

# Headache in cerebrovascular diseases

Jiajie Lu , Wei Liu, Hongru Zhao

**To cite:** Lu J, Liu W, Zhao H. Headache in cerebrovascular diseases. *Stroke & Vascular Neurology* 2020;0. doi:10.1136/svn-2020-000333

JL and WL are joint first authors.

Received 10 January 2020

Revised 3 March 2020

Accepted 9 March 2020

## ABSTRACT

Headache is a common accompanying symptom of cerebrovascular diseases. The most common patterns of headache for different cerebrovascular disorders, aetiology and pathogenesis and diagnostic workup are reviewed with emphasis on distinguishing characteristics. It will be a clinical guide for physicians who treat patients with headache or cerebral vascular disease.

Headaches are divided into primary headaches, secondary headaches, painful cranial neuropathies, other facial pain and other headaches according to the Third Edition of the International Classification of Headache Diseases (ICHD-3).<sup>1</sup>

Migraine, tension-type headache and cluster headache are major primary headaches (table 1).

Item 6 in ICHD-3 is the headache attributed to cranial and/or cervical vascular disorder. It includes headaches attributed to cerebral ischaemic events, non-traumatic intracranial haemorrhage, unruptured vascular malformation, arteritis (such as giant cell arteritis, primary or secondary angiitis of the central nervous system (CNS)), cervical carotid or vertebral artery disorder (such as cranial venous disorder, other acute intracranial arterial disorder, chronic intracranial vasculopathy (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) or mitochondrial encephalomyopathy, lactic acidosis and stroke-like episode syndrome (MELAS)) and pituitary apoplexy.

Headache attributed to cranial and/or cervical vascular disorder is usually acute in onset, throbbing or thunderclap in nature, peaking rapidly and sometimes does not accompany any other local symptoms and signs. Therefore, it is very important to collect detailed history, such as the way of onset, the site, the nature and the intensity of headache and whether it is accompanied with nausea or vomiting. In addition, history, family history and history of medication are also crucial. CT or MRI of brain, transcranial Doppler (TCD), digital subtraction angiography (DSA), lumbar puncture and genetic testing are other optional examinations that may be needed for identifying the possible underlying causes.

In fact, the relationship between headache and cerebrovascular diseases is very complicated. Headache can be the prodromal or core symptom, and also a risk factor of them. In this paper, we will discuss the clinical characteristics of common cerebrovascular diseases that may be associated with headache, and hope to provide a reference for clinical practice.

## HEADACHE CAN MANIFEST AS A MAJOR SYMPTOM OF CRANIOCERVICAL VASCULAR DISEASE

In many of these conditions, such as ischaemic or haemorrhagic stroke, headache is overshadowed by focal signs and/or disorders of consciousness. Headaches associated with ischaemic stroke have no special features, which can be ipsilateral or bilateral, mild to moderate intensity and often recover within 3 months.<sup>2</sup> It is more common in posterior circulation than in anterior circulation. In haemorrhagic stroke, headache is usually severe and torturous. It can be maximal on the day of its onset and localised in accordance with the site of the haemorrhage. Some cerebrovascular diseases can cause headache and stroke simultaneously, such as subarachnoid haemorrhage (SAH), CNS vasculitis, artery dissection, cerebral venous thrombosis (CVT), and so on, in which headache is usually a warning symptom. Therefore, it is essential to be aware of the relationship between headache and cerebral vascular diseases, so that we can timely identify causes and intervene as soon as possible to avoid serious consequences (table 2).

