Curr Pain Headache Rep (2013) 17:334
DOI 10.1007/s11916-013-0334-y

UNCOMMON HEADACHE SYNDROMES (J AILANI, SECTION EDITOR)

Headache Attributed to Cranial or Cervical Vascular Disorders

Siddharth Kapoor

Published online: 13 April 2013
© The Author(s) 2013. This article is published with open access at Springerlink.com

Abstract Cranial or cervical vascular disease is commonly associated with headaches. The descriptions may range from a thunderclap onset of a subarachnoid hemorrhage to a phenotype similar to tension type headache. Occasionally, this may be the sole manifestation of a potentially serious underlying disorder like vasculitis. A high index of clinical suspicion is necessary to diagnose the disorder. Prompt recognition and treatment is usually needed for many conditions to avoid permanent sequelae that result in disability. Treatments for many conditions remain challenging and are frequently controversial due to paucity of well controlled studies. This is a review of the recent advances that have been made in the diagnosis or management of these secondary headaches.

Keywords Headache · Secondary headache · Arteriovenous malformation · Vasculitis · Carotid or vertebral artery pain · Diagnosis · Treatment

Introduction

In the early part of twentieth century, studies on man and lower animals demonstrated that the cranial blood vessels are pain-sensitive structures, capable under special circumstances of giving rise to headache. It was enticing to believe that the distention of certain branches of the external carotid arteries was chiefly responsible for migraine headache and the headache associated with arterial hypertension [1]. Our understanding of causation of headaches including migraine has continued to evolve with overall advances in neuroscience. An emerging concept over the last year has been to view primary headaches as a dysfunction of the neurolimbic network (Table 1) [3], with evidence to suggest that vascular change is neither necessary nor sufficient for migraine [4]. However, this has not challenged the close association of headaches with vascular disease of the head and neck region. The ICHD aptly recognizes that headache related to vascular disease is a secondary headache that may differ from, or mimic the phenomenology of the primary headaches [2].

In a recent report Galletti et al. [5] found that large majority of patients with arteriovenous malformation, in which headache was the main symptom at presentation, attacks mirrored the clinical features of migraine by ICHD-II criteria. This was most correlated with an occipital lobe location of the AVM.

The International Classification of Headache Disorders further defines a diagnosis of "headache attributed to vascular disorder" as definite only when the headache resolves or greatly improves within a specified time after its onset or after the acute phase of the disorder. When this is not the case, or before the specified time has elapsed, the diagnosis is qualified by stating "probably attributed to vascular disorder". Recognizing that these are criteria which cannot be applied in all instances, especially when the headache does not resolve or greatly improves after 3 months, leads to a diagnosis of chronic post–vascular-disorder headache. This time based criteria are arbitrary and controversial.

There are many features of headaches that suggest a secondary headache. The mnemonic 2SNOOP4 secondary headaches, has been utilized for many years as an aid to remember the red flags that should prompt a search for an underlying cause [6•].

- Systemic symptoms (fever, weight loss, fatigue)
- Secondary risk factors (HIV, cancer, immunodeficiency)
- N Neurologic symptoms/signs (altered mental status, focal deficits)

This article is part of the Topical Collection on *Uncommon Headache Syndromes*

S. Kapoor (✉)
University of Kentucky, Lexington, KY, USA
e-mail: sidkapoor@uky.edu

Table 1 Types of headaches attributed to cranial or cervical vascular disorders

1. Headache attributed to ischemic stroke or transient ischemic attack
2. Headache attributed to nontraumatic intracranial hemorrhage
3. Headache attributed to unruptured vascular malformation
4. Headache attributed to arteritis
5. Carotid or vertebral artery pain
6. Headache attributed to cerebral venous thrombosis
7. Headache attributed to other intracranial vascular disorder

(After ICHD-II)

For all vascular headaches, the diagnostic criteria include whenever possible: [2]

A. Headache with one (or more) of the stated characteristics (if any are known) and fulfilling criteria C and D

B. Major diagnostic criteria of the vascular disorder

C. The temporal relationship of the association with, and/or other evidence of causation by, the vascular disorder

D. Improvement or disappearance of headache within a defined period1 after its onset or after the vascular disorder has remitted or after its acute phase

- Onset/ (split-second, thunderclap)
- Older (new after age 50)
- P: prior history/ positional / papilledema / precipitants

Besides the well-recognized red flags, there are other "yellow flags" that should alert the examiner and includes a headache that wakes patient from sleep at night or new-onset side-locked headaches [7••]

