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Pathophysiology of cerebral venous thrombosis--an overview.

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Pathophysiology of Cerebral Venous Thrombosis - An overview

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Abstract

Cerebral venous sinus thrombosis is a disorder with a unique pathophysiology which needs to be described.A Medline search of all articles detailing pathophysiology of CVST was done, using keywords: cerebral venous thrombosis and pathophysiology. In addition, major texts were reviewed for additional references. The pathophysiology of CVST depends on two interconnected events, local signs due to venous infarct, e.g. hemiparesis and global signs due to raised ICP from an obstructed venous system - papilloedema and isolated intracranial hypertension being one of them. Pathophysiology of CVST is diverse and makes it easier to understand the diversity of clinical presentations.

Introduction

The advent of modern non-invasive neuro-imaging techniques has brought into the attention diseases that were rendered uncommon previously, cerebral venous thrombosis being one of them. Current statistics indicate the estimated annual incidence to be 3 to 4 cases per 1 million population and up to 7 cases per 1 million among children.[1] The skewed ratio of its incidence in women of childbearing age is mainly because of predisposing factors such as pregnancy, peurperium, and oral contraceptive use. The fact that it occurs more in the young population differentiates its clinical picture from that of other cerebrovascular pathologies. This review article aims to reinforce the current concepts on the pathophysiology of CVT.

Anatomy

The internal cerebral veins draining blood from the deep cortical veins empty into the Great Cerebral Vein (of Galen). The deep and the superficial cortical veins also drain directly into the great (dural) sinuses via their numerous connections. Blood eventually flows into the internal jugular vein after draining into the straight sinus. This supply is extensive enough to provide for collaterals in case of an occlusion. The superior sagittal and lateral sinuses are commonly (70%) individually involved by thrombosis. In 30%, both are affected, in addition to cortical and cerebellar veins.[2]

Aetiology

Numerous causes have been provided for the development of cerebral venous thrombosis, which can be broadly divided into two categories - Infectious causes - which mainly include migratory involvement of the cavernous sinus from staphylococcus infection of the face and Paranasal sinuses, and the Non-infectious causes - in which systemic conditions such as connective tissue diseases, other granulomatous or inflammatory disorders and malignancies are most common.[2]

Pathophysiology linked to clinical features

Cerebral venous thrombosis refers to complete or partial occlusion of either the main sinus/sinuses or the feeding cortical veins leading to secondary effects of vascular congestion and focal or generalized neurological deficits. The local effects depend on the site of occlusion. A major sinus block leads to intracranial hypertension whereas the deep cortical occlusion would cause localized oedema, venous infarction and petechial haemorrhages. The latter can merge and become large haematomas, which have a characteristic appearance on computed tomographic (CT) scans.[1] Since in majority of instances, the deep cortical veins get involved due to a sinus block, these two scenarios get overlapped and we see a mixed picture. Isolated instances of cortical venous thrombosis without sinus involvement are rare. Formation of thrombi in venous channels draining the brain is a consequence of the characteristic risk factors under the heading of Virchow's triad, which includes local trauma to vessel wall, stasis and a hypercoagulable state, the latter being the most important factor in development of cerebral venous thrombosis.

Several morphological factors leading to development of thrombi in venous channels have been noted. The striking involvement of superior sagittal sinus in majority of the cases can be attributed to the fact that the superficial cortical veins draining into it are doing so against the blood flow in the sinus. This along with the presence of fibrous septa present at inferior angle of the sinus causes turbulence hence rendering it more susceptible to thrombosis. A thrombosed sagittal sinus leads to compression of the arachnoid villi, which drain CSF from the ventricles, leading to raised intracranial pressure and papilloedema.[3] However, hydrocephalus does not develop as the ventricular communication with the subarachnoid spaces remains patent. About one fifth of patients with sinus thrombosis have intracranial hypertension only, without signs of cortical vein thrombosis.[4]

Vasogenic oedema, developing due to disruption of the blood brain barrier and engorgement of the brain interstitium with blood, and cytotoxic oedema resulting from localized ischaemia and damage to intracellular ion channels eventually leading to neuronal swelling, is a characteristic of cerebral venous involvement. Magnetic resonance imaging (MRI) has shown that both cytotoxic and vasogenic oedema occur in cerebral vein thrombosis.[5,6]

The outcomes of such a venous drainage compromise can be two- disruption of the blood brain and blood CSF barrier can lead to haemorrhage and development of haematomas and secondly,venous infarction localized to the area where integrity of the circulation is lost. This outcome would decide the clinical picture that would follow.