### Subarachnoid haemorrhage

Aneurysm rupture is the major cause of non-traumatic SAH, accounting for 85% of all SAHs, whereas 10% of SAH cases are classified as idiopathic perimesencephalic haemorrhage. The remaining cases include intracranial arterial dissection, vascular malformation, CVT and reversible cerebral vasoconstriction syndrome (RCVS).<sup>3</sup> Thunderclap headache is the most common symptom of SAH, in which mortality is 30%–40%.<sup>4</sup> It is a sudden, severe, usually stabbing pain, reaching maximal intensity in less than 1 hour and lasting for



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Neurology, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China

### Correspondence to

Dr Hongru Zhao; tiantan11@163.com

**Table 1** Primary headaches and characteristics

Types	Characteristics
Migraine	Unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, association with nausea and/or photophobia and phonophobia, lasting from 4 to 72 hours.
Tension-type headache	Bilateral, pressing or tightening in quality and mild-to-moderate intensity, lasting from 30 min to 7 days.
Cluster headache	Severe in intensity, strictly unilateral to the orbital, supraorbital and temporal area or in any combination of these sites, lasting 15–180 min and occurring from once every other day to eight times a day.

days or weeks. However, initial misdiagnosis occurs in one-quarter to one-half of patients, which is usually misdiagnosed as migraine. So great attention must be paid to the sudden onset, high intensity and the description of the extreme pain. The attack of thunderclap headache may also be associated with nausea or vomiting (77% of cases), transient loss of consciousness (53% of cases) and nuchal rigidity (35% of cases).<sup>5</sup> SAH occurs during stressful events, such as physical exertion or emotional stress, in about half of the patients. However, these features are not specific to SAH. Following physical examination, analysis of the medical history, CT scan and lumbar puncture help us get final diagnosis.

### CNS vasculitis

CNS vasculitis is a kind of disease that causes inflammation and destruction of brain, spinal cord and meningeal vessels. It is divided into primary vasculitis and secondary vasculitis. Primary angiitis of the central nervous system (PACNS) is defined when vasculitis is confined to the CNS and no other system is involved. Vasculitis is considered secondary when it occurs during systemic inflammation or infection. The pathophysiological mechanism is that infiltration of immune cells within CNS blood vessel walls leading to destruction of the vessel walls. As a result,

thickening of vessel walls with alternating segments of stenosis can occur, resulting in poor blood circulation. On the other hand, weakened vessel walls can lead to ruptured vessels due to an inflammatory process.

PACNS is a rare and severe inflammatory disease. Retrospective analysis showed that there was no significant difference in prevalence between men and women. It accounts for about 1% of all vasculitis, its annual incidence is around 2.4 cases per 1 million people and has no gender differences.<sup>6</sup> The clinical features of PACNS are non-specific, which increases the difficulty of diagnosis. Patients may start with acute stroke, one or more episodes, or subacute onset with chronic headache, dementia, chronic meningitis or changes in personality.<sup>7</sup> Headache is characterised by insidious or subacute onset. The pain usually manifests as a chronic process that lasts for months as the disease progresses. Initially, the intensity is usually of mild to moderate, but it can deteriorate or improve over time; sometimes, headache is associated with cervical pain. Thunderclap headache is almost never reported, and the absence of such sudden attack helps distinguish PACNS from acute neurological conditions like RCVS and SAH. Headache alone is of little diagnostic value, but PACNS should be considered in young

**Table 2** Headache attributed to cerebrovascular diseases with clinical and diagnostic features

Types	Headache features	Diagnostic features
SAH	Thunderclap, acute, severe, long-lasting	Non-contrast-enhanced CT: sensitivity 99% in the first 6 hours, CSF: erythrocytes or xanthochromia
PACNS	Chronic, moderate, diffuse, long-lasting	CSF: lymphocyte and protein increases, MRI: ischaemic lesions in subcortical and deep white matter and grey matter
CAD	Thunderclap, acute, unilateral	CT or MRA: long, irregular stenosis, an occlusion or a dissecting aneurysm
CVT	Acute or subacute, diffuse, long-lasting	MRI: detect brain parenchymal lesions; CT/CTV: high density consistent with the position of venous sinus
MELAS	Migrainous headaches, short-lasting, mild or moderate	MRI: lace sign or ribbon sign
CADASIL	Migraine with (atypical) aura	MRI: white matter hyperintensities in the anterior temporal pole, lacunes; genetic testing: NOTCH3 mutation
RCVS	Thunderclap, acute, severe, relapsing	Angiography: segmental narrowing of branches of cerebral arteries