Thunderclap Headache

Thunderclap headache or a headache that is abrupt or hyperacute in onset is probably the most common phenotype of a headache widely recognized to be associated with a vascular cause. The diagnosis of headache and its causality is easily established when focal neurological deficits accompany the vascular disease and its consequences like hemorrhage (Table 2). This is probably most obvious in case of a ruptured aneurysm resulting in a subarachnoid hemorrhage associated with a classic thunderclap headache. When hemorrhage is not obvious on imaging, CSF analysis may be necessary to evaluate for subtle hemorrhage. When hemorrhage has been reasonably excluded, other etiologies need to be considered and should include cervical artery dissection, cerebral venous sinus thrombosis, pituitary apoplexy and reversible cerebral vasoconstriction syndrome, vasculitis besides others. While vascular headaches can rarely mimic primary headaches, non-vascular causes like spontaneous CSF leaks can also result in thunderclap onset headache

Table 2 Considerations with thunderclap headache

- Subarachnoid hemorrhage
- Arteriovenous malformations
- Reversible cerebral vasoconstriction syndrome
- Dissection
- Vasculitis
- Cerebral venous thrombosis
- Spontaneous intracranial hypotension
- Pituitary apoplexy
- Primary thunderclap headache

[8] with subtle imaging findings that are easily missed. A diligent search for secondary causes is also warranted with all persistent headaches. However the presentation may not be that obvious in conditions that are more gradual in onset. On many occasions vascular disease develops in individuals with pre-existing primary headaches and the only clue is a change of the headache type. A high index of suspicion is especially needed in the elderly who are at risk for developing arteritis with its disabling consequences.

Headache Attributed to Unruptured Vascular Malformation

Headache is occasionally an indirect consequence of the vascular disease such as a result of an infarct or hemorrhage consequent to the vascular pathology. However, headache can occur in the presence of an uncomplicated vascular pathology. This becomes especially challenging when the headache resembles a primary headache disorder like migraine or cluster and does not adhere to the strict ICHD-II definitions of a vascular headache [9]. Previously, occurrence of a primary headache phenotype in a patient with a vascular malformation has been considered to be an incidental finding, but response of the headache, to treatment of the underlying vascular malformation, raises an argument against that notion. Patients with complaints of headaches who are found to have an unruptured aneurysm often presume a direct relationship. In a very eloquent prospective study, Schwedt and colleagues demonstrated approximately 2/3 of patients with pretreatment headaches had substantial reductions in headache frequency following treatment of unruptured aneurysm [10••]. This was consistent with previous retrospective studies by Qureshi [11•] and Kong [12•]. As discussed by all authors, reduction of headache was in part attributed to reduction of anxiety, consequent to reduction of risk of rupture. Another recent prospective study by Choxi et al. arrived at similar conclusions [13]. They concluded that 92.45 % (n=53) of patients who filled both a preoperative and postoperative pain score had a statistically

significant improvement in their headache score over an average period of 32 months. There was no relationship found between headache characteristics and aneurysm size, laterality of aneurysm or method of treatment, i.e., surgical vs. endovascular treatment. It is to be noted that this study had significant limitations, including selecting only patients that had experienced headache prior to the procedure, were treated by a single surgeon, and who filled out questionnaires subsequent to the procedure. Emotional well-being or anxiety was not taken into account. A similar but less robust response was seen in the elderly population treated with an endovascular approach utilizing coils alone, balloon-remodeling technique, and stent-assisted coiling [14].

These and other studies have also remarked upon a small subset of patients who experienced worsening of their headaches in the absence of a complication. This group was the subject of a retrospective study by Baron et al. [15] looking at the development of headache following a variety of endovascular procedures. They also found an initial reduction of headaches following treatment of the vascular malformation. However when patients were followed over a longer term, there was a return of the pre-existing headache. This was usually beyond the limits noted in the ICHD-II criteria (develops within seconds of the procedure and resolves within 24 hours) [2]. Postprocedural headache followed intracranial coiling, acrylic glue embolization, and stenting in order of decreasing probability. Headache after the procedure was higher in women, with comorbid smoking and/or anxiety/depression. The same study also found that further diagnostic testing was low yield. In addition, triptans and dihydroergotamine were used without incident in a small group of pre- and postcoil patients. This suggested that for migraineurs with aneurysm, there may not be an absolute contraindication to these medications. Caution is still warranted, as the numbers were very small to infer overall safety. Another study that raised caution against the newer generation of coils concluded that endovascular embolization of unruptured intracranial aneurysms using bioactive coils, resulted in a higher onset rate of mild headaches and greater temperature elevation after treatment than did use of bare platinum coils due to the inflammatory effect of the polyglycolic acid [16].

In summary, it appears that the headache responds to amelioration of anxiety relating to the knowledge of an aneurysm rather than the pathology itself. When anxiety persists after the procedure, so does the headache over the long term.

