A case of Transient Hyperhomocysteinemia with femoral artery thrombosis due to maternal vitamin B12 deficiency-Case report

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Abstract:
Neonatal thrombosis is a serious event that can cause mortality or severe morbidity. It often requires urgent intervention to restore perfusion. Maternal and newborn related factors, including genetic, acquired prothrombotic risk factors, may affect the occurrence of neonatal thrombosis. We present a case of a full-term neonate who had left femoral artery thrombosis with hyperhomocysteinemia and low vitamin B12 levels and also low maternal vitamin B12 levels. The baby was treated with anticoagulant therapy and vitamin B12 with good recovery.

Keyword: Hyperhomocysteinemia, Neonatal thrombosis

Case summary:
A Term boy baby with birth weight of 2800 grams was delivered by emergency lower segment caesarean section for foetal distress to a primi mother of non-consanguenous marriage. At birth baby transited well and was discharged home on day seven. On the thirteenth day of life mother noticed paucity of left lower limb movements and dusky cold left foot. The baby was not on any drugs. The baby had no cannulation in umbilical or inguinal region. The mother had no history of diabetes and systemic lupus erythematos during antenatal period. Though the mother was non vegetarian in habit, she was taking non vegetarian food only occasionally. There was no history of thrombosis in the family. On examination of the baby, the left lower limb was dusky and cold when compared to right lower limb. The femoral, posterior tibial and dorsalis pedis pulses were absent in left lower limb. Pulses in the right lower limb and both upper limbs were normal. Examination of the other systems and ophthalmic examination were normal. Hair colour was normal. Haematologic work up of the baby revealed haemoglobin of 14 gm/dl and packed cell volume of 45%. Peripheral smear was normal. Blood counts, serum electrolytes, renal function tests and liver function tests were essentially normal.
Prothrombin time, activated partial thromboplastin times were normal. Urine examination was normal. Doppler examination of the left lower limb revealed left femoral artery thrombosis and iliac vessels were normal. The ultrasound didn’t reveal any abdominal masses. Ultrasound cranium was normal. Vascular surgeon consult was sought and the baby was treated with continuous intravenous heparin infusion at a dose of 25 IU/kg/hr and INR of 2-3 was maintained. Since no acquired factors were identified as the cause for thrombosis the baby was investigated for other hypercoagulable states. Investigations revealed elevated serum homocysteine level of 32 micro mol/l (normal range 4.45-15 micro mol/l), serum vitamin B12 was low 134pg/ml (<145pg/ml is deficiency, 145-180 pg/ml is indeterminate and 180-914 pg/ml is normal) and Serum folic acid level was normal. Protein C, Protein S and Antithrombin III levels were normal. Blood investigation of the mother showed haemoglobin of 7 gm/dl and peripheral smear showed dual population of RBCs with both microcytic hypochromic and normochromic macrocytic RBCs a feature of dimorphic anaemia. Mother had low serum vitamin B12 levels of 141pg/ml (<145 pg/ml is deficiency, 145-180 pg/ml is indeterminate and 180-914 pg/ml is normal).

Since the mother had low vitamin B12 levels, the possibility of decreased foetal transfer is very high and baby would be born with less stores of vitamin B12. After birth with low levels of vitamin B12 in the breast milk of deficient mother the baby had low vitamin B12 levels and developed elevated homocysteine levels and manifested with femoral artery thrombosis.

The mother was started on vitamin B12, iron, folic acid and dietary advice. The baby was started on daily oral folic acid (2.5 mg), vitamin B6 (50 mg), vitamin B12 (1 mg). Follow up Doppler examination of the baby revealed clearance of thrombus. Maintenance anticoagulant therapy with warfarin at a dose of 0.1 mg/kg/d was commenced after seven days of heparin and heparin was stopped on twelfth day of its initiation. Warfarin was stopped after three weeks of its initiation.

On follow up the baby had adequate weight gain and no pallor. At third month follow up serum homocysteine and serum vitamin B12 levels returned to normal. The baby was on follow up for past one year and had normal weight gain, normal muscle tone and attained normal developmental milestones.

**Discussion:**

Neonatal thrombosis is a serious event that can cause mortality or severe morbidity. During the neonatal period 5.1 symptomatic thromboses occur per 100 000 births and this accounts for 2.4 admissions per 1000 newborns admitted to intensive care units (1,2). Although catheters are the most common cause of neonatal thrombosis, spontaneous events can also occur. The most common sites of spontaneous thrombus formation in neonates are the renal veins, inferior vena cava, and cerebrovascular veins, while arterial thromboembolic events occur less frequently (1-4). Spontaneous arterial thrombosis is usually aortic and usually catastrophic (5). In our baby spontaneous arterial thrombosis occurred in left femoral artery. During the neonatal period, risk factors for arterial thromboembolic disease attributable to the mother are gestational diabetes, and antiphospholipid syndrome. Risk factors attributable to the baby are asphyxia, neonatal infections, dehydration, polycythemia, indwelling catheters, cyanotic congenital heart diseases and prothrombotic conditions such as protein
C deficiency, protein S deficiency, hyperhomocysteinemia\(^1\)\(^-\)\(^4\). The mechanisms by which hyperhomocysteinemia acts as a thrombogenic risk factor have been only partially elucidated. It has been shown that excess homocysteine has toxic effect on the endothelium. It promotes thrombosis by platelet activation. It increases the levels of von Willebrand factor and thrombomodulin.

