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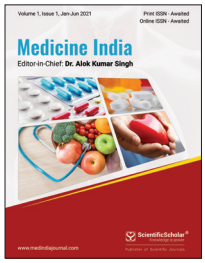

Review Article

Reversible cerebral vasoconstriction syndrome: Considerable differential diagnosis

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ABSTRACT

Background: Headache is the most common symptom in the neurology department of the hospital. This makes it a very important topic to understand more about what causes headaches. There are many causes of headaches and based on the cause, there could be different locations for headaches. One of the causes of the headache could be reversible vasoconstriction in the brain. This type of headache overlaps with a lot of differential diagnoses. Hence, it is important to bring light to this differential diagnosis to improvise the treatment regimen for the patient.

Objectives: The objectives of the study were to study reversible cerebral vasoconstriction syndrome (RCVS) and all the differential diagnosis of headache that overlaps with RCVS.

Methods: We searched the recent studies done on RCVS along with meta-analysis, controlled clinical trials, and cohort studies. We made the differential tables with symptoms, diagnoses, and treatments to bring a better understanding of the overlapping symptoms of different diseases and RCVS.

Result: Understanding the symptoms, diagnosis of RCVS, and other overlapping symptoms of diseases, is helpful to avoid the extra expenditure of the patient. It would also help in leading treatment in the right direction without putting the patient on the experimental drugs.

Keywords: Reversible cerebral vasoconstriction syndrome, Headache, Neurology, Vasoconstriction

INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) is one of the modern neurovascular disorders that were discovered in 1962. Regarding its modern discovery, its etiology and pathophysiology have remained unclear. Features considered under RCVS are thunderclap headaches with reversible segmental vasoconstriction of cerebral arteries. These features mostly take 3 months to recover. RCVS patients may experience complications, such as ischemic stroke, posterior reversible encephalopathy syndrome (PRES), and intracranial, intracerebral, or subdural hemorrhage. Additionally to that, White matter hyperintensities can be noticed in one-third of RCVS patients. Additional symptoms that can be seen regarding the severity of RCVS are seizures and hypertension with stroke-like symptoms.[1]

With the remain of unexplained etiology and pathophysiology mechanisms in most of them, diagnosis and treatment will not be accurate and promising. Regarding RCVS symptoms, many neurovascular and neurological disorders can overlap with these symptoms: Cerebral venous sinus thrombosis (CVST), PRES, cervicocerebral arterial dissections, intracerebral hemorrhage,

pituitary apoplexy, and intracerebral hemorrhage (ICH). Noticing this fact, differentiation between these symptoms should be available for accurate diagnosis. The differential diagnosis had been most of them clear in many studies and research. Studies involved in each disorder had mostly shown the effect of the accuracy of radiological biomarkers above blood tests. Magnetic resonance imaging (MRI) had shown great results in detecting hemorrhage and its location with the finding of any masses. Additional to MRI, a computed tomography (CT) scan was a little preferable regarding its undifferentiation between neurovascular disorders. Some blood tests for coagulation and detecting infection had helped in the diagnosis of many of them.

PATHOPHYSIOLOGY

The presentation of RCVS is temporary and self-limiting. Permanent disability has been observed in almost 10% of patients.[2] Thunderclap headaches, focal deficits, inaugural seizures, and blood surges comprise the main symptoms. They resolve generally within 3 months of onset and are associated with triggers such as physical strain and emotional turbulence. Photophobia, Phonophobia, and pain-related symptoms accompany episodes.[3]

Although roughly 11% of cases develop RCVS iatrogenically, a systematic review of the literature revealed that RCVS was secondary to vasoactive drug usage (41%), and pregnancy (21%), and the remaining cases have various triggers.[4] Although commonly females are affected by RCVS, pediatrically 11 out of 12 observed RCVS patients were male.[5] Observations on the relationship between selective serotonin reuptake inhibitors and serotonergic medication in general with the onset and development of RCVS have been insightful to judicial use of said drugs.[6] Pathophysiological links have been made between RCVS and systematic lupus erythematosus.[7]

A variety of neuroimages findings shed light on RCVS. Diffuse vasoconstriction, accompanied by subarachnoid, intracerebral hemorrhages, and cerebral infarction. Segmental narrowing and dilatation of cerebral arteries are the cruces of the condition. A repeat angiogram will reveal the temporary nature of the string of beads presentation as some vessels may have resolved in a few days. Arterial histology is found to be normal and there is the absence of inflammation, vasculitis, or micro-thrombosis.[3]