Headache Attributed to Arteritis

Headache is the most common symptom with CNS vasculitis. These can either be secondary to CNS involvement in systemic vasculitides or be associated with the rare primary CNS vasculitis. The headache can be generalized or localized, is gradually progressive with periods of remission. This is in contrast to the headache associated with reversible cerebral vasoconstriction syndrome where onset is typically acute with thunderclap headache—extreme head pain peaking in less than 1 min, mimicking that of a ruptured aneurysm. Screaming, crying, agitation, confusion, and collapse are common because of the excruciating pain. Typical headache is bilateral (although it can be unilateral), with posterior onset followed by diffuse pain. Nausea, vomiting, photophobia, and phonophobia in frequently occur [17••].

A symptom that should elicit a careful search for an underlying condition may be stabbing headache. Rampello et al. reported their findings in 26 patients recruited over 10 years, with stabbing headache. More than half of these patients had autoimmune disorders, including multiple sclerosis, Sjogren's disease, systemic lupus erythematosus, Behcet's disease, autoimmune vasculitis, and antiphospholipid antibody syndrome. They speculate that stabbing headache may develop as a result of neuroinflammation and, at least in some cases, may be an epiphenomenon of focal demyelinating lesions of the upper or lower brain stem [18].

A long established cause of secondary vascular headache is Giant Cell arteritis (GCA), which is one of the commonest vasculitides. It is closely associated with polymyalgia rheumatica that also targets the same group of patients, frequently occurring together in the same individual, characterized by focal or diffuse myalgia associated with weakness and weight loss. Diagnosis is suspected when there is new onset temporal headache associated with scalp tenderness. Jaw and tongue claudication may be associated and it is frequently accompanied by visual symptoms (diplopia, or visual loss). This disabling complication may be permanent and hence a high index of suspicion needs to be maintained when encountering patients with a new or change of headache. American College of Rheumatology diagnostic criteria include the following; age of onset greater than 50 years; onset of new headache ; temporal artery abnormality (tender or reduced pulsation) ; elevated erythrocyte sedimentation rate, >50 mm/h using the Westergren method; abnormal arterial biopsy—showing necrotizing vasculitis with predominant mononuclear cell infiltration or granulomatous inflammation [19••]. Biopsy remains the test of choice to establish the diagnosis but given the risk of complications, prompt treatment should ensue. Initial treatment is with corticosteroids. Use of high-dose intravenous steroids as initial therapy is preferred by many, especially when visual complaints are present but this remains highly controversial [20]. The last decade has witnessed a much improved understanding of the immunopathology of GCA, and is impacting the diagnostic approach to patients with GCA. Immunologic studies suggest a much more chronic

course of the disease than previously appreciated. Accordingly, current therapeutic strategies, while successful in managing acute disease, need to be adapted to longer term goals. An overriding challenge is the advanced age of the affected patient population. While immune aging emerges as one of the underlying pathogenic principles in conferring risk for GCA, it also restricts the potential use of more aggressive means to immunosuppress vessel-wall centered chronic inflammation. Other treatment options include the use of methotrexate, azathioprine, cyclosporine [19••], cyclophosphamide [21], atlizumab [22, 23•] among other immune modulating therapy. Atlizumab is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R) interfering with cytokine function. Although GCA is the commonest systemic vasculitis, prospective randomized trials on steroid sparing agents are rare and mostly included only small patient numbers. There is an urgent need for prospective randomized trials with larger patient groups, longer follow-up, and well defined inclusion criteria and criteria for response and relapse, using standardized disease activity scoring systems, in order to be able to give evidence-based recommendations for patients not responding to glucocorticoids alone in the future [24].

Takayasu arteritis (TAK), a disease very similar to GCA, is a rare disorder typically recognized in younger individuals of Asian origin and female gender. This is, however, controversial and studies show that the disease is distributed all over the world and is not restricted to any one ethnic group [25]. Symptoms, signs, and imaging abnormalities that are characteristic of GCA or TAK are often present, albeit in differing frequencies, in both disorders and this may represent skewed phenotypes within the spectrum of a single disorder [26]. In a recent description of this illness in children, the median time lag between the first onset of symptoms and diagnosis was 7.7 weeks. Hypertension was the most common finding on first presentation (93 %), followed by headache (64 %), nausea (64 %) and palpitation (50 %). Ten patients (71 %) had reduced or absent carotid, brachial or femoral pulses in one or more locations. C-reactive protein was elevated in 79 % of the patients and erythrocyte sedimentation rate in 64 %. Vascular imaging showed extensive vasculitis of most major arteries in the body in 86 % of patients. Conservative drug treatment was effective in 50 %. Interventional dilatation of stenosis and surgical therapy, including aortic bypass, resection of aneurysms and nephrectomy, were necessary in the remaining patients [27]. Anti-inflammatory therapy can lead to dramatic improvement in TA. The 5-year survival rate in adults is as high as 94 %. Preventing organ damage is critical in insuring a favorable prognosis [25].

