Review

Reversible cerebral vasoconstriction syndrome: an underestimated cause for thunderclap headache in emergency settings

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Abstract

Thunderclap headache (TCH) is severe and occurs rapidly. It can have many underlying causes with similar presentations causing confusion among clinicians. The most serious underlying condition is a subarachnoid haemorrhage (SAH), which takes priority. Another increasingly recognised cause of a TCH is reversible cerebral vasoconstriction syndrome (RCVS). RCVS can be diagnosed with angiography after an SAH is excluded. RCVS and its differential diagnoses have very similar presentations, thereby making the diagnosis of RCVS difficult; however, there are specific differences that can be observed to correctly identify the condition. RCVS has classical presentations and triggers that should be examined in a comprehensive history to avoid misdiagnosis and unnecessary treatment. Clear guidance on diagnosing RCVS is required, especially in emergency settings. RCVS is generally assumed to have a positive outcome, however, some patients experience further complications such as strokes, seizures, SAHs and, even, death. Because of this, patients with RCVS should be monitored regularly. RCVS can also have self-resolving temporary worsening, which clinicians should bear in mind. Treatment for RCVS aims to manage symptoms and remove any potential triggers. However, there is very limited pharmacological-based evidence for therapy for RCVS and further research is required to determine the best treatment for this condition.

Abbreviations

CAD - Cervical artery dissection
CSF - Cerebrospinal fluid
CT - Computed tomography
CTA - Computed tomography angiography
DSA - Digital subtraction angiography
MRA - Magnetic resonance angiography
PACNS - Primary angiitis of the central nervous system
RCVS - Reversible cerebral vasoconstriction syndrome
SAH - Subarachnoid haemorrhage
TCH - Thunderclap headache

Introduction

Headaches are the most common A&E presentation in the UK.[1] Headaches that are severe and sudden headaches can indicate a serious underlying pathology.[2,3] A potentially life-threatening headache that often presents in A&E patients is a thunderclap headache (TCH): a throbbing, debilitating headache that occurs spontaneously, peaking within one minute, and which can last for weeks later.[4] Primary TCH is diagnosed when all other aetiologies are excluded.[5] TCH has many secondary causes, the most prominent being a subarachnoid haemorrhage (SAH). Another important,

but less-well identified cause for TCH is reversible cerebral vasoconstriction syndrome (RCVS), which occurs when cerebral arteries constrict and dilate abruptly.[6] Symptoms associated with TCH in RCVS can include nausea/vomiting, photosensitivity and phonophobia.[5,6] The incidence of RCVS is unknown, however, it may be more prevalent than realised, possibly due to errors in the diagnosis of RCVS, particularly in emergency settings.[5,7-9] There is no single definitive cause for RCVS, although pregnancy and vasoactive drugs have been linked its development.[7,10] RCVS is primarily diagnosed with radiological findings of segmental cerebral vasoconstriction within 12 weeks of the onset of a TCH. This can be done by digital subtraction angiography (DSA), magnetic resonance angiography (MRA) or computed tomography angiography (CTA).[6,11]

In RCVS, the TCH typically reoccurs an average of four times over four weeks and may be accompanied by neurological deficits.[14] Though most clinical outcomes of RCVS appear to be benign, there are potential future complications, such as strokes, seizures and SAH.[5] A diagnosis of RCVS may help individuals to prepare for potential associated future difficulties. An inaccuracy in the diagnosis of RCVS may have serious complications for the patient later in life.

This review will discuss RVCS as a cause for TCH and how it is managed in emergency settings. This review will be constructed in 4 parts: (1) characteristics and investigations for RCVS; (2) RCVS compared with differential diagnoses of TCH; (3) management and consequences of untreated RCVS; and (4) diagnosis in emergency settings and potential reasons for errors in diagnosis.

Literature search

Articles utilised in this review were predominantly collected from the online database PubMed. Additional online sources used were The Lancet and Google Scholar. Key terms searched for were "reversible cerebral vasoconstriction syndrome" and "thunderclap headache". These terms were used in conjunction with "emergency setting", "diagnosis", "differential diagnosis", "management" and "prognosis". Boolean factors (i.e. "NOT", "AND" and "OR") were used to create an algorithm with the keywords to filter out appropriate papers on PubMed. Articles were excluded if the full text was not freely available and if the publication was not in English. Some papers were also found through searching references of systematic reviews and meta-analyses. Based on relevance, and the inclusion and exclusion criteria, a total of 25 studies were included.

General information and statistical data on RCVS were retrieved from The National Institute for Health and Care Excellence and the National Health Service websites.

