



A Rare Case of Cerebral Venous Sinus Thrombosis (CVST) Induced by Norethisterone Enanthate: Report from a Medical University Hospital in Bangladesh

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Abstract

Cerebral Venous Sinus Thrombosis (CVST) is a rare condition and the association between norethisterone enanthate and CVST in the literature has very seldom been reported. In this case report, a 22-year-old unmarried woman of Bangladesh presented with acute onset of headache and vomiting with history of oral intake of 5 mg norethisterone thrice daily during past 2 years for menstrual disorder. She had no history of seizure, visual disturbances, and neck stiffness, imbalance of gait and weakness of any limbs, any sensory complaints or any episode of unconsciousness during the course of illness. Bilateral papilloedema was present with more marked on left eye and serum homocysteine level was high. A brain CT scan, MRI and Magnetic Resonance Venogram (MRV) revealed thrombosed anterosuperior segment of superior sagittal sinus. She was diagnosed to have CVST due to norethisterone and was treated with low molecular weight heparin, followed by Rivaroxaban, Vitamin B12, Vitamin B6 and Folic acid. She made a complete recovery after one month of intake of rivaroxaban and withdrawn of norethisterone.

Keywords: Cerebral venous sinus thrombosis; Norethisterone enanthate; Hyperhomocysteinemia; Rivaroxaban

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Introduction

Cerebral Venous Sinus Thrombosis (CVST) is rare type of stroke with the annual incidence ranging from 0.22 to 1.57 per 100,000 populations, affecting young individuals and mostly women [1-3]. CVST is identified in increasing frequency due to widespread use of CT scan and MRI [1]. The diseases are presented with more varied clinical spectrum because of its wide range of causes and appearance of symptoms [1,4]. The main causes and risk factors associated with CVST are genetic disposition and acquired prothrombotic states (about 85%) often any precipitating factor such as obstructed labour, infections (otitis, mastoiditis, sinusitis, meningitis), inflammatory systemic disorders (SLE, Behcet's syndrome), hematological conditions such as primary and secondary polycythemia, thrombocytopenia, leukemia, drugs mainly oral contraceptives, mechanical trauma such as head injury, lumbar puncture and neurosurgical procedures, cancer, pregnancy, puerperium and dehydration [4]. More than 90% of the patients present most frequent but least specific symptoms like severe headache [5,6], Seizures, focal neurological deficit, altered consciousness and papilloedema, which can be presented either in isolation or in combination with other symptoms [7]. An increase in plasma concentration of homocysteine due to hyperhomocysteinemia disorder is independent and strong risk factors (27% to 43%) [7]. However, in about 15% cases causes are not found. The best methods for diagnosing CVST are CT scan of brain, MRI and magnetic resonance angiography [8]. Low-molecular-weight heparin in acute phase is the first line treatment choice and antiepileptics in patients with an early seizure and if the patient is on contraceptives, contraceptives containing oestrogens should be avoided [8]. In some cases, more aggressive treatment may be required such as local parental thrombolytics, mechanical thrombectomy and decompressive hemicraniectomy [7].

Case Presentation

A 22-year-old unmarried medical student, presented with history of sudden severe throbbing

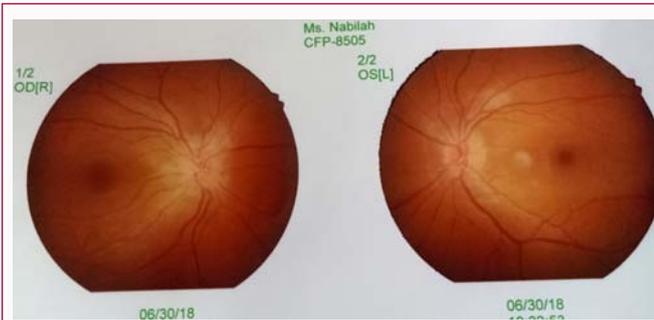


Figure 1: Fundal photograph showing bilateral papilloedema more marked on right eye.

