Clinical Radiology xxx (2017) 1–11

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Review

Reversible cerebral vasoconstriction syndrome: an important and common cause of thunderclap and recurrent headaches

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ARTICLE INFORMATION

Article history:
Received 11 May 2017
Accepted 20 November 2017

Reversible cerebral vasoconstriction syndrome is an intracranial vascular manifestation of a wide variety of diseases. It is the second most common cause of thunderclap headache, the most common cause of recurrent severe secondary headaches, and, in patients <60 years of age, has been reported as the commonest cause of isolated convexity subarachnoid haemorrhage. Radiologically, its key feature is vasoconstriction of the intracranial vessels, a dynamic process that is typically maximal at 2 weeks, varies in its distribution over the course of the disease, and typically resolves after 3 months. It can have haemorrhagic and ischaemic complications and sometimes occurs in concert with posterior reversible encephalopathy syndrome. It also has important associations with dissection and migraine. Rarer atypical cases can present with mild headache, no headache at all, or even a comatose state. This paper provides a detailed review of this syndrome, its pathophysiology, differential diagnosis, imaging findings, and work-up. It also describes the role that high-resolution magnetic resonance imaging (MRI) techniques can have in diagnosing the disease and emphasises the central role that all radiologists have in detecting this important and underdiagnosed condition.

Introduction

In 1998, writing in the journal *Stroke*, Call and Fleming were amongst the first to describe a series of patients with severe headaches and reversible cerebral segmental vasoconstriction.[1] Subsequently the descriptive term "reversible cerebral vasoconstriction syndrome" (RCVS) was coined in 2007 by Calabrese *et al.* It describes a common pathology present in several differing entities, which manifest as reversible vasoconstriction of the intracranial vessels. It typically presents as an acute severe headache, which is commonly thunderclap, and often initially suspicious for a ruptured intracranial aneurysm. Although the vasoconstriction is reversible, several associated complications, including subarachnoid haemorrhage (SAH), ischaemia, infarction, and haemorrhagic stroke, can lead to significant morbidity and mortality.[2–5] Imaging has a key role to play, not just because of clinical uncertainty in diagnosis, but because RCVS is much more common than initially believed and remains under-recognised and untreated. In particular, computed tomography (CT)-negative, lumbar-puncture negative thunderclap headaches may represent a diagnosis of secondary headache due to RCVS, rather than a primary headache.

In this paper, we describe the clinical and radiological findings of RCVS, including its typical and atypical clinical manifestations, differential diagnosis, and complications. In

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https://doi.org/10.1016/j.crad.2017.11.017
0009-9260/

particular, we focus on the radiological features of the syndrome, its important associations, and the variety of factors that influence how it is worked-up. Radiologists, both sub-specialised and general, have a central role to play in diagnosis as patients can present for imaging through a number of routes, including the emergency department, obstetrics, neurology, neurosurgery, and rheumatology.[5]

Epidemiology

RCVS is the most common cause of thunderclap headache in patients without aneurysmal SAH and is the most common cause of recurrent thunderclap headaches.[6] The reported incidence has increased significantly since the first series was published in 2007 by Ducros *et al.* This initial group described 67 cases over a 3-year period at a single institution.[7] A recent Dutch paper by Grooters *et al.* reported an incidence of 8.8% of RCVS in cases of thunderclap headache lasting a minimum of 6 hours presenting to a general hospital.[8] A study from Cheng *et al.* in 2014, from a headache clinic in Taipei reports an incidence of 45.8% in a population with thunderclap headache.[9]

RCVS can occur at any age, including childhood. It is more common in females by at least 2:1, with some reports as high as 10:1. In females, it most often presents in the early to mid-forties and in men, most often a decade earlier.[4,10]

