Translated by E.V. Trushina

Review

https://doi.org/10.23934/2223-9022-2024-13-3-492-500

Reversible Cerebral Vasoconstriction Syndrome

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ABSTRACT Reversible cerebral vasoconstriction syndrome (RCVS) is a collective term used to describe pathological conditions with a similar clinical and radiological picture which is characterized by thunderclap headaches with a sudden onset and reversible segmental (multifocal) constriction of the cerebral arteries. The article is devoted to issues of terminology, genetic and clinical features of RSCV, and also discusses risk factors, differential diagnosis, complications and prognosis. Modern pathogenetic mechanisms and possible approaches to the treatment of this condition are presented.

Keywords: reversible cerebral vasoconstriction syndrome, cerebral vasospasm, thunderclap headache

For citation Ramazanov GR, Magomedov TA, Solovtsova MS, Shevchenko EV, Kovaleva EA. Reversible Cerebral Vasoconstriction Syndrome. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2024;13(3):492-500. https://doi.org/10.23934/2223-9022-2024-13-3-492-500 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study has no sponsorship

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BBB — blood-brain barrier
CI — confidence interval
CNS — central nervous system
CSF — cerebrospinal fluid
CT — computed tomography
CTA — computed tomographic angiography
DSA — digital subtraction angiography
ICH — intracranial hemorrhage
IS — ischemic stroke
MCA — middle cerebral artery
MRA — magnetic resonance angiography
MRI — magnetic resonance imaging
PA CNS — primary angiitis of the central nervous system
PRES — posterior reversible encephalopathy syndrome
RCVS — reversible cerebral vasoconstriction syndrome
SAH — subarachnoid hemorrhage
TCDS — transcranial Doppler sonography

INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) is a group of cerebrovascular diseases characterized by multifocal alternation of segmental vasoconstriction and vasodilation of medium-sized and large cerebral arteries, clinically debuting with a thunderclap headache [1]. More than 35 years have passed since the first description of RCVS by Call et al. (1988), and currently there are more than a dozen synonyms, including: "Call-Fleming syndrome", "thunderclap headache with reversible cerebral vasospasm", "benign angiopathy of the central nervous system", "headache associated with sexual activity", "drug-induced cerebral arteritis or angiitis", etc. [2–4].

Reversible cerebral vasoconstriction syndrome may occur spontaneously, without an obvious cause, but in more than 50% of cases the triggers are intracranial hemorrhage; cervical dissection; postpartum period; use of narcotic drugs (marijuana, cocaine, amphetamine, methylenedioxymethamphetamine), selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine), tricyclic antidepressants (clomipramine, dibenzepine, doxepin), and vasoconstrictors (oxymetazoline, xylometazoline, phenylephrine) [5, 6].

Currently, there is no clear pathogenetic concept of RCVS, nor is there any basic information on prevalence and mortality. Moreover, even with clearly formulated clinical and instrumental criteria, timely verification of the diagnosis is a complex medical task. This is evidenced by the fact that on average, the patient visits a doctor 4 to 5 times from the onset of the disease to diagnosis and treatment, and the mean time is 9 or more days [6]. Since RCVS is a potentially life-threatening condition, such significant diagnostic delays are unacceptable. Currently, there is information about the relationship between RCVS and such conditions as transient global amnesia, takotsubo cardiomyopathy, PRES (Posterior Reversible Encephalopathy Syndrome) [5, 6]. In addition, there is a hypothesis that PRES and RCVS are a pathogenetic continuum of reversible dysfunction of cerebral arteries of varying severity.

The aim of this article is to increase awareness of neurologists, therapists, anesthesiologists about reversible cerebral vasoconstriction syndrome (RCVS).

MATERIAL AND METHODS

To achieve the stated goal, the results of scientific studies devoted to RCVS were analyzed. The literature search was performed in PudMed and ELIBRARY electronic search systems using the keywords: reversible cerebral vasoconstriction syndrome, acute headache, primary angiitis of the central nervous system. For the analysis, scientific articles published between 1988 and 2023 were selected; 30% of the analyzed works devoted to the topic of RCVS were published no later than 5 years ago.

