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Venous Sinus Thrombosis in A Preterm Male Neonate with Elevated Anti-Phospholipid Antibodies: A Case Report

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Abstract

Background: Cerebral venous sinus thrombosis (sinovenous) (CSVT) is a rare and yet an important cause of morbidity and mortality in neonates. The Canadian registry quotes an incidence of 41 per 100,000 newborns per year. Cerebral sinovenous thrombosis is rarely reported in preterm infants. Although it is a potentially devastating condition with poor neuro developmental outcome, the risk factors are still poorly understood and the awareness to diagnose this condition is lacking. Males are at higher risk for both arterial ischemic stroke and for the sinovenous thrombosis.

Case Report: We report a preterm, male neonate with right transverse venous sinus thrombosis, who had perinatal risk factors and elevated antiphospholipid antibodies on follow up. No other known risk factors for thrombosis were identified. High levels of anti phospholipid antibodies in this infant, could have possibly lead to venous sinus thrombosis in neonatal period.

Keywords: Venous Sinus Thrombosis; Antiphospholipid Antibodies; Neonate

Abbreviations: CVST: Cerebral Venous Sinus Thrombosis; APLA: Anti Phospholipid Antibody

Introduction

Cerebral Venous Sinus Thrombosis (sinovenous) (CVST) is a rare yet an important cause of morbidity and mortality in children [1] primarily effecting neonates [1-6]. The risk factors for arterial ischemic stroke and cerebral sinovenous thrombosis in neonates are poorly understood. Males are at higher risk, although the reason for sex predilection is unknown.

The Canadian Pediatric Ischemic Stroke Registry, the largest registry for stroke and neonatal CVST, quotes an incidence of 0.6 per 100,000 population per year [7] and 41 per 100,000 newborns per year, accounting for half of all pediatric cases.

Case Report

A 33 weeks male neonate, weighing 2700 grams was admitted to the neonatal unit at few hours of life. The neonate was born to a 30 years old primigravida by vaginal delivery. There was no history of consanguinity. Antenatal risk factors were pre-eclampsia, glucose intolerance and urinary tract infection. The neonate had delayed cry and required resuscitation with supplemental oxygen. At admission there was mild tachypnea with adequate bilateral air entry which responded to supplemental oxygen. Initially congenital pneumonia was considered and baseline antibiotics were started. Cardiac examination revealed a systolic murmur in the tricuspid region, with no other signs of congestive cardiac failure. Neurological examination showed persistent jitteriness with mild hypotonia and absent neonatal reflexes. Investigations showed normal blood glucose levels and cell counts along with low ionized calcium levels (Ionized calcium - 0.6 mmol/L). Chest radiograph showed 68% cardiothoracic ratio and an initial Echocardiogram (ECHO) revealed asymmetric septal hypertrophy (ASH), mild tricuspid regurgitation (TR) with mild pulmonary arterial hypertension (PAH), which were attributed to perinatal asphyxia and poor maternal glycemic control. Repeat ECHO was normal in follow-up. The neonate developed significant hyperbilirubinemia on fourth day of life (maximum Serum Bilirubin-21 mg/dl; PCV-52 %) along with dehydration, hypernatremia (serum sodium-156 meq/L) and bilirubin encephalopathy. Despite fall in bilirubin levels after two exchange transfusions and phototherapy, encephalopathy persisted leading to the suspicion of meningitis, for which antibiotics were upgraded. However the lumbar puncture was hemorrhagic (CSF gram stain- negative& CSF culture- sterile) .Subsequently the neonate developed bleeding manifestations with coagulopathy and raised fibrin degradation products, suggesting disseminated intravascular coagulation (DIC) and was treated accordingly. The neonate also had persistent jitteriness along with persisting hypocalcaemia. Hence serum PTH levels were done, which were inappropriately normal for the degree of hypocalcaemia. Hence transient hypoparathyroidism was considered, which often manifests in sick neonates. Serum calcium and PTH levels were normalized subsequently, with calcium supplementation (Figure 1).