Causes of hyperhomocysteinemia in newborns include inherited and acquired causes. Inherited causes include genetic defect that causes a marked reduction in the activity of cystathionine-β-synthetase and therefore severe hyperhomocysteinemia (>100 micro mol/L) occur. Acquired causes include folate, vitamin B12 deficiency and newborns of vitamin deficient mother\(^6\). Mild (16 to 24 mol/L), moderate (25 to 100 mol/L) and severe hyperhomocysteinemia (>100 mol/L) are risk factors for occlusive vascular disease, cerebrovascular lesions and thrombosis in children\(^7\).

Falcon CR et al in their study showed that even mild hyperhomocysteinemia was associated with thrombosis\(^8\). Our baby had moderate elevation of homocysteine levels and presented with left femoral artery thrombosis but didn’t have other features of vitamin B12 deficiency like pallor, irritability and hypotonia.

Elevated homocysteine levels may result from low levels of folic acid, and vitamin B12. Homocysteine acquires a methyl group from N5-methylhydrofolate in a reaction catalyzed by the vitamin B12-dependent enzyme methionine synthetase and forms methionine. In folic acid and vitamin B12 deficiency conversion of homocysteine to methionine is impaired due to decreased methionine synthetase activity resulting in the accumulation of homocysteine. Vitamin B12 is the major modulator of total plasma homocysteine in infants younger than 1 year and folate becomes a main determinant of plasma homocysteine at older age\(^9\).

Guerra-Shinohara EM et al in their study showed that maternal concentrations of vitamin B12 and folate determine the vitamin B12 and folate levels in the neonate at birth\(^10\). Mothers with adequate vitamin B12 and folic acid transfers adequate amount of vitamins through the placenta to the fetus and are stored in the liver. Vitamin B12 intake may be limited during the first year of life because of low vitamin content in breast milk and an immature intrinsic factor system. The stores of vitamin B12 in the neonatal liver are expected to cover the requirements of this vitamin during the first year of life. In vitamin deficient mothers there is decreased transfer of vitamins to the fetus and low stores of vitamins are in the liver. The baby may show features of vitamin B12 deficiency like pallor, poor weight gain, irritability and hypotonia\(^11\). Bjorke et al in their study showed that low concentration of vitamin B12 in mothers was associated with lower B12 in their newborns\(^12\). In our baby, the same result was observed. Concentrations of homocysteine and methylmalonic acid are sensitive and specific metabolic markers for vitamin B12 status\(^13,14\). Serum concentrations of the vitamin has poor specificity and sensitivity\(^14\).
Therefore, the assessment of homocysteine and methylmalonic acid offers a useful diagnostic tool. Methylmalonic acid level was not done in our baby.

Doppler ultrasound is the most common imaging technique used in the diagnosis of neonatal arterial or venous thrombosis. Although contrast angiography is considered the gold standard for the diagnosis of thrombosis in adults, it is of limited use in neonates due to its invasiveness. In our baby, hand held life Doppler ultrasound machine was used for the diagnosis of left femoral artery thrombosis. **Fig 3:** Femoral Artery doppler blood flow after resolution of Thrombus

Neonatal thrombosis is treated with anticoagulants and/or thrombolytic agents. Anticoagulants used in newborn are heparin (25 U/kg /per h), low molecular weight heparin (enoxaparin, 1.5 mg/kg; 12 hrly) and warfarin (0.1 mg/kg/d ). Decreased concentrations of plasminogen at birth limit the thrombolytic effects of the thrombolytic agents like streptokinase (2000 U/kg / h), urokinase (4 400 U/kg / hr), and tissue plasminogen activator (0.1 – 0.5 mg / kg / hr). Thrombolytic agents are considered if thrombi are thought to be threatening to life, limb, or organ. Since our baby had no risk to life or limb and was treated with anticoagulants only.

In a 2005 Cochrane review, high dosages of oral vitamin B12 (1 to 2 mg daily) had improvement in serum vitamin B12 similar to intramuscular injections of vitamin B12 in older age groups. There are no specific guidelines regarding the duration of treatment. Duration of treatment of vitamin B12 deficiency is decided by monitoring for improvement of metabolic markers and periodical reassessment of the levels of vitamin B12 and homocysteine. Those with vitamin B12 deficiency will need at least 1 mg of vitamin B12 daily.

Our baby was on daily oral folic acid (2.5 mg), vitamin B6 (50 mg), vitamin B12 (1 mg) and serum homocysteine, serum vitamin B12 levels returned to normal levels after three months of treatment. The baby was on follow up for the past one year and had normal weight gain, normal muscle tone and normal development.

**Conclusion:** Neonatal thrombosis a major catastrophe though rare can cause serious morbidity and fatality. Detailed work up is needed to establish the cause. In the absence of the common risk factors, uncommon causes should be kept in mind especially when dealing with mothers who could be deficient in vitamin B intake. Estimation of biochemical markers like homocysteine, methyl malonic acid in mother and baby may be vital for establishing the diagnosis of vitamin B12 deficiency.
Early identification of the thrombus and its predisposing factors and appropriate management will prevent neonatal mortality and morbidity.

References:


