

Unusual causes of Cerebral Venous Thrombosis

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Abstract

Cerebral venous thrombosis is a relatively uncommon condition afflicting mostly young adults. Thrombosis of cerebral veins or sinuses results in variable and nonspecific clinical features, including headache, lethargy, motor or sensory deficits, seizures, neck stiffness and sometimes fever. A multitude of conditions have been attributed as risk factors for CVT. The more common conditions include hereditary thrombophilia, pregnancy and purperium, postoperative state, intracranial and local infections and the use of oral contraceptives. Frequently, the cause of CVT is multifactorial, and in less than twenty percent of cases no clear risk factor is identified. In this review, we have focused on relatively rare and unusual causes of cerebral venous thrombosis. Many of the conditions described have very few reported cases and the causal relationship is not well established.

Introduction

Thrombosis of the cerebral veins is a distinct cerebrovascular disorder that most often affects young adults and children.¹ The first detailed description of cerebral venous thrombosis (CVT) in a human was given by Ribes in 1825.² Cerebral venous thrombosis is far more common than previously assumed and estimated annual incidence is 3 to 4 cases per 1 million population and up to 7 cases per 1 million among children.¹ The spectrum of its clinical presentation is extremely wide and course is highly variable.¹⁻³

A host of conditions can cause or predispose to CVT. They include all known surgical, gynecologic-obstetric, and medical causes of deep vein thrombosis as well as a number of local or regional causes, either infective or noninfective, such as head trauma, brain tumours and arterial infarcts. CVT is often multifactorial, meaning that the identification of a risk factor or even of a cause should not deter a search for other causes.² Some of the more common and well established risk factors include inherited thrombophilia (e.g. factor V Leiden mutation, protein C and S deficiency), acquired prothrombotic state (pregnancy, purperium and postoperative period), systemic disease (e.g. Behçet syndrome, systemic lupus erythematosus), neoplasia (e.g. leukemia, systemic carcinoma), systemic infectious disease (e.g. septicemia), local causes (e.g. otitis, mastoiditis) and use of oral contraceptives.⁴ A prothrombotic risk factor or a direct cause is identified in about 85 percent of patients with

sinus thrombosis. Often, a precipitating factor, such as head injury or obstetrical delivery, causes sinus thrombosis in a person with a genetically increased risk.¹ In a recently published multicenter study³, 44% patients with CVT had one risk factor, 33% had two, and 6% had 3 or more risk factors for CVT. In only 17% patients, no risk factor could be identified.

We will review some of the rather unusual and rare risk factors or associations of CVT published in the literature. Many of these are isolated case reports and hence a true association between the risk of CVT and mentioned condition remains uncertain.

Trivial Trauma

The mechanical causes of sinus thrombosis are head injury, direct injury to the sinuses or the jugular veins and neurosurgical procedures.¹ However, CVT associated with minor or trivial trauma is reported in only few cases.

Jumping from a rock

Röttger et al.⁵ described two cases of CVT associated with very minor trauma. The first case was of a 49 year old woman who jumped from a small rock 1 m in height. She suffered instantaneous, severe occipital headache associated with transient impairment of hearing and vision. Her other associated risk factors included smoking and the use of contraceptives. She had marked meningism but no focal neurological deficits. CVT was confirmed by magnetic resonance imaging (MRI). Her evaluation for other hereditary thrombophilic conditions was normal.

Sneezing

The second case of Röttger et al. [5] was of a 18 year old woman who developed severe occipital headache after a sneezing attack. She was using oral contraceptives. Her neurological examination showed meningism and bilateral papilloedema. CVT was confirmed by computerized tomography (CT) venography. No inherited or acquired thrombophilic factors were detected. The authors have suggested a combination of acceleration trauma, and a sudden rise in intracranial pressure (ICP) resulting in damage to the endothelial layer of sinuses and cerebral veins as the probable mechanism of CVT in these patients with minimal trauma.⁵

Closed head injury

Saad et al.⁶ described the case of a 10-year old female cheerleader who fell from a height of approximately 6 to 10 feet during practice and landed on the back of her head. She had no loss of consciousness or focal neurologic deficits. She had one episode of emesis on route to the emergency room and another during the hospital stay for observation. Her initial CT head was read as negative and she was discharged from the hospital. She later developed vomiting which was initially treated as gastroenteritis. On persistence of nausea and vomiting, a head CT was repeated which showed hyperdensity in right transverse sinus, which was confirmed as sinus thrombosis on a CT venogram.