CAD, cervical artery dissection; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; CSF, cerebrospinal fluid; CTV, CT venography; CVT, cerebral venous thrombosis; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episode syndrome; MRA, magnetic resonance angiography; PACNS, primary angiitis of the central nervous system; RCVS, reversible cerebral vasoconstriction syndrome; SAH, subarachnoid haemorrhage.

adults without cerebrovascular risk factors when they present a history of subacute or chronic headache with focal deficits, seizures, altered cognition or disorders of consciousness.

At present, no specific laboratory indicators are used to diagnose PACNS. Cerebrospinal fluid examination is an important diagnostic tool. In most cases of PACNS confirmed by tissue biopsy, the content of lymphocyte and protein in cerebrospinal fluid increases, and the sugar content is normal.<sup>8</sup> The most common imaging manifestation is cerebral infarction, which usually develops on both sides, involving the cortex, subcortex and meninges. White matter hyperintensities are common in the T2-weighted image/fluid attenuated inversion recovery phase of magnetic resonance. The gold standard of diagnosis of PACNS is that subcortical combined with soft meningeal biopsy finds primary vascular transmural damage and vascular destructive inflammatory response.

### Artery dissection

Cervical artery dissection (CAD) is divided into internal carotid artery dissection and vertebral artery dissection (VAD), in which blood flows into the wall of the cervical artery to form an intramural haematoma, which leads to stenosis, occlusion or aneurysmal changes of the artery.

Carotid dissection is the cause of stroke in 20% of young people. The average age of onset is 44 years.<sup>9</sup> The pathophysiological mechanism of dissection is still unclear. Hypertension, migraine (especially migraine without aura), neck trauma and new infections (intracranial or systemic infections) are considered risk factors for carotid artery dissection.<sup>10</sup> In most cases, headache and neck pain can be the initial symptoms. The headache or neck pain is likely caused by the direct tear in the blood vessel wall. Blood vessels, like arteries, have many nerves surrounding them. Irritation of the vessel wall likely leads to a series of events, including proinflammatory neurotransmitters from the perivascular nerve terminals. This may cause pain away from the area of the dissection.<sup>11</sup> A retrospective study of carotid artery dissection and VAD found that 57% of patients had headache symptom.<sup>12</sup> Headache associated with CAD has no special manifestation and sometimes it mimics other headaches such as migraine, cluster headache or thunderclap headache. Headache is often acute and continuous for days or longer, and located at the same side of the affected cervical vessel. If the patient only suffers from neck pain, the degree is often mild to moderate, and if he has headache with or without neck pain, the intensity is usually moderate to severe.<sup>13</sup> Headache is more common in posterior circulation stroke than in anterior circulation, and the reasons have been speculated as follows. First, there are more dense vessels and abundant trigeminal nerve distribution in the posterior circulation system; second, the posterior cerebral arteries and superior cerebellar arteries supply part of the dura mater; third, the posterior circulation vessels might be more susceptible to spreading depolarisations.<sup>14</sup>

CAD can be identified by a variety of different imaging modalities including CT angiography (CTA), MRI and DSA. Each of them offers their own advantages and disadvantages based on the clinical scenario. Therefore, the final diagnosis of carotid artery dissection should be made by combining the medical history, clinical manifestations and dynamic imaging findings.

### Cerebral venous thrombosis

CVT is a special type of cerebrovascular disease characterised by obstruction of cerebral venous reflux, often accompanied by intracranial hypertension. The annual incidence of CVT is 1/250 000.<sup>15</sup> CVT is a common cause of cerebrovascular diseases in young people. The age of onset is mostly between 20 and 50 years old. The ratio of male to female is 1–1.5:5, which is the result of sex-specific risk factors such as oral contraceptives, pregnancy and puerperium. About 85% of patients have one or more risk factors, including hereditary or secondary thrombogenic tendency<sup>16</sup> (eg, factor V Leiden mutation, thrombin G20210A mutation, protein C, protein S or antithrombin III deficiency), pregnancy, postpartum or oral contraceptives, acute or chronic infections or inflammatory diseases, blood system diseases, tumours or injuries, but some patients have unknown causes.