Behcet's syndrome (BS) is a chronic relapsing vascular inflammatory disease of unknown etiology with high morbidity and mortality. In a study of clinical patterns of CNS disease in a group of patients with BS, headache was the most common symptom (86.6 % of cases), pyramidal affection (signs of upper motor neuron lesions/hemiplegia) was reported in 33.3 %, attacks of disturbed conscious level in 26.6 %, and cranial nerve affection in 6.5 %. Of the patients, 66.6 % with clinical features of neuro-Behcet (NBS) had statistically significant radiographic evidences of cerebrovascular disease. Patients with NBS had significantly higher disease activity index score. Radiographic findings and flow abnormalities were significantly less in patients on immune suppressants and antiplatelet drugs. BS patients with clinical neurologic disease were found to have radiographic findings suggestive of cerebral vascular disease with high disease activity index score. Drugs like immunosuppressants and oral antiplatelets might retard cerebral vascular disease progression and flow abnormalities, respectively [28]. Migraine without aura did prove to be the most frequent type of headache in BS patients (with and without neurological involvement) and there were no differences in the frequency of the different pattern of headache between BS patients and controls [29].

Primary angiitis of the CNS also needs to be considered in the differential though its occurrence is being challenged. Many of the patients previously diagnosed as such, may have RCVS [30]. Other differentials not discussed in detail include polyarteritis nodosa, Kawasaki disease, Wegener's granulomatosis, systemic lupus erythematosus, and vasculitits secondary to infections.

Carotid or Vertebral Artery Pain

Head and neck pain as a consequence of cervical artery dissection (carotid and vertebral) has been recognized for many decades. The location of the pain is variable and can involve, in isolation or in combination, any part of the head, face and neck, usually ipsilateral to the pathology; however, bilateral and diffuse headache can occur, even when the dissection is unilateral. The pain can sometimes be very localized with a predilection for the frontal, orbital, temporal and upper cervical regions. It can also simulate migraine, cluster headache or carotidynia [31]. Horner's syndrome; cranial-nerve palsy; tinnitus; and, rarely, cervical-root injury are the most common associated symptoms that attract attention to the secondary nature of the pain [32••]. It has also been shown that the risk for cervical artery dissection (CAD) is doubled for any migraine [33]. It has hence been postulated that CAD may explain the increased risk of ischemic strokes associated with migraines. The group participating with CADISP (Cervical Artery Dissection and Ischemic Stroke Patients, a multinational European network) [34] also found both migraine with and without aura to be more frequent in patients with cervical artery

dissection, as compared to healthy controls and stroke patients without a dissection. Within patients with a dissection, presence or absence of migraine did not impact the prevalence of strokes, arterial distribution, or other clinical or prognostic features [35••]. In a separate study in the same cohort of patients, the authors found that patients with carotid artery dissection were older, more often men, more frequently had a recent infection (odds ratio of 1.59), and tended to report less often a minor neck trauma in the previous month (OR=0.75 [0.56–1.007]) compared to patients with vertebral artery dissection. Clinically, patients with internal carotid artery dissection more often presented with headache at admission but less frequently complained of cervical pain or had cerebral ischemia than patients with vertebral artery disease. It was also noted that multiple concomitant dissections tended to cluster on the same artery type rather than involving both a vertebral and carotid artery [36]. An important cause of dissection is fibromuscular dysplasia, which is a nonatherosclerotic, noninflammatory vascular disease that primarily affects women in the prime of their life. It commonly involves the renal, carotid, and vertebral arteries. In one of the largest cohort of fibromuscular dysplasia patients [37], the most common clinical manifestations noted were hypertension, headaches, pulsatile tinnitus, and dizziness, but dissection, aneurysm, transient ischemic attack, and stroke also occur with a high frequency. Headaches were a common symptom (60.0 % of patients), with classical migraine-type headaches reported in 32.2 %. Severe headaches occurred weekly in 13.1 % of patients and daily in 12.5 % of patients. Since the affected population, also has one of the highest prevalence for migraine, a high index of suspicion needs to be maintained.

Once the pathology is clinically suspected, prompt confirmation of the diagnosis and commencing treatment for the underlying condition is warranted. There is class I evidence that contrast-enhanced CT angiogram, MR angiogram and catheter-based contrast angiography are all useful for diagnosis of cervical artery dissection (level of evidence: C) [38••]. Regarding treatment , there is class IIa evidence that for patients with symptomatic cervical artery dissection, anticoagulation with intravenous heparin (dose adjusted to prolong the partial thromboplastin time to 1.5 to 2.0 times the control value) or low-molecular weight heparin (in appropriate dose) followed by warfarin [dose adjusted to achieve a target INR of 2.5 (range 2.0 to 3.0)], or oral anticoagulation without antecedent heparin, can be beneficial for 3 to 6 months, followed by antiplatelet therapy with aspirin (81–325 mg daily) or clopidogrel (75 mg daily, level of evidence: C) [38••].