Infection

Intracranial infections and infections adjacent to cranial cavity including mastoid and inner ear are well known causes of CVT. Association of remote systemic infections and CVT is not very clear.

Abdominal tuberculosis

Kakkar et al. have reported two cases of CVT in patients with abdominal tuberculosis.⁷ First case was of a 35 year old female who had 2-month history of diarrhea, intermittent fever, fatigability, and weight loss. She developed sudden impairment of speech and memory, delusions, nodding movements of head and irrelevant talking. Her CT scan showed old right frontal infarct and a left parieto-occipital infarct. A day later she developed focal seizures with secondary generalization and right hemiparesis and died later. Her autopsy confirmed abdominal tuberculosis. Additionally, she had thrombosis of cortical veins and sagittal sinus. She also had bilateral tonsillar and left uncus herniation. The second case was of a 36 year old female who had fever, abdominal pain, attacks of intestinal obstruction and loose motions intermittently. She developed focal and generalized seizures. On autopsy, she had evidence of abdominal tuberculosis. Her brain showed thrombosis of superior sagittal sinus and cortical veins, and haemorrhagic infarct in the left parietal cortex.

Falciparum malaria

Kirshnan et al. reported 3 cases of falciparum malaria who had fever, altered consciousness and seizures.⁸ CT scans revealed haemorrhagic infarctions of cortex and sub-cortical white matter with features of venous infarction. Sagittal sinus thrombosis was confirmed by angiography in two patients and autopsy in one patient. Infection with Plasmodium falciparum was confirmed by peripheral blood

smears. Two of the three patients also had Plasmodium vivax infection.

Herpes simplex

Chan et al. have reported a case of presumed herpes simplex encephalitis with right transverse and sigmoid sinus thrombosis.⁹ A 48 year old man with one week history of fever, flu-like symptoms and bitemporal throbbing headache developed generalized tonic-clonic seizure. He had bilateral papilloedema. His CT scan of the brain showed acute haemorrhages over right anterior frontal and posterior temporal regions. Digital subtraction angiography confirmed the thrombosis of transverse and sigmoid sinuses. The diagnosis of herpes simplex encephalitis was made on the basis of clinical triad of fever, headache, and convulsion and CT findings of frontotemporal haemorrhages and oedema.

Surgery

Cardiopulmonary bypass

Emir et al. have reported the case of an 8 year old child with antiphospholipid syndrome and ventricular septal defect (VSD).¹⁰ This child underwent a cardiopulmonary bypass for the repair of VSD. On the first postoperative day, she remained comatose after recovery from anaesthesia and removal of pharmacologic paralytic agents. CT scan of the brain showed dural sinus thrombosis and severe cerebral oedema. The dural sinus thrombosis was confirmed by angiography. Diagnostic evaluation revealed elevated anticardiolipin antibodies, both IgG and IgM. The presence of antiphospholipid antibodies were thought to have contributed to CVT. A case of CVT is reported after Fontan procedure.¹¹

Medications

Androgens

The association between oral contraceptives and cerebral venous thrombosis is well established. However, the role of androgens in CVT is not clearly defined. Sharaian et al.¹² reported the case of a 22 year old male body builder who was following an exercise program for 5 years and was using once or twice a week nandrolone decaonate 25 mg intramuscularly for 5 months prior to developing intense bitemporal headache, recurrent vomiting and papilloedema. CT scan of head revealed cord sign. MR venogram showed superior sagittal and transverse sinus thrombosis.

Thalidomide

Thrombotic events have been described in patients treated with thalidomide for various conditions.¹³ Pagnoux et al. reported the case of a 68-year old woman who was diagnosed with antiphospholipid antibody syndrome based on positive serology.¹³ She was started on thalidomide due to increasing requirements of prednisone. She was also anticoagulated with warfarin. She developed left hemiparesis. MRI revealed superior sagittal sinus thrombosis and an ischaemic lesion. Her INR was 2.4 at that time. Her thalidomide was continued at a lower dose, but she later developed left femoro-popliteal venous thrombosis while the INR was 2.37. Thalidomide was subsequently discontinued.

High-Voltage Brain Injury

Sure et al.¹⁴ reported the case of a 19 year old male who while climbing on top of a railway carriage contacted a 15,000 V railway overhead cable with alternating current (16.67 Hz). He was thrown from the top of the wagon to ground 3 m below. He also suffered ignition of his clothes that was extinguished. He suffered headaches before losing consciousness. CT scan of the head showed multilobulated right hemispheric parenchymal bleeding accompanied by subarachnoid haemorrhage and subgaleal haematoma. He died 8 days after injury secondary to intracerebral swelling. In addition to the above findings, autopsy also revealed thrombosis of cerebral veins but not the sinuses.