Although there is uncertainty over the pathophysiology of RCVS, the key mechanism leading to vasoconstriction is alterations in vascular tone. This may be caused by various mechanisms such as endothelial dysfunction, oxidative stress, and sympathetic overactivity. The close correspondence of RCVS with PRES supports the involvement of epithelial dysfunction as it plays a central pathophysiological role in PRES. Various hormonal and biochemical such as estrogen, endothelin-1, serotonin, nitric oxide, and prostaglandins have been suggested to contribute. Other factors involved in angiogenesis such as the placental growth factor, soluble endoglin, and the soluble placental growth factor have also been under the spotlight. Genetic predisposition has been observed and may affect the severity of the clinical course for certain individuals. Increased vasoconstriction was observed in cases with genetic polymorphism in the gene for brain-derived neurotrophic factor. It was observed that a large proportion of postpartum RCVS patients, around 70%, used serotonin selective reuptake inhibitors or other serotonergic drugs.[2] Rare, crucial inciting factors such as hyperosmolar hyperglycemic state and Illicit drugs such as marijuana and cocaine have also been seen to induce RCVS.[8]

PRES often present in association with RCVS and they may share a common pathophysiology. Autonomic dysregulation and oxidative stress have been postulated to be possible mechanisms in RCVS.[2] PRES almost exclusively occurs in clinical situations with arginine vasopressin (AVP) hypersecretion, such as eclampsia and sepsis, it has been hypothesized that AVP axis secretion precipitates PRES. Its common pathophysiology with RCVS may open new areas of understanding of RCVS.[9]

RCVS AND DIFFERENTIAL DIAGNOSIS FOR HEADACHES

Neurological disorders are considered a challenging science till our century. This fact is mainly due to the remain of unclear etiology and pathophysiology of these disorders leading to unpromising diagnoses and treatments. With all of the evolution of medicine, understanding neurological disorders with accurate diagnosis is still challenging especially due to the overlap of the symptoms and combination of many disease's symptoms.[10]

In even one symptom, the type of symptom may differ its diagnosis, for example, headache is the most common symptom in neurological disorders, but headache in the temporal region gives a different diagnosis compared with headache in the occipital region. In cerebral venous thrombosis as an example, it is hard to confirm the diagnosis according to the severity of symptoms differ, from minor symptoms that overlap with migraine to sub-acute symptoms that need accurate description from patients. Arteriovenous infections, thrombosis, or even hemorrhage are more challenging in differentiating between their symptoms according to the similarity of symptoms, as well as in many different neurovascular diseases.[11]

RCVS is considered one of the neurological chronic disorders and radiological as well. RCVS is not a disease with a specific etiology, it is a group of diseases that need concentration

on the described symptoms. RCVS visible signs and symptoms that person suffers from is a mainly frequent period of severe pain that take 3 months. Headache is mostly diagnosed in RCVS when having Thunderclap headache or in minor cases migraine-like symptoms. Besides the visible symptoms, patients with RCVS are on the side of reversible vasoconstriction in cerebral vasculatures.[10]

The understanding of the pathophysiology of changes in a vascular tone that leads to hemorrhage or infection is the opener key to the world of etiology of RCVS leading to the exact diagnostic methods in our hands. This fact was in scientists' minds till starting studies to evaluate the future. Unfortunately, studies are yet under confirmation as the pathophysiology is not fully clear. Contrary to that, many methods and clinical experiments had been done to come up with a clear accurate diagnosis.[11]

Many studies involved in understanding the etiology of vascular tone changes in RCVS patients were done with control studies for the accuracy of the results. Brain biopsy was one of the methods in taking a step to visualize a visible understanding of RCVS. Brain biopsy results confirmed no detection of any histological changes in the vasculature of the RCVS patient's brain. This study proved patients with RCVS are having normal vasculature in both functioning and histologically. Cerebral vascular tone deregulation is stimulated in RCVS patients mainly due to endothelial dysfunction according to the overlapping of RCVS and PRES, which gives endothelial dysfunction a forward step into the pathophysiology of RCVS. Sympathetic overactivity had also been suggested in the deregulation of cerebral vascular tone in surges of blood pressure, pheochromocytoma, and sympathomimetic vasoactive substances ingestion. Besides these methods it was detected also oxidative stress which is playing important role in the deregulation of cerebral vascular tone. Different studies have shown biochemical factors and hormones influencing on deregulation of cerebral vascular tone. Hormones such as serotonin, estrogen, endothelin-1, and prostaglandins have been shown to affect vasoconstriction and thrombosis that lead to rupture or hemorrhage.[11]