In addition, there is class IIb evidence supporting the consideration of carotid angioplasty and stenting when ischemic neurological symptoms have not responded to antithrombotic therapy after acute carotid dissection (level of evidence: C) [38••]. The safety and effectiveness of pharmacological therapy with a b-adrenergic antagonist, angiotensin inhibitor or non-dihydropyridine calcium channel antagonist (verapamil or diltiazem) to lower blood pressure to the normal range and reduce arterial wall stress are not well established (level of evidence: C)

Independent of dissections, occurrence of headaches has been described with performance of cerebral and carotid angiogram, endovascular and surgical manipulation of the carotid and vertebral vessels.

Intracarotid or intravertebral injection of contrast induces a diffuse severe headache with a burning sensation which resolves spontaneously. The injection can also trigger a migraine attack in a person who has migraine. A very specific subtype of headache has been reported after balloon inflation or embolization of an AVM or aneurysm. It is a severe pain of abrupt onset, localized in specific areas according to the artery involved, occurring within a few seconds of the procedure and disappearing rapidly [2]. In a recent study, frequency of headache after internal carotid stenting was 39.1 % as compared to 21.9 % angiography alone. The headache commonly arose in a short period after the procedure and was relieved in 10 minutes. In both cases headache was mild, ipsilateral, frontotemporal in location, pressing in nature, and arose frequently and resolved within 10 minutes after the procedure. Both types of headache were related to severe stenosis, however described as pressing after carotid stenting and burning after angiography [39].

Headache Attributed to Cerebral Venous Thrombosis

Cerebral venous thrombosis (CVT) is a rare type of cerebrovascular disease that can occur at any age, including in neonates, and it accounts for 0.5 % of all strokes. CVT is more common than previously thought and it is recognized as a nonseptic disorder with a wide spectrum of clinical presentations, numerous causes, and usually a favorable outcome with a low mortality rate [40]. Isolated headache as the sole presenting manifestation of CVT has also been described [41] with variable estimates of its occurrence [42]. When present the most frequent characteristics were: recent onset rapidly progressive severe headache with a persistent course; unilateral location and throbbing quality. Rarely, the headache may mimic migraine or cluster headache [41]. In another series of patients, the quality of headache was reported as throbbing, band like, thunderclap, and other (pounding, exploding, stabbing). The location of headache was reported as unilateral, localized or diffuse by an equal number of patients [43]. The spectrum of clinical symptoms reflects the degree of venous congestion, which depends not only on the extent of thrombosis in the deep veins but also on the territory of the involved vessels and the establishment

of venous collaterals [44]. Oral contraceptive intake, pregnancy, and the puerperium are responsible for the vast majority of CVT occurring in young women, usually in association with other prothrombotic risk factors, particularly congenital thrombophilia [45]. Some cases have been described recently where CVT is emerging as a complication of spontaneous intracranial hypotension [46–48] MRI with combined with magnetic resonance angiography are the best diagnostic methods. D-dimer concentrations are raised in most patients but normal D-dimers do not rule out CVT, particularly in patients who present with isolated headache [40]. Heparin is the first-line treatment, but in a few cases more aggressive treatments, such as local intravenous thrombolysis, mechanical thrombectomy, and decompressive hemicraniectomy, may be required [40••]. There is no contra-indication for further pregnancies when this occurs in relationship to pregnancy, but a permanent contra-indication for all estrogen-based contraception [45].

Headache Attributed to Other Intracranial Vascular Disorder

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by the association of severe headaches with or without additional neurological symptoms and a 'string and beads' appearance on cerebral arteries, which resolves spontaneously in1 to 3 months. RCVS is spontaneous in a third of the patients and secondary in the other two-thirds. The main pattern of presentation (94 % of patients) was multiple thunderclap headaches recurring over a mean period of 1 week. Various complications were observed, with different time courses. Cortical subarachnoid hemorrhage (cSAH), intracerebral hemorrhage, seizures and reversible posterior leukoencephalopathy were early complications, occurring mainly within the first week. Ischemic events occurred significantly later than hemorrhagic events. The different time courses of thunderclap headaches, vasoconstriction and strokes suggest that the responsible vasospastic disorder starts distally and progresses towards medium sized and large arteries [49••]. RCVS and primary angiitis of the central nervous system (PACNS) can affect both the medium and the small vessels. The diagnosis of small-vessel cerebral arteriopathies requires a high level of clinical suspicion, astute interpretation of imaging findings, and a detailed examination of the skin, eye, or other organ systems [50]. RCVS has about a ten percent overlap with posterior reversible encephalopathy syndrome(PRES) [51•], with many shared associations and etiologies and a hypothesis of shared pathophysiology. It has been hypothesized that either the episodes of systemic hypertension lead to hyperperfusion, or cerebral vasoconstriction and therefore hypoperfusion result in vasogenic edema observed in PRES [52]. Mainstay of treatment remains calcium-channel blockers including intravenous nimodipine [49••], intravenous prostacyclin [53] and intra-arterial delivery of milrinone [54], nimodipine [55], verapamil [56] that have been reported to be beneficial.