Initial cranial ultrasound on fourth day of life showed prominent basal ganglia. However, the MRI brain was done on 10th day of life revealed right sided transverse sinovenous thrombosis , bilateral intraventricular hemorrhage with parenchymal hemorrhages in both temporal lobes, right occipital lobe and in the deep white matter. Initially the sinovenous thrombosis was attributed to both antenatal and neonatal risk factors like sepsis with disseminated intravascular coagulation. Incidentally there

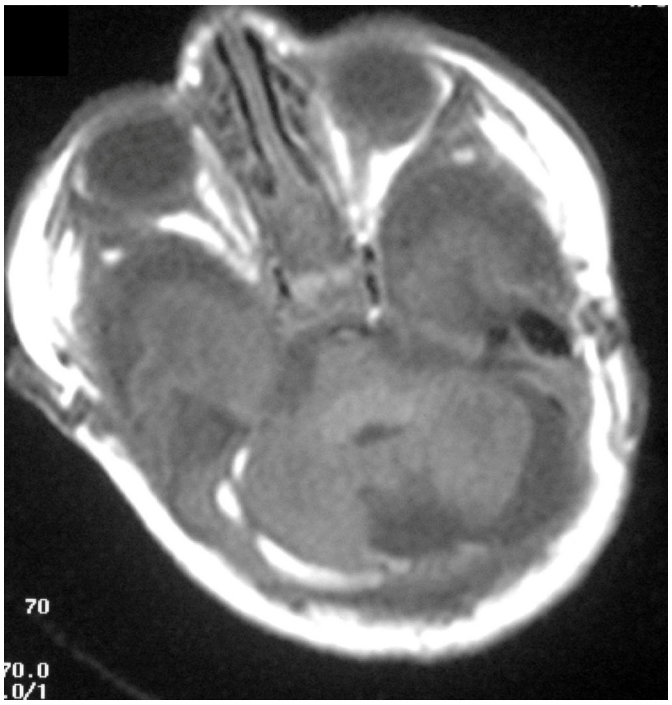

Figure 1: Axial T1W image through the posterior fossa reveals distended right transverse sinus with hyper intense luminal signal, consistent with sub acute thrombus: Right Transverse Sinus thrombosis.

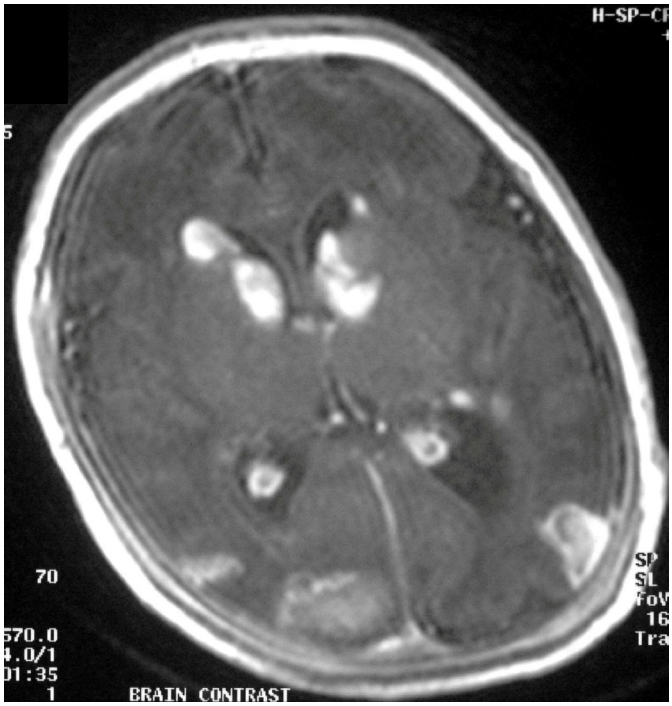

Figure 2: Axial T1W image through the body of lateral ventricle reveals bilateral intraventricular hemorrhage and parenchymal hemorrhages in bilateral temporal, right occipital and in the deep white matter.

were bilateral adrenal hemorrhages, which resolved in follow up. As the neonate showed improvement in the neurological status from 10th day onwards, oral spoon feeds as well as breast feeding was initiated and the neonate was subsequently discharged on 24th day (Figure 2).

