Review Article

Mechanism of neuronal injury in Cerebral Venous Thrombosis

Uzma Usman, Mohammad Wasay

Department of Neurology, The Aga Khan University, Karachi.

Abstract

The impact of CVT on the brain is wide spectrum, ranging from completely normal parenchyma to brain oedema and/or haemorrhage. Multiple factors relate to neuronal injury in CVT including; dural sinus pressure, increased venous flow velocities, collateralization of venous channels, rate of occlusion, development of cytotoxic and vasogenic oedema, recanalization and accelerated myelination. It is suggested that recanalization of occluded vein, as well as, the presence or absence and the efficiency of intracranial venous collaterals, may have an impact on the extent of brain tissue damage and hence the prognosis of acute CVT.

Introduction

Cerebral venous thrombosis (CVT) is an uncommon condition and knowledge regarding cerebral venous circulatory disturbances and the mechanism of neuronal injury is scarce. Cerebral venous thrombosis (CVT) is regarded as a continuing process of imbalance between prothrombotic and thrombolytic processes that results in the formation and later on progression of thrombus in the cerebral venous sinus.[1,2]

The mechanism of neuronal injury in CVT has been a subject of great interest by researchers. The impact of CVT on the brain is wide spectrum, ranging from completely normal parenchyma to brain oedema and/or haemorrhage.[3-5]

The outcome of venous thrombosis depend upon the cerebral blood flow, cerebral venous pressure and cerebral perfusion pressures. Only in the circumstances, when venous occlusion results in significant raise in cerebral venous pressure that is sufficient to lower cerebral perfusion pressure to the extent that auto-regulation is hampered, neuronal injury results.[3]

Multiple factors relate to the extent of neuronal injury in CVT including; dural sinus pressure, venous flow obstruction, collateralization of venous channels, rate of occlusion, development of cytotoxic and vasogenic oedema, recanalization of venous channels and development of infarction and haemorrhage. Although these factors are inter linked and one factor leads to another one, we will discuss these factors separately for simplicity.

Mechanism of neuronal injury in CVT could be attributed to four pathophysiologic stages of CVT.

1. Increased dural sinus pressure
2. Venous flow obstruction
3. Development of cytotoxic and vasogenic edema
4. Infarction and haemorrhage

Increased Dural sinus pressure

Thrombosis of dural sinus especially superior sagittal sinus leads to rise in dural sinus pressure. This pressure could range from mild to severe and is probably one of the most important factor underlying initial symptomatology of CVT. The dural sinus pressure seem directly related to the severity of parenchymal injury. Fong and his colleagues identified five stages of brain parenchymal changes on MR imaging, corresponding with the dural sinus pressure in acute setting.[6] These stages included stage 1; no parenchymal change, stage 2; brain swelling, no signal change, stage 3; parenchymal signal change, stage 4; severe oedema with or without haemorrhage, stage 5; massive oedema and or haemorrhage.

Rather higher pressure readings may be anticipated in case of chronic obstruction as recanalization and collateralization try to minimize the parenchymal injury.[6-8]

Bousser[3,4] and several others[9,10] have described certain factors that result in various degrees of infarction after venous occlusion. Presence of collateral channels and recanalization are important as all venous occlusions do not necessarily end up in the neuronal injury or infarction. Massive brain oedema can be the only consequence in Superior Sagittal Sinus thrombosis.[3,4]

Location of occlusion may be important. One study showed that occlusion of posterior SSS leads to significantly reduced Cerebral blood flow and haemoglobin oxygen saturation.[11] Increased dural sinus pressure may lead to reduced capillary perfusion pressure[12] and increased cerebral blood volume.[13] Reduction of capillary perfusion pressure and increased cerebral blood volume may lead to neuronal injury at this stage.

Venous flow obstruction

Increment in venous flow velocity in course of venous occlusion is well acknowledged by several studies

conducted in humans and animal models.[14-16] Stolz et al[14] used transcranial duplex sonography (TCCS) for the evaluation of venous drainage patterns in acute CVT. They reported 69% of patients exhibiting pathological venous flow. When the veins get thrombosed, there is increase in back pressure, resulting in reversal of flow direction (predominantly in setting of transverse sinus and straight sinus thrombosis) and increase in flow velocity. In the setting of transverse sinus occlusion, compensatory increase in flow velocity in the contra lateral sinus is also documented. In sigmoid sinus thrombosis, increased flow velocity may lead to enhanced drainage into cavernous sinus.