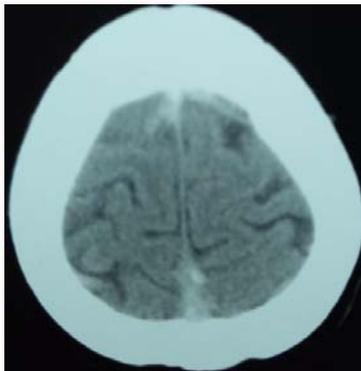


Figure 2: Noncontrast CT scan of brain showing dense clot sign.

headache and several episodes of vomiting ten days back that persisted. Her menstrual cycles were irregular with intermittent episodes of heavy bleeding since menarche. She has been taking norethisterone 5 mg thrice daily for past 2 years as prescribed, which she continued during her recent onset of symptoms. She gave no history of seizure, visual disturbances, imbalance of gait, and weakness of any limbs, any sensory complaints or any episode of unconsciousness during the course of illness. She gave no preceding history of fever, joint pain, skin rash or photosensitivity. No such prior illness or positive family history of such type of illness. No history of diabetes, hypertension, CAD-atherosclerotic disease or stroke. On examination at the time of presentation she was conscious, alert and could move all limbs normally. Vitals were normal. Pupils were 2.5 mm, equally reacting to light, bilateral papilloedema more marked on left eye (Figure 1), deep tendon reflexes were normal, plantar was bilaterally flexor, no neck stiffness was present. Cardio vascular, respiratory and per abdominal examinations were unremarkable.

Investigations

Routine blood investigations including complete blood count, biochemistry were within the normal limits except D-dimer which was $>4 \mu\text{g/mL}$ (reference value $<0.5 \mu\text{g/mL}$), Thrombophilia profile including ANA, anti-PLP antibodies, factor V Leiden mutation were also within normal ranges but serum homocysteine level was elevated ($46.5 \mu\text{mol/L}$). A brain non contrast CT scan showed thrombosis in the posterior portion of the superior sagittal sinus that appeared as a dense triangle, the dense or filled delta sign (Figure 2). Contrast MRI showed a central isodense lesion in superior sagittal sinus with surrounding enhancement (Figure 3). This appearance is the MRI equivalent of the CT-empty delta sign (Figure 4). MRV of brain revealed intermittent foci of non-filling within superior sagittal sinus;

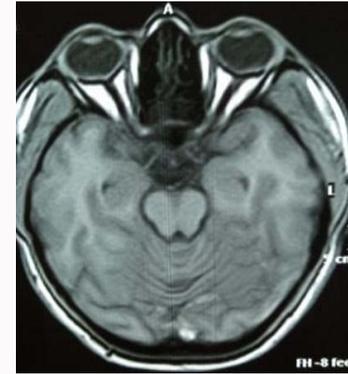


Figure 3: MRI of brain T1WI no cortical.

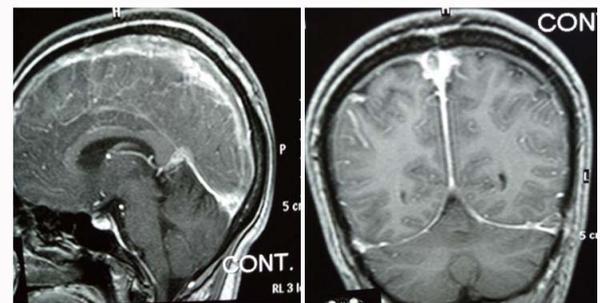


Figure 4: MRI of brain with contrast showing empty delta sign (equivalent delta sign of CT).

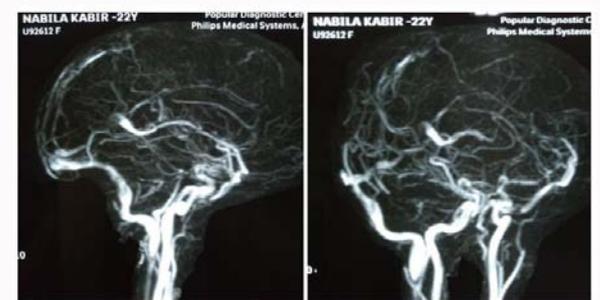


Figure 5: MRV of brain showing intermittent hypointense foci of non-filling are noted within the superior sagittal sinus.

great cerebral veins appeared congested, cortical veins were not adequately visualized (Figure 5).