A variety of methods such as investigations, laboratory tests, radiological tools, and clinical integrations are conducted under the diagnostic methods and biomarkers in RCVS patients. Diagnosis decision is not simple to be done according to the overlap with other diseases such as aneurysmal subarachnoid hemorrhage (SAH). According to that, some steps should be taken in the beginning before starting the diagnostic tools and methods. Starting with taking a history of RCVS patients is a significant step in determining the diagnosis. The following step is considered in taking well and accurate physicals. Next to that point, we can start laboratory tools like CSF tests, blood tests that detect inflammation such as white blood cell (WBC) count test, and also red blood cell test and protein levels will be helpful, then radiological tests come lately.[12]

Radiological imaging as Transcranial Doppler Sonography (TCDs) is considered one of the diagnostic methods helping in discovering RCVS. TCDs had detected elevation in internal carotid artery velocity and middle cerebral elevation RCVS patients. Corresponding to TCDs, Serial TCD examinations are more favorable and accurate according to their detection of the related etiology of elevation of cerebral arterial velocity in RCVS. In parallel to TCDs, CT angiography (CTA) and non-contrast CT are included as a diagnostic method for RCVS to detect hemorrhages like subarachnoid, or even intracranial strokes that non-contrast CT can detect.[12]

Another radiological diagnostic method and etiological detection are MRI. T2 FLAIR-weighted imaging of MRI is demonstrating both cerebral edema and subarachnoid hemorrhage (SAH) in RCVS patient's brain. In contrast, diffusion-weighted imaging (DWI) can only detect infarction of watershed area. Findings in susceptibility-weighted imaging had evaluated diagnosis in revealing intracranial hemorrhage. Radiological vascular methods can take part in the diagnosis of RCVS, such as catheter angiography, Perfusion imaging, and vessel wall Imaging (MR VWI) as in general they detect the presence of hemorrhage, stroke, or even vascular structure changes.[12]

Even though RCVS is not fully diagnosed clearly, suffering RCVS patients should be given treatments to eliminate their symptoms at least. Treatment discovery for RCVS is not yet in our hands but contrary to that, some useable pharmacological treatments are advised to be given to RCVS patients and to be the role of RCVS treatment. The most commonly and widely used pharmacological treatment is calcium channel blockers, such as nimodipine or verapamil is considered one of the treatments that RCVS patients had used with effective results in treating vascular tone. Besides calcium channel blockers, corticosteroids are also used as a treatment for RCVS. Corticosteroids are used in RCVS according it is important to function in the prevention of SAH and vasospasm. Additionally to that, controlling other symptoms such as seizures by antiepileptic treatments is required.[13]

Last but not least, with all the missing information about neurological disorders in general and specifying RCVS etiology and pathophysiology, it was managed to come up with using available treatments to treat and eliminate RCVS patients' symptoms. His management was mainly due to the efforts in studies on RCVS patients. In addition to that, studies also helped in detecting some methods that can be used as diagnostic biomarkers in RCVS patients.[13]

BAIN HEMORRHAGES VERSUS RCVS

Hemorrhage is defined as bleeding from vessels as a result of a stroke or rupture in vessels. Vessels of all types and sizes can rupture leading to hemorrhage. Hemorrhages in the brain can take many places regarding the affected vessel. Many neurological disorders are considered hemorrhagic disorders as intracranial hemorrhage, intracerebral hemorrhage, and pituitary apoplexy. Many neurological disorders are considered hemorrhagic disorders as intracranial hemorrhage, intracerebral hemorrhage, pituitary apoplexy, RCVS, CVST, and SAH. Regarding the similar sharing symptoms in stroke-like symptoms, it is important to diagnose them and come up with promising diagnostic biomarkers.

Intracranial hemorrhage is one of the neurological disorders known for bleeding in the intracranial vault. Intracranial hemorrhage frequently overlaps in diagnosis with intracerebral hemorrhage (ICH) and SAH. Regarding this overlap, it is important to differentiate them by diagnostic biomarkers. The differentiation will be a result of understanding the etiology and pathophysiology of all of them. To do and evaluate that, control studies should be done. With the evolution of studies, Scientists named Call and Flemming discovered a neurovascular disorder that includes stroke-like symptoms and other overlapping symptoms such as hemorrhage known as RCVS. Regarding the modern discovery of RCVS, it is preferable to use RCVS in comparison with other neurological disorders that share similar symptoms to differentiate and diagnose them.[14,15]

RCVS as mentioned before is a neurovascular disorder and rare as well regarding its modern discovery. RCVS had known for its distinguished symptom in thunderclap headaches besides other symptoms. RCVS can be correlated to pregnancy and exposure to certain drugs. In addition, factors influencing vascular tone can lead to RCVS. Factors such as LSD, cannabis, cocaine, steroids, intracranial or extracranial disorders (head and neck surgery, CSF hypotension, head trauma, and spinal subdural hematoma), headache disorders (primary thunderclap headache, exertional headache, migraine, and benign sexual headache), catecholamine-secreting tumors (bronchial carcinoid tumors, glomus tumors, and pheochromocytoma,), and vascular associations (cervical artery dissection, fibromuscular dysplasia, endovascular procedures, unruptured intracranial aneurysm, and carotid endarterectomy).[14]

