Pakistan Journal of Neurological Sciences (PJNS)

Volume 13 | Issue 3 Article 10

9-2018

Cerebral venous thrombosis At high altitude

Maryam J Syed
Sindh Medical College, Jinnah Sindh Medical University, Karachi,

Wasim Alamgir
2Military Hospital, Rawalpindi

Mohammad Wasay
Aga Khan University, Karachi, mohammad.wasay@aku.edu

CEREBRAL VENOUS THROMBOSIS AT HIGH ALTITUDE

Maryam J Syed *MBBS*[1], **Wasim Alamgir** *FRCP*[2], **Mohammad Wasay** *MD, FRCP, FAAN*
[1]Sindh Medical College, Jinnah Sindh Medical University, Karachi, [2]Military Hospital, Rawalpindi
[3]Aga Khan University, Karachi

Correspondence to: *Mohammad Wasay MD, FRCP, FAAN Professor, Department of Neurology Aga Khan University Stadium Road, Karachi 74800, Pakistan*
Phone: 9221 4930051(office) Email: mohammad.wasay@aku.edu

Date of submission: *April 12, 2018* ***Date of revision:*** *June 05, 2018* ***Date of acceptance:*** *June12, 2018*

ABSTRACT

Cerebral Venous Thrombosis (CVT) is one of the rarest causes of stroke. It is described as complete or partial occlusion of the sinuses or cortical veins of the brain. A relationship between high altitude (HA) and cerebral venous thrombosis has been long suspected due to various case reports and studies, however, the exact underlying mechanisms and etiologies are highly complex and debatable. In this article review we discuss the incidence etiologies, risk factors, clinical presentations and management of CVT at high altitude. CVT majorly affects young people [2]. It presents with a wide variety of clinical presentations due to the complexity of cerebral venous architecture and a combination of edema, increased intracranial pressure and venous infarct. Numerous etiologies have been suggested for the incidence of CVT; varying from dehydration, increased blood viscosity leading to endothelial injury, immobility, inflammation, genetic expression of certain prothrombotic entities, triggering of the coagulation cascade, platelet dysfunction and underlying coagulation disorders. Individuals with history of coagulation abnormalities should be screened for underlying thrombophilias and cautiously ascend to higher altitudes. CVT should be considered in all neurological clinical presentations at high altitude. High altitude trekkers should be educated on how to keep hydrated and avoid immobility, exposure to extreme cold and seeking immediate help for symptoms like headache and disturbed mental status.

KEYWORDS: Cerebral Venous Thrombosis, High Altitude, Venous Thrombosis, coagulopathy, stroke

INTRODUCTION: CVT accounts for 1% of all strokes. Occurrence of CVT at high altitude is also a rare phenomenon, however, the numerous anecdotal records from the past and the recently documented case reports of CVT occurring in the context of high altitude have urged the scientific community to find plausible etiologies that help explain the underlying mechanisms involved. The exact prevalence of CVT at high altitude remains undiscovered due to the challenges faced at determining the risk factors and asymptomatic hypercoagulable states of climbers ascending to high altitudes [1]. The case reports that are available are few in number and without controls. CVT majorly affects young people [2]. It presents with a wide variety of clinical presentations due to the complexity of cerebral venous architecture and a combination of edema, increased intracranial pressure and venous infarct [2, 28]. The inconsistency in the clinical findings of CVT makes it immensely challenging to diagnose in the context of high altitude with several other commonly occurring conditions such as Acute Mountain Sickness or High Altitude Cerebral Edema being the much more probable causes. High Altitude is associated with increased propensity for developing a hypercoagulable state by multiple studies and case reports [5 -10]. Various etiologies have been suggested for the incidence of CVT; varying from dehydration, increased blood viscosity leading to endothelial injury, immobility, inflammation, genetic expression of certain prothrombotic entities, triggering of the coagulation cascade, platelet dysfunction and underlying coagulation disorders. Despite much speculation, contradictory evidence is also present, negating that hypobaric hypoxia, such that is experienced at a HA is involved in increased thrombosis [3]. CVT may be associated with poor outcome depending on the timely

nature of diagnosis and treatment and the extent of the thrombosis. Bilateral or extensive thrombosis coupled with underlying coagulation disorder is associated with poor prognosis. Understanding the pathophysiology and the risk factors can help prevent incidence of CVT at high altitude as well as educate physicians and climbers about prompt diagnosis, treatment, screening and appropriate preventive measures.

