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Systematic review of reversible cerebral vasoconstriction syndrome

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Abstract

Reversible cerebral vasoconstriction syndrome (RCVS) is a cerebrovascular disorder associated with multifocal arterial constriction and dilation. RCVS is associated with nonaneurysmal subarachnoid hemorrhage, pregnancy and exposure to certain drugs. The primary clinical manifestation is recurrent sudden-onset and severe ('thunderclap') headaches over 1–3 weeks, often accompanied by nausea, vomiting, photophobia, confusion and blurred vision. The primary diagnostic dilemma is distinguishing RCVS from primary CNS arteritis. Diagnosis requires demonstration of the characteristic 'string of beads' on cerebral angiography with resolution within 1–3 months, although many patients will initially have normal vascular imaging. Many treatments have been reported to ameliorate the headaches of RCVS, but it is unclear whether they prevent hemorrhagic or ischemic complications.

Keywords

headache; reversible cerebral vasoconstriction syndrome; stroke; systematic review; vasospasm

Reversible cerebral vasoconstriction syndrome (RCVS) has been proposed as a unifying term for a variety of previously named similar syndromes, including Call–Fleming, 'thunderclap' headaches with reversible vasospasm, benign angiopathy of the CNS, postpartum cerebral angiopathy, migrainous vasospasm, migraine angiitis, and drug-induced cerebral arteritis or angiopathy [1]. The mean age of onset is 42 years, and it affects more women than men. RCVS is possibly caused by a transient dysregulation of cerebral vascular tone, leading to multi-focal arterial constriction and dilation [2–4]. Approximately 60% of the cases are secondary to a known likely cause, mainly occurring during the postpartum period or after exposure to vasoactive substances. The syndrome is generally self-limited and has a low incidence of recurrence [2,5]. The main clinical manifestation is recurrent sudden-onset and severe (thunderclap) headaches over 1–3 weeks, often accompanied by nausea, vomiting, photophobia, confusion and blurred vision [2]. The major complications are localized convexity nonaneurysmal subarachnoid hemorrhage (22%) and ischemic stroke or intracerebral hemorrhage (7%), which may leave permanent residual neurological deficits

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[4]. RCVS may be under-recognized and frequently misdiagnosed because it can mimic common conditions such as migraine and ischemic stroke from common causes [6,7]. The clinical and imaging manifestations of RCVS are often indistinguishable from several conditions that cause cerebral arterial stenosis, such as primary CNS arteritis (PCNSA). However, the clinical course, prognosis and management may be quite different. The combination of more frequent cerebrovascular imaging with noninvasive techniques and the escalating use of vasoactive drugs make it likely that cerebrovascular specialists will encounter a growing number of patients on the RCVS spectrum [7].

Methods

The purpose of this article is to assess the currently available literature on patients with RCVS. We sought published articles that reported unique patient clinical information with the diagnosis of RCVS. We searched PubMed with this query: reversible AND (intracranial OR intracereb* OR intercereb* OR cerebrum OR cerebral OR brain) AND (vasoconstrict* OR vasospasm*) AND (stroke OR strokes OR cerebral vascular accident). Our search was performed in April 2010, and limited to full articles published prior to 1 January 2010. No other limits were used. This search produced 84 results. We reviewed titles, abstracts or full articles to determine if our inclusion criteria were met. We found 33 articles that matched our inclusion criteria.

Results

We identified four case series matching our inclusion criteria:

- A prospective series of 56 patients with recurrent thunderclap headaches of whom 22 had proven initial vasoconstriction [8];
- A prospective series of 67 cases, all of whom had initial cerebral arterial vasoconstriction and resolution on repeat angiography [9];
- A retrospective series of 25 patients with thunderclap headache, who also had radiologically proven RCVS [10];
- A prospective series of 32 patients who had RCVS and in whom sequential transcranial color-coded sonography was performed on the middle cerebral artery for 3 months [1].

We identified 214 individual patients reported in the literature to have RCVS. The majority of these patients (180) were part of the aforementioned case series. The other 34 cases were in individual case reports or small series that had clinically and radiographically proven RCVS and showed reversibility on repeat angiography [5,11–27]. Three of these cases were children under 18 years of age [11].