Occurrence of headaches is a well-known manifestation of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) which is a result of mutation of the NOTCH3 gene. This leads to deposition of the NOTCH3 cleavage product in the vascular smooth-muscle cells both in cerebral and extracerebral vessels [57]. Sathe and colleagues recently describe their experience in twenty confirmed cases. Recurrent acute confusional episodes associated with migraine in adults appeared to be a phenomenon unique to CADASIL [58] Prolonged aura and atypical aura has also been described previously [59] as a concerning feature of migraines, when associated with white matter disease on imaging, should prompt further genetic testing. Headaches associated with unexplained combination of neurological and non-neurological disease in a patient or kindred, a mitochondrial inherited disorder should be suspected and appropriate diagnostic measures initiated. Genetic testing should be guided by the phenotype, the biopsy findings, and the biochemical results [60]. Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and CoQ10 deficiency (primary or secondary) would be important diagnostic considerations. Sumatriptan has been described to be effective in treatment of headaches associated with MELAS [61].

Pituitary apoplexy remains an important diagnostic consideration for patients presenting with thunderclap headache and should be considered a neuroendocrine emergency. Apoplexy can occur in association with pregnancy, general anesthesia, bromocriptine therapy, and pituitary irradiation, but most commonly occurs in patients with no known history of a pituitary tumor. Clinical symptoms range from relatively mild symptoms including acute headache, nausea to loss of vision, diplopia, and reduction in visual fields to adrenal crisis, coma, and sudden death. Paucity of objective findings including normal physical examinations, CT scans, and cerebrospinal fluid have also been reported. MRI is the preferred imaging modality for correct diagnosis [62••].

Conclusion

Secondary vascular headaches represent a group of diverse disorders that range from hyperacute to subacute in presentation, with a progressive course. They may be easily missed and mistaken for a primary headache disorder. Prompt

recognition and early treatment is essential to avoid some preventable complications. Treatment recommendations are generally controversial, based on tradition and lack evidence of benefit or clear superiority of one treatment. Future research will be essential to address the many unanswered questions.

Conflict of Interest Dr. Siddharth Kapoor received payment for development of educational presentations including service on speakers' bureaus from Allergan.