PREVALENCE

The true prevalence of RCVS remains unknown due to the difficulty of diagnosing this disease. Nevertheless, it has been established that RCVS is more often diagnosed in women [6]. Thus, the ratio of men and women with verified RCVS in European, North American and Chinese studies was 1:2.6, 1:4.3 and 1:10.2, respectively [7, 8, 9]. Another gender-specific feature of RCVS is the average age of onset of this disease in men, which is 10 years younger than in women (30 years versus 40 years, respectively) [9]. In an Italian study, the frequency of RCVS verification in patients with ischemic stroke under 45 years of age was 13% [10]. Although there is no precise data on the prevalence of RCVS, Patel S.D. et al. (2021) reported that more than 1000 patients with RCVS are hospitalized annually in the United States, with an average age of 47.6 years [11].

Despite the presence of such a definition as “reversible” in the term, RCVS is a potentially life-threatening condition, with a mortality rate of 5–10%. However, 90% of patients have a favorable functional outcome of the disease [12]. The incidence of severe RCVS accompanied by focal neurological symptoms is significantly higher in European and North American countries [10].

ETIOLOGY

It was established that RCVS may occur spontaneously, without an obvious cause, or be secondary to a known trigger (25–60% of cases) [11]. Moreover, one patient may have two or more triggers. There are a large number of reports of

factors that provoke RCVS, such as prolonged loud laughter, crying or coughing, bathing in cold or hot water, sexual activity, which are more likely to be coincidental than a pattern [13–15].

The established causes of RCVS can be divided into iatrogenic, which are a consequence of the use of various drugs or diagnostic and therapeutic manipulations, or induced by drug use, as well as associated with other pathological conditions and diseases. Well-known drug triggers of RCVS include the use of over-the-counter sympathomimetics, antimigraine drugs, treatment with interferon, immunoglobulin, erythropoietin, selective serotonin reuptake inhibitors, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, and transfusion of blood components [1]. A medical diagnostic and treatment procedure capable of RCVS inducing is cerebral digital subtraction angiography. In addition to iatrogenic ones, there is a special group of RCVS provoked by the use of narcotic psychoactive substances such as cocaine, methamphetamine, methylenedioxymethamphetamine, tetrahydrocannabinoid. The third group of RCVS causes includes conditions and diseases, among which are the early postpartum period, cervical arterial dissection, subarachnoid hemorrhage (SAH) of both aneurysmal and non-aneurysmal origin, cerebral venous thrombosis, migraine, catecholamine-producing tumors, antiphospholipid syndrome [16–18]. Although a significant number of medications and drugs are well-known RCVS inducers, the bulk of the above-mentioned triggers is the early postpartum period, which accounts for about 50–60% of all cases [19]. The onset of RCVS in the early postpartum period usually occurs between 1 and 6 weeks after an uncomplicated pregnancy. It should be noted that the onset of symptoms may occur several days or months after exposure to the trigger [20].

PATHOGENESIS

Since the etiology of RCVS is heterogeneous, the underlying pathophysiological mechanisms are multifaceted, which complicates the formation of a unified pathogenetic concept. Moreover, according to Singhal A.B. et al. (2011), histological examination of the brain performed in 17% of patients with RCVS did not reveal any abnormalities in any case [1]. A case report of RCVS with histological and electron microscopy examination of the cerebral arteries revealed no abnormalities either, except for a focal area of subendothelial thickening of the posterior cerebral artery [21].