Cause

Reversible cerebral vasoconstriction syndrome has been reported to occur in various clinical settings, and although the pathophysiology is not clearly understood, a disturbance in the control of cerebrovascular tone seems to be the final common pathway [28]. It is associated with nonaneurysmal subarachnoid hemorrhage and neurosurgical procedures, the postpartum period, many vasoactive and other drugs, sexual activity, and numerous other conditions including pheochromocytoma and porphyria [1,2,5,7,[20],21,24,29,30]. Frequently no cause can be identified [24]. Cerebrospinal fluid (CSF) examination, extensive serological tests, and biopsies of the brain and temporal arteries have shown no abnormalities in patients with RCVS [7].

There is evidence to suggest that many factors associated with vasospasm from aneurysmal subarachnoid hemorrhage (catecholamines, endothelin-1, calcium, serotonin, nitric oxide and prostaglandins) may play a similar role in the pathophysiology of vasoconstriction in RCVS [7]. As vascular tone and diameter is dependent on vascular receptor activity and sensitivity, a sudden or evoked central vascular discharge may underlie the alteration and reversible nature of RCVS, and contribute to the severe and acute headache seen with this disorder, which may involve the fact that cerebral blood vessels are densely innervated with sensory afferents from the first division of the trigeminal nerve and dorsal root of C2 [28]. It has been noted that there is a strong association between female sex hormones and hormonal fluctuations with RCVS [8]. The underlying mechanism of RCVS is likely to be multifactorial [8].

Clinical manifestations

The clinical manifestations of RCVS are incompletely characterized. Peak incidence appears to be between the ages of 20 and 50 years, and women have been reported to be affected more often than men [2,4,8–10]. A history of migraine, pregnancy or recent exposure to vasoactive agents has been frequently reported [2,7,10,28]. The onset is usually recurrent sudden-onset and severe headaches that are often accompanied by nausea, vomiting, photophobia, confusion and blurred vision [7,28]. Seizures and focal neurological deficits have been infrequently reported, usually after onset of the headaches [2]. A prospective study of 67 patients with RCVS observed over 3 years reported that the main pattern of presentation (94%) was recurrent thunderclap headaches, which occurred over a mean period of 1 week [2,9]. Localized convexity nonaneurysmal subarachnoid hemorrhage (22%), intracerebral hemorrhage (6%), seizures (3%) and posterior reversible leukoencephalopathy (9%) were all early complications, occurring mainly within the first week [2,3]. Ischemic events, including transient ischemic attacks (16%) and cerebral infarction (4%), occurred later than hemorrhagic events, mostly during the second week [2,4]. Transient ischemic attack symptoms were most commonly visual loss, followed by unilateral sensory symptoms, aphasia and hemiparesis [2,9].

Prognosis

The natural history of RCVS is unclear due to a lack of standard diagnostic criteria. However, because reversibility of the cerebrovascular angiographic abnormalities is necessary for the diagnosis, it would appear that many, if not most, patients have a full recovery without residual symptoms. There may also be a lag in the resolution of the clinical or angiographic features after either has resolved. In the long term, 71% had no evidence of disability and 29% had only minor disability; 61% reported no evidence of cognitive impairment and 31% reported only minor problems. In this series one patient had a relapse. The authors reported that the presence of stroke was the major determinant of persistent morbidity. Although ultimately reversible, severe vasoconstriction can lead to ischemic stroke, presumably through hypoperfusion of the brain territory of the affected artery. The mechanism of subarachnoid and intracerebral hemorrhage occurrence in RCVS is unclear. Despite the overall favorable long-term prognosis of RCVS, some patients will develop stroke, and rare deaths have been reported. The incidence of stroke in RCVS is unclear, with studies reporting between 7 and 50% [7–10]. Fulminant vasoconstriction resulting in progressive symptoms or death has been reported in exceptional cases [3,7,28]. Recurrence of this syndrome has been reported only rarely [7,28].

Diagnosis

Since the most common clinical manifestation of RCVS is recurrent thunderclap headache, the diagnosis should always be considered in this setting. Other entities that can be present

with thunderclap headache include aneurysmal subarachnoid hemorrhage, intracerebral hemorrhage, cerebral venous sinus thrombosis, cervicocerebral arterial dissection and pituitary apoplexy. Idiopathic thunderclap headache is an exclusionary diagnosis for those patients who do not exhibit features of any of the above diagnoses [28]. Evaluation for these other conditions is warranted, which will usually include CT scan of the head, followed by CSF examination for subarachnoid hemorrhage. MRI and magnetic resonance angiography of the brain and vessels of the head and neck can be helpful to narrow the differential diagnosis.

