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Original Research Article

Cortical venous thrombosis in high altitude; result of an observational study

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ABSTRACT

Background: High altitude, an extremely rare cause of cortical venous thrombosis (CVT) has no literature review available signifying the relation between two as per date. The aim of this study is to establish the relation of exposure to high altitude and occurrence of CVT in properly acclimatised healthy individuals exposed to high altitude having no pre-existing morbidities.
Methods: An observational type of prospective study was conducted at a tertiary care centre in North India. Patients who were sent back from a high-altitude area with CNS symptoms (headache to coma) were included in the study. Magnetic resonance imaging (MRI) and magnetic resonance venography (MRV), blood investigations including complete blood count and D-dimer were done as routine examinations in all these patients. MRI and MRV findings were recorded and analyzed for features of CVT.
Results: Twenty-eight patients with an average age of 31.5 years (23-51 years) were included in the study. All patients had CNS symptoms; with headache being the common symptom. In the patients of CVT, there were MRI features of parenchymal infarct in 7 (25%), hemorrhagic infarct in 11 (41.6%), subarachnoid hemorrhage in 7 (25%) and mass effect in 3 (8.4%) patients. MRV revealed involvement of multiple sinus involvement more common than single sinus involvement, of which most commonly involved sinuses were Superior sagittal sinus and transverse sinuses. D-Dimer levels were significantly raised in 23 (83%) patients.
Conclusions: High altitude though a rare cause, can be the single most important contributory factor in the development of CVT in healthy acclimatised individuals with no predisposing factors. The physicians dealing with such patients at high altitude should be well aware of the scenario as early diagnosis via imaging and prompt management can drastically reduce mortality in this potentially lethal but treatable conditions.

Keywords: CVT, High altitude, MRI, MRV

INTRODUCTION

Cerebral venous thrombosis (CVT) is a complete or partial occlusion of main sinuses, sinus or cortical feeding veins leading to venous congestion resulting in focal or generalised neurological deficits.[1] The cause of CVT can be attributed to local and systemic causes. Systemic causes include hormonal (most commonly oral contraceptives), post op condition, hypercoagulable states, malignancy dehydration to name a few. Local causes are mostly trauma and infection. In approximately 25 % of the cases, no cause has been determined.[1,2]

CVT has an extremely non-specific and subacute presentation. Non-specific symptoms range from mild headache to focal or generalised neurological deficits. It

takes about 02 to 03 weeks to fully manifest. CVT accounts for only 1 to 2 percent of strokes in adults. The non-specific and the sub-acute presentation contribute to making diagnosis of CVT very difficult.[2,3]

In our setting, the diagnostic difficulty is compounded as such the exposure to high altitude usually occurs in hostile field in conditions where there is lack of advanced imaging and other specific investigations helping us to reach the diagnosis.

High altitude as a cause of CVT is extremely rare with not much research done on this subject, though cases of CVT due to exposure to high altitude have been well documented before.

The aim of this study is to establish a direct correlation between exposure to high altitude and occurrence of CVT in otherwise healthy soldiers exposed to high altitude with proper acclimatisation and no pre-existing morbidities.

METHODS

The prospective study was conducted at a tertiary care hospital in North India from March 2010 to Oct 2018. The patients included in this study were those patients who were sent ack from high altitude areas due to CNS symptoms ranging from headache to coma. All these patients underwent MRI and MRV in a Siemens 1.5 T MRI.

Protocols

Protocols of MRI varied according to the clinical status of the patient for unstable or uncooperative patient: iltrafast imaging with just a 3 D T1 SE and a Ss 3 D PC MRV (total imaging duration of 4 mins 30 secs).

For cooperative and stable patients: Additional DWI, FLAIR coronal T2* and T2 axial images (total imaging duration-9 minutes and 30 secs).

All these patients underwent investigations like CBC, platelet counts, ESR, protein C and S, PBS and Hb electrophoresis to screen for underlying blood disorders and hypercoagulability states

RESULTS

There were 28 patients who were diagnosed with CVT. All the patients in the study were males with an average age of 31.5 years (23 to 51 years). The patients were apparently healthy prior to this evaluation as the routine medical examination as well as laboratory investigations done before induction into high altitude were normal and they were free from any discernible diseases or comorbidities.

