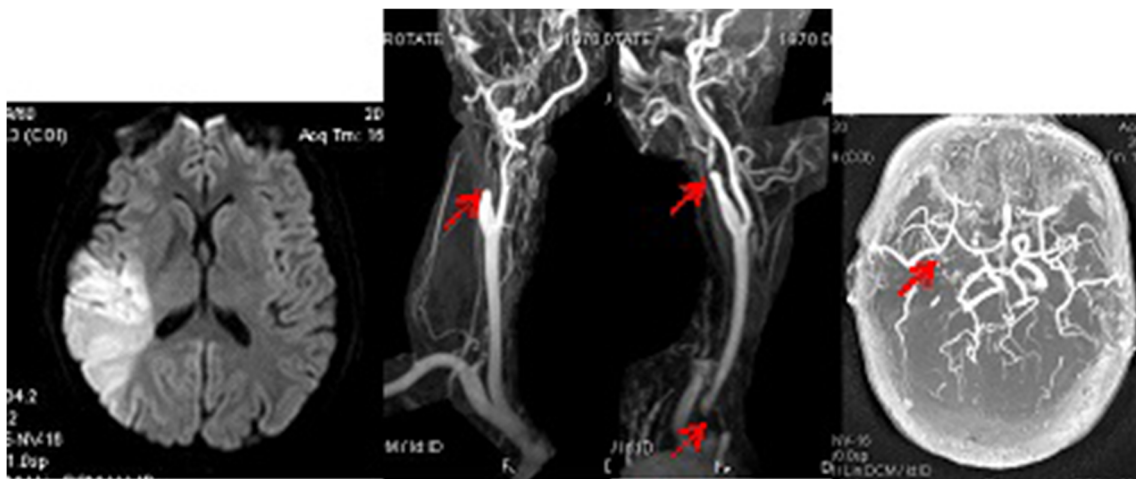
Fig. 2 A 40-year-old woman who developed a holocephalic headache and dizziness four days after an uncomplicated delivery. On examination, her blood pressure was normal. She had mild left-sided weakness. Imaging shows the **a** diffusion-weighted imaging sequence on MRI and **b** MRA of the head and neck. A large right middle cerebral artery infarct is noted in the setting of a posterior MCA branch occlusion (*arrow*), with multiple arterial dissections in the anterior extracranial circulation (*arrows*)

Headache is a common presentation of PRES, described by patients of all ages. In a small series of 16 patients, Yoon et al. reported that headache was present in 25 % [53]. PRES is more common in women, even after adjusting for eclampsia/pre-eclampsia, which is PRES with a specific trigger. The headache characteristics are strongly dependent on the triggering factor causing PRES, as well as the cerebrovascular complications of ischemic infarct, ICH, and SAH. Ischemic infarct is an early sign of irreversible cerebral damage associated with adverse outcomes [9, 13]. RCVS should be excluded in these patients [46]. While cerebral hemorrhage is less common than infarction in PRES, minute hemorrhage, ICH, and sulcal SAH can be found on MRI [52, 58] (Fig. 1). Cerebral hemorrhage, seen in approximately 15 % of MRIs with PRES, may be more common among patients with allogeneic bone marrow transplantation or anticoagulant treatment, whereas blood pressure levels may have no influence on the bleeding risk [54, 58]. A statistically significant association has been reported between edema severity on FLAIR sequences and bleeding risk [59]. MR or conventional cerebral angiography should be considered early in cases of suspected PRES to identify and prevent those complications.

Treatment of PRES consists of correction of underlying cause and symptomatic management of the various complications. In cases of severe PRES, 44 % of survivors have been found to have severe functional impairment, with hyperglycemia at presentation and increased time to causative-factor control as predictors of poor outcome [60].

Headache in Acute Hemorrhagic Stroke

Acute hemorrhagic stroke includes ICH and SAH. Other causes of hemorrhagic cerebrovascular disease that can present with headache include CVT with hemorrhage into venous infarcts as well as epidural and subdural hemorrhage. Compared to ischemic stroke, hemorrhagic stroke is more commonly associated with headache at presentation.

Intracerebral Hemorrhage (ICH)

The frequency of onset headache in ICH is variable, at 34.4–58 % [19, 25, 27, 61]. Patients with headache are significantly more likely to be female and younger, and are likely to have radiographic evidence of intraventricular or subarachnoid hemorrhage, moderate to severe hydrocephalus, transtentorial herniation, and midline shift [62]. Patients with onset headache tend to have ICH in infratentorial and lobar regions rather than in deep locations [62, 63]. With lobar hemorrhages, a Chinese study found that those most likely to present with headache are occipital (66.7 %), temporal (61.5 %), and frontal (47.4 %) [64]. Headache location tends to be bilateral rather than focal in both deep and lobar hemorrhages [17].