Venous flow obstruction causes raised intracranial pressure (ICP) leading to blood brain barrier (BBB) disruption, resulting in decreased cerebral blood flow.[13] These abnormal venous flow and flow velocities found out to be remarkably associated with headaches and papillaoedema.[14,15] Raised intracranial pressure as a result of these haemodynamic changes is the possible explanation.[6,14,15,17,18] Valdueza and coworkers[15] were the first to correlate the venous haemodynamics to clinical findings in CVT. They elucidated the declining consciousness level to be directly related to the extent of venous flow velocity. Venous outflow obstruction leads to moderate enlargement of extracellular spaces. Experimental studies in cats showed that SSS occlusion alone may not lead to BBB disruption while thrombosis of cortical veins is invariably associated with BBB disruption leading to extensive haemorrhagic cerebral infarction.[19]

Presence of collaterals is an important determinant of Neuronal injury in case of venous outflow obstruction. Small cerebral veins drain blood from brain into larger veins such as the Vein of Galen. These bigger veins empty into dural sinuses which themselves are ultimately drained mainly by the internal jugular veins.[2,4] The brain surface is provided with Pial collaterals and larger anastomotic channels through which the cerebral venous system is interconnected. Owing to these widespread anastomoses between cortical veins, venous territories are not as well defined as the arterial territories.[2-4] These collaterals help in maintaining adequate cerebral flow and perfusion pressure in the event of occlusion of large veins where only small portion of vein is blocked, sparing the anastomotic channels.[2-4,14] Hence, cerebral infarction only ensues when venous blood does not find the alternate route due to the thrombus that is occluding collaterals.[3,5,14] This good collateralization of cerebral venous system in addition to slow propagation of thrombus elucidate the gradual onset of symptoms over the period of weeks and months.[1-4] However, large number of cases present with acute onset of symptoms which most likely represents acute thrombosis of a large sinus or corti-

cal vein over a subacute or chronic thrombotic process.[2,4,14] Corollary to the venous thrombosis, new collaterals are formed in these venous vessels[1,3] but this neo-vascularization is a slow process and does not have any impact in acute setting rather aids in the reversal of neurological deficits over a period of time.[3,4]

The rate of occlusion of cerebral veins is imperative in determining the outcome of venous thrombosis.[2,3] The slower the rate of occlusion (as seen in tumor), the lesser would be the chance of parenchymal damage. The reason being the greater time availed for collateralization due to the slow rate. Quite the reverse is true in the event of rapid occlusion that often results in haemorrhagic infarction.[3] Animal studies have shown that aged brain is likely to be more vulnerable to early and extensive hypoperfusion. Otsuka[20] demonstrated age related increase in the rate and size of venous infarct following cortical vein occlusion in 38 rats.

Recanalization of occluded vein or sinus may play an important role in minimizing neuronal injury and promoting neurological recovery. Studies have shown that recanalization is associated with favourable outcome in patients with CVT.[14] CVT results in infarction only in 50% of cases.[14,21] Large areas of the brain are only functionally or metabolically disturbed but not irreversibly damaged as contrary to arterial cerebral ischaemia that usually is a monophasic abrupt thrombotic process and there is only a small penumbra.[1] Thus lesions secondary to CVT may or may not be resolved over a period of time.[9,10]

It is plausible that early recanalization of occluded vein, as well as, the presence or absence and the efficiency of intracranial venous collaterals, may have an impact on the extent of brain tissue damage and hence the prognosis of acute CVT.[14,22] Animal model of CVT in rats revealed initial increase in lesion volume up to 5 hours secondary to cytotoxic oedema. Subsequent recanalization of occluded veins or improvement of collateral drainage and recovering metabolism possibly attribute to the reduction in the volume of lesions at 48 hours.[22] Mullins and colleagues[10] tried to relate parenchymal abnormalities with clinical outcome in 13 patients. DW imaging in these patients disclosed three lesion types with variable outcome; 1-lesions with elevated diffusion that resolved, consistent with vasogenic oedema; 2-lesions with low diffusion that persisted, compatible with cytotoxic oedema in patients without seizure activity; and 3-lesions with low diffusion that resolved in patients with seizure activity. Based on above mentioned findings, it is conceivable that resolution of these lesions could be attributable to recanalization and recovery of cerebral blood flow.[10] This theory is further confirmed by the use of venous transcranial duplex sonography (TCCS) in the study conducted by Stolz et al[14] that revealed normalization of venous

TCCS on day 90 after the onset of symptoms of thrombosis and MRA recanalization after 6±2 months. Normalized TCCS may also reflect functionally sufficient venous collateral pathways.[14]

Recanalization of venous sinuses after treatment has been demonstrated by various studies using MRI and MRVenogram.[23-24] Straub reported a case of transverse sinus thrombosis in a young woman with protein S deficiency who developed ipsilateral peripheral facial palsy during course of her illness that resolved completely.[25] This complete resolution seems to be concomitant with the recanalization of the transverse sinus.