The development of RCVS apparently requires not only the presence of a trigger, but also a predisposition of the body. Despite the complex mechanisms, Chen S.P. et al. (2022) identified 9 tangentially oriented links of this syndrome: dysregulation of cerebral arterial tone, sympathetic hyperactivity, excessive oxidative stress, damage to the blood-brain barrier (BBB), altered trigeminovascular nociceptive system, genetic predisposition, sex hormones and inflammation [21, 22]. Pathogenetically, it best fits the picture of reversible cerebral vasoconstriction syndrome triggered by surgery on the vessels of the brain in genetically predisposed individuals [23]. Thus, according to this concept, a trigger with increased sympathetic activity acts on a genetically predisposed patient [24]. Then, at the moment of overexcitation of the sympathetic nervous system, there occurs a release of vasoconstrictors such as catecholamine, neuropeptide Y and endothelin-1, which induces a violation of cerebrovascular tone regulation and debuts with dilation of distal arterioles due to an increased trigeminovascular reflex [24]. Dilation of distal arterioles, capillaries and meningeal collaterals ultimately leads to stretching of perivascular nociceptive nerve fibers and, as a consequence, to headache. Excessive pulsatile blood flow against the background of fluctuations in arterial pressure forms the basis for increased permeability of the BBB, which further increases the dysfunction of cerebral arterial tone, as well as the severity of headache. In response to excessive pulsatile cerebral blood flow and dilation of distal arterioles, large and medium cerebral arteries constrict, resulting in centripetal spread of vasoconstriction [20]. Persistent sympathetic hyperactivity leads to endothelial dysfunction and excessive oxidative stress, further dysregulating cerebral arterial tone, which reduces the capacity for endogenous endothelial restoration. Vasoactive metabolites formed in response to free radicals, such as 8-iso-PGF2α, penetrate into the perivascular space, maximizing vasoconstriction [22]. Along with vasoconstriction, inflammation of the vascular wall may develop [24]. Increased BBB permeability and excessive pulsatile blood flow may cause complications such as PRES, SAH, and intracerebral hematoma. In addition, abrupt stretching of small

pial arterioles can lead to reperfusion injury and rupture of these vessels and, as a consequence, SAH. Vasoconstriction of large and medium-sized cerebral arteries can lead to cerebral hypoperfusion and acute ischemia [21].

CLINICAL MANIFESTATIONS AND CEREBRAL COMPLICATIONS

The main clinical manifestation of RCVS is a sudden, intense, thunderclap headache reaching its maximum intensity within 1 minute. The patient describes such cranialgia as the most severe pain he or she has ever experienced. The duration of the pain syndrome can reach 10 days, and in some cases is accompanied by symptoms of focal brain damage. The incidence of severe headache in patients with RCVS reaches 94–100%; and in 70–76% of cases, it may be the only symptom [17, 25]. Cases of non-specific, mild or progressive headache in patients with RCVS were described. Very rarely, RCVS occurs without headache and debuts immediately with cerebral focal symptoms [26]. Typical headache in patients with RCVS is bilateral (less often unilateral), starts from the occipital region and spreads diffusely throughout the head. It is often accompanied by nausea, vomiting, photo- and phonophobia; which requires differential diagnosis with SAH and meningitis, and concomitant neck pain should serve as a reason to exclude cervical dissection [7]. In 94–100% of patients, headaches are recurring, with an average of four thunderclap headache episodes developing over the next 4 weeks [23, 27–30]. Headache recurrence can be provoked by Valsalva-like activity – cough, laughing, defecation, sexual activity [28, 30]. Almost half of the patients develop headache after regression of vasoconstriction, which can be present for more than 12 months [31]. It should also be remembered that 5–10% of the patients develop a relapse of RCVS [32]. Boilet R. et al. (2019) described a series of clinical observations with the simultaneous development of RCVS and transient global amnesia, which may indicate similar pathogenetic mechanisms of the two conditions [5].

Seizures and focal neurological deficit are observed in 33% and 8–43% of patients with RCVS, respectively [18, 28, 29, 33]. Focal neurological deficit in a patient with RCVS requires the exclusion of such cerebral complications as intracranial hemorrhage (ICH), development of acute cerebral ischemia, as well as posterior reversible encephalopathy syndrome (PRES) [34, 37]. According to the study by Topcuoglu M.A. et al. (2016), the incidence of ICH in patients with RCVS was 43% [34, 35]. Female gender and a history of migraine are independent risk factors for ICH in patients with RCVS [36]. Convexity subarachnoid haemorrhage (SAH), intracerebral and subdural hematomas were detected in 38%, 13% and 1.9% of patients, respectively [35]. In 1/3 of patients, SAH was bilateral. Primary computed tomography (CT) examination of the brain reveals signs of convexity SAH in 90%, and in 10% - only during a repeat examination. Moreover, in 23% of patients, SAH of a new location was observed during CT of the brain in dynamics [35]. The features of SAH in patients with RCVS are location in convexity (35%), limitation by 1–3 sulci, more often frontal localization (51%) [36]. As a rule, SAH develops 2–4 days after the onset of the thunderclap headache [36, 37]. The incidence of such complications of RCVS as ischemic stroke (IS) and PRES, according to the study by Chen S. et al. (2008), is 20% and 9%, respectively [38–40].

