Neonatal Immune Thrombocytopenia

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Abstract

Background : Neonatal immune thrombocytopenia, a consequence of transplacental transfer of antiplatelet antibodies can result in serious bleeding with disastrous consequences in the otherwise healthy newborn.

Methods : Over 2 years at a service hospital, 5 mothers with chronic autoimmune thrombocytopenia and one with maternal alloimmunisation delivered, which comprised the study sample.

Results : Of these, two ladies suffered episodes of thrombocytopenia in the current pregnancy. They were provided platelet transfusions and intravenous immunoglobulins. All patients delivered vaginally. Cord blood platelet was normal in all cases. Three babies developed thrombocytopenia, two due to autoimmune and one alloimmune pathology. The nadir of thrombocytopenia occurred in 36-72 hours with recovery taking place in 10 days. The clinical manifestations were petechiae, ecchymosis, gastric bleed and oozing from vitamin K injection site. Two of the affected babies were provided intravenous immunoglobulins and one steroids. Only one of the two mothers who suffered thrombocytopenia during pregnancy and was provided intravenous immunoglobulins was associated with neonatal thrombocytopenia, an inconsistent relation. It was also observed that antenatally provided immunoglobulins raised effectively maternal rather than fetal platelet counts. However, postnatal immunoglobulins were efficacious in thrombocytopenic neonates.

Conclusion : Thus inspite of several therapeutic and preventive modalities being described, the optimum management strategy of immune mediated perinatal thrombocytopenia is yet in evolution.

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Key Words : Immunoglobulins; Immune thrombocytopenia; Neonate

Introduction

Thrombocytopenia is a serious disorder affecting 15-40% of critically ill neonates [1,2]. It is a consequence of several etiological factors e.g. prematurity, dysmaturity, perinatal asphyxia, infections, parenteral nutrition and appears several days after birth. Of increasing concern is the occurrence of thrombocytopenia (TP) in healthy neonates soon after birth. Its frequency in a normal cohort of newborns is not clearly defined because platelet counts are not routinely performed in asymptomatic babies [3-5]. Due to immune mechanism, transplacental passage of antiplatelet antibodies can lead to widespread platelet destruction in the fetus and newborn. Consequently serious bleeding manifestations could occur [6]. Immune fetal TP has been ascribed to two main etiologies viz maternal alloimmunisation where maternal platelets are devoid of an antigen of paternal origin on the fetal platelets and maternal idiopathic TP where the autoantibodies can recognise an antigen on maternal as well as fetal platelets [7]. We present an experience of neonatal immune TP at a service hospital.

Material and Methods

Over a period of two years, mothers who were likely to deliver babies with immune mediated TP were enrolled in the study. They included mothers who suffered from idiopathic thrombocytopenic purpura (ITP) and those who gave a history of a immune TP affected neonate in the previous childbirth. Exclusion criteria included associated conditions which could result in fetal/neonatal TP viz PIH, HELLP syndrome, SLE, acute infection, splenomegaly and cytotoxic drugs/radiation therapy. The HIV status was checked in all mothers and positive cases excluded. In the enrolled mothers history of previous treatment received for ITP viz steroids, immunoglobulins (IVIG), platelet transfusions (PT), splenectomy and laboratory parameters such as platelet counts and platelet associated antibody estimation was noted. History of previous fetal/neonatal loss due to bleeding diathesis was recorded. Bleeding manifestations in the current pregnancy and platelet estimations performed were noted. Specific treatment received during the current pregnancy i.e. steroids, IVIG and platelet transfusions was recorded. At birth, cord blood platelet estimation was carried out. A detailed clinical examination was conducted to exclude prematurity, dysmaturity, asphyxia, intrauterine infections and congenital malformations which could be associated with TP. A daily

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clinical examination noted evidence of bleeding manifestations. The platelet estimation was carried out daily and SOS for 5 days and then biweekly. In case TP occurred, the treatment modality adopted viz steroids, IVIG and platelet transfusions was recorded. In thrombocytopenic neonates due to maternal ITP, steroids and IVIG were provided to alternate cases. However, in TP due to alloimmunisation, IVIG was provided. Platelet transfusion was provided when the neonatal platelet counts were < 0.3 lacs/cmm. Platelet estimation was carried out by collecting a sample of blood in EDTA and estimating platelet count in a Neubauer chamber after using platelet diluent. In case of TP, a countercheck was carried out by studying the peripheral blood smear to exclude pseudo thrombocytopenia due to aggregation. The results obtained were tabulated and critically analysed to study the association between maternal vs neonatal platelet counts, maternal clinical status with neonatal platelet counts, the course of neonatal TP and the association of neonatal platelet counts with clinical manifestations of bleeding.