CVT can present four clinical syndromes: isolated intracranial hypertension, focal neurological deficit, diffuse encephalopathy and cavernous sinus syndrome. Severe headache is the first and most common symptom of CVT and reported by 60%–90% of patients.<sup>17</sup> Headache associated with CVT is elicited by intracranial hypertension. It has no specific features, but it is usually diffuse, progressive and severe, and associated with other signs of intracranial hypertension. It can be unilateral and sudden (even thunderclap), or mild, and sometimes mimics migraine. It worsens with manoeuvres that increase intracranial pressure and is usually refractory to common analgesics.<sup>18</sup> Headache often accompanies with focal neurological symptoms, but in 10% of patients can be the only symptom.<sup>19</sup> Thirty to forty per cent of patients develop acute symptomatic seizures, with approximately 80% of seizures occurring actually before the diagnosis has been established. Superficial venous system thrombosis and brain parenchymal lesions generally have focal neurological deficit while deep venous system thrombosis often presents mental disorder, gaze paralysis, diffuse encephalopathy or coma.<sup>20</sup> Given the absence of specific characteristics of headache caused by CVT, it should be considered in the patients with recently persistent headache, especially in the presence of a potential prethrombotic state.

The diagnosis of CVT depends more on imaging. Magnetic resonance venography (MRV) and CT venography (CTV) are both appropriate for diagnosis of CVT, but the former has more advantages for the visualisation of brain parenchymal lesions. In theory, DSA is still the gold standard for the diagnosis of CVT. However, it is not routinely used because of its invasiveness and the risk



of increased intracranial pressure caused by improper operation. Diagnostic accuracy of CTV and MRV for the cerebral venous system diseases is higher. MRV with GRE (gradient recalled echo) or SWI (susceptibility weighting imaging) sequences can maximise diagnostic accuracy, especially in patients with acute CVT and suspected isolated cortical venous thrombosis.<sup>21</sup>

### **Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episode syndrome**

MELAS is the most common maternal hereditary mitochondrial encephalomyopathy. It is associated with mitochondrial DNA gene and nuclear DNA (nucleus) gene mutations, which causes the disorder of mitochondrial protein synthesis and oxidative phosphorylation. The age of onset is generally under 45 years old.<sup>22</sup> Eight-four to ninety-nine per cent of patients have stroke-like seizures. Fifty-four to ninety-one per cent of patients present with pulsatile headache accompanied with frequent vomiting. The migrainous headaches can precipitate stroke-like episodes. On the other hand, the headache attack is more severe during the stroke-like episodes. In most of the patients, headaches were short-lasting and often mild or moderate intensity.<sup>23</sup> The high prevalence of migraine in MELAS is independent of sex, phenotype or genotype. Epilepsy, myoclonus and stroke-like episodes are more frequent in MELAS cases with migraine than without migraine. Moreover, migraine is a phenotype of MELAS and an early manifestation of mitochondrial respiratory chain dysfunction in the CNS.<sup>24</sup>

The level of lactic acid in blood and cerebrospinal fluid and the lactic acid peak in magnetic resonance spectroscopy are important evidence for patients suspected of MELAS. The brain MRI of patients with MELAS often shows diffusion limited in temporal, parietal and occipital cortex during stroke-like attack, which means layered necrosis, also called 'lace sign' or 'ribbon sign'. Some patients had basal nucleus calcification, brain atrophy and ventricular enlargement. The characteristic morphological changes of muscle biopsy in patients with MELAS display typical ragged-red fibres by modified Gomori staining, and strong succinate dehydrogenase (SDH) reactive blood vessels by SDH staining. From the molecular genetic mechanism, genetic mutation at site of A3243G in the MT-TL1 gene encoding tRNA was found in 80% of patients with MELAS, and mutations at site of T3271C or A3252G can also cause MELAS.<sup>25</sup>

