International Journal of Clinical and Experimental Neurology, 2017, Vol. 5, No. 1, 5-8
Available online at http://pubs.sciepub.com/ijcen/5/1/2
©Science and Education Publishing
DOI:10.12691/ijcen-5-1-2

Hyper Homocysteinemia Related Cerebral Venous Sinus Thrombosis –Presenting as Generalised Tonic-Clonic Seizure –A Case Report

Soumyabrata Roy Chaudhuri[1,*], Deep Das[2], Subhayan Bhattacharya[3], Subhankar Chakraborty[4], Kingshuk Bhattacharjee[5]

[1]Senior Registrar, KPC Medical College, 1F, Raja Subodh Chandra Mullick Road Jadavpur, Kolkata West Bengal, India
[2]Consultant Neurologist, Woodlands Hospital, Alipore Road, Alipore, Kolkata, West Bengal, India
[3]Post Graduate Trainee, Dept. of Tropical Medicine, School of Tropical Medicine, Chittaranjan Avenue, Kolkata, West Bengal, India
[4]Consultant Internist, Anandalok Hospital, D.K.7/3Salt lake City, Kolkata, West Bengal, India
[5]Assistant Manager, Medical Services, Biocon LTD, Kolkata
*Corresponding author: soumya.academics@gmail.com

Abstract Cerebral venous sinus thrombosis (CVST) is a neuromuscular disorder with protean manifestation requiring a high index of suspicion. Early diagnosis is sometimes lifesaving. It is particularly challenging is to establish an accurate etiology as it guides the clinician for long term thrombo-prophylaxis. We report a young female with no conventional risk factors for CVST, who presented with headache, generalised seizures and prolonged loss of consciousness. Her work-up revealed an elevated serum homocysteine level which might be a possible causative association in the etiopathogenesis of this neuromuscular condition.

Keywords: *hyperhomocysteinemia, young, female, CVST*

Cite This Article: Soumyabrata Roy Chaudhuri, Deep Das, Subhayan Bhattacharya, Subhankar Chakraborty, and Kingshuk Bhattacharjee, "Hyper Homocysteinemia Related Cerebral Venous Sinus Thrombosis –Presenting as Generalised Tonic-Clonic Seizure –A Case Report." *International Journal of Clinical and Experimental Neurology*, vol. 5, no. 1 (2017): 5-8. doi: 10.12691/ijcen-5-1-2.

1. Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon form of cerebrovascular stroke that mostly affects young adults and can be precipitated by a variety of conditions [1,2,3]. The clinical symptoms may vary from severe headache (70-90%), focal lateralized signs (25%-75%), seizures (30-40%) as well as behavioral symptoms such as delirium, amnesia, and disturbances in consciousness. In some of the patients the clinical symptoms develop slowly whereas in a few the symptoms are non-specific requiring a high index of clinical suspicion to pick up the diagnosis. Therefore, it is not too unjustified that there does not exist a definite clinical syndrome [4].

In European population, the estimated annual incidence is 3-4 cases per million and three fourth of the adult cases are seen in women [5], although data from Indian sub-continent is scanty. The common associations are procoagulant states like infections, neoplasm, pregnancy, puerperium, systemic diseases, oral contraceptive (OCP) use, dehydration, hyper viscosity and coagulopathies. Female preponderance is attributed to gender specific risk factors (GSRF) such as OCP use, pregnancy and hormone replacement therapy (HRT). [6] Behcet's syndrome is reported as an important causative factor of CVST (33% -36%) from the Middle East countries (Persian Gulf region, North Africa and Turkey mainly). Among the cerebral venous sinuses the superior sagittal sinus (SSS) and the transverse sinuses are the most frequently affected with affection rates of 72% and 70% respectively. More than one sinus is affected in one third of the patients [7], and multiple sinus thrombosis usually bears a greater case fatality rate [8] We report on an young female, without GSRF, who developed SSS thrombosis and in whom relevant investigations related to known etiological factors were found to be normal except for a moderately elevated serum homocysteine level.

2. Case Report

A 38 year old Indian female without significant medical comorbidities was admitted to the Intensive Care Unit with history of recent onset severe headache, followed by generalised tonic-clonic seizures with loss of consciousness for the next 24 hours. She was normotensive and not on OCP. CNS (central nervous system) examination of the obtunded patient including fundoscopy revealed bilateral up going plantar response. Plain CT (computed tomography) head revealed bilateral limited fronto-parietal hypo densities. She was started on intravenous anticonvulsants and osmotic agents but had a breakthrough seizure 30 hours post-ictus and remained

obtunded for another eight hours. After regaining consciousness, she had slurred incoherent speech, with impaired recognition and orientation. She improved gradually and a CE (contrast enhanced) MRI was done which showed altered signal intensities at bilateral high frontal regions. Blood biochemistry, hematology and collagen profiles were within normal limits. CSF (cerebro spinal fluid) analysis was also normal. (Table 1).

Post stabilization, she was switched to oral anticonvulsants. Her speech and orientation improved and normalized over time. A low grade persistent headache however remained, which prompted a radiology review raising possibility of thrombus in the superior sagittal sinus (SSS) –empty delta sign depicted by arrow in Figure 1.

Table 1. Initial Pertinent Laboratory Investigations

TEST REPORT STATUS	RESULT (Patients' Value)	BIOLOGICAL REFERENCE INTERVAL
BLEEDING TIME	01 MIN 15 SEC	2-9 min
CLOTTING TIMRE 03 MIN 25 SEC	03 MIN 25 SEC	2-4 SEC
PLATELET COUNT	350 x 10^9/L	150-400 x 10^9/L
INTERNATIONAL NORMALISED RATIO	1.08	0.9-1.2
TSH (THYROID STIMULATING HORMONE)	4.67 mIU/L	0.5-5 mIU/L
FREE T4	0.905 ng/mL	0.77-1.55 ng/mL
TOTAL LEUCOCYTE COUNT	10.6 x 10^9/L	4-10 x 10^9/L
NEUTROPHIL	6.7 x 10^9/L	2-8 x 10^9/L
ESR	50 mm/hr	< 30 mm/hr
C REACTIVE PROTEN (CRP)	32 mg/dL	< 3 mg/dL
SODIUM	141 mmol/L	135-145 mmol/L
POTASSIUM	4.6 mmol/L	3.5-5 mmol/L
CPK (CREATININE KINASE)	504 mcg/L	10-120 mcg/L
GLYCOSYLATED HAEMOGLOBIN	5.5%	< 5.7%
ANF (hep2)	NEGATIVE	
SERUMCREATININE	0.68	0.5-1.1 mg/dL
AntidsDNA	NEGATIVE	
pANCA	NEGATIVE	
C ANCA	NEGATIVE	
TOTAL CHOLESTEROL	193 mg/dl	< 200 mg/dL
LOW DENSITY LIPOPROTEIN	112mg/dL	< 100 mg/dL
HIGH DENSITY LIPOPROTEIN	45 mg /dl	> 60 mg/dL
TRIGLYCERIDE	180mg/dl	< 150 mg/dL

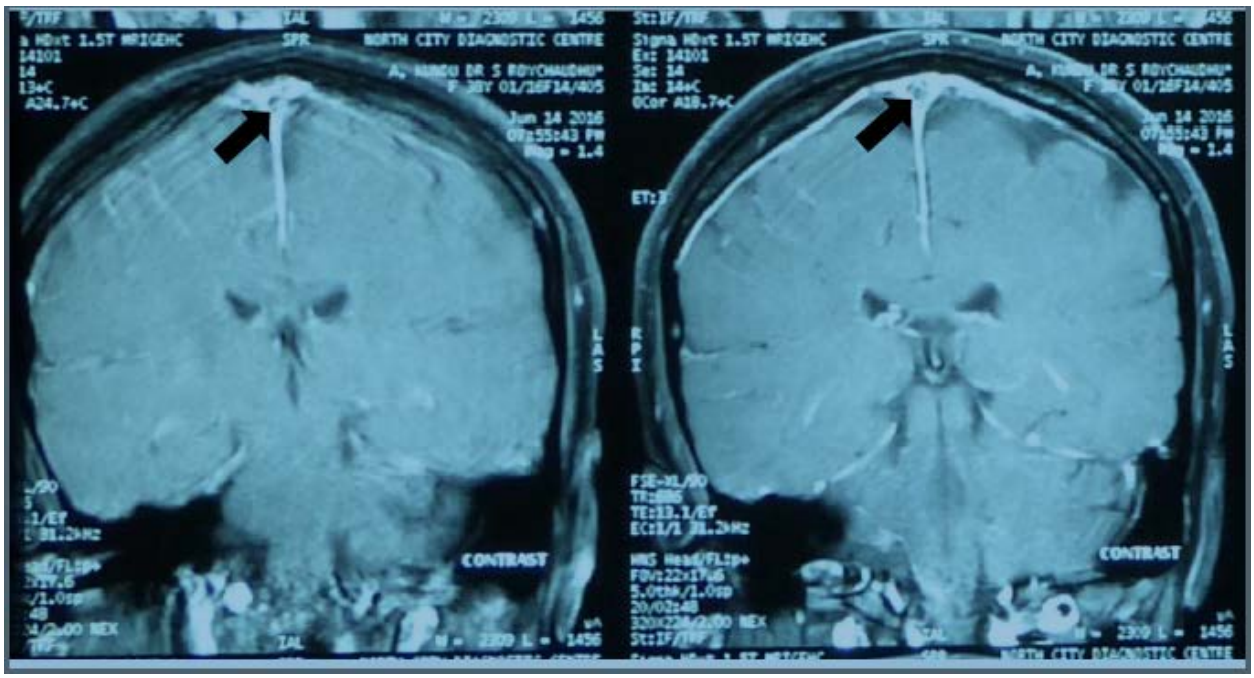

Figure 1. Contrast enhanced MRI of brain revealing empty delta sign (arrow)

Table 2. Pertinent Laboratory Investigations

TEST REPORT STATUS	RESULTS	BIOLOGICAL REFERENCE INTERVAL
PROTEIN C ACTIVITY, PLASMA	135	67 -195
PROTEIN S ACTIVITY, PLASMA	64	55 - 123
PTT (TEST)	31.9	30.0 - 43.0
DRVV SCREEN (TEST)	38.2	30.0 – 43.0
LUPUS ANTICOAGULANT	ABSENT	ABSENT
ANTI PHOSPHOLIPID IGG ANTIBODIES,SERUM	2.9	NORMAL RANGE : <12
HOMOCYSTEINE, SERUM / PLASMA	19.36	HIGH WITH FOLATE SUPPLEMENTATION <12 WITHOUT FOLATE SUPPLEMENTATION <15
ANTITHROMBIN ACTIVITY, PLASMA	120	70 -122
ANTI – PHOSPHOLIPID IGM ANTIBODY, SERUM	1.5	NORMAL RANGE : <12

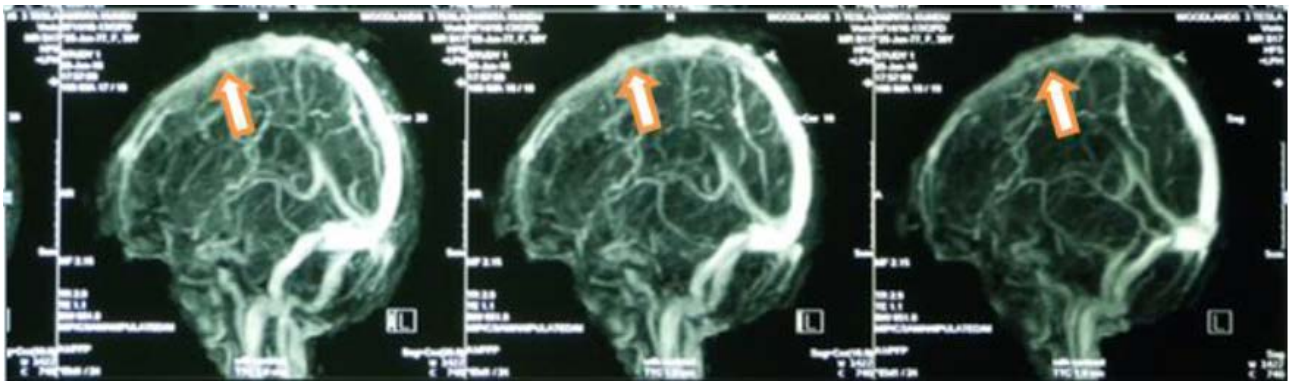

Figure 2. Contrast enhanced Magnetic resonance venogram revealed residual thrombosis in the superior sagittal sinus

Meanwhile her serum pro-coagulation profile reports became available which revealed elevated levels of serum homocysteine (Table 2).

A contrast enhanced MR venogram was then done which showed *thrombi filling the central part of superior sagittal sinus* (Figure 2). The patient was started on weight adjusted low molecular weight heparin and over the next week was switched to oral anticoagulation and is doing well till her last follow-up till six months.

3. Discussion

Homocysteine is an alpha amino acid which originated primarily from methionine which is a by- product of protein metabolism. Under normal condition homocysteine is converted to cystathione and then to cysteine (via the transulfuration pathway requiring enzyme cystathione beta synthase) which is then excreted via the urinary route. Vitamin B6 is required as a co-factor in this pathway. Deficiency of the enzyme cystathione beta synthase thus causes homocysteinuria, an inborn error of metabolism. There is another pathway namely the remethylation pathway which requires methylene tetrahydrofolate reductase (from folate metabolism) which helps methionine synthetase to convert homocysteine back to methionine .Vitamin B 12 is a cofactor in this reaction and any pathology in this pathway leads to hyperhomocysteinemia.