The predominant clinical features were either headache, hemiparesis, speech and gait abnormalities, seizures, cranial nerve involvement, altered sensorium or coma. The distribution of these symptoms is shown in Figure 1.

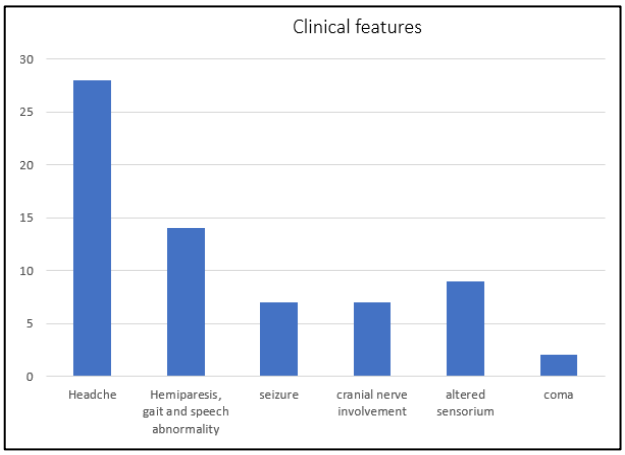

Figure 1: Clinical features in patients diagnosed with CVT.

MRI findings in CVT patients

The findings on MRI in all the patients diagnosed with CVT are shown in Figure 2. The predominant MRI finding was hemorrhagic infarct in 11 (41.6%) patients followed by parenchymal infarct in 7 (25%), subarachnoid hemorrhage in 7 (25%) and mass effect in 3 (8.4%) patients.

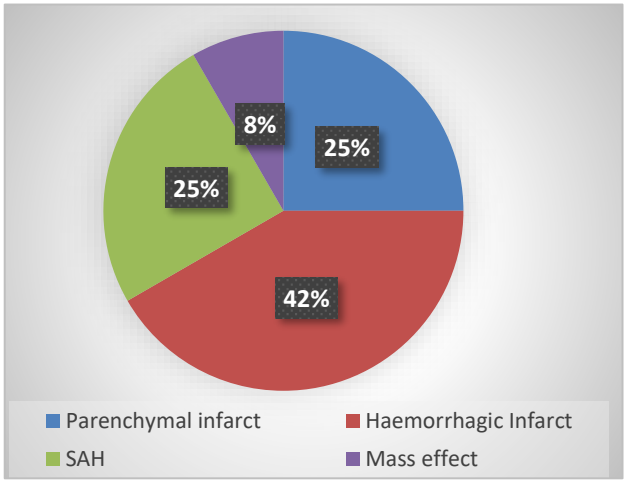

Figure 2: MRI findings in CVT.

MRV findings in CVT patients

The specific MRV features in our study showed involvement of superior sagittal sinus (SSS) and transverse sinus (TS) in 9 (33.3%) patients followed by various different combination of sinus involvement as shown in Figure 3. Multiple sinus involvement was more common than single sinus involvement, most commonly involved sinuses were Superior sagittal sinus and transverse sinuses.

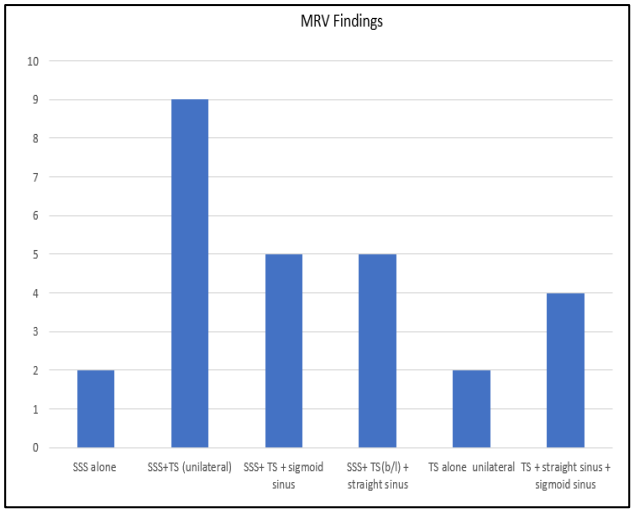

Figure 3: MRV findings in CVT.

The D-dimer levels were evaluated and 24 (83.3%) patients had significantly high (>500 ng/ml) values as shown in Figure 4.