### **Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy**

CADASIL associated with subcortical infarction and leucoencephalopathy is a non-atherosclerotic arteriopathy caused by Notch 3 gene mutation and is the most common cause of hereditary stroke in adults. The clinical features include migraine, psychiatric symptoms, progressive cognitive decline and recurrent stroke. Migraine usually occurs before the age of 20, and white matter abnormalities in T2 phase on MRI are common between

the ages of 20 and 30. Motor dysfunction, apathy, executive dysfunction and dementia caused by ischaemic stroke often occur between the ages of 40 and 70.<sup>26</sup> Although other types of migraine have been reported, the most common type of headache in 40% of cases is migraine with aura (MA).<sup>27</sup> MA in CADASIL is the most commonly typical aura with visual or sensory symptoms. Frequency of migraine can vary, but a majority of patients have less than one attack per month, as high as 80% in one 2015 study.<sup>28</sup> Women with CADASIL are more likely to have migraine aura than men. The characteristics of migraine are different from those of the general population. The aura period is longer and more complex. Nowadays it is recognised that MA is an undisputed risk factor for ischaemic stroke. Several mechanisms like genetic predisposition, hypercoagulability, increased platelet aggregability, hyperviscosity, and so on are speculated to be involved.<sup>29</sup> In CADASIL, up to 70% biopsy-confirmed patients have ischaemic events, which tend to occur repeatedly and manifest in many ways.

The diagnosis of CADASIL in patients with headache can be particularly challenging, as headache may precede other clinical or radiographic clues. For young patients with MA, ischaemic events, psychiatric symptoms and progressive cognitive impairment, CADASIL should be fully considered. The latest diagnostic criteria proposed by Japan are that the age of onset is less than 55 years old; at least two clinical manifestations are accorded with: subcortical dementia, long bundle sign, pseudobulbar palsy, stroke-like attacks with focal neurological deficits, mood disorders, migraine; autosomal dominant inheritance; white matter lesions involving the anterior temporal lobe detected by MRI and CT; excluding white matter malnutrition; mutations in exons 2–24 that result in the acquisition or deletion of cysteine residues; and GOM (granular osmiophilic material) is found under pathological electron microscopy.<sup>30</sup>

### **Reversible cerebral vasoconstriction syndrome**

RCVS was first reported in 1988 by Call and Fleming. It used to be called Call-Fleming syndrome. RCVS often presents as a recurrent episode of severe thunderclap headache, and accompanied by diffuse segmental stenosis of intracranial artery, which can recover within 3 months. The pathogenesis of headache may include reversible dysregulation of cerebral arterial tone, autonomic overactivity, endothelial dysfunction and oxidative stress.<sup>31</sup> The peak age of RCVS is 42 years old and is considered a common cause of stroke in young adults.<sup>32</sup> The underlying causes of RCVS are unclear, but there are many triggers involved. Common causes include drug exposure (selective serotonin reuptake inhibitors, phenylpropanolamine, pseudoephedrine, cyclophosphamide, tacrolimus), marijuana use, pregnancy and puerperium, blood transfusion, head trauma, cervical or spinal cord injury, neurosurgery, and so on.<sup>33</sup>

Thunderclap headache is usually recurrent in a few days or weeks, often bilateral and lasting about 1–3 hours, accompanied by nausea and vomiting. Headaches are often caused by exertion, sexual activity, Valsalva manoeuvre, mood, bath and/or shower. Seventy-five per cent of patients have headache accompanied with fluctuating focal neurological dysfunction and epileptic seizures. Acute headache caused by RCVS may be a warning sign before stroke.<sup>34</sup> Although thunderclap headache is similar to RCVS and SAH, a few details help distinguish between them: they have common onset and localisation, but in RCVS, headache lasts for up to 3 hours while in SAH it can last for days or weeks; in contrast to the numerous episodes of RCVS, single episodes are usually described in SAH.