In view of CVST, procoagulant work up was done at three months of age, which showed absence of factor V Leiden mutation, normal protein C levels and low protein S levels (Subsequently normalized at 6 months). Interestingly anti β2 glycoprotein-1 IgG antibody levels were elevated (at 3 months-32.5 G units/ mL). However anti β2 glycoprotein-1 IgM antibodies, Lupus anticoagulant and IgG and IgM isotypes of Anticardiolipin were negative. To fulfill the criteria for APLA syndrome, repeat APLA levels done at 6months of age showed persistent positivity (anti β2 glycoprotein 1 IgG antibody levels-18.5 G units/ml). Normal levels of antibodies in neonates are not available, however the prescribed cutoff is <5 units/ml. Both values in the index case were well over these levels. Antibodies retested at 6months interval showed high levels. Anti double stranded DNA was positive with titers of 73 (>40 significant) at one year of life, but became negative at 2 years of age. Both parents prothrombotic work up showed normal protein C & S levels. Since APLA syndrome in neonates is associated with maternal SLE, the mother was evaluated for SLE. She had 4 +ANA (coarse speckled pattern), positive double stranded DNA, while remaining asymptomatic. Immuno dot test to detect the nature of antibodies showed weakly positive Sm antibody. However her APLA work up was negative.

Follow-up

Developmental assessment at the age of 33 months (by Denver developmental screening test) showed normal gross motor, language, socio-personal milestones with delay in fine motor quadrant. Initial eye examination at six months showed bilateral convergent non paralytic squint and subsequently at 33months, the power in the right eye was- 2.0, and in the left eye was- 2.75 with spectacles, for which unilateral occlusion was advised. Evaluation for hearing revealed normal Brainstem Auditory Evoked Responses at three and six months of corrected age. In view of APLA positivity, infant was started on aspirin (75 mg), which was continued till two and half years of age.

Discussion

The neonates are at highest risk for thrombosis when compared to any other age group, due to their physiological prothrombotic status. Various physiological as well as pathological factors in pre natal, natal or postnatal period can predispose to neonatal CVST. The most frequently involved sinuses in neonate are the superior saggital sinus and lateral sinuses [8]. The deep sinovenous system is less frequently involved. Cortical venous thrombosis is even rare.

Index neonate had multiple known predisposing perinatal risk factors such as preeclampsia, glucose intolerance and urinary tract infection in mother [1]. There was perinatal asphyxia and significant hyperbilirubinemia with dehydration and hypernatremia (highest serum sodium level of 156 meq/ l).Also the neonate had sepsis with meningitis and disseminated intravascular coagulation [1,8] which were reported risk factors [9]. Apart from these, persistently elevated antiphospholipid antibodies could possibly have lead to thrombotic event in neonatal period.

Canadian stroke registry [1] reported the role of these perinatal and prothrombotic risk factors in a cohort of 160 children, including neonates. Acute systemic illnesses were present in 84 percent of neonates. Perinatal complications (51%) were most frequently present, followed by dehydration (30%). A strong association has been quoted between preeclampsia [1,3,10], prothrombotic disorders and neonatal venous thrombosis [11-13], along with dehydration, sepsis and meningitis. Tests for prothrombotic disorders performed in 123 patients, showed 32 % abnormal results. Presence of anticardiolipin antibody being the most frequent abnormality,(IgG titers: 15- 60 IgG phospholipid units /ml). Index case manifested lethargy, poor feeding, hypotonia and depressed

neonatal reflexes, which are commonly described in CVST1,[11,12,14-16]. Seizures which were frequently associated with poor outcome were absent in this case. However EEG or amplitude-integrated EEG was not performed. There are no consistent recommendations for anticoagulants or thrombolytic therapy in neonatal CVST, more so with disseminated intravascular coagulation [1-4]. Hence, the index case received supportive neuro developmental care, while aspirin was started in view of the positive APLA work up. However, a single center prospective study by Mahendranath et al. [17] reported that the anticoagulant therapy (standard or low molecular weight heparin or warfarin) improves outcomes in neonates and children. Anticoagulant therapy was associated with reduction in thrombus propagation and aided in early recanalization of the thrombus. Literature states 34% poor neuro developmental outcome [1,3,4,12] with predominant motor impairment, more so with thalamic and sub cortical haemorrhages [4,12], which were present in the index case. Hence, close monitoring & neuro developmental follow up is vital to detect deficits as well as recurrent thrombosis.

Conclusions

A preterm male neonate presents with right transverse venous sinus thrombosis in the setting of early & persistent anti-beta 2 GP1 antibodies, a rare thrombotic disorder associated with both maternal and neonatal risk factors.

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Authors Contribution

S C: Recruited patient, collected the data, and drafted the manuscript; **K M**: Edited the manuscript; **J A**: Necessary hematological Workup, edited the manuscript; **S S**: Follow up of the neonate, edited the manuscript; **P K**: Edited the manuscript; **J N**: Drafted and edited the manuscript.

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