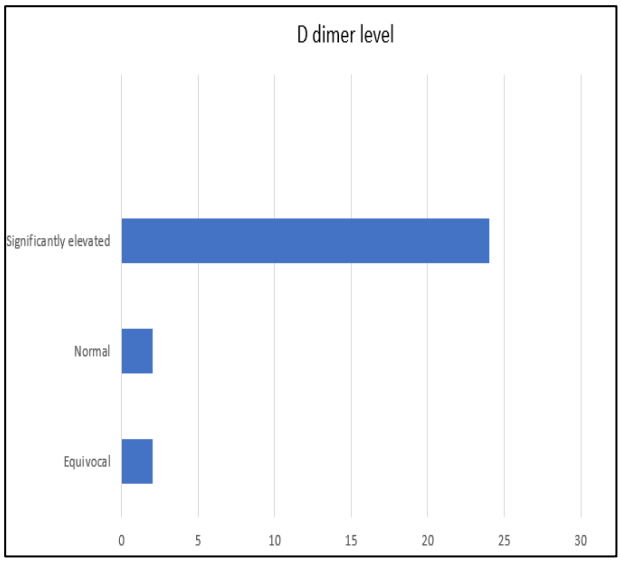

Figure 4: D-Dimer levels in CVT patients.

Out of the 28 patients who had CVT, all had elevated D dimer, one patient with normal D dimer had a brain stem glioma, one patient with equivocal D dimer had SAH, one of the patients with elevated D dimer had a right MCA territory infarct and another with elevated D dimer was found to be normal on imaging

DISCUSSION

CVT has been well known for more than 200 years. There are wide variety of causes leading to CVT which have been divided broadly into endocrine disturbances, haematological/immunological abnormalities, connective tissue and other inflammatory disorders, and neoplastic causes.

Sinus occlusion can be either due to the development of a prothrombotic state or turbulence due to direct disturbance of venous flow (e.g., compression, low flow states), or by infiltration or inflammation of the sinus wall (e.g., the arteritis). Nearly a quarter of the cases of CVT are idiopathic.[4-7]

Although high altitude is a known cause of CVT, there has been review of literature mostly on isolated case reports in mountain climbers only. We haven't come across a large cohort of patients presenting with CVT after being exposed to high altitude, also most of the cases reported to have CVT had hypercoagulability as risk factor. Our cases were healthy individuals and had no such risk factors.

Hypoxia at high altitude leads to a physiological response which are mediated by a complex physiological interplay of respiratory, renal, haematological and metabolic mechanisms. Also increased erythropoiesis as a result of hypoxia and the fluid shift mechanism further contributes to it. Soon within few seconds of exposure to hypoxia, the beginning of prothrombotic state ensues.

Hypoxia is the main stimulus for increase red cell production. On ascent to high altitude, the expression of hypoxia inducible factors (HIFs) is induced by renal hypoxia. These factors are transcription factors which induces other genes like VEGF, erythropoietin, endothelin and adrenomedullin.[8] Erythropoietin (Epos) peaks values after 1-2 days to exposure to hypoxia and then fall to a new plateau at about twice that present at sea level by in the 2nd week.[9]

The haemoglobin concentration rises by an average of about 5 gm/dL within a week of stay at high altitude. It results in the rise of haematocrit from an average value of 40 to 45 to about 60. The rising haematocrit in turn increases the viscosity of blood predisposing it to thrombosis.

The fluid dynamics across capillary membrane causes a significant shifting of fluid from intravascular to extravascular compartment. A large part of this response is mediated through HIFs. They lead to activation of nitric oxide synthase (NOS) and production of nitric oxide which acts as a vasodilator.[10]

The dynamics of coagulation mechanism is also influenced indirectly by the alveolar ventilation. The hypoxia triggers the peripheral chemoreceptor leading to increased alveolar ventilation.[11] With increased alveolar ventilation, there is ongoing insensible loss from respiratory pathway leading to dehydration. Also, respiratory alkalosis is created in the body as a result of loss of carbon dioxide from the respiration. The kidney increases its bicarbonate excretion to about 13% as a response to the respiratory alkalosis. This bicarbonate excretion, along with an increase in renal sodium and water excretion is called hypoxic diuretic response.[12-14]

The end result of all these mechanisms is reduction of approximately1 to 3 L total body water and 38% increase in blood viscosity depending on the duration of stay at high altitude.[15] Additionally, other factors in the environmental setup like constrictive clothing, restriction of movement and reduced water intake contributes even more to dehydration and stasis of blood flow.

