CASE REPORT

NEONATAL THROMBOCYTOPENIC PURPURA: REPORT OF TWO CASES AND REVIEW OF LITERATURE

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ABSTRACT

Introduction: Severe neonatal thrombocytopenia is a hematological emergency that can be due to increased platelet destruction(*such as immune-mediated and peripheral platelet consumption*) or congenital failure of platelet production. The definitive diagnosis of the underlying cause of neonatal thrombocytopenic purpurais based on both clinical and laboratory findings.**Case report**; We present two infants with persistent severe thrombocytopenia of distinct aetiologies: neonatal alloimmune thrombocytopenic purpura and hepatitis B virus exposure. Their clinical course, haematological profile and treatments are discussed.**Conclusion**: This reportreiterates the need to think laterally while considering the differential diagnoses of neonatal thrombocytopenic purpura. Moreover, ithighlightsits treatment challenges in peripheral health facilities, especially in resource-limited settings.

Keywords: Neonatal thrombocytopenic purpura, Differential diagnoses, Haematological profile

INTRODUCTION

Severe neonatal thrombocytopenia (less than 50,000/ul) is a hematological emergency. It is rare in apparently healthy newborns but its incidence ranges from 2.4% to 5.0% among infants admitted to the neonatal intensive care unit (NICU).[1,2]Neonatal thrombocytopenia is often due to increased platelet destruction (*such as immune-mediated and peripheral platelet consumption*) or congenital failure of platelet production including amegakaryocytic thrombocytopenia and thrombocytopenia absent radius (TAR) syndrome.[3-5]Also, neonatal thrombocytopenia can occur in perinatal asphyxia and pre-eclampsia, perhaps related to hypoxia and decreased maternal platelet level respectively.[2,6]The definitive diagnosis of neonatal thrombocytopenia is based on both clinicaland laboratory findings.

Neonatal alloimmune thrombocytopenia purpura (NATP) occurs when fetal platelets contains paternal antigen that is recognized as foreign by maternal immunity, eliciting immunoglobulin G (IgG) antiplatelet antibodies that cross placenta and destroy fetal platelets.[7]This is the platelet equivalent of Rhesus disease of the newborn.[7]The incidence of NATP is 1 in 4,000 to 5,000 live births .[7] Affected infants typically develop generalized petechiae and purpura in the early neonatal period, but they are otherwise healthy. Intracranial hemorrhage may be present in up to 30% of severe cases.[7,8] Laboratory confirmation is by detecting antiplatelet alloantibodies in mother's serum while DNA sequencing of parental blood identify platelet antigen genotypes.[7,9]

Furthermore, congenital viral infections such ascytomegalovirus and hepatitis B virus (HBV) can lead to neonatal thrombocytopenia by increased peripheral platelet consumption.[10] They induce platelet aggregation and loss of sialic acid from platelet membrane.[11]There is a paucity of report on thrombocytopenia in HBV-exposed neonates in the

literature. In a population-based cohort study in Sweden, HBV increased the risk of preterm birth and its associated morbidities.[12]In addition, Salemi *et al*found that adverse neurological outcome occurred more frequently in infants of HBV-positive mothers. [13] However, none of these studies reported symptomatic neonatal thrombocytopenia as a perinatal outcome.[12,13]

Considering the dearth of data on neonatal purpurain HBV-exposed infants and the scarcity of sophisticated diagnostic tools to aid clinicians to confirm NATP, this report highlights the clinical features, management and outcome of two Nigerianinfants with these possible underlying causes of thrombocytopenic purpura, while reviewing relevant literatures.

CASE REPORT

The following infants who had generalized purpura in the early neonatal period were deliveredat the Mother and Child Hospital Ondo, by unrelated parents. Both of them had severe thrombocytopenia. Their clinical features, diagnoses and outcome are detailed below:

Case 1: A male neonate delivered at home to a 23-year-old Para2^{+0} woman on May 23, 2014. Pregnancy was booked and the antenatal period was uneventful. There was no prolonged bleeding in the mother. There was no peripartum pyrexia. The infant had spontaneous regular breathing at birth.

However, hepresented on the 3rd day of life with complaints of fever and poor feeding of two days duration. He was well hydrated,anicteric, acyanosed and systemic examinations were normal.Generalized petechial haemorrhages and purpura were noticed on his trunk and extensor surfaces of his extremitieson the second day on admission. (Figure 1A)There was no active bleeding from the orifices.Bleeding time was prolonged. Serial complete blood count results showed persistent severe thrombocytopenia (Table 1).

The diagnosis was neonatal alloimmune thrombocytopenic purpura (NATP)and probableneonatal sepsis. He was treated with intravenous cefuroxime and gentamicin as well as intravenous vitamin K 1mg/kg daily for 3 days.He had exchange blood transfusions (EBTs) on the 2nd and 4th day on admission using suitable freshly donated blood.Platelet concentrate was not available.He was referred to a tertiary institution for platelet transfusionand possible anti-platelet antibody immunoassay due to persistent thrombocytopenia.