Open Access This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Ray BS, Wolff HG. Experimental studies on headache: pain-sensitive structures of the head and their significance in headache. Arch Surg. 1940;41:813–56.
2. Headache Classification Subcommittee of the International Headache Society. The International classification of headache disorders: 2nd edition. Cephalalgia. 2004;24(Suppl 1):9–160.
3. Maizels M, Aurora S, Heinricher M. Beyond neurovascular: migraine as a dysfunctional neurolimbic pain network. Headache J Head Face Pain. 2012;52:1553–65.
4. Goadsby P. Pathophysiology of migraine. Ann Indian Acad Neurol. 2012:15–22.
5. Galletti F, Sarchielli P, Hamam M, et al. Occipital arteriovenous malformations and migraine. Cephalalgia. 2011;31:1320–4.
6. • Dodick DW. Pearls: headache. Semin Neurol. 2010;30:74–81. *These articles detail findings seen with dangerous headaches that merit further investigation.*
7. •• De Luca GC, Bartleson JD. When and how to investigate the patient with headache. Semin Neurol. 2010;30:131–44. *These articles detail findings seen with dangerous headaches that merit further investigation.*
8. Famularo G, Minisola G, Gigli R. Thunderclap headache and spontaneous intracranial hypotension. Headache J Head Face Pain. 2005;45:392–3.
9. Vargas BB. The impact of unruptured intracranial aneurysm repair in headache management: putting the data into clinical practice. Cephalalgia. 2011;31:1071–3.
10. •• Schwedt TJ, Gereau RW, Frey K, Kharasch ED. Headache outcomes following treatment of unruptured intracranial aneurysms: a prospective analysis. Cephalalgia. 2011;31:1082–9. *Is the only prospective study looking at headache outcomes in unruptured aneurysms.*
11. • Qureshi AI, Suri MF, Kim SH, et al. Effect of endovascular treatment on headaches in patients with unruptured intracranial aneurysms. Headache. 2003;43:1090–6. *Are seminal studies in the field that first looked at headache outcomes in unruptured aneurysms.*
12. • Kong DS, Hong SC, Jung YJ, Kim JS. Improvement of chronic headache after treatment of unruptured intracranial aneurysms. Headache. 2007;47:693–7. *Are seminal studies in the field that first looked at headache outcomes in unruptured aneurysms*.
13. Choxi AA, Durrani AK, Mericle RA. Both surgical clipping and endovascular embolization of unruptured intracranial aneurysms are associated with long-term improvement in self-reported quantitative headache scores. Neurosurgery. 2011;69:128–33. discussion 133-124.
14. Gu DQ, Duan CZ, Li XF, He XY, Lai LF, Su SX. Effect of endovascular treatment on headache in elderly patients with unruptured intracranial aneurysms. AJNR Am J Neuroradiol. 2012. doi:10.3174/ajnr.A3353.
15. Baron EP, Moskowitz SI, Tepper SJ, et al. Headache following intracranial neuroendovascular procedures. Headache J Head Face Pain. 2012;52:739–48.
16. Takigawa T, Matsumaru Y, Nakai Y, et al. Bioactive coils cause headache and fever after endovascular treatment of intracranial aneurysms. Headache J Head Face Pain. 2012;52:312–21.
17. •• Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol. 2012;11:906–17. *An excellent in depth review of this condition.*
18. Rampello L, Malaguarnera M, Rampello L, Nicoletti G, Battaglia G. Stabbing headache in patients with autoimmune disorders. Clin Neurol Neurosurg. 2012;114:751–3.
19. •• Nahas SJ. Headache and temporal arteritis: when to suspect and how to manage. Curr Pain Headache Rep. 2012;16:371–8. *An excellent in depth review of this condition*.
20. Hayreh SS, Biousse V. Treatment of acute visual loss in giant cell arteritis: should we prescribe high-dose intravenous steroids or just oral steroids? J Neuroophthalmol Off J N Am Neuroophthalmol Soc. 2012;32:278–87.
21. Quartuccio L, Maset M, De Maglio G, et al. Role of oral cyclophosphamide in the treatment of giant cell arteritis. Rheumatology (Oxford). 2012;51:1677–86.
22. Unizony S, Arias-Urdaneta L, Miloslavsky E, et al. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. Arthritis Care Res. 2012;64:1720–9.
23. • Schafer VS, Zwerina J. Biologic treatment of large-vessel vasculitides. Curr Opin Rheumatol. 2012;24:31–7. *A recent update into emerging therapies.*
24. Kotter I, Henes JC, Wagner AD, Loock J, Gross WL. Does glucocorticosteroid-resistant large-vessel vasculitis (giant cell arteritis and Takayasu arteritis) exist and how can remission be achieved? A critical review of the literature. Clin Exp Rheumatol. 2012;30:S114–29.
25. Brunner J, Feldman BM, Tyrrell PN, et al. Takayasu arteritis in children and adolescents. Rheumatology (Oxford). 2010;49:1806–14.
26. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? Medicine (Baltimore). 2009;88:221–6.
27. Zhu WH, Shen LG, Neubauer H. Clinical characteristics, interdisciplinary treatment and follow-up of 14 children with Takayasu arteritis. World J Pediatr. 2010;6:342–7.
28. Mohammed RH, Nasef A, Kewan HH, Al SM. Vascular neurobehcet disease: correlation with current disease activity forum and systemic vascular involvement. Clin Rheumatol. 2012;31:1033–40.
29. Volpinari S, Monaldini C, Capone JG, et al. Headache in Behcet's disease: case-control study and literature review. Reumatismo. 2009;61:174–81.
30. Neel A, Auffray-Calvier E, Guillon B, et al. Challenging the diagnosis of primary angiitis of the central nervous system: a single-center retrospective study. J Rheumatol. 2012;39:1026–34.
31. Biousse V, D'Anglejan-Chatillon J, Massiou H, Bousser MG. Head pain in non-traumatic carotid artery dissection: a series of 65 patients. Cephalalgia. 1994;14:33–6.
32. •• Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. Lancet Neurol. 2009;8:668–78. *An excellent in depth review of this condition*.