Unilateral headaches tend to be ipsilesional rather than contralesional for supratentorial hemorrhages. Infratentorial hemorrhage headaches are typically diffuse, commonly described as migraine-type (40 %) or tension-type (25 %) [19]. In comparison to ischemic stroke, ICH headache is more frequently associated with nausea and vomiting in the first two days and tends to precede focal neurologic signs [17]. Patients with ICH headache are also significantly more likely to have meningeal signs and a Glasgow Coma Scale score less than 10 on presentation compared to those without headache [62]. The mean duration of headache is 58 hours to 3.94 days [17, 25]. Headache with ICH is also typically described as severe [25].

It is commonly thought that ICH headache is the result of hemorrhage causing mass effect and mechanical stretch of nociceptive afferents of the trigeminovascular system at the base of the skull [19]. Other proposed mechanisms include a massive increase in intracranial pressure, tearing and distension of the ventricular wall, abrupt rise of arterial blood pressure in the early hours after hemorrhage, and direct irritation of the trigeminovascular system by blood at the base of the skull, especially for patients with infratentorial ICH. [62, 63]. One study demonstrated that ICH patients with headache are more likely to have a history of infection or inflammation in the 15 days prior to hemorrhage, as well as higher body temperature, leukocyte count, erythrocyte sedimentation rate, IL-6 level, and TNF-α level, compared to those without headache. This suggests that the mechanism of headache may be related to inflammation and cerebral edema [61].

A recent study demonstrated that patients with ICH with onset headache had increased 30-day mortality, even after adjusting for age, gender, ICH location, and intraventricular hemorrhage [63]. Another prospective study did not find any difference in three-month mortality, Canadian Stroke Scale, or modified Rankin Scale between those with and without headache, but the residual cavity volume was significantly higher in those with headache [61].

Subarachnoid Hemorrhage (SAH)

The oft-quoted aphorism that the headache of a SAH is "the worst headache of my life" lacks specificity and sensitivity in determining the presence of SAH. A headache caused by aneurysmal rupture is notable for acuity of onset rather than extreme severity of pain. In a prospective community-based Dutch study, patients presenting with thunderclap headache were evaluated and divided into diagnoses of aneurysmal SAH, perimesencephalic SAH, and benign thunderclap headache. Among patients with aneurysmal SAH, 50 % had almost instantaneous headache, while 19 % had gradual onset of headache over minutes. Associated signs and symptoms

included loss of consciousness (26 %), transient focal symptoms (33 %), seizures (7 %), double vision (5 %), and vomiting (69 %). Half were associated with physical exertion. In contrast, patients with perimesencephalic (non-aneurysmal) hemorrhage were less likely to have almost instantaneous headache (35 %), loss of consciousness (4 %), or transient focal symptoms (9 %). However, thunderclap headache with transient focal neurologic symptoms is not specific for SAH, as it can also be seen with benign thunderclap headache [65]. The Ottawa SAH Rule is a clinical decision rule that may help to standardize the investigation of acute headache among patients suspected of having SAH. A very high sensitivity (100 %) but low specificity (15 %) was found with the following criteria: age 40 years or older, neck pain or stiffness, witnessed loss of consciousness, onset during exertion, thunderclap headache (instantly peaking pain), or limited neck flexion on examination. The Ottawa SAH Rule was not applied for patients with new neurological deficits, previous aneurysms, previous SAH, brain tumors, or history of recurrent headaches (three or more episodes over the course of six months or greater) [66].

A sentinel headache is a sudden severe headache occurring in the days to weeks prior to SAH. The reported frequency of sentinel headache has varied from 15 % to 60 %, but the clinical significance and mechanism are unclear. The report of headache occurring before SAH could be coincidental or reflect recall bias. On the other hand, a headache prior to SAH could be due to changes in aneurysmal size or to minor bleeding from the aneurysm. In a study in which sentinel headache was defined as a sudden, severe, never previously experienced headache of unknown character and intensity, lasting at least an hour, and occurring in the four weeks prior to the index SAH, patients with sentinel headache had a tenfold increase in early rebleeding, which increased the odds of death and reduced the odds of survival with good or functional outcome [67].

Cerebral Venous Thrombosis (CVT)

The occurrence of cerebral venous thrombosis has been associated with oral contraception, thrombophilia, cancer, sepsis, and dehydration [68]. Headache is the most frequent presenting symptom of CVT, and may be the only clinical presentation in 15–40 % of patients. There is no typical pattern of headache, which may be diffuse or bilateral in the majority of patients, but can be unilateral and throbbing, mimicking a migraine. In a study of 30 patients presenting with only headache, characteristics of headache associated with CVT included recent persistent headache, thunderclap headache, or pain worsening with straining, sleep/lying down, or Valsalva maneuvers [69]. In a study of 100 patients with isolated headache, 93 % patients had a complete recovery and 4 % died or were dependent, with no significant difference between early and late isolated headache [70]. Neurological

worsening was more frequent within early isolated headache patients. Headache can occur due to venous thrombosis alone or venous infarction, with or without ICH or SAH [71].