RCVS is mainly diagnosed if a patient fulfills the following criteria: (1) Segmental cerebral artery vasoconstriction seen on the magnetic resonance angiography, (2) no evidence of SAH, (3) normal CSF analysis (protein, leukocytes, and glucose), (4) severe headache with/without neurological findings, and (5) reversibility of angiographic abnormalities within 12 weeks. Regarding that, the pathophysiology of RCVS is more related to vascular vessels of the cerebral arteries, sympathetic overactivity, and the breakdown of the blood-brain barrier. Considering this information, it is important to study other disorders that overlap with RCVS to differentiate between them.[14]

Intracerebral hemorrhage (ICH) is a neurological disorder and is considered a subtype of stroke. ICH is a devastating condition whereby a hematoma is formed within the brain parenchyma with or without blood extension into the ventricles. Regarding the understanding of its definition, the risk factors are almost expected. Chronic hypertension, amyloid angiopathy, and vascular malformations are the main risk factors. Regarding these life-threatening symptoms, it is important to understand and study the etiology of ICH and its pathophysiology as well.[15]

The etiology of ICH had studied the causes and factors that lead to it in many involved studies. ICH was divided into primary and secondary. The division was due to the presence or absence of pathological or structural. Primary hemorrhage bleeds account for 85% of all ICH and are related to chronic hypertension or amyloid angiopathy. Secondary hemorrhage is considered to be related but not limited to bleeding diathesis (iatrogenic, congenital, and acquired), vascular malformations, neoplasms, hemorrhagic conversion of an ischemic stroke, and drug abuse. The absence of structural pathology as malignant tissue or vascular anomalies. Factors affecting ICH are age, chronic hypertension, and location of the clot. It was visible that the main factor that increases the chance of ICH is chronic hypertension at 60%. This change was due to the etiology of chronic hypertension as it is considered that lipohyalinosis and degenerative changes of penetrating arterioles result in Charcot-Bouchard aneurysms in the small arterial vessels supplying deep cerebral structures. ICH hematomas are most commonly seen in the posterior fossa, pons, basal ganglia, and thalamus. Contrary to that, secondary hemorrhage is classified as evidence of structural pathologies, such as vascular anomalies or malignant tissue. Cerebral hematomas may also be secondary to a primary or metastatic lesion. Vascular lesions include arteriovenous malformations, cerebral aneurysms, aortic-venous fistulae, and cavernous angiomas these are often the cause of ICH in the young. Additionally to that, congenial and acquired bleeding diathesis is a common factor in ICH.[15]

Cerebral parenchymal hemorrhages are often classified as primary injury and secondary injury as well. With the evolution of studies, it was noticed that ICH can be seen in three phases, (1) the initial extravasation of blood into the parenchyma, (2) subsequent bleeding around the clot causing expansion, and (3) swelling or edema around the hematoma. Primary injury is considered in acute bleeding which causes a sudden increase in mass in the parenchyma of

the brain which in turn causes compression and disruption of the surrounding neuronal tissue. As the consequence of acute bleeding, the brain parenchyma recruits inflammatory cytokines and thrombin, which causes edema or tissue swelling around the acute hemorrhage considered a secondary injury.

Diagnostic methods and tools were done on ICH patients in a controlled study to get promising diagnostic biomarkers for ICH. Non-contrast CT is a promising tool in the diagnosis of ICH. This promise is mainly due to the ability of CT scans to differentiate the intracranial pathology that included SAH, ischemic stroke, and mainly ICH. In addition, it can confirm hemorrhage location, and size and distinguish mass as well. Patients having hyperdensity within the parenchyma, with surrounding hypodensity that reveal and indicate perivascular edema can be detected by CT scan. CTA had considered another tool in discovering ICH and clotting of vessels. The diagnosis of a vascular abnormality can also be useful before clot evacuation in the emergent setting. Another diagnostic tool that helps in diagnosis is MRI (T2 MRI) weighted and gradient-echo sequences had helped in revealing old clots but have the downfall of taking more time and being less readily available.[15]

Regarding the pathophysiology and diagnostic biomarkers, studies in treatments of ICH should start. Treatments for ICH in stroke-like symptoms such as headache from hypertension due to hematoma expansion should be controlled by pharmacological treatments of elevated blood pressure. Hyperglycemic patients having ICH should be also given medication to control sugar levels. Another treatment that may depend on severity is the "Surgical intervention for supratentorial ICH.". This had mainly been done in a clinical trial within 72 h of surgery but it was not helpful. Undergoing studies are working on treatments of ICH that have the benefit of less parenchymal brain trauma.