33. Rist PM, Diener HC, Kurth T, Schurks M. Migraine, migraine aura, and cervical artery dissection: a systematic review and meta-analysis. Cephalalgia. 2011;31:886–96.
34. Debette S, Metso TM, Pezzini A, et al. CADISP-genetics: an International project searching for genetic risk factors of cervical artery dissections. Int J Stroke Off J Int Stroke Soc. 2009;4:224–30.
35. •• Metso TM, Tatlisumak T, Debette S, et al. Migraine in cervical artery dissection and ischemic stroke patients. Neurology. 2012;78:1221–8. *A large number of patients with an uncommon condition are studied and issues of specific interest to headache experts is addressed in this article.*
36. Debette S, Grond-Ginsbach C, Bodenant M, et al. Differential features of carotid and vertebral artery dissections: the CADISP study. Neurology. 2011;77:1174–81.
37. Olin JW, Froehlich J, Gu X, et al. The United States registry for fibromuscular dysplasia: results in the first 447 patients. Circulation. 2012;125:3182–90.
38. •• Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/ SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Vascular medicine. 2011;16:35–77. *Consensus guidelines on a variety of conditions.*
39. Gunduz A, Goksan B, Kocer N, Karaali-Savrun F. Headache in carotid artery stenting and angiography. Headache. 2012;52:544–9.
40. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6:162–70.
41. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. J Neurol Neurosurg Psychiatry. 2005;76:1084–7.
42. Timoteo A, Inacio N, Machado S, Pinto AA, Parreira E. Headache as the sole presentation of cerebral venous thrombosis: a prospective study. J Headache Pain. 2012;13:487–90.
43. Wasay M, Kojan S, Dai AI, Bobustuc G, Sheikh Z. Headache in cerebral venous thrombosis: incidence, pattern and location in 200 consecutive patients. J Headache Pain. 2010;11:137–9.
44. van den Bergh WM, van der Schaaf I, van Gijn J. The spectrum of presentations of venous infarction caused by deep cerebral vein thrombosis. Neurology. 2005;65:192–6.
45. Bousser MG, Crassard I. Cerebral venous thrombosis, pregnancy and oral contraceptives. Thromb Res. 2012;130 Suppl 1:S19–22.
46. Costa P, Del Zotto E, Giossi A, et al. Headache due to spontaneous intracranial hypotension and subsequent cerebral vein thrombosis. Headache. 2012. doi:10.1111/j.1526-4610.2012.02261.x.
47. Schievink WI, Maya MM. Cerebral venous thrombosis in spontaneous intracranial hypotension. Headache. 2008;48:1511–9.
48. Rozen TD. Pachymeningeal enhancement on MRI: a venous phenomena not always related to intracranial hypotension (Resolving pachymeningeal enhancement and cerebral vein thrombosis). Headache. 2013. doi:10.1111/head.12003.
49. •• Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain. 2007;130:3091–101. *An excellent in depth review of this condition.*
50. Singhal AB. Diagnostic challenges in RCVS, PACNS, and other cerebral arteriopathies. Cephalalgia. 2011;31:1067–70.
51. • Mortimer AM, Bradley MD, Stoodley NG, Renowden SA. Thunderclap headache: diagnostic considerations and neuroimaging features. Clin Radiol. 2012;68(3):e101–13. *An excellent in depth review of this condition.*
52. Lemmens R, Smet S, Wilms G, Demaerel P, Thijs V. Postpartum RCVS and PRES with normal initial imaging findings. Acta Neurol Belg. 2012;112:189–92.
53. Grande PO, Lundgren A, Bjartmarz H, Cronqvist M. Segmental cerebral vasoconstriction: successful treatment of secondary cerebral ischaemia with intravenous prostacyclin. Cephalalgia. 2010;30:890–5.
54. Bouchard M, Verreault S, Gariepy JL, Dupre N. Intra-arterial milrinone for reversible cerebral vasoconstriction syndrome. Headache. 2009;49:142–5.
55. Linn J, Fesl G, Ottomeyer C, et al. Intra-arterial application of nimodipine in reversible cerebral vasoconstriction syndrome: a diagnostic tool in select cases? Cephalalgia. 2011;31:1074–81.
56. French KF, Hoesch RE, Allred J, et al. Repetitive use of intra-arterial verapamil in the treatment of reversible cerebral vasoconstriction syndrome. J Clin Neurosci. 2012;19:174–6.
57. Joutel A, Andreux F, Gaulis S, et al. The ectodomain of the Notch3 receptor accumulates within the cerebrovasculature of CADASIL patients. J Clin Invest. 2000;105:597–605.
58. Sathe S, DePeralta E, Pastores G, Kolodny EH. Acute confusional migraine may be a presenting feature of CADASIL. Headache. 2009;49:590–6.
59. Gladstone JP, Dodick DW. Migraine and cerebral white matter lesions: when to suspect cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Neurologist. 2005;11:19–29.
60. Finsterer J. Inherited mitochondrial disorders. Adv Exp Med Biol. 2012;942:187–213.
61. Iizuka T, Sakai F, Endo M, Suzuki N. Response to sumatriptan in headache of MELAS syndrome. Neurology. 2003;61:577–8.
62. •• Schwedt TJ, Matharu MS, Dodick DW. Thunderclap headache. Lancet Neurol. 2006;5:621–31.