DSA is still the gold standard for its diagnosis. The sensitivity of brain CTA/magnetic resonance angiography in the diagnosis of RCVS is about 80%. Typical manifestations are multiple beaded stenosis of intracranial vessels, most of which last 1–2 weeks after headache attack. TCD can dynamically detect intracranial blood flow rate, which is of great significance in displaying cerebral vasospasm.<sup>35</sup>

In order to improve the diagnostic accuracy of RCVS, a new diagnostic score RCVS2 has been developed. The scores include R (recurrent or single thunder-like headache, positive predictor), C (intracranial involvement, negative predictive factor), V (vasoconstriction, positive predictive factor) and S (gender and SAH, positive predictor), ranging from –2 to 10, and 10 means probable RCVS. The combination of clinical features and imaging results is necessary for the diagnosis of RCVS.<sup>36</sup>

## SUMMARY

In a word, we need to keep in mind the relationship between headache and cerebrovascular diseases. When it comes to the condition in which headache presents as a major symptom, especially acute in onset, throbbing or thunderclap in nature and peaking rapidly, we need to consider the possibility of following diseases such as SAH, CAD, CVT, RCVS, and so on. A comprehensive combination of characteristics of headache, detailed medical history, physical examination and necessary laboratory and imaging examinations are very important for identifying the aetiology. Good prognosis is based on clear aetiology and individualised precise treatment.

**Contributors** JL and WL proposed the overall structure and drafted the manuscript. HZ provided critical feedback and helped shape the manuscript. All authors contributed to the final version of the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially,

and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## ORCID iD

Jiajie Lu <http://orcid.org/0000-0002-0865-8240>

## REFERENCES

- Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders. In: *Cephalalgia*. 3rd ed, 2018; 38: 1–211.
- Oliveira FAA, Sampaio Rocha-Filho PA. Headaches attributed to ischemic stroke and transient ischemic attack. *Headache* 2019;59:469–76.
- Ducros A, Boussier M-G. Thunderclap headache. *BMJ* 2013;346:e8557.
- Sherlock M, Agha A, Thompson CJ. Aneurysmal subarachnoid hemorrhage. *N Engl J Med* 2006;354:1755–7.
- Yang C-W, Fuh J-L. Thunderclap headache: an update. *Expert Rev Neurother* 2018;18:915–24.
- Salvarani C, Brown RD, Christianson T, et al. An update of the Mayo clinic cohort of patients with adult primary central nervous system vasculitis: description of 163 patients. *Medicine* 2015;94:e738.
- Hajj-Ali RA, Calabrese LH. Diagnosis and classification of central nervous system vasculitis. *J Autoimmun* 2014;48–49:149–52.
- Beuker C, Schmidt A, Strunk D, et al. Primary angiitis of the central nervous system: diagnosis and treatment. *Ther Adv Neurol Disord* 2018;11:1756286418785071.
- Giannini N, Ulivi L, Maccarrone M, et al. Epidemiology and cerebrovascular events related to cervical and intracranial arteries dissection: the experience of the city of Pisa. *Neurol Sci* 2017;38:1985–91.
- Debette S. Pathophysiology and risk factors of cervical artery dissection: what have we learnt from large hospital-based cohorts? *Curr Opin Neurol* 2014;27:20–8.
- Sheikh HU. Headache in intracranial and cervical artery dissections. *Curr Pain Headache Rep* 2016;20:8.
- Diamanti S, Longoni M, Agostoni EC. Leading symptoms in cerebrovascular diseases: what about headache? *Neurol Sci* 2019;40:147–52.
- Gallerini S, Marsili L, Bartalucci M, et al. Headache secondary to cervical artery dissections: practice pointers. *Neurol Sci* 2019;40:613–5.
- Wang Y, Cheng W, Lian Y, et al. Characteristics and relative factors of headache caused by cervicocerebral artery dissection. *J Neurol* 2019;266:298–305.
- Devasagayam S, Wyatt B, Leyden J, et al. Cerebral venous sinus thrombosis incidence is higher than previously thought: a retrospective population-based study. *Stroke* 2016;47:2180–2.
- Lauw MN, Barco S, Coutinho JM, et al. Cerebral venous thrombosis and thrombophilia: a systematic review and meta-analysis. *Semin Thromb Hemost* 2013;39:913–27.
- Silvis SM, de Sousa DA, Ferro JM, et al. Cerebral venous thrombosis. *Nat Rev Neurol* 2017;13:555–65.
- Cumurciuc R, Crassard I, Sarov M, et al. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. *J Neurol Neurosurg Psychiatry* 2005;76:1084–7.
- Mehta A, Danesh J, Kuruvilla D. Cerebral venous thrombosis headache. *Curr Pain Headache Rep* 2019;23:47.
- Ferro JM, Canhão P, Boussier M-G, et al. Early seizures in cerebral vein and dural sinus thrombosis: risk factors and role of antiepileptics. *Stroke* 2008;39:1152–8.
- Coutinho JM, Gerritsma JJ, Zuurbier SM, et al. Isolated cortical vein thrombosis: systematic review of case reports and case series. *Stroke* 2014;45:1836–8.
- Marques-Matos C, Reis J, Reis C, et al. Mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes presenting before 50 years of age: when a stroke is not just a stroke. *JAMA Neurol* 2016;73:604–6.
- Kraya T, Deschauer M, Joshi PR, et al. Prevalence of headache in patients with mitochondrial disease: a cross-sectional study. *Headache* 2018;58:45–52.
- Vollono C, Primiano G, Della Marca G, et al. Migraine in mitochondrial disorders: prevalence and characteristics. *Cephalalgia* 2018;38:1093–106.
- El-Hattab AW, Adesina AM, Jones J, et al. Melas syndrome: clinical manifestations, pathogenesis, and treatment options. *Mol Genet Metab* 2015;116:4–12.