Differential diagnosis of aneurysmal SAH and RCVS-associated SAH is important. The latter is characterized by a discrepancy between the prevalence of SAH (1–3 sulci) and the severity of vasoconstriction, which is often diffuse [36]. In addition, in 80% of patients with aneurysmal SAH, only one episode of a thunderclap headache develops at the onset of the disease, while 85–100% of patients with RCVS have about four such episodes [37]. The headache pattern allows differentiation between primary angiitis of the central nervous system (PA CNS) and RCVS. In the first case, the headache is often “dull” in nature (51%), and very rarely thunderclap one (6%) [38].

The severity of cerebral vasoconstriction in patients with RCVS is associated with the risk of developing acute cerebral ischemia and PRES. Thus, Chen S. et al. (2008) using transcranial Doppler ultrasonography found that blood flow velocity in the middle cerebral artery (MCA) exceeding 120 cm/s, as well as the Lindegaard ratio of 3 or more, increase the risk of developing IS and PRES (50% versus 0%, p=0.01, and 75% versus 4%, p=0.003, respectively) [39]. Moreover, Topcuoglu M.A. et al. (2016) using cerebral computed tomography and digital subtraction angiography (DSA) found that early distal vasoconstriction is associated with the formation of intracerebral hematomas and SAH, and delayed proximal one - with the development of ischemic stroke [34]. One study found that the

combination of vasoconstriction of the M1 MCA and P2 posterior cerebral artery segments has the highest risk of developing PRES and acute cerebral ischemia (odds ratio 11.6; 95% confidence interval (CI) 2.06–67.85; p=0.005) [39]. Thus, it was established that cerebral hemorrhagic complications in patients with RCVS develop within the 1st week, and IS and PRES – between the 2nd and 3rd weeks [34].

DIAGNOSIS

Diagnostic criteria for RCVS include the presence of thunderclap headaches and angiographically confirmed vasoconstriction of two or more cerebral arteries [3]. It should be noted that these criteria have not been validated in prospective studies.

There are several neuroimaging techniques used to diagnose and monitor RCVS, including computed tomography (CT), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA).

With regard to cerebral DSA, it should be noted that this diagnostic method is the "gold standard" with 100% sensitivity for RCVS [40, 41]. A characteristic angiographic symptom of RCVS is alternating areas of stenosis and dilatations of the cerebral arteries (string of beads sign) [42]. The advantage of the method is the ability to visualize vasoconstriction of small-caliber arteries, as well as the possibility of local intra-arterial delivery of a pharmacological drug. The disadvantages are the invasiveness of the method, and the risk of developing contrast-induced nephropathy and other rare complications, the incidence of which ranges from 0.3 to 5% [43, 44]. Currently, DSA in patients with RCVS is considered as a reserve diagnostic method. Cerebral DSA, having 100% sensitivity to detect luminal signs of RCVS, does not allow us to evaluate parenchymatous changes of the brain. The angiographic pattern of vasoconstriction helps perform differential diagnosis of RCVS and primary CNS angiitis. In contrast to the diffuse uniform concentric vasoconstriction in RCVS, PA CNS is characterized by uneven, jagged eccentric stenosis of the cerebral arteries, which is the result of chronic inflammation and destruction of the vascular wall [38].