Low Serum Carnitine

Hypoxia at birth is the leading risk factor among prenatal complications that could lead to cerebral thrombosis.¹⁵ Ezgu et al. reported two newborns with hypoxic-ischemic encephalopathy who had CVT and carnitine deficiency.¹⁶ The first neonate was born at 37 gestational weeks by Caesarean section and the other was born at 40 gestational weeks. Both had severe hypoxia at birth. The arterial pH in first neonate was 6.9 and in second neonate it was 6.8. Both of them had MRI which showed right superior cerebral vein thrombosis in the first neonate and thrombosis of superior sagittal sinus and right transverse sinus in the second. Carnitine levels were checked as part of another study and the carnitine levels were low in both suggesting carnitine deficiency. The authors suggested that the carnitine deficiency could have contributed in the thrombus formation as not all infants with grade 3 encephalopathy have cerebral thrombosis.¹⁶

Inflammatory Bowel Disease

Ulcerative colitis

Murata et al.¹⁷ have reported the case of a 19 year old male with severe active ulcerative colitis who developed severe headache and fatigue in the course of treatment for ulcerative colitis. His post contrast CT scan of brain and MRA revealed thrombosis of right transverse sinus and superior sagittal sinus.

Crohn's disease

Singh et al.¹⁸ have reported the case of a 19 year old female with Crohn's disease. She initially presented with history of abdominal pain, bloody diarrhea and weight loss. Her diagnostic studies were consistent with Crohn's disease. She was started on treatment for that. During the course of treatment, she developed central visual loss in one eye. Clinical examination showed bilateral papilloedema and signs of chronic uveitis. Her magnetic resonance imaging showed thrombosis of superior sagittal sinus and left transverse sinus.

The authors of the above reports have suggested the presence of hypercoagulable state in inflammatory bowel disease. However, its exact role in clinical thrombotic complications is uncertain. Both of these patients were treated with high dose steroids before developing neurological symptoms. Authors of one report suggest the possible contribution of corticosteroid in inducing hypercoagulable state.¹⁷

Intracranial Hypotension

Sopelana et al.¹⁹ have reported the case of a 56 year old male who had increasingly severe headache, nausea and vomiting. The headache had strong postural component and worsened on standing up and improved on lying down. The patient had been doing vigorous exercise in the preceding month. His neurological examination was normal. His MRI showed thrombosis in the right transverse, sigmoid, jugular and superior sagittal sinuses which was confirmed on angiography. Additionally, the MRI also showed features of intracranial hypotension characterized by flattening of the pons, decrease in the size of interpeduncular fossa, obliteration of the chiasmatic cistern and descent of the cerebellar tonsils. The authors have suggested that the intracranial hypotension may have resulted in a rise of venous volume and slowing of circulation. Berroir et al. have also reported two cases of CVT with spontaneous intracranial hypotension.²⁰ Lumbar puncture has also been associated with cerebral venous thrombosis.¹ One of the explanation provided is that low cerebrospinal fluid pressure after a lumbar puncture causes a downward shift of the brain, with traction on the cortical veins and sinuses. Deformation of the venous walls may induce thrombosis.¹

Demyelinating disease

Maurellia et al.²¹ have reported the case of a 48 year old female who had two episodes of brainstem demyelination in the course of one month. Her brain MRI findings were suggestive of a demyelinating disease and the initial MRV was normal. She received a lumbar puncture and was subsequently started on high dose intravenous (IV) steroids. A few hours after the lumbar puncture, she developed postural headache which worsened three days later and became associated with nausea and vomiting. A CT scan of the head at that time showed a right basal ganglia infarct. MRI and MRA showed thrombosis of straight sinus, torcular Herophili and superior sagittal sinus. The diagnostic work up for prothrombotic states was non-revealing. The authors postulated the combination of lumbar puncture and use of IV steroids as the possible cause of CVT.