CVST VERSUS RCVS

RCVS is known as a radiological and neurological disorder that was discovered in 1962. It was discovered mainly by its famous symptom known as a thunderclap headache. In addition, patients had shown thunderclap headaches with or without hemorrhage and infection of brain vasculature. Stroke-like symptoms are also involved in patients diagnosed with RCVS. Regarding the discovery of RCVS, studies were involved in understanding its pathophysiology. These studies were in place to help mainly in diagnosis by confirming diagnosis methods and biomarkers for RCVS.

Studies had shown many factors that may affect the vasculature tone which in turn can lead to hemorrhage. Factors such as cannabis, cocaine, LSD, and binge alcohol consumption had shown an effect on vascular tone. Additionally to that, nicotine patches, noradrenergic, and selective serotonin reuptake inhibitors also affected in increase the vasoconstriction of vessels. Patients suffering from depression and using selective serotonergic antidepressants are having the chance to have changes in vascular tone regarding the effect of antidepressants. Other factors and treatments that may develop RCVS symptoms are nasal decongestants interferon-alpha, steroids, bromocriptine, triptans, cyclosporine, epinephrine, and ergots.

Compared to RCVS, many neurovascular disorders share similar findings and symptoms. According to that fact, understanding and searching the etiology and pathophysiology of neurovascular disorders are important in differentiating between symptoms. CVST is considered one of the neurovascular disorders with a rare percentage and mostly affects young people.

CVST appeared symptoms are mainly in headaches that range from mild to severe depending on the severity of CVST. Corresponding to headache, other neurological symptoms can be seen depending on the severity of CVST like epilepsy, neurological defects, or even coma and death. It is mostly been contributed with 0.5% of stork depending on the stage as well. With all CVST symptoms that can be seen it's similar to RCVS symptoms, differentiating the diagnosis of both need clearance of the etiology and pathophysiology of them.

As mentioned before about the understudies in the pathophysiology of RCVS, it is CVST turn to take part in studies to understand its pathophysiology. CVST pathophysiology to be visibly clear, experiments and studies must be done, and according to the results, CVST will be clearer. Despite that fact, general and available diagnostic tools should take part as well to find a way in understanding the pathophysiology of CVST. Some methods and studies were impressively helpful and others only detected changes inside the CVST patients that can give an overlapping diagnosis with neurovascular disorders.

Animal models were the first volunteer studies that were done in understanding CVST. Several types of animal models were volunteered in this study. Types used are known in animals generated with ligations of superior sagittal sinus or thrombus animal models that use injection thrombi or ferric chloride. Concerning the model's difference, each type explained CVST in its way. By many expiations, it was confusing to understand the pathophysiology of CVST.

According to this, histological studies were involved only in rate experiments that were suggested for accurate understanding according to the similarity features of rates with human features. This study had taken a method that was done by inserting a water-swellable rubber and implanting

it into the SSS. SSS occlusion had been detected in CVST patients with noticing of edema also in the brain parenchyma in this study. With all of these animal studies, it was shown that CVST is induced mainly by intracranial injuries such as intracranial tumors, brain abscesses, and traumatic brain injury or inflammation in the brain like meningitis.

The radiological method like MRI is considered one of the tools for detecting changes in CVST patients. According to many MRI screenings in CVST animals and patients, MRIs only helped detect damaged vasculature or hemorrhage that can be seen in severe cases, without finding a specific marker to diagnose CVST, differentiate it from RCVS, or even neurovascular disorders. Blood tests were more helpful in detecting some blood tests that can detect coagulation like plasma protein levels test, prothrombin time or thrombin time test, detecting inflammation by WBC count test, as were detected an increase in WBC count, neutrophils exactly were noted significantly high in CVST patients in comparison with healthy people. Corresponding to that were noted behavioral changes like anxiety and depression.

Besides these tools, morphology was detecting in CVST patients a distortion in the surrounding veins as well it was detecting intricate vascular pathways around the venous sinus that occluded. Corresponding to the morphology, imaging tools like T2WI and DWI scanning detected occlusion in SSS as well as brain edema. Besides these findings, it was shown higher ADC values in CVST patients compared with normal healthy people.

To combine, the diagnosis of CVST patients had shown an increase in ICP, intracranial hypertension with constant CSF, and cerebral blood flow according to the airtight rigid structure of the skull cavity to other changes that were shown. Compared to RCVS, these are some differentiating changes that were noted in CVST patients.

Compared to RCVS, CVST also remains without specific treatment according to the fact that CVST remains with neither fully unclear etiology nor pathophysiology. Contributing to this fact, replacement of available pharmacological treatment had been given to eliminate the symptoms and treat the coagulation. Anticoagulant therapy is been used in CVST patients most commonly according to its effectiveness with CVST patients confirmed in many studies. Beside Anticoagulant therapy, heparin treatments were concluded under treatments of CVST. Corresponding to these most common ways of treating CVST, chemical thrombolysis, and mechanical thrombectomy is favorable to be used in severe stage.[16]

CERVICOCEREBRAL ARTERIAL DISSECTIONS VERSUS RCVS

RCVS is one of the challenging disorders known as a neurovascular disorder. The main marker symptom for RCVS is mainly thunderclap headaches. Rather than a headache, the patient has hemorrhage or stoke-like symptoms regarding vasoconstriction. The etiology and pathophysiology mechanisms are not fully clear as it was discovered in 1962. This was mainly the first challenging point. In addition to that, stroke-like symptoms and headache symptoms can overlap with other stroke and neurological disorders such as cervicocerebral artery dissections.

Cervicocerebral artery dissections are considered one of the disorders that share similarities with RCVS. Cervicocerebral artery dissections were found due to environmental causes like road accidents, trivial forces, or even cervical manipulations. The notable and distinguished point of this disease is mainly the appearance of neck pain in the early stage of cervicocerebral artery dissections. Besides neck pain, neurological defects can be also seen but this is more common in the late stage. Corresponding to these symptoms, other symptoms can be seen depending on the patient's severity in cervicocerebral artery dissections. These symptoms are ataxia, headache, vomiting, dysphagia, and visual disturbance.[17]

To understand cervicocerebral artery dissections, it is important to look up studies and experiments that were done on cervicocerebral artery dissections patients. Research and studies were done on 18 patients in age between 28 and 53 to evaluate the understanding of cervicocerebral artery dissections. The study included two patients with more than one artery affected, others were most commonly affected in internal carotid arteries compared with vertebrobasilar arteries. According to their description of symptoms, symptoms were migraine or headache and hypertension.[17]

According to the similarity of symptoms between RCVS and cervicocerebral artery dissections, patients were gathered in one group in the control study compared to normal people to compare diagnostic method results. Diagnostic results were very limited according to the contrary variation of results in cervicocerebral artery dissections patients. CT was not a beneficial method in the diagnosis of those patients. Contrary to CT, arteriography was a helpful diagnostic method and excluded dissection in severe cases.[17]

Treatment according to the unclear expiation and knowledge of this disease, treatment of these patients will only depend on available treatments. Cervicocerebral artery dissections were recommended to use anticoagulation treatments (heparin or/and warfarin) in the early stage of cervicocerebral artery dissections. Contrary, in the severe stage surgery, is a better option according to the severity to save a patient's life. Last but not least, comparing this information with RCVS's information on diagnostic methods, it is clearer now to differentiate between them in symptoms and diagnosis.[17]

PITUITARY APOPLEXY VERSUS RCVS

A neurovascular disorder RCVS is one of the overlapping disorders with many neurological disorders. This fact was mainly due to the overlap of symptoms such as headache known as thunderclap headache as well stroke-like symptoms may appear depending on the severity which can overlap with neurological disorders or with stroke or hemorrhage in the brain as pituitary apoplexy as well. RCVS is a rare and new disorder as it was discovered in 1962. This fact is leading to the remain of unclear facts about its etiology and pathophysiology. RCVS is known for changing vasculature tone without changing the histology of vasculature.

Acute symptomatic pituitary apoplexy is one of the life-threatening disorders in neuroendocrine disorders. Pituitary apoplexy is a rare condition that ranges in the severity of hemorrhage from acute to sub-acute hemorrhage of the pituitary gland's tumor, in more common words; it is hemorrhage in the macroadenoma or adenoma of the pituitary gland.[18]

Symptomatic pituitary apoplexy can show hemorrhage symptoms like headache that range according to the stage of pituitary apoplexies such as nausea, reduction of consciousness, pituitary deficiencies, and visual disturbance such as visual field defects, decreased vision, and ophthalmoplegia. Besides these symptoms, pituitary dysfunction symptoms are detected such as fever without inflammatory cause, disturbance of one or more hormone regulations, and decrease in blood supply.[18,19]