- 26 Vinters HV, Zarow C, Borys E, *et al.* Review: vascular dementia: clinicopathologic and genetic considerations. *Neuropathol Appl Neurobiol* 2018;44:247–66.
- 27 Liem MK, Oberstein SAJL, van der Grond J, *et al.* Cadasil and migraine: a narrative review. *Cephalalgia* 2010;30:1284–9.
- 28 Guey S, Mawet J, Hervé D, *et al.* Prevalence and characteristics of migraine in CADASIL. *Cephalalgia* 2016;36:1038–47.
- 29 Zhang Y, Parikh A, Qian S. Migraine and stroke. *Stroke Vasc Neurol* 2017;2:160–7.
- 30 Mizuta I, Watanabe-Hosomi A, Koizumi T, *et al.* New diagnostic criteria for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in Japan. *J Neurol Sci* 2017;381:62–7.
- 31 Choi HA, Lee MJ, Chung C-S. Cerebral endothelial dysfunction in reversible cerebral vasoconstriction syndrome: a case-control study. *J Headache Pain* 2017;18:29.
- 32 Ducros A. Reversible cerebral vasoconstriction syndrome. *Lancet Neurol* 2012;11:906–17.
- 33 Jensen J, Leonard J, Salottolo K, *et al.* The epidemiology of reversible cerebral vasoconstriction syndrome in patients at a Colorado comprehensive stroke center. *J Vasc Interv Neurol* 2018;10:32–8.
- 34 Ducros A, Wolff V. The typical thunderclap headache of reversible cerebral vasoconstriction syndrome and its various triggers. *Headache* 2016;56:657–73.
- 35 Burton TM, Bushnell CD. Reversible cerebral vasoconstriction syndrome. *Stroke* 2019;50:2253–8.
- 36 Rocha EA, Topcuoglu MA, Silva GS, *et al.* RCVS<sub>2</sub> score and diagnostic approach for reversible cerebral vasoconstriction syndrome. *Neurology* 2019;92:e639–47.