SEARCH METHODOLOGY

Comprehensive literature search was done on search engines PubMed and Google Scholar using the keywords "Cerebral Venous Thrombosis", "High Altitude" and "Venous Thrombosis". The following search query was used in PubMed: ("Cerebral Venous Thrombosis" [MeSh]) OR (Cerebral Venous Thrombosis[Title] AND High Altitude[Title]) OR (Cerebral Venous Thrombosis[Title] OR High Altitude) OR (Cerebral Venous Thrombosis at High Altitude[Title]). Inclusion criteria consisted of articles from journals that were PubMed indexed and published in the last 20 years. A total of 40 articles were reviewed, out of which 32 were included in the final paper. The references in papers found to be eligible were taken into account and screened for relevant information. The full text of all acceptable papers was accessed and read thoroughly. A comprehensive table of all pertinent information was made for easy access during article writing. Literature related to pathophysiology of venous thrombosis due to hypoxia was selected according to its relevance and recentness.

HIGH ALTITUDE (HA)

Barometric pressure decreases at an exponential rate as higher altitudes are reached, leading to a decrease in the partial pressure of Oxygen, which results in brain receiving less oxygen, hence inducing hypoxia [4]. CVT has been mostly described to occur between altitudes ranging from 2500m to 5500m [1]. It has been proposed that activation of coagulation factors leading to a prothrombotic state is rate dependent, i.e the more rapid the ascent to HA, higher the risk of developing CVT [5, 10]. Comparatively, gradual ascent to HA and well-acclimatized individuals pose a lesser risk of thrombosis. A study held in India compared 1692 patient profiles comparing incidence of thrombosis in extremely HA (>5000m) and sea levels found that there was a 30 times higher incidence of CVT at HA [8]. Similarly, a study done on healthy, young soldiers at 3500m found a 30 times higher incidence of thrombosis [5]. Another study found that lowlanders posted at 3883m had 30-44 times increased incidence of deep vein thrombosis [6]. It was suggested that acute exposure to hypoxia solely cannot predispose to thrombosis without significant underlying shift in hemostasis [11]. There is a lack of good studies to determine the exact cause of hypercoagulability in HA especially since most of current studies in the West are performed in artificially simulated hypoxic environment. CVT can occur in lower than average altitude in people with pre-existing underlying prothrombotic state. Prolonged duration of stay is also associated with higher incidence of CVT as illustrated by various case reports. Table 1 shows incidents of CVT in high altitude.

TABLE 1: CASE REPORTS AND STUDIES WITH ASSOCIATED ALTITUDES AT WHICH CVT INCIDENCE OCCURRED.

Author, Publication Type, Date	Altitude (meters above sea level)
Song et al[26] – case series (1986)	5200m
Bolous et al[11] – case report (1999)	3000m
Anand et al[8] – case series (2001)	3000m-5999m
Saito et al[19] – case report (2003)	5000m
Torgovicky et al[10] – case report (2005)	10,000m-13,000m
Skaiaa and Stave[27] – case report (2006)	8201 m
J. Kotwal et al[5] - cohort study (2007)	3500m
Nair et al[17] – case report (2008)	4572m
Cheng et al[9] - case report (2009)	4000m
Grabe et al[18] – case report (2012)	4877m
Shrestha et al[13] – case report (2012)	5600m
Hassan et al[12] – case report (2013)	2200m
Nair et al[7] – case report (2016)	6400m
Te DP et al[16] – case report (2017)	4000m
Kim et al[15] – case report (2017)	5970m
A.K. Paliwal et al[30] – case series (2018)_	3000m-3800m

AGE

At HA, CVT is typically observed in young to middle aged individuals [1]. Extremes of ages have also been reported with a 75-year-old man with an underlying

case of hyperhomocysteinemia developing deep CVT at an altitude of 2200 m for 3 days [12] and a 19-year-old female developing sinus vein thrombosis after a high altitude training of 2 months [10].