Computed tomography scan of the brain will be normal in the majority of patients with RCVS, but may show convexity subarachnoid and/or intracerebral hemorrhage when they occur. The CSF examination is usually normal, but has been reported to show minor abnormalities such as pleocytosis of up to 15 nucleated cells, small numbers of erythrocytes and/or minimally elevated protein in the range of 50–60 mg/dl [9].

Magnetic resonance imaging of the brain during the first week is normal in most patients, but up to 20% may demonstrate a thin, convexity subarachnoid hemorrhage without evidence of aneurysm [13]. Intracerebral hemorrhage occurs in up to 10% of cases. In the same series, up to 10% of patients had MRI abnormalities consistent with posterior reversible encephalopathy syndrome [9]. The coexistence of this syndrome with RCVS noted in several case reports suggests a possible common pathogenetic mechanism with disturbance of vascular tone. Radiographic evidence of infarction, often in the arterial border zone regions, may be seen during the second week. The earlier occurrence of hemorrhage and later appearance of infarcts may suggest that the more distal arteries are involved at the onset, and a centripetal spread of vasospasm towards the more proximal arteries follows after [3].

Magnetic resonance angiography reveals diffuse segmental arterial constriction in up to 90% of cases, although occasionally the initial study may be negative, and a second study 1–2 weeks later may be required to demonstrate the abnormalities. Large- and medium-sized arteries are more commonly affected, and the degree of affection to smaller arteries remain unclear as the angiographic techniques are not sensitive to small arteries [9]. Catheter angiography remains the gold standard test to demonstrate the characteristic ‘string of beads’ pattern of alternating areas of arterial stenosis and dilation in cases where noninvasive vascular imaging is inconclusive. By definition, the cerebrovascular abnormalities are transient, and should demonstrate complete resolution on repeat imaging 1–3 months later.

Transcranial ultrasound has been used to follow the course of cerebral arterial vasospasm in RCVS. It has been demonstrated that the blood flow abnormalities, as demonstrated by the mean flow velocity in the middle cerebral artery window and the Lindegaard index (the ratio of middle cerebral artery velocity to extracranial internal carotid artery velocity), may persist well beyond resolution of the clinical manifestation [1]. Markedly abnormal values, such as those observed in vasospasm after aneurysmal subarachnoid hemorrhage, are uncommon (13%), but when present may serve as a tool to predict which patients will develop ischemic complications such as cerebral infarction [1].

As the most difficult diagnostic dilemma clinicians face is to distinguish RCVS from PCNSA, a few key points can be helpful [28]:

- RCVS occurs more commonly in women than men at a ratio of approximately 3:1, as opposed to PCNSA, where no sex predilection is noted;

- Symptoms in RCVS develop rapidly, whereas symptoms in PCNSA tend to develop more slowly. Also in PCNSA, a gradual-onset headache is typically accompanied by other neurological symptoms that may dominate the picture, such as confusion, focal neurological deficits or seizures. While these symptoms can also develop in RCVS, they are less common;
- The CSF examination is typically normal or shows minimal abnormalities in RCVS, whereas in PCNSA, 90% or more of patients show significant abnormalities;
- Brain abnormalities on MRI are more frequently seen in PCNSA than RCVS;
- Reversibility of cerebrovascular abnormalities within 1–3 months is the rule for RCVS, which is less often the case for PCNSA.

In some cases the diagnosis will remain unclear despite extensive evaluation by imaging and CSF analysis, and brain biopsy may be necessary, although the sensitivity of biopsy for the diagnosis of PCNSA is certainly not 100%, and the true sensitivity is unclear [31].

Treatment

Treatment of RCVS is currently based on expert opinion and reported case series. Randomized controlled trials do not yet exist and will be difficult to perform due to the difficulty in diagnosis, relative rarity of the condition and the spontaneous resolution of the syndrome in the majority of cases. There is general agreement that discontinuation of potentially offending drugs such as serotonergic agents and sympathomimetics should occur [17,20]. Observation may be sufficient in mild cases, although many authorities advocate empiric treatment for patients who exhibit severe angiographic abnormalities, particularly when cerebral ischemia develops [31]. Calcium channel blockers, such as nimodipine, nifedipine or verapamil, have been used in most patients where treatment was reported [8,9,11,24,25,32,33]. A commonly reported regimen consists of an initial intravenous administration of nimodipine at a rate of 1–2 mg/h, followed by an oral regimen (30–60 mg every 4 h) tapered over the course of several weeks. Treatment is typically given for 4–8 weeks, although the optimal duration is unclear [9]. The dose should be titrated and supportive measures taken to avoid systemic hypotension, which could precipitate cerebral infarction in the border zone arterial territories. Transcranial ultrasound measurement of systolic velocities in intracranial arteries has been used to assess treatment efficacy [1]. The efficacy of treatment varies considerably between reports, ranging from 40 to 80% [9]. The variability in reported treatment success may result from small sample sizes and/or variable definitions of treatment success, which have included cessation of headaches, resolution of vasospasm, or lack of further neurological symptoms and/or stroke. In refractory cases, intra-arterial nimodipine, papaverine or milrinone have been used with good results reported, although experience is limited to case reports [12,26].

Other treatment modalities have been reported less often. Corticosteroids were used in several case reports [18,19,23,24]; while there are preclinical data that corticosteroids may prevent or ameliorate vasospasm in subarachnoid hemorrhage, conclusions regarding their efficacy cannot be made from the aforementioned studies because calcium-channel blockers were used simultaneously. Moreover, the rationale behind the use of corticosteroids may reflect the initial diagnostic uncertainty between RCVS and PCNSA, until additional evidence such as brain biopsy or repeat angiography is available. Another study examined the use of intravenous magnesium sulfate in four patients with postpartum RCVS and reported good results [16,27].

Conclusion

Despite the extensive knowledge that has been acquired concerning RCVS over the last two decades, many uncertainties still exist, primarily resulting from our incomplete understanding of the underlying pathophysiology. Prompt recognition of the syndrome and its precipitating factors in patients presenting with recurrent thunderclap headaches is important, since treatment of these factors, such as discontinuation of offending drugs, may prevent further morbidity. Distinction from PCNSA is a significant challenge, and is often a matter of clinical judgment. Identification of the subset of patients that will develop ischemic or hemorrhagic complications remains problematic. Last, optimal treatment in individual cases is still unclear. Hopefully, future research will allow us to address these issues, and better understand this complex and fascinating cerebrovascular syndrome.

Expert commentary & five-year view

Reversible cerebral vasoconstriction syndrome remains poorly characterized, misdiagnosed and under-recognized, mainly owing to the lack of specific diagnostic tests, any diagnostic criteria and lack of clinical trials. There are a few hypotheses regarding the mechanism involving the segmental vasoconstriction but the exact pathogenesis remains unknown. Most physicians, including many neurologists, have limited knowledge about RCVS. Misdiagnosis is common because the clinical, radiological and angiographic abnormalities are often indistinguishable from conditions that cause irreversible or progressive arterial narrowing, such as primary cerebral vasculitis. With advances in neuroimaging, especially noninvasive cerebral angiography techniques, and with the increasing use of vasoactive drugs, it is likely that stroke physicians will encounter an increasing number of patients with vasoconstriction-induced stroke. Hopefully we will have more systematic reviews and controlled randomized clinical trials to support the exact pathogenesis and criteria for the diagnosis for RCVS in the future.

Key issues

- Reversible cerebral vasoconstriction syndrome (RCVS) is a transient dysregulation of cerebral vascular tone leading to multifocal arterial constriction and dilation.
- The primary clinical presentation is recurrent and severe thunderclap headaches over 1–3 weeks, often accompanied by nausea, vomiting, photophobia, confusion and blurred vision.
- RCVS can occur without identifiable cause, during pregnancy or the puerperium period, and as a response to certain medications or illicit drugs.
- The primary diagnostic dilemma is distinguishing RCVS from primary CNS arteritis.
- Treatment is empirical and includes calcium-channel blockers and possibly high-dose corticosteroids.
- Prognosis is uncertain, but most patients do well and recover completely.

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