According to these life-threatening symptoms, the intervention of diagnostic methods must participate in order of understanding the etiology with the pathophysiology of pituitary apoplexy. Although pituitary apoplexy is considered an urgent diagnosis, some lines should be added to hurry in diagnosis with a proper and accurate diagnosis as well. Studies were involved in diagnostic methods which were mainly searching for the fastest way in detecting this disorder. These studies were grouping pituitary apoplexy patients into three groups according to the severity from A to C, (A) acute, (B) subacute, and (C) non-acute. The acute group was of patients having acute headaches and detecting the failure of cortisol levels. Compared to group A, group B is with half of acute headache symptoms. The c group is patients without acute headaches.[24]

Diagnostic tools were experienced on these patients as CT, but they could not detect hemorrhage in the pituitary gland. Besides CT, MRI was helpful and considered one of the pituitary apoplexy diagnostic methods as it was detecting the changes and hemorrhage in tumors of the pituitary gland. This helpful study was only able to subtype pituitary apoplexy to understand its stage of it without full information on both etiology and pathophysiology. Corresponding to radiological findings, hypopituitarism and prolactin level changes were detected in pituitary apoplexy patients in the studies.[18,19]

Despite the fact of detecting the diagnostic methods without explanation of etiology and pathophysiology, treatment remained with the available treatments. Surgery is the main step to stopping the hemorrhage, especially in severe cases. Forward step after surgery, hormonal replacement medication is advoked to use depending on hormonal disturbance from one patient to another. Last but not least, it was managed with help of studies to differentiate in diagnosis between RCVS and pituitary apoplexy.[18]

TREATMENTS

Regarding the fact of the modern discovery of RCVS in 1962, the etiology and mechanism of pathophysiology have remained unclear explanations. Regarding that, treatments as well are only depending on suffering symptoms only. Unfortunately, there is no form of treatment to be only for RCVS. Contrary to that, available treatments and surgeries can help in reducing symptoms.

RCVS had been known with vasoconstriction and changes in the vascular tone. Regarding that, vasodilators should be described to those patients. Vasodilators as calcium channel blockers will help in the dilation of vessels by reducing systolic blood pressure and so compromise cerebral perfusion in patients with severe vasoconstriction. Another vasodilator is Nimodipine, it is widely used and has better elective action on cerebral circulation.[20]

Regarding headaches, it is mostly advised Valsalva maneuvers for headaches in a few days or even weeks depending on the severity of the headache. Monitoring of elevated blood pressure is also thought to decrease headache severity. Noting that reducing the number of episodes and severity of the headache, both prospective and retrospective studies suggest that it does not affect the time course of cerebral vasoconstriction. Other treatments that can vary from one patient to another depending on the suffering symptom are treating seizures by antiepileptics treatment.

Last but not least, treatments and methods can vary from one patient to another regarding the symptoms, but most commonly in severe cases milrinone, nimodipine, and epoprostenol administered intra-arterially, and balloon angioplasty with variable success have been used as well as medications for reducing headache.

DISCUSSION

RCVS is a neurovascular disorder that affects individuals in middle-aged of their life. RCVS patients suffer mainly from headaches known as thunderclap headaches. Additional to headaches, minor symptoms occur such as nausea, vomiting,

neurological deficits, and cerebrovascular diseases. The severity of RCVS can increase the chance of occurrence of seizures as well as elevation of blood pressure. Regarding symptoms, segmental arterial constriction may occur with resolving within 3 months. Regarding studies, it affects more commonly women aged between 20 and 50 years.

RCVS can occur both spontaneously or by triggers. Triggers that increase the chance of RCVS include vasoactive drugs such as triptans and selective serotonin reuptake inhibitors, alcohol, Puerperium, sexual activity, and tumors such as Pheochromocytoma and Paraganglioma. Additionally to that, in 2020 there were studies involved with SARS-Cov-2 and RCVS. It was noted that SARS-CoV-2 may trigger RCVS because of the direct interaction of the virus with endothelial cells and Angiotensin-converting enzyme type 2 receptors, with subsequent possible alterations of vessel caliber.

With study evolutions, the pathogenesis and the etiology remain unexplained. This fact is thought because RCVS is likely to be underdiagnosed as a result of RCVS being the final diagnosis in approximately 0.26% of patients presenting to the emergency department due to headaches. Regarding the remaining pathophysiology unclear, many studies were involved in understanding. Studies had shown a key feature of understanding RCVS as they found that oxidative stress and endothelial dysfunction are probably the main factors contributing to the pathogenesis of RCVS. In addition, it was thought transient deregulation in cerebral vascular tone can be a cause of RCVS. Biopsy in studies had shown no evidence of inflammation in the brain.

Studies contributed to RCVS pathophysiology and diagnosis had added two important points for managing patients with suspected RCVS. (1) RCVS could be misdiagnosed as a primary headache in patients with no complications. (2) In patients with negative CT findings and thunderclap headache, RCVS should be considered as a differential diagnosis and the patient should be followed up with radiological diagnostic biomarkers not <2 weeks after a regular visit.

