Postpartum cerebral venous thrombosis associated with protein S deficiency: A case report

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ABSTRACT

There is a decline in the levels of protein S during pregnancy due to an increase in its binding protein. Thus, protein S deficiency increases the risk of thrombosis and may lead to poor pregnancy outcomes. In the setting of a hypercoagulable state during pregnancy, it is difficult to interpret protein S levels when measured with other tests of thrombophilia in pregnancy. The rate of developing thrombotic events is higher in those pregnant females with a deficiency of any natural anticoagulant like protein S. We report the case of a recently delivered female with multiple intracranial hemorrhages and cerebral venous thrombosis associated with protein S deficiency. This case highlights the need to extensively identify all risk factors of thrombosis in newly delivered females for the early and effective management of postpartum thrombosis.

Key words: *Cerebral venous thrombosis, Coagulopathy, Postpartum, Protein S deficiency*

The incidence of stroke is higher in women compared to men in the age group of <30 years [1]. The incidence of cerebral venous thrombosis (CVT) was found to vary from 4.3 to 210 strokes per 100,000 deliveries [2]. Even though uncommon, it is a leading cause of mortality and morbidity in antenatal women. A largest reported series of pregnancy-related strokes was conducted by James *et al*. from the west. They studied 2850 cases of pregnancy, of which 766 were ischemic strokes and 50 (2%) were cortical venous thrombosis [3]. The exact etiology of CVT remains unidentified in a significant proportion of cases, but the increased risk of ischemic strokes can be attributed to the several prothrombotic physiological changes that occur in pregnancy.

Even though there had been some studies from India on postpartum CVT [4], all these studies were done in the South Indian population and there is a scarcity of data on the North Indian women. We report the case of a recently delivered female with CVT and multiple intracranial hemorrhages associated with coagulopathy and mild protein S deficiency.

CASE REPORT

A 25-year-old female presented with complaints of seizures, altered behavior, irrelevant talk slurring of speech, headache, and difficulty in breathing for 2 days. She had delivered her fourth child 13 days back at full term by normal vaginal delivery. Delivery was non-institutional and there were no complications during delivery or postpartum. Seizures occurred twice in the past few days involving all four limbs with frothing from her mouth. There was no history of tongue bite and post-ictal depression. She had also complained of a headache for 2 days on the left side of the head which was not associated with nausea or vomiting. There was no history of diabetes, hypertension, and any other chronic medical or surgical illness in the past. She never smoked tobacco, drank alcohol, or consumed illicit drugs. The systemic examination was normal. Glasgow Coma Scale was E4V5M6, bilateral plantar reflexes constricted and sluggishly reacting, power in both upper and lower limbs was 4/5.

Magnetic resonance imaging of her brain was suggestive of hemorrhagic infarct in the left temporal region extending to the left insular cortex and gangliocapsular region with transtentorial herniation with the left transverse sinus thrombosis with sigmoidal sinus and jugular venous thrombosis. According to the neurosurgical experts, she did not require any intervention and was admitted and managed in the medical ward. Her day-to-day routine investigation report is shown in Table 1 in chronological order. Urine dipstick was negative for sugar and albumin. Her blood group was B positive.

The patient was symptomatically better but her general condition was poor. Her sample was sent for special tests of coagulation profile on day 5 of admission for suspicion of clotting diathesis, the report is shown in Table 2. Her non-contrast computerized tomography scan of the head was done on day 5 of admission that suggested the expansion of hemorrhagic infarct. The condition of the patient did not improve clinically. Thus, she