Hypercoagulable state has been attributed as one of the major risk factors in the development of CVT. Mutations in genes encoding for coagulation factors, increased basal production of these factors in certain physiological and pathological states and certain malignancies and autoimmune disorders lead to an imbalance between prothrombic and antithrombotic factors. Mathieu Zuber, in his study, showed a strong association between mutation of factor V leiden , a cofactor in the activation of the prothrombin, and the occurrence of CVT and found this mutation to be the most common coagulation defect in CVT patients.[7] In addition, levels of d-dimer, a breakdown product of fibrin, have been shown to be a sensitive indicator of the presence of cerebral sinus thrombosis and normal D dimer levels make the presence of CST very unlikely.[8] This is however, still a subject of much debate.

The association of Pregnancy and puerperium with cerebral venous thrombosis can be explained by the fact that there is a state of compensated, accelerated intravascular coagulation as is necessary for maintenance of the uterine-placental interface and preparation for the haemostatic challenge of delivery. This is achieved by a physiological increase in production of coagulation factors that induce a prothrombotic state.

Clinically an arterial and a venous stroke may have similar presentation as there is great overlap between the signs and symptoms resulting from neuronal damage, and compromise of function. This has been noted especially in the involvement of cortical veins with patent sinuses where a 'stroke like' episode is seen.[9] However, there are differences that have been noted. A venous stroke usually presents with an insidious and gradual onset of neurological deficits and the involvement of the brain does not follow a major arterial territory. Whereas arterial cerebral ischaemia usually is a monophasic abrupt thrombotic process and there is only a small penumbra, CVT is a continuing process of disequilibrium between prothrombotic and thrombolytic mechanisms; large areas of the brain are only functionally or metabolically disturbed but not irreversibly damaged. Intracranial bleeding in SVT is a consequence of increased venous and capillary pressure and thus occurs more frequently than in arterial thrombotic disease in which capillary pressure is reduced by the thrombosis and bleeding occurs during reperfusion of tissue damaged by ischaemia. This explains the greater incidence of haemorrhagic infarcts in venous occlusions compared to the arterial ones.

The most frequent symptoms and signs of cerebral venous thrombosis were found to be headache, focal seizures with or without secondary generalization, paresis

(uni- or bilateral) and papilloedema.[10] Pseudo tumor cerebri, a syndrome many patients of cerebral venous thrombosis present with, develop as a result of increased pressure in the affected dural sinus. In fact, patients with a pseudo tumor cerebri syndrome should undergo angiography or brain MRI before being labeled idiopathic.[11]

Growth of the thrombus and the good collateralization of the venous vessels probably explain the usually gradual onset of symptoms, frequently over weeks and months.[2,12] In contrast to arterial thrombi, spontaneous resolution of venous thrombi does occur. This explains the large number of patients with complete reversibility of their neurological deficit, as there is a large area of only transiently and reversibly disturbed cerebral tissue.[12]

Furthermore, mechanisms underlying cerebral venous thrombosis and deep venous thrombosis of other areas (e.g. the leg) are probably different. First, cerebral veins and sinuses have a continuous blood flow and no valves[13], whereas venous flow in the limbs is not continuous but requires the presence of valves and the activity of muscles. Secondly, the factors that appear to precipitate deep venous thrombosis including immobilization do not increase the risk of cerebral venous thrombosis. Moreover, there is a stronger association of deep venous thrombosis with cancers than cerebral venous thrombosis.[14]

Complications and prognostic factors

Parenchymal oedema with venous infarction and haemorrhage complicate up to 50% of venous sinus thromboses.[2] Pulmonary embolism , even though encountered infrequently in patients with cerebral venous thrombosis, carries a poor prognosis.[15] Hypopituitarism may result from cavernous sinus thrombosis.[16] Also, association between CVT and arteriovenous malformations have been described in several instances but it is not clearly known which is the primary event. In a significant number of patients, persistent focal seizures may develop requiring long term anti epileptic therapies. The main cause of acute death in CVT patients was found to be neurologic, the most frequent mechanism being transtentorial herniation.[17]

Long term prognosis is generally good in these patients but some factors might contribute to a bad outcome. These include old age, involvement of deep veins, concomitant CNS infection or cancer, or if the patient presents in coma or haemorrhage.

Recent advances in imaging especially Diffusion weighted Imaging and perfusion Imaging may be helpful in differentiating arterial from venous stroke. These imaging techniques not only provide important information regarding pathophysiology but may have a prognostic role.

Conclusion

CVT has two major manifestations linked to the pathophysiology, focal, due to cortically based venous infarction, with seizures, stroke like presentation. The other scenario is global, with a depressed level of consciousness and high intracranial pressure due to venous engorgement and back pressure. These are often intermixed in patients. Venous infarction, unlike arterial, is often slower in onset, insidious, often associated with seizures, good recovery of neurological function in the majority of cases.

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