Characteristics and investigations for RCVS

The main presentation of RCVS is a TCH, which often occurs with several conditions, including SAH, primary angiitis of the central nervous system (PACNS), cervical artery dissection (CAD) and central venous thrombosis (see **Table 1**). In RCVS, the TCH usually occurs without any additional symptoms, is bilateral and short-lived.[5,14] Common triggers for RCVS have been identified, including the use of vasoactive drugs and antimigraine medication, sexual activity, postpartum state, and selective serotonin reuptake inhibitors.[7,10] Identifying these triggers using a detailed history could be used to suggest RCVS. Moreover, a correct diagnosis of RCVS could prompt patients to steer clear of these triggers to reduce the chances of a TCH. Angiography can be used to diagnose RCVS; however, studies have shown that angiography is not routinely performed in patients with an undetermined TCH.[2] Ducros *et al*. recommends performing a second angiogram if RCVS is suspected and the first angiogram is normal.[14] This is due to the first angiogram usually being performed within 1 week of the onset of symptoms whilst the maximum vasoconstriction of the middle cerebral arteries occurs at around 16 days after onset of symptoms.[14]

Table 1. Differential diagnosis of a TCH.[6,15]

	Presentation	Diagnosis
SAH	• Sudden onset of headache • Neck pain and neck stiffness are common • Transient loss of consciousness	• CT scan within 6 hours • Lumbar puncture after 6 hours
PACNS	• Usually subacute/chronic onset of headache	• Angiography • Abnormal CSF
CAD	• Neck pain and headache • Risk factors: recent trauma, connective tissue disease, hypertension, migraines and large vessel arteriopathies	• Head and neck CTA
Cerebral venous thrombosis	• Associated symptoms include papilledema, seizures, neurological deficit, distorted mental state • Usually aged <50 years • Hypercoagulopathy following events (e.g. surgery, postpartum) increases risk	• CT or MR venogram

CT, computed tomography; CTA, computed tomography angiography; CSF, cerebrospinal fluid; MR, magnetic resonance.

RCVS compared with differential diagnoses of TCH

Symptoms associated with a TCH are similar in many of the differential diagnoses of this condition, and to RCVS, which makes it difficult to distinguish between the conditions without additional imaging. Several differences between the clinical manifestations of RCVS and its differential diagnoses have been observed[15] and are discussed below.

SAH SAH is the most prevalent underlying cause for TCH.[16] It has been found that 50% of patients with SAH experience TCH.[17] SAH and RCVS present very similarly, although some differences in their clinical manifestations have been reported. TCHs in SAHs are usually unilateral on the side of the haemorrhage, whereas TCHs in RCVS is typically generalised or occipital. Additionally, TCH in RCVS tends to be shorter-lived than in SAHs.[4, 6, 15]

Without appropriate treatment, an SAH has a substantial mortality and morbidity rate; therefore, initial assessment of TCH must focus on SAH.[17] Computed tomography (CT) and lumbar puncture are highly sensitive preliminary assessments to detect SAH in patients with TCH. However, many differential conditions, including RCVS, cannot be identified by these assessments alone. If the CT and lumbar puncture are negative and SAH is ruled out, it is advised to perform an angiogram.[15]

PACNS PACNS is a rare inflammatory disease of the brain and spinal cord.[6] Distinguishing between PACNS and RCVS can be extremely difficult as PACNS patients present with a TCH and have similar angiograms.[10] Additional testing, such as a lumbar puncture, may be useful as abnormalities in cerebrospinal fluid (CSF) can be observed in ~90% of patients with PACNS, whereas CSF is usually normal in RCVS patients.[11] Analysis of symptoms may also aid in distinguishing between the two. For example, multiple TCH has never been reported in PACNS but is a classic feature of RCVS.[10] Additionally, symptoms gradually develop in PACNS, while symptoms in RCVS occur rapidly.[7] Furthermore, vasoconstriction is typically reversed within days after onset in RCVS but this is not the case for PACNS.[9,11]

CAD The typical presentation of CAD differs from RCVS in several ways. Headache in CAD is usually accompanied by neck, ear and face pain, which are not identifying features of RCVS.[14] Patients with CAD can also present with Horner's syndrome, comprised of miosis, ptosis and anhidrosis.[7] Testing for suspected CAD should include

ultrasound and angiography.[18] Also, it is important to note that CAD has been shown to be comorbid with RCVS;[5,18] although, it is unknown whether RCVS causes CAD or vice versa.