All the above factors reduce the volume of intravascular fluid which leads to increase viscosity of the blood. This, together with increased expression of inflammatory cytokines produces a favourable environment for development of thrombosis in an individual staying at high altitude for prolonged intervals.[16] Volume depletion and polycythaemia are implicated as causes of CVT in cases of high-altitude exposure. Polycythaemia with relative hyper viscosity and increase in CBF (cerebral blood flow) results in increase intracranial pressure (ICP). This raised ICP compromises the low-pressure venous system. Cerebral venous occlusion as a result of thrombosis leads to venous congestion and elevated venous pressures. There is resultant interstitial oedema and decreased CSF absorption which may result in rupture of venous structures and localised haematoma formation. At the initial stages there is extensive collateral circulation causing compensation of the situation, which explains the subacute presentation.

Isolated CVT without sinus involvement is extremely rare. Contiguous transverse and sigmoid sinus involvement is seen in 90% cases and deep cerebral veins involvement accounts for only 10% of the cases. This data also commensurate with our findings. Since the findings of MRI in the very early (< 5 days) or very late (> 30 days) is equivocal, MRA is required only in these stages of the evolution of the thrombus for a definitive diagnosis. Addition of MRA to MRI helps us to avoid the possibility of increased false negatives.[17,18]

The MRI findings maybe equivocal in the first five days or at more than 30 days is because the imaging characteristics of a thrombus changes as per its temporal evolution.[19] An acute thrombus appears isointense on T1WI because of the presence of deoxyhaemoglobin, and the same appears hypointense on T2WI. The hypointense thrombus on T2WI can be easily missed as it appears similar to normal blood flow. In the late sub-acute phase i.e. (5 to 30 days period) as there is methaemoglobin formation from deoxyhaemoglobin. The signal is hyperintense on both T1and T2WI, giving the thrombus a bright appearance. This sub-acute period is the only period where a definitive diagnosis can be made on MRI alone. Similarly, a chronic persistent thrombus of more than 30 days duration is hypointense on T1WI and hyperintense on T2WI but thrombus recanalization might give a heterogenous appearance.[20]

As MRI alone might be insensitive in diagnosing acute and chronic thrombus, the addition of MRV (Magnetic resonance venography) sequence to MRI helps us in correcting and accurately reaching up to the diagnosis. The thrombus is visualised as a filling defect (loss of signal) in the background of hyperintense flowing blood in contrast enhanced MRV. However, a subacute hyper intense thrombus may mimic blood flow in a sinus, a pitfall which it shares with TOF imaging. In PC MRV (post contrast MRV), however the hyperintensity of thrombus in T1 WI is not a disadvantage and hence it could be the preferred method of MRV while imaging CVT.[20]

Imaging of CVT has direct and indirect components. Imaging of the clot itself is a direct component whereas imaging of parenchymal effects of the clot is an indirect component. A combination of MRI and MRV is able to adequately image both of these components. Faster algorithms have aided in imaging. The protocols have been modified according to the clinical status of the patient. Uncooperative patient due to altered sensorium had only 2 sequences 3D T1WS with Ss 3D PCMRV which took only 4 minutes 30 secs of imaging time. FLAIR, T2W axial, DWI (to differentiate between venous congestion and cytotoxic oedema), T2*(for haemorrhage) sequences were added in case of cooperative patient in addition to T1WS with Ss 3D PCMRV sequences which added just 5 more minutes to the total imaging time.

Our study included previously healthy patients with no known comorbidities who presented with CVT after exposure to high altitude thereby implying that high altitude was a singular most important factor for their developing CVT. A combination of clinical features, D dimer and a high index of suspicion were considered as screening tools in view of many constraints in a harsh and inhospitable terrain. D dimer levels correlate very well to risk of having CVT.

CONCLUSION

High altitude though a rare cause can be a single most important contributory factor in the development of CVT in healthy acclimatised individuals with no predisposing factors. A good knowledge of the non-specific symptoms and sub-acute presentation of CVT is essential and important in physicians who deal with patients at high altitude as early and adequate imaging can help reduce mortality and morbidity in this potentially lethal but treatable condition.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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