Cerebral CT and CT angiography (CTA) are the first instrumental diagnostic method performed on patients admitted to hospital with thunderclap pain. The absolute advantage of CTA is its high availability. The sensitivity of CTA for detecting vasoconstriction in patients with SAH is 80% [45, 46]. The disadvantages of this method are exposure to X-ray radiation and the risk of developing contrast-induced nephropathy. Native CT is a reliable method for detecting SAH with sensitivity and specificity approaching 99.99%. The optimal method for identifying such parenchymal manifestations of RCVS, as cerebral ischemia and PRES, is to use magnetic resonance imaging (MRI) in FLAIR (Fluid Attenuated Inversion Recovery) and DWI (Diffusion-Weighted Imaging) modes, respectively.

Cerebral MRI and MRA have the advantages over CT and CTA of no X-rays or need for a contrast agent, thus not exposing the patient to the risk of developing contrast-induced nephropathy. Compared with CT, MRI is the optimal method for verifying such parenchymal complications of RCVS as acute cerebral ischemia and PRES. Claustrophobia and the presence of paramagnetic substances in the patient's body limit the use of MRI. Cerebral MRA has a sensitivity of 80% for detecting signs of vasoconstriction [40, 45, 46]. The use of a contrast agent during MRI may be required for differential diagnosis, for example, with inflammatory diseases of the brain. Contrast-enhanced vascular wall MRI (VW-MRI) may be a useful method for differential diagnosis of RCVS with such arteriopathies as PA CNS, vasculitis and cocaine vasculopathy. Thus, according to the results of the study by Mandell D.M. et al. (2012), thickening of the cerebral artery wall in the absence of contrast accumulation is a characteristic feature of RCVS, in contrast to other arteriopathies, in which simultaneous wall thickening and marked contrast accumulation are observed [47]. In some cases, it may be necessary to differentiate between cerebral vasoconstriction and intracranial atherosclerosis, where contrast-enhanced T1-weighted VW-MRI demonstrates contrast accumulation in the vascular wall, as opposed to RCVS. Intracranial atherosclerosis is also characterized by eccentric thickening of the arterial wall in contrast to the uniform concentric vasoconstriction associated with RCVS [47]. MRI is the optimal diagnostic tool for visualizing parenchymal complications of RCVS [40, 46, 48]. Hyperintense cerebral arteries on FLAIR images may indirectly indicate a decrease in blood flow through them due to vasoconstriction [47]. However, it should be taken into account that this sign has low specificity, and may be a manifestation of thrombotic occlusion or atherosclerosis [49, 50]. In the case of cerebral infarction, two radiological scenarios are

possible. The first involves the formation of small cortical foci of acute cerebral ischemia that occur during the first week as a result of hypoperfusion caused by vasoconstriction of arterioles [12]. The second is the formation of large, wedge-shaped foci of infarction in areas of adjacent blood supply [12]. Ischemic foci do not develop simultaneously, but as vasoconstriction progresses [38]. On the one hand, this is a dynamic process with the possibility of escalation of the severity of neurological deficit, and on the other, this prevents the simultaneous formation of malignant cerebral ischemia and an unfavorable outcome of the disease.

Transcranial doppler (TCD) ultrasound reveals signs of cerebral vasospasm in 69–81% of patients with RCVS [39]. The noninvasiveness and high availability of this method make it extremely attractive. An analysis of five studies showed the sensitivity of TCD to detect vasospasm of 67% (95% CI, 48–87); while a pooled analysis of three studies found a sensitivity of 62% (95% CI, 11–72) for the verification of anterior cerebral artery vasospasm using TCD [41]. Monitoring the severity of cerebral vasospasm using TCD allows one to evaluate the therapeutic response, which is another significant advantage of this technique [49]. At the onset of the disease, the blood flow velocity according to TCD data may be within normal values, reaching peak values within the next 3 weeks [50].

Currently, there are no laboratory tests to confirm or refute RCVS. However, toxicological examination of biological fluids can establish a trigger for RCVS [51]. Detection of signs of inflammation in the cerebrospinal fluid (CSF) or determination of a high titer of antineutrophil cytoplasmic antibodies in the blood allow one to suspect meningitis or vasculitis, respectively [52]. In addition, CSF analysis allows differentiation of RCVS from PA CNS which is characterized by an increase in protein concentration and an oligoclonal type of IgG synthesis [53]. The importance of differential diagnosis is dictated by the differences in treatment regimens for RCVS and diseases that mimic it, which include PA, CNS vasculitis, cerebral venous thrombosis, and inflammatory cerebral amyloid angiopathy [54].