GENDER

There's an evident gender disparity in the documentation of CVT at high altitude, with a significantly higher incidence of CVT in males [1]. Most of the stronger studies were done on stationed soldiers and male trekkers [2,3,5,6,7,8]. and majority of the case reports document male patients [11, 12,15,16,17,18,19]. Mountaineering is a male-dominated sport [14]. Women have additional risk factors such as oral contraceptive pills and pregnancy that predisposes them to venous thrombosis. Reported cases of females developing CVT at HA always had an existing underlying risk factor. A young female developing sinus vein thrombosis at HA had a history of oral contraceptive use that she claimed to have stopped taken 3 years prior to the incident [10]. Similarly, Shrestha et al. reported another female with heterozygous mutation of Factor V Leiden and low plasma levels of protein S suffered from CVT at 5600m [13]. A 39-year-old female was reported to develop bilateral deep subcortical infarction in combination with Acute Mountain Sickness [9].

CONGENITAL THROMBOPHILIAS

A pre-existing prothrombotic state, such as congenital thrombophilias, appears to the most common risk factor for developing CVT in a HA setting. A systemic review showed 9 out of 14 reported cases had an underlying hypercoagulable state with secondary polycythemia and Factor V Leiden mutations being the most common [1]. Heterozygous Factor V Leiden mutation increases the risk of thromboembolism by seven fold, whereas homozygous mutation increases the risk by eight-fold [20]. Bolous et al reported a case of sudden onset of right sided hemiplegia and aphasia secondary to CVT at 3000m in a 42-year-old man with congenital protein C deficiency, while Nair et al shares a case of a patient with a Protein S levels of 36% (normally 70-123%) presenting with CVT coupled with DVT. Both cases were distinct for positive family history of hypercoagulability [17]. Grabe et al recorded a case of homonymous hemaniopia from deep CVT leading to infarction of the optic tract and lateral geniculate nucleus at 4800m with an underlying heterozygous Factor V Leiden mutation and elevated Factor VIII levels [18]. Nair et al reports a case of 35-year-old patient with both intra-arterial and venous thrombosis at multiple sites including the superior sagittal sinus with an increased Plasminogen Activator Inhibitor 1 (PAI-1) due to 4G/4G genotype polymorphism [7]. Hassan et al brings to attention a case of a rare association between protein S deficiency and hyperhomocysteinemia that resulted in severe deep CVT [12].

OTHER RISK FACTORS

Factors that predispose to CVT formation include infections, head trauma, malignancy and drugs with prothrombotic tendencies. On HA, additional risk factors to consider are dehydration, immobility, polycythemia and changes in hemostasis. Dehydration secondary to reduced water intake, increased physical exertion as well as vomiting and diarrhea due to AMS can predispose to increased hemoconcentration [9,13]. Hemoconcentration also increases due to eventual acclimatization which leads to polycythemia and increased blood viscosity. The process of acclimatization brings about numerous changes in blood physiology leading to a higher risk of thrombus formation. Whilst full acclimatization is achieved, hematocrit is believed to have increased by 50% [20]. Significant increase in hemoglobin levels, hematocrit and RBC count is reported in various studies done on HA [5, 6]. Increased blood viscosity increases mean PTT and causes endothelial damage leading to clot formation. Polycythemia also results in increased cerebral blood flow, subsequently increasing intracranial pressure which in turn disrupts the cerebral venous blood flow. Although most cases of CVT at HA are observed in lowlanders acutely exposed to high altitude conditions, a few cases have also been observed in well acclimatized individuals native to such conditions. A case of vein of Galen thrombosis was observed in a permanent citizen of the Tibetan plateau (4000m) with an additional risk factor of recent history of trauma (bilateral acetabular fracture), high blood pressure, history of smoking and hemoglobin of 191 g/L [16]. Similar case of a well acclimatized man presenting with occlusion of superior sagittal and right transverse sinuses around his 45th day at 5000m altitude, with an additional risk factor of pre-existing brain sinus narrowing and anomalies [19]. 10%-30% of the population is believed to have structural brain sinus anomalies. Extreme cold can trigger coagulation cascade [23].

SUGGESTED MECHANISMS

The precise etiopathology of thrombosis at HA is obscure. The literature contains conflicting studies

offering a wide array of plausible explanations regarding the underlying mechanisms that lead to a hypercoaguable state at HA. Hypoxia-induced customization of hemostasis and coagulation factors results in simultaneous changes in multiple components of blood, predisposing to thrombosis.

ROLE OF INFLAMMATION

Gupta et al emphasized the presence of an active proinflammatory response to hypoxia employing innate and adaptive immune cells resulting in aggravated venous thrombosis. This proinflammatory state develops in response to HA due to the action of Hypoxia-induced factor 1-alpha (HIF-1a) on NLRP3 gene expression leading to formation of NLRP3 inflammasome [21]. This study documents the presence of NLRP3, caspase-1 and IL- β in individuals who formed venous thrombosis. Additionally, another contributing factor is believed to be endothelin-1-mediated and interleukin-6-mediated endothelial activation and related inflammatory response [15].