Treatment

Patient was treated with low molecular weight heparin followed by newer oral anticoagulants, rivaroxaban. Anti-oedema measures were taken until oedema resolved and the patient became asymptomatic. There were no further episodes of headache and vomiting during 10 days stay in the hospital. She was discharged with oral anticoagulants and multivitamins (Vitamin B12, Vitamin B6, Folic acid). She was also advised to avoid prothrombotic conditions such as avoiding norethisterone and was advised to consult with gynecologist for alternate treatment of menorrhagia. The patient followed up after one month and was completely asymptomatic following oral intake of rivaroxaban. Her papilloedema resolved and MRV of brain revealed re-canalization and she was advised to continue oral rivaroxaban for 6 months and continue to avoid Norethisterone.

Discussion

CVST is a rare disease and grave condition leading to disability and death [9]. Bangladesh is a densely populated country, according to the United Nations estimation in 2016 total population was 160 million [10]. If five (05) cases of CVST are developed in one million populations based on current incidence then it is expected that around 815 cases would be reported each year in Bangladesh [3]. Moreover, women of reproductive age between 15 and 49 years, 27% as contraception used oral pill [11] which was 14% in 1983 [12]. In Bangladesh, widely use of oral pill as contraceptive may increase the risk of developing CVST. Several studies have demonstrated cause-and-effect relationship between oral contraceptive and development of CVST, OR 5.6 and 95% CI 4.0 to 7.9 [13]. Large numbers of observational studies have revealed that combined oral contraceptives are associated with two fold to six fold increased risk of venous thrombosis [14]. In oral contraceptive formulations, the Oestrogen compound (ethinyloestradiol) is thought to cause the increased risk of thrombosis. Reduction of ethinyloestradiol compound in the dose of oral contraceptive would result in a reduced risk of venous thrombosis [9]. This case report also provided history of taking norethisterone 5 mg thrice daily for two (02) years before diagnosis of CVST for the treatment of irregular and excessive bleeding during menstruation. So far our knowledge this is the first case, an unmarried woman with history of taking norethisterone reporting from Bangladesh. The patient was also having increased serum homocysteine level. Similar type of case was reported in married women, norethisterone induced CVST presenting as superior sagittal sinus thrombosis that had pre excising hyperhomocysteinemia [14] and another case of norethisterone induced CVST presenting as subarachnoid haemorrhage in a patient of menorrhagia [15]. Homocysteine is a common amino acid in blood and formation of cysteine and methionine, which can be further used by the body. Due to genetic abnormalities of enzymes or deficiencies of cofactors (Folic acid, Vitamin B12, Vitamin B6), which blocked the pathways to either cysteine or methionine then homocysteine levels may rise. Chronic kidney diseases, alcoholism and certain medications may also increase serum homocysteine level. Although hyperhomocysteinemia is considered as a risk factor for Deep Vein Thrombosis (DVT) and stroke but clear evidence has not been established for an increased risk of CVST [16]. To reduce elevated level of plasma homocysteine, vitamin supplementation primarily with folic acid, Vitamin B6 and Vitamin B12 has been found to be effective [17].

Despite recent advancement in the recognition of CVST due to MRI and MRV, thrombophilia profile, diagnosis and management can be difficult because of the wide range of multiple risk factors and the absence of a uniform treatment approach [13]. Treatment of CVST is mainly provided through specialist services [18]. In Bangladesh, care seeking behaviour is primarily from unqualified providers and absence of strong referral linkage which may delay in diagnosis and initiation of the treatment of CVST patient. No guidance on CVST service design exists in Bangladesh.

Conclusion

This case report will contribute findings from developing countries in the global evidence of CVST. As more research are still required in the pathophysiology, diagnosis and management of CVST, this largest tertiary level Medical University of Bangladesh can

contribute in the global network as well as develop strategy for the country.

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