Management and consequences of untreated RCVS

RCVS should be managed by temporarily avoiding potential triggers, such as sexual intercourse, vasoactive drugs, and exercise.[7,10] Symptomatic treatment, such as analgesia and rest, are recommended. Blood pressure monitoring is also suggested.[14] Furthermore, it is fundamental to support patients' emotional and mental wellbeing. Suggested pharmacological treatment is comprised of various combinations of calcium channel blockers, corticosteroids, and intravenous magnesium.[19] Nimodipine, a calcium channel blocker, has been found to decrease the intensity and frequency of headaches in selected patients.[20] However, there is no data on the effectiveness of nimodipine in the treatment of RCVS from randomised control trials.[21] Glucocorticoids are sometimes used to treat RCVS, but some studies show no benefit or, even, potential worsening of the condition.[9] This is complicated by glucocorticoids being beneficial in the treatment of PACNS, which presents very similarly to RCVS.[22] Delaying treatment of PACNS for a few days with glucocorticoid steroids has not been found to increase adverse effects; thus, glucocorticoids may be held off until a more definitive diagnosis is achieved. Subsequently, if RCVS is diagnosed, glucocorticoids should be avoided. Intravenous magnesium has been shown to suddenly relieve symptoms of RCVS in 2 patients in whom treatment with calcium channel blockers and corticosteroids had not been successful.[23] This indicates a potential area of research for the treatment of RCVS.

The prognosis of RCVS is generally thought to be good as most patients' headaches resolved within days or weeks without any lasting symptoms.[13] However, studies have shown that some patients experience further complications post-diagnosis.[9,14] Patients have been reported to develop long term vasoconstriction, which led to ischaemic stroke and, in some cases, death.[13,19] Haemorrhagic strokes have also been reported after RCVS, with the underlying mechanism being uncertain.[19] Other possible subsequent conditions include seizures and SAH.[5] To prevent these outcomes, clear guidance on monitoring patients diagnosed with RCVS should be created. Furthermore, additional research is required to elucidate the mechanisms behind RCVS-associated strokes, seizures, SAHs and mortality. This may aid in the development of prophylactic measures for patients diagnosed with RCVS.

Some patients have temporary worsening that self-resolves.[19] Katz *et al*. reported that most participants with clinical worsening recovered shortly after the time of worsening.[19] With accurate diagnosis, clinicians can anticipate reversible worsening and prevent unnecessary testing and treatment.

Diagnosis in emergency settings and potential reasons for errors in diagnosis

Studies have demonstrated the inadequacy of the diagnosis of RCVS, particularly in emergency settings.[2] Kim *et al*. found that patients with RCVS needed to be seen by emergency physicians 4.7 times, with symptoms persisting for 9.3 days on average before receiving a precise diagnosis.[2] It was suggested that this may have been due to similar presentations to those of ruptured aneurysms.[2] These findings are not truly representative of the population as the data are derived from a small cohort of just 18 participants. Despite this, the study presents confusion among clinicians in the diagnosis of RCVS. Miller *et al*. show how appropriate imaging can be used to distinguish differential diagnoses from RCVS.[10] If RCVS is suspected after ruling out SAH, Tan and Flower recommend first performing an MRA or CTA based on availability, following this with a DSA if the MRA/CTA is negative and RCVS is still suspected.[24]

Furthermore, Ducros *et al*. highlighted a key issue in the diagnosis of RCVS, with some patients having normal MRAs upon initial testing.[5] There was a variation of between 1 and 2 weeks from the onset of headache and visible vasoconstriction on MRA.[5] This shows that an initial normal MRA cannot rule out RCVS. Moreover, physicians may struggle to make an accurate diagnosis due to the intensity in an emergency setting. To help with this, an awareness of the possible causes of TCH may be helpful if SAH is ruled out. A summary sheet with the various conditions and their presentations could be compiled for reference in emergency departments.

Conclusion

RCVS is becoming more recognised. Currently, there are still no clear guidelines for the diagnosis and management of RCVS. It is recommended to perform an angiogram after an SAH has been ruled out, with peak vasoconstriction being visible at 16 days after onset of symptoms. There are several triggers for RCVS that should be avoided in individuals with suspected or diagnosed RCVS. In most instances, RCVS self resolves without further complications; however, RCVS can increase the risk of stroke, SAH and death, which should be monitored. Furthermore, RCVS has similar presentations to other conditions that present with a TCH, although there are certain differences that can be observed. There is no evidence-based pharmacological treatment for RCVS; hence, more research is required to identify appropriate treatment. A potential area of future research is magnesium infusion in the treatment of a TCH in RCVS. Management should include supportive measures, such as analgesia, avoidance of triggers and support for each patient's mental well-being.

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