There are many conditions predisposing to CVST, which may be seen alone or in combination. The known conditions are sinusitis, trauma, surgery, hypercoagulable states (antiphospholipid syndrome, protein C and protein S deficiency, anti-thrombin deficiency, vasculitis, pregnancy, puerperium, usage of OCPs, nephrotic syndrome, malignancy etc.

Arterial vascular disease and lower limb deep vein thrombosis has a direct correlation with hyperhomocysteinemia and the strength of the correlation is well established. Many studies have also looked at the role of hyperhomocysteinemia in venous thromboembolism (VTE) [9,10,11,12].

Association of CSVT and hyperhomocysteinemia however remains putative. It has been observed in a study trail in patients' with proven CSVT the total homocysteine remains an independent risk factor for CSVT when a multivariate analysis is performed. [13]. Of interest is the observation by this authors that a significant association exist between a post methionine (PMC) load increments of homocysteine in subjects with CSVT. A homozygous state for MTHFR mutation was also looked into, but failed to reach statistical significance in multivariate analysis. When confounding risk factors like smoking, factor 5, liden mutation, anti-phospholipid antibodies were eliminated, the odds ratio (OR) for CSVT with isolated homocysteinemia was 5.2. However, whether higher levels of total homocysteine translated into more severe or significant disease pattern remains to be ascertained.

4. Conclusion

The reported case highlights the absence of conventional procoagulant risk factors and other known precipitants of CVST thus tempting to classify this as an idiopathic or cryptogenic CVST. However, presence of an elevated homocysteine level might serve as a pointer towards a cause-effect relationship. Further large scale prospective studies are required to evaluate the importance of estimation of serum homocysteine level in cases of CVST, especially where a clear risk factor has not been identified.

If such a relationship were to be found, it might have an implication on the risk of recurrence and duration of anti-coagulation therapy along with folate and vitamin B12 supplementation in this group of patients.

Limitations

The case in discussion is an isolated case and has low level of evidence. It is only an effort to stimulate interest in the mind of the reader about the various established and yet to be proven novel risk factors in this not so common condition which may be potentially life threatening.

Conflicts of Interest

All authors declare that none of them have any potential conflicts of interest with regard to the present case report.

Consent Form

Patient consent form has been procured prior to the case report study. The patient's identity has not been disclosed at any point of time.

References

[1] Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008; 117: 93-102.

[2] Stam J. Thrombosis of the cerebral veins and sinuses. New Engl J Med. 2005;352:1791-98.

[3] Allroggen H, Abbott RJ. Cerebral venous sinus thrombosis. Postgrad Med J. 2000; 76:12-15

[4] Ozcan TA, Meral H, Ozben S, Tiras R, Hakyemez H, Ozturk O, Mutlu A, Balci BP, Cokar O and Ozer F. Cerebral venous sinus thrombosis: gender differences in ten years' experience. Düşünen Adam: The Journal of Psychiatry and Neurological Sciences.2013; 26 (3), 281-258

[5] Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005; 352:1791-8.

[6] Amoozegar F, Ronksley PE, Sauve R, Menon BK. Hormonal Contraceptives and Cerebral Venous Thrombosis Risk: A Systematic Review and Meta-Analysis. Frontiers in Neurology. 2015;6:7.

[7] Hussain ME, Momin A, Mahmudul Islam M, Haque SKR, Sharmin Jahan S, Hoque MH. A Young Man with Cerebral Venous Thrombosis and Hyperhomocystinemia. *American Journal of Medical Case Report., 2016; 4:(4): 115-117.*

[8] Patil VC, Choraria K, Desai N, and Agrawal S. Clinical profile and outcome of cerebral venous sinus thrombosis at tertiary care center. J Neurosci Rural Pract. 2014 ;5(3): 218-224.

[9] den Heijer M, Koster T, Blom HJ, Bos GM, Briet E, Reitsma PH, Vandenbroucke JP, Rosendaal FR. Hyperhomocysteinemia as a Risk Factor for Deep-Vein Thrombosis. *N Engl J Med.* 1996; 334:759-762.

[10] Simioni P, Prandoni P, Burlina A, Tormene D, Sardella C, Ferrari V, Benedetti L, Girolami A. Hyperhomocysteinemia and deep-vein Thrombosis. A case-control study. *Thromb Haemost*. 1996; 76:883-6.

[11] Brattström L, Tengborn L, Lagerstedt C, Israelsson B, Hultberg B. Plasma homocysteine in venous thromboembolism. *Haemostasis*. 1991; 21: 51-57.

[12] Amundsen T, Ueland PM, Waage A. Plasma homocysteine levels in patients with deep venous thrombosis. *Arteriosclerosis Thrombosis and Vascular Biology* 1995; 15: 1321-1323.

[13] Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, & Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. Blood 2003; 102(4), 1363-1366. Accessed March 04, 2017.