Cerebrovascular Disorders of Pregnancy that Present with Headache

During pregnancy and the postpartum period, women may have new-onset headaches that are generally primary, but may be secondary to acute stroke. Pregnancy is a time of increased stroke risk, with many cerebrovascular diseases presenting with headache [72]. The prevalence of headache during pregnancy is reported to be as high as 35 %, generally due to migraine in over 80 % of women with a history of pregestational headache [73]. However, in the rare cases of women with new-onset headache during pregnancy, over half are secondary headache. During pregnancy, and particularly in the postpartum period, women may complain of headache related to cerebrovascular complications of pregnancy, either associated with or independent of elevated blood pressure [74]. The risk of cerebrovascular disease, including ischemic stroke, ICH, and CVT, is significantly increased during the six weeks after delivery. Kamel et al. found that an elevated risk of thrombosis persisted until at least 12 weeks after delivery, although the absolute increase in risk beyond six weeks after delivery was low [75•].

As noted in a review of pregnancy-related stroke hospitalizations by Kuklina et al., the risk of pregnancy-related stroke complications is increasing [76]. Between the periods 1994–1995 and 2006–2007, the rate of any stroke (SAH, ICH, acute ischemic stroke, TIA, CVT, or unspecified) among antenatal hospitalizations increased by 47 % (from 0.15 to 0.22 per 1,000 deliveries) and among postpartum hospitalizations by 83 % (from 0.12 to 0.22 per 1,000 deliveries). At the end of the study period (2006–2007), the overall prevalence of pregnancy-related stroke hospitalizations was 0.71 hospitalizations per 1,000 deliveries. The increased risk of these headache-associated cerebrovascular diseases during pregnancy appears to be due to the increasing prevalence of traditional vascular risk factors present in women who are delaying pregnancy until an older age [77].

Headache is a prominent presenting symptom in hypertensive disorders of pregnancy (HDP) such as pre-eclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. These disorders, in which headache may be accompanied by visual disturbance, alteration in consciousness, confusion, and clonus, increase the immediate risk of pregnancy-related ischemic and hemorrhagic stroke, especially in the peripartum period. Pre-eclampsia is defined as hypertension (severe, defined as systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 110 mm Hg) in association with thrombocytopenia, impaired

liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbance [78]. Eclampsia occurs when a seizure accompanies the symptoms of pre-eclampsia. However, a seizure may be the initial symptom of a hypertensive disorder of pregnancy. The headache associated with HDP is not particularly distinctive, characterized as generally holocephalic pain of variable severity without a distinct positional component. Other headaches occurring during pregnancy such as migraine, tension-type, and post-dural puncture headaches are rarely confused with a headache associated with elevated blood pressure. After surviving a hypertensive complication of pregnancy, the woman is still at increased risk of suffering an ischemic stroke in the future. The combination of HDP and preterm delivery has been shown to confer a 3.22-fold greater risk of future stroke [79].

A history of primary headache disorder is associated with an increased risk of complications of pregnancy. The incidence of preterm delivery is higher in women suffering from migraine or tension-type headache than women who do not experience headache. The association between headache, either migraine or tension-type, and adverse perinatal outcomes was shown to be statistically significant regardless of pre-eclampsia [80]. Women who experience migraine headaches are also at increased risk of hypertensive complications of pregnancy.

Headache may herald the risk of acute stroke in other pregnancy-related disorders not associated with elevated blood pressure, such as CVT, RCVS, and arterial dissection. Headache is associated with cerebral postpartum angiopathy, a variation of RCVS, which is generally not associated with elevated blood pressure. Women in the postpartum period are at increased risk of intracranial and extracranial arterial dissection, which can present with headache or neck pain, followed by focal neurological symptoms of an acute ischemic stroke due to arterial occlusion or thromboembolism (Fig. 2). Pregnancy, fibromuscular dysplasia, and migraine headache all increase the risk for arterial dissection, with resultant acute ischemic stroke. Spontaneous arterial (coronary, aortic, cerebral) dissection occurs during pregnancy or the postpartum period, especially in older or multiparous women. The etiology of this predilection for arterial dissection in the peripartum period is unknown, but may be related to hormonal changes in the intima and media of the arterial wall or to hemodynamic stress (increased cardiac output in pregnancy). Arterial dissections associated with pregnancy can occur simultaneously at multiple sites in multiple intracranial and extracranial vessels.

Conclusions

While most headaches are relatively benign, some headache types, both primary and secondary, increase the risk of acute stroke. A headache may herald an immediate or eventual cerebrovascular event. A focused history with appropriate imaging can generally diagnose headaches that are due to cerebrovascular disease. The determination of whether a headache is due to an acute ischemic stroke or an acute ischemic stroke mimic is critically important, so that effective and safe decisions about immediate intervention can be made. Headache, especially in the immediate postpartum period, may indicate an increased risk for stroke complications of pregnancy, with the need for lowering of elevated blood pressure.

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