Regarding RCVS symptoms that were confirmed in many studies, these symptoms can overlap with many neurovascular disorders or cerebrovascular disorders. PRES, CVST, pituitary apoplexy, and intracranial hemorrhage (ICH) to other cerebrovascular disorders, can overlap with RCVS diagnosis. Regarding that, diagnostic biomarkers should be available in diagnosis and differentiate each of the disorders. PRES clinically presents with headache, visual alterations, and seizures.

	Reversible cerebral vasoconstriction syndrome	**cerebral venous sinus thrombosis**	**Cervicocerebral arterial dissections**	**Pituitary apoplexy**	**Intracranial hemorrhage**
Pathophysiology	Remain unclear (mostly known in changing of vasculature tone)	Intracranial injuries, tumors and infection	Environmental causes e.g., (motor cycle accidence)	Bleeding into a pre-existing benign tumor of the pituitary gland or by death of an area of tissue	Compressing the brain stem
Symptoms and duration	Symptoms: Thunderclap headache, neck pain Duration: 3 months	Symptoms: Headache, neurological symptoms. Duration: up to 1 month	Symptoms: Neck pain and neurological defects Duration: 3–6 months	Symptoms: Reduce consciousness, pituitary deficiencies and visual disturbance Duration: 8 weeks	Symptoms: Headache, nausea, vomiting Alterations in levels of consciousness Weakness/numbness in face, arm or leg (usually on one side) Vision loss Seizures Duration: 1 month
Diagnostic tools	TCDs, CT and MRI	Prothrombin time or thrombin time test, WBC test and T2WI and DWI scanning	CT scan and arteriography	MRI	CT and MRI
Treatments	Self-limited (Calcium channel blockers)	Anticoagulant therapy and mechanical thrombectomy	Self-limiting (anticoagulation treatments (heparin or/and warfarin)	Self-limiting medications as hormonal regulations and surgery	Self-limiting. (Stopping the bleeding, removing the clot and relieving pressure on the brain)

DWI: Diffusion-weighted imaging, MRI: Magnetic resonance imaging, CT: Computed tomography, WBC: White blood cell

Studies contributed to studies RCVS had used radiological methods according to its accuracy and faster results compared to blood tests. Non-contrast CT was first used in imaging RCVS patients regarding its availability compared to other radiological tool. CT scan results in RCVS were shown negatively in more than half of the cases, while intracranial hemorrhage was a helpful tool in detecting the hemorrhage with its location. CT scan studies had detected the most affected regions of the brain in RCVS patients, it was shown the most frequent location was the frontal lobe in about 79% of cases, the second level was the parietal region in 31% of cases, followed by the occipital and temporal lobes that were rarely involved (only 23 and 10% of cases). In addition, CT detected 90% of cases of RCVS that SAH was present.

Compared to CT, MRI studies were involved in helping in the diagnosis of RCVS. MRI is frequently performed in suspecting RCVS to detect complications such as intracerebral bleeding and exclude other differential diagnoses. DWI had shown ischemic stroke in RCVS as they are usually seen in bilateral and manifest in arterial watershed distribution this is due to cerebral vasoconstriction. In addition, MR angiography is important in evaluating the presence of segmental vasoconstriction of cerebral arteries in RCVS. DWI detected RCVS usually affects large-to-medium-sized arteries with an appearance of alternating areas of constriction and dilatation. It has been giving a typical "string of beads" or "sausage on a string" appearance. A new MRI technique, VWI is the gold standard in differentiation between RCVS and vasculitis. VWI shown in RCVS there is a thickening of the vessel wall with no or mild enhancement, whereas in vasculitis vessel wall enhancement tends to be prominent and persistent.

Digital subtraction angiography (DSA) is one of the extremely important tools to evaluate cerebral arterial, the most affected vessels as the basilar artery and the carotid siphon. In addition, DSA can be used to prove the reversibility of vasoconstriction after intra-arterial administration of Verapamil.

RESULTS AND CONCLUSION

Many neurological and neurovascular disorders have remained with unclear etiology and pathophysiology. Contrary to that fact, studies involved in many of them had used the available methods and tools as well as treatments to help suffering individuals and reduce and eliminate their symptoms. Results had shown the great effect of many vasodilators on RCVS in treating them as calcium channel blockers. In addition, radiological tools such as MRI, CT, and fMRI had a great impact on the understanding of pathophysiology and diagnosis.

Author's Contributions

Srijamya mentored the team and proposed the topic and roadmap for it. Srijamya and Ruba Nageh worked in the editing work together. Arjun was active in literature search and writing the manuscript. Pearl did statistical study and helped in writing the manuscript.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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