Table 1: Results of patient's blood tests in a chronological order

Days	1	2	3	5
Hemoglobin (g/L)	11.4		11.4	10.5
White blood cells (×109/L)	7500		7400	7200
Platelets (×10^9/L)	2.44		2.50	2.45
Erythrocyte sedimentation rate			26	
Total bilirubin (mg/dl)	0.5		0.8	0.4
Total protein (g/dl)	6.6			
Albumin (g/dl)	3.3			
Alanine transaminase (U/L)	46		36	43
Aspartate aminotransferase (U/L)	34		34	35
Alkaline phosphatase (U/L)	120		118	110
Serum glucose (mg/dl)	98			
Blood urea (mg/dl)	35		28	21
Serum creatinine (mg/dl)	0.8		0.8	0.7
Total calcium (mg/dl)	8.5		9.2	
Serum phosphorus (mg/dl)	3.6		3.9	
PT (control – 11.5 s)	11.6	12.0	11.0	11.6
International normalized ratio	1.0	1.0	0.9	1.0
APTT (control 27.6 s)	26.8		24.8	25.6
D-Dimer (ng/ml)	666		820	
Total cholesterol (mg/dl)	133			
Triglyceride (mg/dl)	98			

Table 2: Results of patient's coagulation protein assays

Parameters	Patients report	Expected normal range
Fibrinogen (mg/dl)	857	238–498
Factor VIII (%)	288	50–150
Protein C (%)	110	70–140
Protein S (%)	42.8	57.6–112.5

was transferred to the neurology department in a superspecialty hospital for further management.

DISCUSSION

Women who have recently delivered are at increased risk of developing CVT, while there does not seem to be an increased risk of CVT during pregnancy. Mostly, the first 15 days after delivery are associated with the postpartum strokes, as found in several studies [3,5]. In a study by Aaron *et al*., the onset of symptoms was <10 days after birth in 53% of the population followed by 10–20 days after birth in 16% of the population [6]. Cerebral venous/venous sinus thrombosis was commonly seen in multipara females. Aaron *et al*. found that 39% of the multigravida had a history of thrombotic events in the previous pregnancies [6].

Several inherited and acquired prothrombotic states have been identified in recent years. However, the exact etiology of CVT remains unidentified in a significant proportion of cases. Cakmak *et al.* [7] found that prothrombotic risk factors were present in 75% of CVT patients and Aaron *et al*. [6] found that 38% of patients had multiple factors.

Protein S is a Vitamin K-dependent natural anticoagulant protein which functions as a cofactor that aids in the action of activated protein C in the degradation of clotting factors Va and VIIIa. There are two forms of protein S in the plasma: The free form (40%) which is the predominantly active form and has functional cofactor activity; and the bound form linked to the complement C4b-binding protein (60%). Protein S deficiency may be hereditary or acquired. The hereditary form is a rare cause of thrombophilia, with an autosomal dominant inheritance. The frequency of the occurrence of its deficiency is approximately 1 in 500 individuals [8]. Pregnancy is a predisposing risk factor for acquired protein S deficiency, which is being found in 9.7% of cases of pregnancy-associated CVT [6]. The decline in the levels of protein S is attributed to the elevated C4b-binding protein during pregnancy. Evidence suggest that protein S levels decline in the second trimester during normal pregnancy but they return to normal levels toward term and postpartum [5].

Of the various coagulopathies that might be associated with CVT, elevated factor VIII was the most common protein anomaly (14.6%) seen by Aaron *et al*. [6] and also the most common risk factor found in patients with CVT by Cakmak *et al*. [7]. The enhanced thrombin formation and/or the induction of acquired APC resistance by the high factor VIII levels may increase the risk of venous thrombosis.

Plasma fibrinogen levels rise during pregnancy and remain elevated during the puerperium. Increased plasma fibrinogen level is suggestive of a hypercoagulable state and increases the possibility of thrombosis [9]. In addition, there is evidence that non-O blood group subjects present an increased risk of venous thrombosis compared to those carrying the O blood group. The presence of ABO antigens on von Willebrand factor (vWF) might protect against its clearance, and hence, individuals with blood type O have been shown to have ~25% lower levels of vWF and factor VIII in plasma [10].

CONCLUSION

CVT is a major cause of stroke in Asian pregnant women compared with women elsewhere. In the premise of the physiological state of thrombophilia in pregnancy and puerperium, the presence of multiple prothrombotic markers may lead to venous thrombosis. Hence, there is a need to be vigilant about the warning signs of CVT in newly delivered women with institutional admission at the earliest. It is essential to investigate and identify the risk factors for pregnancy-associated prothrombotic states for significant long-term management of postpartum CVT.

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