Pathophysiology

A reversible dysregulation of intracranial arterial tone is thought to be the common underlying mechanism shared by processes which trigger RCVS. The exact process is unknown and is believed to relate to autonomic over-activity, endothelial dysfunction, and oxidative stress.[2,5,6,11,12] RCVS is well documented in association with sympathomimetic activity, either from exogenous vasoactive substances or from endocrine secreting tumours such as phaeochromocytoma. It is also often associated with posterior reversible encephalopathy syndrome (PRES), suggesting the importance of endothelial dysfunction in the disease.[6,13] Markers for oxidative stress have also been correlated with disease severity, notably urinary 8-iso prostaglandin F2α, which is a marker for vasoconstriction and oxidative stress that has been found to correlate with the severity of vasoconstriction.[11] Importantly, histopathology in RCVS patients who have undergone biopsy show no histological changes in the cerebral vessels to suggest inflammatory or vasculitic processes.[2,3,] It has also been proposed that the vasoconstriction of RCVS starts in smaller distal vessels and progresses proximally to larger arteries.[7]

The aetiology of the thunderclap headache is also uncertain, and has been postulated as related to the innervation of the vasculature via the first division of the trigeminal nerve and via sympathetic pathways from the brainstem; however, the typical evolution of the illness, and the occurrence of RCVS without thunderclap headache, does not suggest a clear underlying causal mechanism.[5,14]

Approximately 50% of cases of RCVS have identifiable triggers.[2,5,6] Most often this involves vasoactive substances, including prescribed agents such as adrenergic agonists, selective serotonin reuptake inhibitors, tacrolimus, and also illicit substances, including amphetamines, cocaine, and marijuana. The delay between exposure and development of RCVS can range from a few days to months and can involve first doses, long-term use, or excessive dosing.[6,7] Post-partum triggers account for approximately 10% of identifiable causes, which in a third of cases are combined with other known causes, such as vasoconstrictors used in epidural anaesthesia and post-partum haemorrhage.[6] Post-partum RCVS usually occurs within 3 weeks of labour but is reported up to 6 weeks later.[14,15] Other important reported causes include carotid endarterectomy, migraine, and increasingly an association with dissection of the extracranial cervical arteries is recognised.[16–18] A more complete list is presented in Table 1.[2,3,19]

Clinical course

Thunderclap headache

Thunderclap headache is the classic presenting symptom of RCVS and occurs in 95% of cases. In 75%, it is the only symptom.[5–7,18] Onset is very rapid, usually peaking within 1 minute, often in seconds. It is typically associated with a severe emotional response including confusion, screaming, and collapse.[5–7] It's distribution is usually in the occipital regions bilaterally, which quickly spreads diffusely. Unilateral symptoms have been reported in approximately one-fifth of patients.[20] Headache usually, but not always, lasts <3 hours, which can help differentiate it from SAH.[6] Headaches that last only a few minutes to several days have, however, also been reported, as have milder and progressive headaches.[2,3] Photophobia, phonophobia, nausea, and vomiting also often occur.[2,3] Typically there are recurrent attacks during a period of up to 3 weeks and between severe exacerbations, moderate headache often

Table 1
Triggers of reversible cerebral vasoconstriction syndrome.[2,3,19]

Vasoactive agents
Therapeutic medications: selective serotonin/serotonin-noradrenaline reuptake inhibitors, non-steroidal anti-inflammatory drugs, ergot alkaloids, triptans, nasal decongestants, cyclophosphamide, oral contraceptives, erythropoietin
Illicit agents: marijuana, cocaine, amphetamines
Pregnancy and post-partum
Peripartum period, eclampsia, pre-eclampsia, HELLP syndrome, blood transfusions.
Metabolic and endocrine derangements
Hypercalcaemia, porphyria, catecholamine secreting tumours including carcinoid tumours and phaeochromocytoma
Autoimmune associations
Anti-phospholipid antibody syndrome, thrombotic thrombocytopenia purpura, Intravenous immunoglobulin
Vascular abnormalities
Dissection of craniocervical vessels, cerebral aneurysms

HELLP, haemolysis, elevated liver enzymes, and low platelets.

Please cite this article in press as: Arrigan MT, et al., Reversible cerebral vasoconstriction syndrome: an important and common cause of thunderclap and recurrent headaches, Clinical Radiology (2017), https://doi.org/10.1016/j.crad.2017.11.017