Results

Over a period of two years, five mothers with chronic ITP were admitted in the hospital. One other patient with no past history of TP delivered a neonate with features of immune TP. Of these, two were primigravidas, three 2nd gravidas and one 3rd gravida. The clinical profile and treatment received in the mothers is as shown in Table 1. During the current pregnancy, two of the patients suffered episodes of TP. Both of these had babies who were mildly affected not requiring treatment in the previous pregnancy. Two of the mothers with ITP had positive antiplatelet antibodies detected in the non pregnant state. The ladies who suffered TP during pregnancy of < 0.5 lacs/cmm were provided platelet

transfusions. IVIG was provided to two patients. All the patients delivered vaginally at term.

Cord blood platelet counts were within normal limits in all cases. However three of the neonates manifested TP within 36 to 48 hours after birth. Their platelet profile, treatment provided and correlation with maternal status is as shown in Table 2. The 1st baby manifested TP by 36 hours and bleeding viz petechiae and gastric bleed by 40 hours. She was born to a mother who had splenectomy performed previously for ITP and was on steroids during pregnancy. The platelet count ranged from 0.5 lacs to 1.85 lacs/cmm. The baby was provided steroids for two weeks. The 2nd baby manifested TP at 72 hours of age in the form of ecchymosis and gastric bleed. The platelet count ranged from 0.3 lacs to 2.1 lacs reaching the nadir at 72 hours after birth. This baby was provided a platelet transfusion and IVIG in the dosage of 400 mgms/kg/day for two consecutive days with a gradual improvement in platelet counts over 7 days. The third neonate was born to a primigravida with no past history suggestive of immune mediated TP. She did not suffer any adverse antenatal influences. The neonate, vigorous since birth, suffered oozing from vitamin K injection site. In addition she developed widespread ecchymosis. All investigations including coagulation profile were normal except for a thrombocytopenia which ranged from 0.25 lacs to 2.25 lacs on recovery. The maternal platelet counts were normal. A diagnosis of neonatal alloimmune thrombocytopenia (NAIT) was made and a platelet transfusion along with IVIG provided as a slow infusion for two consecutive days with gradual recovery of platelet counts over the next 10 days. Parental platelet typing revealed the mother to be HPA 1a negative and the father HPA 1a positive, thus suggesting alloimmunisation as the cause of TP in this baby. Ultrasound examination of the head

Table 1
Maternal clinical profile vs neonatal platelet counts

Case No.	Maternal status	Maternal platelet nadir	Treatment antenatal	Neonatal platelet nadir
1.	Chronic ITP	2.0 lacs	Nil	1.8 lacs
2.	Chronic ITP Splenectomy + Steroids	0.4 lacs	IVIG+PT	0.5 lacs
3.	Chronic ITP	1.75 lacs	Steroids	1.75 lacs
4.	Chronic ITP Splenectomy done	0.50 lacs	IVIG+PT	1.5 lacs
5.	Chronic ITP	2.4 lacs	Nil	0.3 lacs
6.	Alloimmunisation	2.2 lacs	Nil	0.25 lacs

ITP - Idiopathic thrombocytopenic purpura, IVIG - Intravenous immunoglobulin, PT - Platelet transfusion

Table 2
Neonatal thrombocytopenia - maternal status vs neonatal platelet counts (lacs/cmm)

Case No.	Maternal status	Maternal PC nadir	UC	Neonatal PC N	D	RD	Clinical features	Treatment
1.	Chronic ITP Splenectomy done	0.4	1.8	0.5	2	7	Petechia Gastric bleed	Steroids
2.	Chronic ITP	2.4	1.65	0.3	3	7	Ecchymosis Gastric bleed	IVIG + PT
3.	Alloimmune	2.2	-	0.25	2	10	Bleed injection site + ecchymosis	IVIG + PT

UC - Cord blood, N - Nadir, D - Day, RD - Recovery day, PT - Platelet transfusion

and abdomen and CT scan of head excluded intracranial and abdominal bleed in the babies. All the mothers with affected neonates were warned of the recurrent risk in subsequent pregnancies.