Down's Syndrome

Tarlaci et al.²² reported the case of a 25 year old male with Down's syndrome who had a generalized tonic-clonic seizure with prolonged post-ictal period. Initial evaluation was unremarkable. A day later, he developed left hemiparesis, became somnolent and had more seizures. His MRI showed bifrontal venous haemorrhages with subacute thrombosis in the right transverse and posterior part of the sagittal sinus. His evaluation for prothrombotic risk factors was unremarkable. The only significant laboratory abnormality was an elevated ESR of 50 mm in 1st hour. Though Down's syndrome is associated with some commonly encountered pathologies that are considered as risk factors for CVT, none of those was found in this patient.

Moya Moya Syndrome

Kikuta et al.²³ have reported the case of a 54 year old female who had developed right hemiparesis at the age of 45 and was found to have a left thalamic infarct. At that time, her angiography revealed bilateral internal carotid artery occlusion at their origin. Though her angiographic findings were somewhat atypical for moya moya disease, based on the previously reported findings, she was diagnosed as a case of moya moya disease and underwent bilateral extracranial-intracranial bypass. Seven years later, she developed sudden left hemiparesis and was found to have a right thalamic haemorrhage. Initially, the haemorrhage was attributed to moya moya disease, however, her clinical sta-

tus worsened and she developed partial seizures. Repeated CT scan revealed another basal ganglia haemorrhage. An MRI study at that time showed dural sinus thrombosis which was confirmed on angiography. Angiography also showed that the previously done bypass was patent bilaterally. Her laboratory evaluation subsequently showed protein C deficiency on two different occasions. With this information, the patient was diagnosed to have moya moya syndrome associated with congenital protein C deficiency instead of moya moya disease. Her CVT was attributed to protein C deficiency.

Blood disorders

Evans syndrome

Evans syndrome is characterized by immune thrombocytopenia and autoimmune haemolytic anaemia. Yilmaz et al.²⁴ reported the case of a 19 year old male patient with Evans syndrome who was treated with prednisolone, several pulses of methylprednisolone, and intravenous immunoglobulin therapies. He also had splenectomy at the age of 9. He also developed chronic hepatitis B infection which was treated with lamivudine. At the age of 19, when he was in haematologic remission and was not getting any treatment except lamivudine, he developed severe headache, and vomiting for 3 days and had a generalized convulsive seizure on the day of admission. His MRA showed extensive thrombosis in the left lateral, left sigmoid and straight sinus, along with internal jugular vein. His laboratory evaluation for prothrombotic states revealed heterozygous mutation in prothrombin G20210A gene.

Idiopathic hypereosinophilic syndrome

The idiopathic hypereosinophilic syndrome is a leukoproliferative disorder marked by a sustained overproduction of eosinophils and a distinct predilection to damage specific organs, especially cardiovascular system. It is characterized by persistent eosinophilia ($>1,500/\text{mm}^3$) without underlying cause. Schulman et al.²⁵ have reported the case of a 11 year old boy who was being treated with prednisone for eosinophilic cellulitis when he developed headaches, vomiting and raised intracranial pressure. His CT scan of the brain showed cord and empty delta signs. He worsened despite treatment with IV heparin. Repeat CT scan demonstrated features of transtentorial brain herniation. An autopsy was refused.

Bone marrow transplantation

Bertz et al.²⁶ have reported three cases of bone marrow transplant recipients who were on immunosuppressive therapy including methylprednisolone and cyclosporine when they developed neurologic symptoms. One patient had generalized seizures, one had headaches, and one had both the symptoms. The magnetic resonance imaging in each one of them showed thrombosis of cerebral venous sinuses. The laboratory studies for prothrombotic factors were normal except for factor V Leiden mutation in one patient. The authors have suggested that bone marrow transplant recipients who are on immunosuppressive therapy may be at higher risk for CVT.

High Altitude

Cerebral venous thrombosis has been seen in people who climb to high altitudes of about 5000 meters (m).²⁷ The altitude range has been described between 2200 m to 5500 m. Interestingly, this has been seen that the venous thrombosis sometimes occurs when the person descends from high altitude to lower altitude. Volume depletion and polycythemia are given as a plausible explanation for CVT on high altitude.²⁷

In summary, cerebral venous thrombosis is a relatively uncommon but devastating neurological disorder with many associated conditions or risk factors. The index of suspicion for CVT should be higher to diagnose it early in unusual situations. Cerebral venous thrombosis should be considered in all patients with unexplained neurological symptoms, especially headache, seizures and signs of raised intracranial pressure. Though CVT is described in association with many different conditions, the causal relationship is not well established. Often there are multiple risk factors in a single individual and it is difficult to ascertain what was the actual cause. Multiple risk factors may have a synergistic effect on the risk of developing cerebral venous thrombosis.

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