ROLE OF FACTOR VIII, PAI-1 AND PLATELET ACTIVITY

Kicken et al attributed the increase in thrombin levels mediated by increased Factor VIII levels to be the cause of increased hypercoagulability at HA. Factor VIII levels were presumed to be increased due to the oxidative stress in circulation due to tissue hypoxia, asserting that hypoxia alters the "redox status" of the blood [6]. This study also found that platelet aggregation was reduced at HA, attributing to increased ADP and epinephrine. Antithrombin levels, D-dimers and coagulation factors remained unchanged as compared to sea levels. Interestingly, subjects which were pretreated with Vitamin E had a reduced incidence of venous thrombosis [6]. On the other hand, Kotwal et al studied the effect of high altitude on hemostasis at induction, 3 months and 8 months and reported a significant rise in platelet count and platelet activation factors (BTG and PF4). This study also reported a significant rise in hemoglobin, PAI-1 activity and plasma fibrinogen, asserting a positive relationship between the latter two and postulating the significance of PAI-1 in "tilting the balance" towards thrombosis by decreasing fibrinolytic activity. Kotwal et al also emphasized that platelet aggregation in the context of thrombosis was not a reliable method, instead BTG and PF4 measured on ELISA assay were more illustrative of platelet activity [5].

Martin et al contradicts aforementioned findings by analyzing the kinetics of clot formation using thromboelastography to study the effects of hypoxia at 4250 m and 5300m on coagulation [3]. It was found that exposure to hypoxia decreases blood coagulability [3].

ROLE OF INCREASED SYMPATHETIC ACTIVITY

Hypoxia is also believed to trigger the body's sympathetic response and increased sympathetic activity has a strong relationship with stroke [20, 22]. Constantly increased norepinephrine activates platelet hyperfunctioning leading to a hypercoagulable state [22].

Clinical Features and Diagnostic Challenges

There's a considerable variation in the clinical features associated with CVT. Severity of the presentation is contingent with the extent of the thrombosis, sinuses involved and development of venous collaterals [12]. Most common signs and symptoms include headaches, focal neurological deficits, seizures and altered mental status [1, 2]. Other symptoms include papilledema and behavioral changes. Both cytotoxic and vasogenic cerebral edema are associated with CVT [28]. These present with an acute onset and the headaches are often associated with vomiting, confusion and loss of consciousness. Deep CVT involving the thalamus, basal ganglia and subcortical white matter presents as serious neurological emergency [12,16,18].

More common neurological conditions associated with high altitude are High-altitude headache (HAH), Acute mountain sickness (AMS) and High altitude cerebral edema (HACE). These render the accurate diagnosis difficult due to several overlapping clinical features. For example, HACE presents as altered mental status, ataxia of gait, and psychiatric changes that can lead to deep coma. Table 2 illustrates the clinical features of patients who developed CVT at HA.

TABLE 2: PUBLICATIONS CITING CVT INCIDENCE AT HA WITH ASSOCIATED CLINICAL FEATURES.

PUBLICATION	CLINICAL FEATURES
BOLOUS ET AL[11]	Sudden onset of right hemiplegia, aphasia, right facial droop and tonic-clonic seizures
KIM ET AL[15]	Weakness in right arm and hand coupled with headache.
HASSAN ET AL[12]	Global headaches and vomiting for 6 days
CHENG ET AL[9]	Headache, dizziness and vomiting, drowsiness and GCS of 8. Tetraplegia.
TORGOVICKY ET AL[10]	Frontal headache
TE DP ET AL[16]	Reduced consciousness and reduced muscle strength.
NAIR ET AL[17S]	Presentation: Sudden onset severe bifrontal headache, vomiting and drowsiness. Day 6: partial motor seizures of right face and right arm. Day 9: right sided flaccid hemiplegia with cranial nerve VII involvement.
GRABE ET AL[18]	Intermittent headaches and somnolence followed by right homonymous hemianopia and right hemiparesis along with right hemi-sensory deficit.
SAITO ET AL[19]	Gait disturbance, aphasia, visual field narrowing, agraphia, coordination deficit and paresthesia of upper limbs.
SHRESTHA ET AL[13]	Sudden onset headache, aphasia and right upper quadrantanopia.
NAIR ET AL[7]	Altered mental status and seizures.
SKAIAA AND STAVE[27]	Severe headache, vomiting and mild drowsiness on two separate occasions (2001 and 2004)

DIAGNOSIS

Neuroimaging plays a vital role in the diagnosis and clinical outcome [31]. Two most common imaging modalities used to confirm diagnosis of CVT are CT scan and MRI, and MRV when not visualized in MRI [1, 32]. There are alterations in the intensity of the thrombus depending on its age [31]. Most common sinuses to be affected is the superior sagittal sinus and transverse sinus [1, 2]. Kim et al weren't able to locate any indication of thrombosis except for vasogenic edema with a hemorrhagic component on MRI [15]. D-dimer level can be effective to diagnose restricted sinus involvement or in older individuals, however, there is a chance of false negative results and its role in diagnosis remains controversial [24, 32]. Imaging modality of choice to visualize deep CVT is MRI T1W1 [12]. Family history of coagulation disorders should raise suspicion for CVT for anyone presenting with neurological findings at HA. Nair et al demonstrated that PA1-1 polymorphism lead to widespread thrombosis at multiple sites including aorta, bilateral iliac arteries, middle cerebral artery and CVT of superior sagittal sinus [7].

PROGNOSIS

The main determinant of prognosis is timely diagnosis and treatment. Hemorrhage is a common sequela of CVT and worsens clinical outcome [11]. Most cases of CVT show good recovery with a combination of quick

anticoagulation and rehabilitation [29]. Failure to anticoagulated results in poor prognosis [9, 29]. 25% of patients with CVT deteriorate despite adequate anticoagulation [2]. Overall mortality rate associated with CVT is 34.2% [29]. Bilateral CVT (which male up 3%-8% of all CVT) and deep CVT present with severe clinical features and are associated with poor clinical outcome [2,9,16,18]. According to the International Study of Cerebral Vein and Dural Thrombosis (ISCVT) 13% had poor neurological outcome whereas 4.3% were recorded to have died during the acute phase. Bushnaq et al demonstrated that the most significant predictor of poor prognosis to be altered or decreased mental status. Other indicators for poor prognosis are seizures, papilledema, hyponatremia (<139mEq/L), low platelet count (<225x109/L) and involvement of more than one sinus [2]. Endovascular therapy has been used as a salvage intervention, however there's not much evidence to support its efficiency in decreasing mortality. Delaying thrombectomy can result in fibrosing of the thrombus leading to permanent neurological damage [2].

TREATMENT

Treatment of choice for CVT at HA is anticoagulation with subcutaneous Low Molecular Weight Heparin [32]. In the acute phase of the disease, first concern should be to stabilize and prevent cerebral herniation [28]. Decompressive surgery is strongly suggested for acute CVT with parenchymal involvement [32]. Use of acetazolamide, steroids and thrombolysis in acute CVT is discouraged [32]. For medically-refractory cases, mechanical thrombectomy can be considered [31]. Long term anticoagulation with warfarin or newer oral anticoagulants (NOACs) may be required for variable periods.

PROPHYLAXIS

LMWH and Warfarin are proven to be acceptable prophylaxis against hypercoagulabity at HA. Use of oral anticoagulants after an episode of CVT to prevent further incidence has low evidence of impact and not recommended [32].
Oral Contraceptive Pills should be discontinued by females before embarking on a HA journey.

FUTURE DIRECTIONS

The exact incidence and mortality rate of CVT on a HA is unknown. Almost all epidemiological studies about CVT are based on normal altitude, not taking in account the additional risk factors associated with hypobaric hypoxia. Most high altitude studies were done on male, middle-aged soldiers or mountaineers without proper controls, this gives rise to bias and inaccuracy. Multi-center academic collaborations between institutions investigating incidence of high altitude-associated CVT can help improve the current understanding about involved risk factors. A case control study will be useful in identifying risk factors for high altitude CVT. Future intervention trials could be planned targeting high risk populations. Determining the precise altitude at which the risk of developing CVT increases significantly can help caution susceptible individuals. Although screening for thrombophilias is not recommended for CVT at normal altitude [32], studies showing a strong relationship between the two should prompt further research on whether thrombophilia screening should be incorporated in the diagnostic protocol for CVT cases presenting at a HA setting. Those set to experience hypobaric hypoxic conditions should also get routine blood counts to screen for polycythemia and thrombocytosis. Screening for Vitamin B12 and Folate levels can help detect a state of hyperhomocysteinemia. Health care professionals should also be trained to consider and diagnose CVT in patients with neurological symptoms. Availability of imaging modalities such as CT and MRI scan can lead to quicker diagnosis and treatment. More research should be focused on the underlying pathophysiology and mechanisms involved with hypoxia-associated CVT to create effective prophylaxis, protocols and treatment plans.

CONCLUSION

Cerebral Venous Thrombosis occurring at high altitude is a neurological emergency that requires timely diagnosis and treatment. It has complex underlying mechanisms and etiologies as well as numerous clinical presentations. Understanding the predisposing factors to this phenomenon can lead to effective preventive measures, quicker diagnosis and management. Individuals with history of coagulation abnormalities should be screened for underlying thrombophilias and cautiously ascend to higher altitudes. CVT should be considered in all neurological clinical presentations at high altitude. High altitude trekkers should be educated on how to keep hydrated and avoid immobility, exposure to extreme cold and seeking immediate help for symptoms like headache and disturbed mental status. Patients with no contraindications to anticoagulation should be immediately anticoagulated with appropriate drugs.

References

1. Zavanone C, Panebianco M, Yger M, Borden A, Restivo D, Angelini C, Pavone A, Grimod G, Rosso C, Dupont S. Cerebral venous thrombosis at high altitude: a systematic review. Revue neurologique. 2017 Apr 1;173(4):189-93.
2. Bushnaq SA, Qeadan F, Thacker T, Abbas M, Carlson AP. High-Risk Features of Delayed Clinical Progression in Cerebral Venous Thrombosis: A Proposed Prediction Score for Early Intervention. Interventional Neurology. 2018;7(6):297-307.
3. Martin DS, Pate JS, Vercueil A, Doyle PW, Mythen MG, Grocott MP, Caudwell Xtreme Everest Research Group. Reduced coagulation at high altitude identified by thromboelastography. Thrombosis and haemostasis. 2012 Jun 1;107(6):1066.
4. Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes. The Lancet Neurology. 2009 Feb 1;8(2):175-91.
5. Kotwal J, Apte CV, Kotwal A, Mukherjee B, Jayaram J. High altitude: a hypercoagulable state: results of a prospective cohort study. Thrombosis research. 2007 Jan 1;120(3):391-7.
6. Kicken CH, Ninivaggi M, Konings J, Moorlag M, Huskens D, Remijn JA, Bloemen S, Lancé MD, De Laat B. Hypobaric Hypoxia Causes Elevated Thrombin Generation Mediated by FVIII that is Balanced by Decreased Platelet Activation. Thrombosis and haemostasis. 2018 May;118(05):883-92.
7. Nair V, Yanamandra U, Kumud R, Ghosh K. PAI-1 polymorphism as a cause of severe high altitude associated arteriovenous thrombosis. BMJ case reports. 2016 Nov 23;2016.
8. Anand AC, Jha SK, Saha A, Sharma V, Adya CM. Thrombosis as a complication of extended stay at high altitude. National Medical Journal of India. 2001 Jan 1;14(4):197-201.
9. Cheng S, Chng SM, Singh R. Cerebral venous infarction during a high altitude expedition. Singapore Med J. 2009 Aug 1;50(8):e306-8.
10. Torgovicky R, Azaria B, Grossman A, Eliyahu U, Goldstein L. Sinus vein thrombosis following exposure to simulated high altitude. Aviation, space, and environmental medicine. 2005 Feb 1;76(2):144-6.
11. Boulos P, Kouroukis C, Blake G. Superior sagittal sinus thrombosis occurring at high altitude associated with protein C deficiency. Acta haematologica. 1999;102(2):104-6.
12. Hassan KM, Kumar D. Reversible diencephalic dysfunction as presentation of deep cerebral venous thrombosis due to hyperhomocysteinemia and protein S deficiency: Documentation of a case. Journal of neurosciences in rural practice. 2013 Apr;4(2):193.
13. Shrestha P, Basnyat B, Küpper T, van der Giet S. Cerebral venous sinus thrombosis at high altitude. High altitude medicine & biology. 2012 Mar 1;13(1):60-2.
14. https://www.nytimes.com/2010/05/23/sports/23guides.html
15. Kim JH, Kim SJ, Kim HY. Right Hand Weakness and Headache During Ascent to Mount Everest: A Case of Cerebral Venous Infarction. The neurologist. 2017 May 1;22(3):98-100.
16. Ye DP, Zhang SL, Xu QH, Wei LJ. A case of Galen vein thrombosis occurring after bilateral acetabular fractures in the Tibet plateau–what can we learn?. Chinese Journal of Traumatology. 2017 Oct 1;20(5):308-10.
17. Nair V, Mohapatro AK, Sreedhar M, Indrajeet IK, Tewari AK, Anand AC, Mathew OP. A case of hereditary protein S deficiency presenting with cerebral sinus venous thrombosis and deep vein thrombosis at high altitude. Acta haematologica. 2008;119(3):158-61.
18. Grabe HM, Bapuraj JR, Wesolowski JR, Parmar H, Trobe JD. Homonymous hemianopia from infarction of the optic tract and lateral geniculate nucleus in deep cerebral venous thrombosis. Journal of Neuro-Ophthalmology. 2012 Mar 1;32(1):38-41.
19. Saito S, Tanaka SK. A case of cerebral sinus thrombosis developed during a high-altitude expedition to Gasherbrum I. Wilderness & environmental medicine. 2003 Dec 1;14(4):226-30.
20. Segler CP. Prophylaxis of climbers for prevention of embolic accidents. Medical hypotheses. 2001 Oct 1;57(4):472-5.
21. Gupta N, Sahu A, Prabhakar A, Chatterjee T, Tyagi T, Kumari B, Khan N, Nair V, Bajaj N, Sharma M, Ashraf MZ. Activation of NLRP3 inflammasome complex potentiates venous thrombosis in response to hypoxia. Proceedings of the National Academy of Sciences. 2017 May 2;114(18):4763-8.
22. Preckel D, von Känel R. Regulation of hemostasis by the sympathetic nervous system: any contribution to coronary artery disease?. Heart Drug. 2004;4(3):123-30.
23. Polderman KH. Hypothermia and coagulation. InCritical Care 2012 Apr (Vol. 16, No. 2, p. A20). BioMed Central.