Cytotoxic and vasogenic oedema

Cytotoxic and vasogenic oedema are both considered to occur in the setting of CVT.[9,10,26,27] It has been conventionally described that blood brain barrier is prone to get damaged in the setting of raised retrograde venous pressure. Hence, leakage of fluid (vasogenic oedema) ensues with increase post capillary venules pressure and opening of tight junctions.[10] Alternatively, increased venous pressure leads to increased intracranial pressure, decreased capillary perfusion pressure and remarkably decreased cerebral blood flow. This causes translocation of water content from the extracellular to the intracellular space (cytotoxic oedema) where water movement is more restricted, a mechanism in keeping with patterns observed in acute arterial infarction.[9,10,26]

Many studies have looked at the mechanism of cytotoxic oedema in patients with CVT and role of microcirculatory changes in experimental CVT models in relation to cytotoxicity and brain damage.[22,27-30] Kirsten[9] used diffusion weighted imaging in 12 patients with acute CVT to confirm that cytotoxic oedema would also occur in acute human cerebral venous infarction (CVI). Eight regions of non-haemorrhagic lesions, consistent with cytotoxic oedema, were detected in seven patients within 2 days of symptom onset. In addition to this, they found resolving cytotoxic oedema when those patients were followed beyond 2 days of symptoms onset. Kirsten's finding were in line with the research done by Rother[22] who induced venous thrombosis in rats by injecting thrombogenic material into the superior sagittal sinus that showed marked decrease in parenchymal ADC at 30 minutes, followed by a steady increase in diffusion (in keeping with vasogenic oedema) pattern over the period of 2 days. This may also show the gradual progression of venous thrombosis. The resultant oedema, if present in brainstem or basal ganglia may contribute to the development of hydrocephalus by obstructing aqueduct or foramen of Monro respectively. Thus, development of cytotoxic and vasogenic oedema represent an important landmark in CVT cascade. Neuronal injury at this point is still reversible and has been shown by many studies.[31]

Infarctions and haemorrhage

Infarctions and haemorrhage are endpoints of CVT cascade. These are most important determinants of neuronal injury and long term outcome of patients.[32] Haemorrhagic tendency in venous thrombosis is more frequent as contrary to arterial thrombosis[1], occurring approximately in 10-50% of cases.[2] Haemorrhagic infarctions principally affect the cortex and gray-white matter junction.[1-3,5] The bleeding in CVT is attributable to increased venous and capillary pressure.[1,2] Small cortical veins are vulnerable to rupture in the setting of these haemodynamic changes, resulting in bleeding on the cortical surface.[6] Sudden development of venous occlusion due to thrombus, rather slow developing occlusion is presumably responsible for the haemorrhagic infarction.

Studies in various animal models ascertained that rupture of cortical veins is fundamental in the development of haemorrhagic infarction.[13] Findings reported by Gotoh et al[13] are also in line with this theory. They evaluated blood brain barrier disturbance in cats by occluding superior sagittal sinus and cortical veins and noticed significant rise in intracranial pressure, cerebral blood volume and brain water content with SSS occlusion but haemorrhage ensued essentially following superficial cortical veins occlusion, depicting breakdown of blood brain barrier and resultant leakage of blood through these ruptured cortical veins. Alteration of cerebral microvasculature is considered to be the cause of haemorrhage in CVT.[28,33] Exact mechanism of vascular injury in CVT is not well known. One study showed increase in calpain expression manifested by loss of microtubule - associated -protein 2 in experimental CVT model. Calpains are intracellular proteases that are activated by increased intracellular calcium with protolytic activity mainly against cytoskeleton.[34]

Accelerated myelination

Focal accelerated myelination is a pathological state and conventionally has a known association with Sturge-Weber syndrome. There are anecdotal reports of association of CVT with accelerated myelination. Porto L et al[35] reviewed serial MR scans, MR angiography, conventional angiography and the clinical progress of three children with accelerated myelination and found 2 out of 3 children with accelerated myelination had an underlying cerebral sinovenous thrombosis. They proposed that cerebral venous thrombosis with the consequent restriction of venous outflow could be a possible key factor in the induction of accelerated myelination. The exact association of accelerated myelination and neuronal injury in patients with CVT is not well understood.

In conclusion, multiple factors contribute to neuronal injury in patients with CVT. These include dural sinus pressure, increased venous flow velocities, collateralization of venous channels, rate of occlusion, development of cytotoxic and vasogenic oedema, recanalization and possibly accelerated myelination. It is suggested that recanalization of occluded vein, as well as, the presence or absence and the efficiency of intracranial venous collaterals, may have an impact on the extent of brain tissue damage and hence the prognosis of acute CVT. Neurological recovery or long term outcome is dependent on extent of neuronal injury and early recanalization of occluded sinuses.

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