Case Report

Reversible diencephalic dysfunction as presentation of deep cerebral venous thrombosis due to hyperhomocysteinemia and protein S deficiency: Documentation of a case

Kaukab Maqbool Hassan, Dheeraj Kumar

Department of Neurology, Command Hospital, Alipore, Kolkata, India

ABSTRACT

A 45-year-old man presented with global headache, vomiting and abnormal behavior after cross-country run at high altitude. There was no seizure, loss of consciousness, fever or head injury. He was conscious, abulic and uncooperative with normal vitals. There was no focal neurological deficit. Non contrast computed tomography scan of head was normal. Magnetic resonance imaging of brain showed venous infarct in bilateral thalami, left basal ganglia and periventricular white matter. Magnetic resonance venography revealed thrombosis involving internal cerebral veins, septal veins, thalamostriate veins, vein of Galen and proximal portion of straight sinus. His condition steadily improved on low molecular weight heparin bridged with oral anticoagulation for one year. At two months, serum homocysteine was 31.51 µmol/l (5.46-16.2 µmol/l) and protein S was 49.00% (77-143.00%). He received methylcobalamin, pyridoxine and folic acid. After 16 months, he was asymptomatic with partially recanalized deep cerebral veins and serum homocysteine falling to 16.50 µmol/l (5.46-16.2 µmol/l).

Key words: Deep cerebral venous thrombosis, headache, hyperhomocysteinemia, protein S deficiency, vasogenic edema

Introduction

Diagnosis of cerebral venous thrombosis (CVT) is commonly overlooked or delayed because of the remarkable diversity of its clinical symptoms, modes of onset, and neuroimaging signs.[1] Hyperhomocysteinemia is an independent risk factor for CVT, increasing the risk four to seven fold.[2,3] There are anecdotal reports of high altitude as cause of CVT.[4] Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) pattern in venous infarcts is very different from that of arterial infarcts, being mostly suggestive of vasogenic edema, which probably explains the much better recovery after CVT.[1]

Access this article online	
Quick Response Code:	Website: www.ruralneuropractice.com
	DOI: 10.4103/0976-3147.112767

We document a case of reversible diencephalic dysfunction due to deep cerebral venous thrombosis (DCVT) caused by hyperhomocysteinemia and protein S deficiency, probably precipitated by dehydration and extreme cold at high altitude.

Case Report

A 45-year-old man, alcohol consumer, non-smoker, without co-morbidities, presented with abnormal behavior for 3 days and global headaches with vomiting for 6 days developing few hours after a cross-country run of 13 km at 7,000 ft. There was no seizure, loss of consciousness, fever or head injury. He was afebrile, conscious, abulic and uncooperative with normal vitals. Rest of the examination was normal.

A non contrast computed tomography scan of head was normal. Magnetic resonance imaging (MRI) brain showed hyperintense signal in bilateral thalami, left basal ganglia and periventricular white matter on T1 and T2-weighted images (T1WI, T2WI) and fluid attenuated inversion recovery image (FLAIR), and hyperintense internal cerebral

Address for correspondence:
Col K M Hassan, Department of Neurology, Command Hospital, Alipore, Kolkata - 700 027, India. E-mail: kaukabm.hassan@gmail.com

veins suggestive of subacute thrombosis [Figure 1a and b]. DWI revealed heterogeneous signal intensity without hypointensity on ADC map corresponding to vasogenic edema [Figure 2a and b]. Gradient echo image showed susceptibility artefacts compatible with hemorrhagic component of venous infarct [Figure 2c]. Magnetic resonance venography (MRV) did not reveal the deep venous system, which was visualized on T1WI indicating thrombosis, while superior sagittal and lateral sinuses were patent [Figure 3].

His condition steadily improved on low molecular weight heparin (LMWH) bridged with acitrom. Mini mental status examination improved from 20/30 to 29/30 by 3 weeks. At 2 months, he was asymptomatic with serum homocysteine of 31.51 μmol/l (5.46-16.2 μmol/l), and at this time, after discontinuation of acitrom for 2 weeks, the protein S was 49.00% (77-143.00%), and protein C 118.40% (70-140.00%); factor V Leiden mutation, methylene tetrahydrofolate reductase (MTHFR) gene mutation (C677T) and prothrombin gene G20210A mutation were not detected. Anti-phospholipid IgG antibody was 4.53 GPL U/ml (0.5-10.0) and IgM antibody was 2.77 MPL U/ml (0.5-10.0). Anti-neutrophil cytoplasmic antibody and rheumatoid factor were negative.

He was treated with methylcobalamin, pyridoxine and folic acid. Oral anticoagulation was continued for 1 year only. After 16 months, he remained asymptomatic with normal MRI brain [Figure 4] and partially recanalized deep cerebral venous system on MRV, and serum homocysteine fell to 16.50 μmol/l (5.46-16.2 μmol/l).

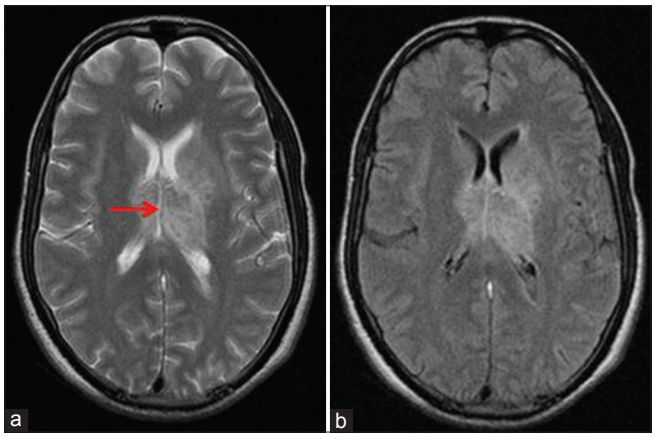

Figure 1: T2WI and FLAIR MRI sequences showing abnormal hyperintensity in the thalamus bilaterally, extending into left basal ganglia and periventricular white matter (a, b respectively), hyperintense signal on T2WI in the internal cerebral veins diagnostic of thrombosis of the deep venous system (red arrow) (a)

Discussion

Clinical severity of CVT depends on extent of thrombosis, territory of involvement, establishment of venous collaterals, and chronicity of thrombus.[5] Patients with chronic course, unlike those with acute onset, may show papilledema on fundoscopy. Isolated thrombosis of the different sinuses and veins results in diverse clinical pictures.[1] Patients with isolated thrombosis of the lateral sinus present mostly as isolated intracranial hypertension characterized by headache and papilledema or diplopia (caused by sixth nerve palsy) even without other focal neurological signs.[1,6] DCVT, the least common form of CVT, can present as neurological emergency with life-threatening bilateral destruction of thalamus, basal ganglia, and subcortical white matter.[7] The natural course for DCVT can be dismal, being often diagnosed only at postmortem examination, with survivors often suffering severe neurologic compromise.[5]

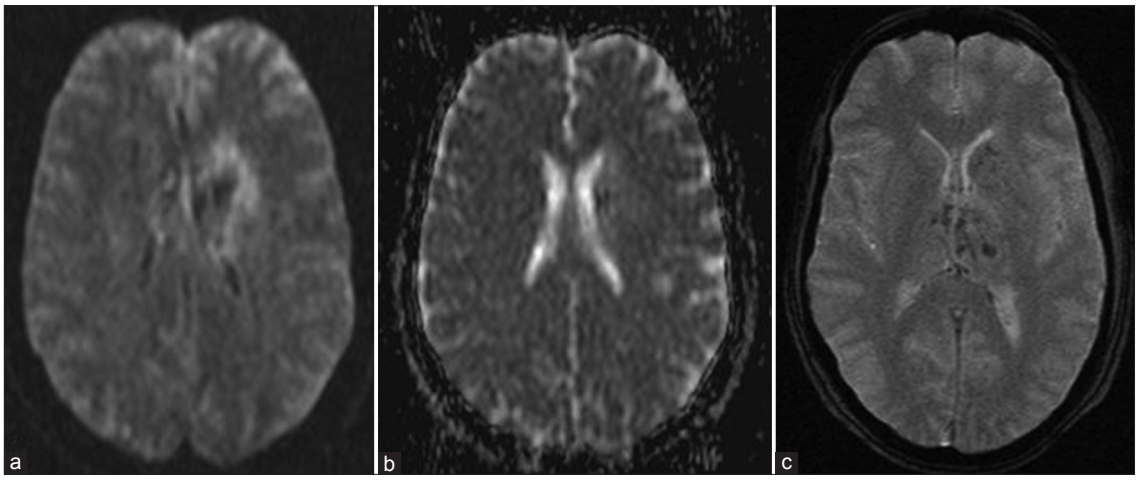

Figure 2: Diffusion-weighted imaging showing heterogenous signal intensity in region of left thalamus, basal ganglia and periventricular white matter (a), Apparent diffusion coefficient map showing near normal signal intensity without evidence of diffusion restriction (b), Gradient echo image showing susceptibility artefacts in the left thalamus and basal ganglia compatible with hemorrhagic component of venous infarct (c)

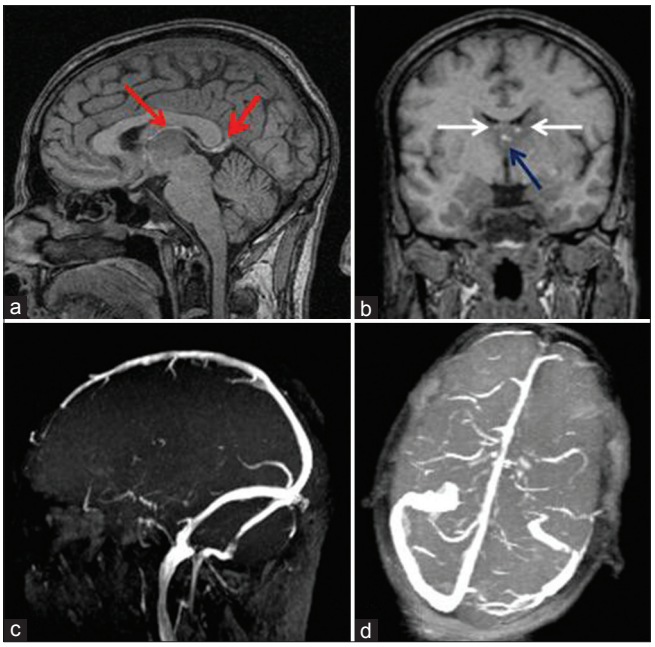

Figure 3: Hyperintense signal in internal cerebral vein (thin red arrow) and vein of Galen (thick red arrow) diagnostic of thrombosis of deep venous system on sagittal T1WI (a), hyperintense signal in both thalamostriate veins (white arrows) and internal cerebral vein (blue arrow) diagnostic of thrombosis of deep venous system on axial T1WI (b), MRV shows absent flow in the deep cerebral veins (c), with patent sagittal and transverse sinuses (c, d)

In a retrospective review of 49 patients with DCVT, the presenting features were confusion, coma, or mental status changes (76%); headache (63%); nausea and/or vomiting (41%); hemiparesis (33%); seizure (14%); fever (12%); papilledema (10%); and aphasia (6%).[8] Isolated mental status changes may be the only presentation as in this case. DCVT should be considered in the differential diagnosis of unexplained coma, akinetic mutism, abulia, and bilateral thalamic lesions due to meningitis, encephalitis, and basilar artery stroke.[7] It is possible for patients to recover, if collateral venous drainage develops.[5]

Many medical, surgical and obstetric disorders can either cause or predispose to CVT [Table 1].[1,6,9] Thrombophilia screening for coagulation factor abnormalities and presence of antiphospholipid antibodies is recommended in diagnostic work up.[2] Recent studies have emphasized the role of hyperhomocysteinemia in CVT.[2,3] Hyperhomocysteinemia results from interaction between genetic and acquired determinants such as deficiencies of folic acid, pyridoxine, and cobalamin which are involved in the metabolic pathways of homocysteine.[2] DCVT has been documented in a lady taking oral contraceptive who was found to have protein C deficiency,[7] and in early pregnancy due to protein S deficiency.[10]

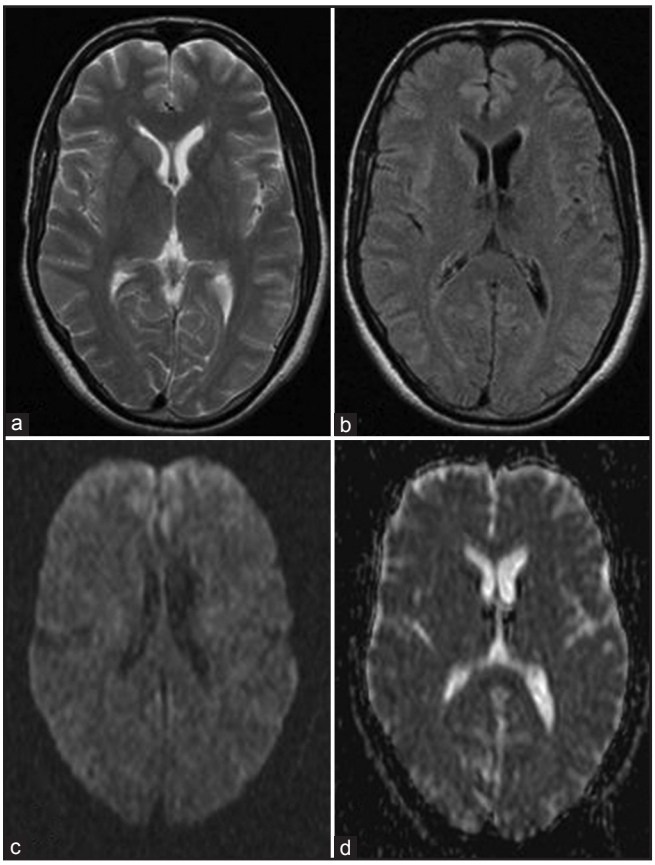

Figure 4: Normal appearing T2WI (a) and small area of gliosis in both thalami on FLAIR image (b), normal DWI and ADC images at 16 months follow-up (c, d)

MRI confirms the diagnosis of DCVT by demonstrating clot in the deep cerebral veins.[7] The gold standard for diagnosis is the combination of MRI to visualize the thrombosed vessel and MRV to detect non-visualization of the same vessel,[1] as was seen in this patient [Figure 3]. T1WI and T2WI may be normal in up to 30% of cases, and in other patients localized or diffuse brain swelling with abnormal signal suggestive of edema, infarction, or haemorrhage may be found. Various patterns have been reported on DWI in CVT.[1] Extensive diminution of the ADC from cytotoxic edema is irreversible in arterial infarct while vasogenic edema in venous infarct from disruption of blood-brain barrier is reversible,[11] as in our patient [Figures 1, 2, and 4]. On ADC map, the most common pattern in CVT is a heterogeneous signal intensity with normal or increased ADC value corresponding to vasogenic edema and far less commonly cytotoxic edema.[1,11] The MR features in this case reflect the underlying pathophysiology of venous congestion with impaired but viable neuronal tissue.

In a retrospective review of treatment outcome for DCVT, heparin or local thrombolysis was associated with improved survival-mortality of 13% versus 48% for

Table 1: Prothrombotic states predisposing to cerebral venous thrombosis with specific diagnostic tests

Prothrombotic states	Specific diagnostic test(s)
Genetic prothrombotic states	
Antithrombin III deficiency	Plasma based assay done at least 6 weeks after onset of CVT
Protein C deficiency	
Protein S deficiency	
Factor V Leiden Mutation	Surrogate test for activated protein C resistance or factor V Leiden mutation study
Prothrombin G20210A mutation	Prothrombin G20210A mutation study
Hyperhomocysteinemia	Serum homocysteine assay
Acquired prothrombotic states	
Puerperium	-
Pregnancy	-
Antiphospholipid antibody syndrome	For lupus anticoagulant, activated partial thromboplastin time and dilute Russell viper venom time.
	Anti-cardiolipin antibodies IgG, Ig M, IgA.
	Laboratory testing should be done on 2 or more occasions at least 12 weeks apart
Hyperhomocysteinemia	Serum homocysteine, B12, folic acid assays
Dehydration	Tests relevant to underlying condition
Nephrotic syndrome	
Malignancy	
Elevated Factor VIII, von Willebrand's factor	
Other prothrombotic states	
Inracranial infections	
Connective tissue diseases	
Hematological malignancies	
Paroxysmal nocturnal hemoglobinuria	
Drugs – androgens, danazol, oral contraceptive pills, L-asparaginase, tamoxifen	
Trauma – head injury, neurosurgical procedures	

"untreated" patients, despite similar initial severity and time to treatment in both groups. Most survivors had full recovery or only mild disability,[12] as our patient of DCVT. Vitamin supplementation with folic acid, pyridoxine, and cobalamin lowers the plasma levels of homocysteine in most cases.[2] In our patient homocysteine reached normal level with vitamin replacement, though the clinical significance of this is not known.[2] Vitamin K antagonists may be continued for 3 to 6 months, keeping target INR of 2.0 to 3.0, in patients with provoked CVT (associated with a transient risk factor), while these may be continued for 6 to 12 months in patients with unprovoked CVT. For patients with recurrent CVT, venous thromboembolism after CVT, or first CVT with severe thrombophilia (i.e., homozygous prothrombin G20210A; homozygous factor V Leiden; deficiencies of protein C, protein S, or antithrombin; combined thrombophilia defects; or antiphospholipid syndrome), indefinite anticoagulation may be considered.[6] Since, our patient possibly had transient risk factors in form of dehydration in setting of extreme cold, he was anticoagulated for 12 months for isolated protein S deficiency.

In conclusion, differential diagnosis of subacute encephalopathy should include DCVT, since early diagnosis and treatment are gratifying. This case documents the rare association of protein S deficiency and hyperhomocysteinemia as causes of DCVT probably precipitated by dehydration due to exertion at high altitude. This case also emphasizes that DCVT can produce extensive venous congestion and vasogenic edema without early infarction and demonstrates that excellent clinical recovery from DCVT is possible with timely anticoagulation.

References

1. Bousser MG, Ferro JM. Cerebral venous thrombosis: An update. Lancet Neurol 2007;6:162-70.
2. Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. Blood 2003;102:1363-6.
3. Ventura P, Cobelli M, Marietta M, Panini R, Rosa MC, Salvioli G. Hyperhomocysteinemia and other newly recognized inherited coagulation disorders (factor V leiden and prothrombin gene mutation) in patients with idiopathic cerebral vein thrombosis. Cerebrovasc Dis 2004;17:153-9.
4. Basnyat B, Cumbo TA, Edelman R. Acute medical problems in the Himalayas outside the setting of altitude sickness. High Alt Med Biol 2000;1:167-74.
5. Spearman MP, Jungreis CA, Wehner JJ, Gerszten PC, Welch WC. Endovascular thrombolysis in deep cerebral venous thrombosis. AJNR Am J Neuroradiol 1997;18:502-6.
6. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, *et al*. Diagnosis and Management of Cerebral Venous Thrombosis: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2011;42:1158-92.
7. Gladstone DJ, Silver FL, Willinsky RA, Tyndel FJ, Wennberg R. Deep cerebral venous thrombosis: An illustrative case with reversible diencephalic dysfunction. Can J Neurol Sci 2001;28:159-63.
8. Crawford SC, Digre KB, Palmer CA, Bell DA, Osborn AG. Thrombosis of the deep venous drainage of the brain in adults: Analysis of seven cases with review of the literature. Arch Neurol 1995;52:1101-8.
9. Leys D, Cordonnier C. Cerebral venous thrombosis. Ann Indian Acad Neurol 2008;11:S79-87.
10. Burneo JG, Elias SB, Barkley GL. Cerebral venous thrombosis due to protein S deficiency in pregnancy. Lancet 2002;359:892.
11. Keller E, Flacke S, Urbach H, Schild HH. Diffusion-and perfusion-weighted magnetic resonance imaging in deep cerebral venous thrombosis. Stroke 1999;30:1144-6.
12. Smith AG, Cornblath WT, Deveikis JP. Local thrombolytic therapy in deep cerebral venous thrombosis. Neurology 1997;48:1613-9.

How to cite this article: 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. J Neurosci Rural Pract 2013;4:193-6.
Source of Support: Nil. **Conflict of Interest:** None declared.