24. Hashami L, Rakhshan V, Karimian H, Moghaddasi M. Diagnostic Value of D-Dimer's Serum Level in Iranian Patients with Cerebral Venous Thrombosis. Neurology international. 2016 Jun;8(2):6310-.
25. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke. 2004 Mar 1;35(3):664-70.
26. Song SY, Asaji T, Tanizaki Y, Fujimaki T, Matsutani M, Okeda R. Cerebral thrombosis at altitude: its pathogenesis and the problems of prevention and treatment. Aviation, space, and environmental medicine. 1986 Jan;57(1):71-6.
27. Skaiaa SC, Stave H. Recurrent sagittal sinus thrombosis occurring at high altitude during expeditions to Cho Oyu. Wilderness & environmental medicine. 2006 Jun 1;17(2):132-6.
28. Stam J. Thrombosis of the cerebral veins and sinuses. New England Journal of Medicine. 2005 Apr 28;352(17):1791-8.
29. Luo Y, Tian X, Wang X. Diagnosis and Treatment of Cerebral Venous Thrombosis: A Review. Frontiers in aging neuroscience. 2018 Jan 30;10:2.
30. Paliwal AK, Gupta M, Peeyush P, Sharma V. Imaging the diverse presentations of cerebral venous thrombosis occurring at high altitude area in Armed Forces personnel: Case series. Medical Journal Armed Forces India. 2018 May 28.
31. Dmytriw AA, Song JS, Yu E, Poon CS. Cerebral venous thrombosis: state of the art diagnosis and management. Neuroradiology. 2018 May 11:1-7.
32. Ferro JM, Bousser MG, Canhão P, Coutinho JM, Crassard I, Dentali F, di Minno M, Maino A, Martinelli I, Masuhr F, de Sousa DA. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis–endorsed by the European Academy of Neurology. European Stroke Journal. 2017 Sep;2(3):195-221.

Conflict of interest: Author declares no conflict of interest.
Funding disclosure: Nil

Author's contribution:
Maryam J Syed; concept, data collection, data analysis, manuscript writing, manuscript review
Wasim Alamgir; concept, manuscript writing, manuscript review
Syed Danish Naseem; data collection, data analysis, manuscript writing, manuscript review
Mohammad Wasay: concept, data collection, data analysis, manuscript writing, manuscript review