Discussion

Thrombocytopenia occurs in 7-8% of all pregnancies [8]. The healthy appearing mother with TP may have either benign gestational TP which does not affect the fetus or immune mediated TP which could have serious consequences [9]. Neonatal immune TP is due to the transplacental transfer of circulating maternal antiplatelet antibodies. Autoimmune antibodies present in cases of maternal autoimmune TP recognise maternal as well as fetal platelet antigens and thus generally induce both maternal and fetal TP. The risk of hemorrhage is reported to occur mainly during delivery. In contrast, maternal alloantibodies developed against a fetal platelet alloantigen inherited from the father, induce a severe fetal TP but is associated with normal maternal platelet counts. TP in the thus affected fetus may occur as early as 18th week of gestation and carries the risk of severe antenatal cerebral hemorrhage and/or porencephaly warranting specific antenatal management [10-13].

The lady with ITP usually gives a history suggestive of TP prior to pregnancy. The platelet counts of such a patient should be regularly assessed during pregnancy. The pregnancy of a patient with normal platelet counts and a past or family history suggestive of NAIT must be carefully monitored, as the fetus could suffer the risk of serious hemorrhage necessitating antenatal therapy. Recurrence risk of both allo and auto immune thrombocytopenia is high, with the sibling being more severely affected than the previous child. Antiplatelet antibody assays of mother's and baby's blood, antigen typing of father's platelet will help determine the risk of neonatal immune TP. If a fetus is at risk of severe TP from either auto or alloantibodies, the fetal platelet count should be measured by cordocentesis antenatally or fetal scalp blood sampling antepartum.

In our series, only two of the offspring of the five mothers with chronic ITP suffered TP, an incidence of 40% which is in concordance with other reports [14-16]. It was also observed that of the two neonates who suffered in relation to maternal ITP, only one was associated with TP in the mother. Thus there appears to be an inconsistent relation between maternal and neonatal platelet counts in immune mediated TP. The discrepancy between maternal and neonatal platelet status can be attributed to two mechanisms viz (i) a chronic state of compensated thrombocytolysis in the mother which balances platelet destruction in the mother but not the neonate (ii) a different presentation of epitopes of fetal and adult platelets [17]. The mother's

pre existing platelet count however, may have some predictive value, in that severe maternal TP prior to delivery or disease activity necessitating splenectomy appears to predict a higher risk of fetal thrombocytopenia [18].

In our series, in all the cases, cord blood platelet levels were normal. The nadir of TP occurred between 36 and 72 hours after birth. This finding is in concordance with the observation of Dreyfus et al, who noted the average nadir to occur at day 3 with recovery taking place within a mean of 8 days as compared to 10 days in our series [19]. It was observed that the degree of TP as well as the clinical manifestations were the most severe in the infant affected by alloimmunisation, a finding in concordance with other workers [20,21]. None of our babies suffered intracranial hemorrhage which is known to occur in almost 20% of neonates with immune TP [22].

Therapy of NATP is the administration of IVIG with or without steroids to the mother beginning in the 2nd trimester. Delivery of the thrombocytopenic fetus should preferably be operative. After delivery if severe TP persists, transfusion of phenotypically matched platelets and IVIG will raise the platelet counts. In maternal ITP, treatment includes antenatal steroids and/or IVIG if not effective, followed by the administration of the same to the affected baby. Occasionally, platelet transfusion is required when life threatening bleed eg intracranial hemorrhage is anticipated. In our series, in the neonates affected by ITP, both steroids as well as IVIG were effective. Other infrequently used modalities in the mother include anti Rh(D), cyclophosphamide, danazole and splenectomy.

One of the infants of the two mothers provided IVIG antenatally suffered TP thus suggesting that prenatal immunoglobulin therapy more effectively raised maternal rather than fetal platelet levels, an observation also made by Marzusch [23]. However, postnatally administered IVIG was effective in raising neonatal platelet counts and in preventing life threatening hemorrhage, an observation of other workers as well [24].

Neonatal immune TP is increasingly being recognised as an important cause of mortality and morbidity in an otherwise healthy neonate. As this condition is often silent and delayed, it appears that systematic neonatal platelet estimations with subsequent screening for immune mechanism would be the only effective way to detect the condition early. Aggressive screening for autoimmune disease in mothers of thrombocytopenic neonates and careful monitoring of subsequent pregnancies and deliveries could prevent severe deleterious effects in the offspring. Several modalities directed at both prevention and treatment have been

described. However, the optimum management of immune TP in both mothers and their babies is in evolution. For the clinician, the appropriate management modality is as yet uncertain making it a fertile ground for research.

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