In order to improve the quality of diagnostics and, first of all, differential diagnosis with PA CNS, the RCVS2 (Reversible Cerebral Vasoconstriction Score) scale was developed [55]. A score of 5 points or more on this scale has 99% specificity and 90% sensitivity for RCVS [55].

TREATMENT

Treatment of patients with RCVS is symptomatic and consists of eliminating the trigger, the use of calcium channel blockers, analgesics, antiemetics, antiepileptic drugs in the event of an epileptic seizure, refusal to use glucocorticosteroids (GCS) and non-hormonal anti-inflammatory drugs [16, 56–58].

There are currently no randomized trials on the treatment for RCVS. Nevertheless, if the trigger is identified, its effect must be discontinued. Since a significant number of patients with RCVS develop complications such as ICH, acute cerebral ischemia, and PRES, diagnosis and treatment should be performed in the intensive care unit. Calcium channel blockers (nimodipine, nifedipine, nicardipine, and verapamil) have been successfully used to treat cerebral vasospasm [16, 56, 57]. However, the optimal duration of drug administration remains unclear. Although there is currently no convincing evidence of the benefits of any of the calcium channel blockers listed above, nimodipine is considered the first-line drug.

Intravenous (1–2 mg per hour) or oral administration of nimodipine at a dose of 30–60 mg every 4 hours leads to a reduction in headache in 64–83% of patients [16, 56]. Regardless of the chosen route of drug administration, nimodipine therapy should be continued for 4-8 weeks [56]. Despite the lack of evidence, headache in patients with RCVS can be effectively relieved with acetylsalicylic acid [59]. Hadhiah K.M. et al. (2021) described a clinical case of successful treatment of refractory cerebral vasoconstriction using intravenous administration of a selective phosphodiesterase inhibitor, milrinone [59]. Intra-arterial administration of calcium channel blockers effectively eliminates cerebral vasospasm, and can also be used as a differential diagnostic test to exclude vasculitis. In patients with vasculitis, the administration of vasodilators, including intra-arterially, is not accompanied by the elimination of vasoconstriction.

Oral administration of verapamil and nicardipine is also possible for the treatment of patients with RCVS [16, 57]. Cases of effective treatment of cerebral vasoconstriction refractory to nimodipine using intra-arterial verapamil and intrathecal nicardipine were described [33, 60]. The possibility of

endovascular balloon angioplasty for refractory cerebral vasoconstriction was also reported [61].

The use of glucocorticosteroids (GCS) in patients with RCVS is associated with adverse functional and clinical outcomes. In 47% of patients who received GCS, an unfavorable clinical outcome (modified Rankin Scale of 4–6 points) of the disease was observed compared with 17% of patients who were not prescribed this type of treatment [58]. Nevertheless, patients with RCVS are often exposed to unnecessary risk by prescribing GCS for fear of missing and leaving untreated PA CNS.

CONCLUSION

Despite the fact that reversible cerebral vasoconstriction syndrome is reversible, the consequences of this syndrome are irreversible in some cases, are the cause of disability, and in 5% of cases - death. In this regard, patients with reversible cerebral vasoconstriction syndrome should be diagnosed and treated in the intensive care unit. All patients with a newly developed thunderclap headache are recommended to undergo neuroimaging, the minimum volume of which is computed tomography and computed tomographic angiography of extra- and intracranial cerebral arteries. In case of reasonable suspicion of reversible cerebral vasoconstriction syndrome even with normal CT and CTA picture, it is necessary to repeat these examinations in 2-3 weeks, since this period is the peak of cerebral vasoconstriction. Reversible cerebral vasoconstriction syndrome can cause both intracranial bleeding and acute cerebral ischemia.

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Received on 12/01/2024
Review completed on 20/03/2024
Accepted on 14/08/2024