However,the referral plan was not accepted by the parents due to financial constraints. Second line antibiotic was commenced as per unit protocols. Euglycemia was maintained at a glucose infusion rateof 6mg/kg/minute and he was later fed with expressed breast milk as tolerated. However,he died suddenly on the 14th day on admission due tointraventricular haemorhage; post-mortem lumbar puncture yielded a uniformly bloody cerebrospinal fluid (CSF) that did not clot. Parents counseled on relevant antenatal management options of fetomaternal alloimmune thrombocytopenia in future pregnancies.[8]

Case 2: A male infant delivered to a primiparous woman in March 2015 via spontaneous vertex delivery. Pregnancy was not booked.Mother did not have any febrile illness with a rash in the antenatal period. There was no prolonged rupture of membrane and no peripartum pyrexia. She was HBVsAg positive; result retrieved third day post-partum. Baby was not asphyxiated.His birth weight was 3.6kg. He received prophylactic intramuscular vitamin K 1mg stat and was discharged home.

However, the infant presented with petechial haemorrhages on the third day of life. Other physical examination findings were normal. Complete blood count confirmed thrombocytopenia ($18x10^3$cells/μL). Other cell lines were normal. Bleeding time was prolonged but clotting profile was not achieved. He was managed as a case of severe thrombocytopenia in HBV-exposed infant. The differential diagnosis was neonatal sepsis.

He was treated with intravenous cefuroxime 100mg/kg/day 8hrly and IV Gentamicin 5mg/kg/day 12hrly. Freshly donated blood in

aliquots of 20ml/kg was transfused on the 1st and 3rd day on admission but there was persistent thrombocytopenia. Typical haematological profile of the infant while on admission is shown on table 1. He received HBV vaccine and immunoglobulin on the 5th day of life; the delay was due to parental financial constraints. He was referred for platelet transfusion in a tertiary centre after 5 days on admission.

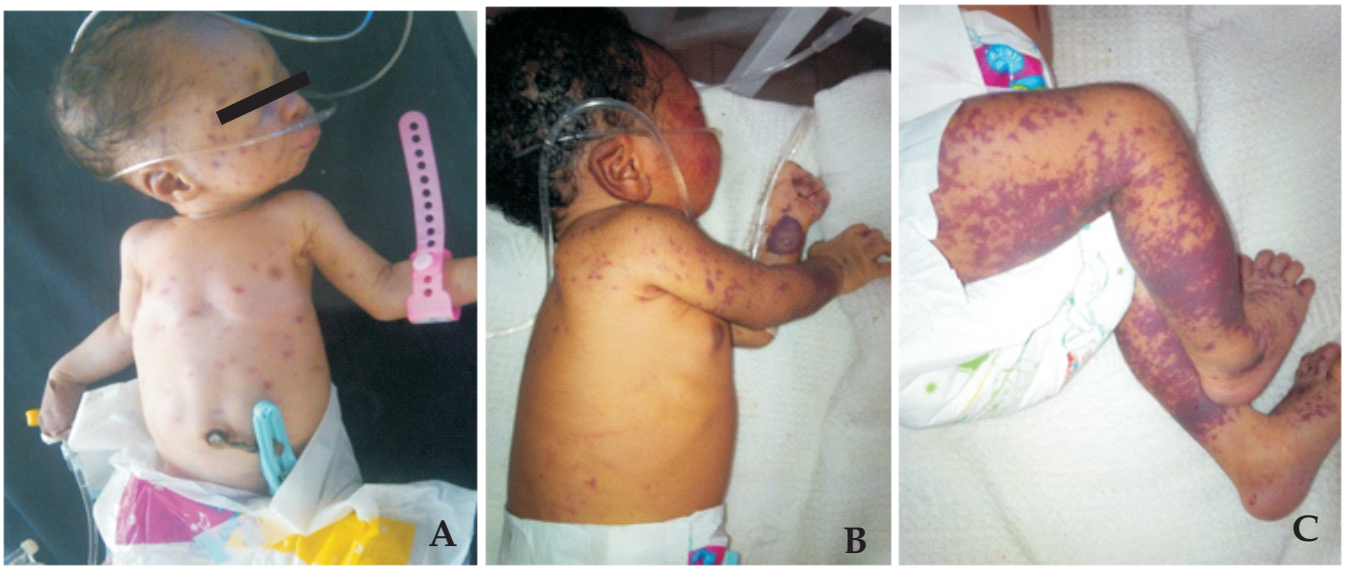

Figure 1A-C: Neonatal thrombocytopenic purpura in two Nigerian infants;A:Generalized petechiae and purpura in a suspected case of neonatal alloimmune thrombocytopenic purpura; B&C: HBV-exposed infant with generalized purpura worse on the lower extremities.

Table 1: Selected complete blood count results of the infants on admission

Cases	Complete Blood counts				
	WBC (x10^3/µL)	**Hematocrit**(%)	**Platelet**(x10^3/µL)	**Lymphocyte**(%)	**Neutrophil**(%)
NATP					
Day 3	20.7	40.5	**14.0**	10.1	86.7
,5	2.7	43.7	**4.0**	38.9	57.5
,7	8.4	42.0	**7.0**	34.0	62.8
HBV-exposed					
Day 3	16.5	36.8	**18.0**	24.7	72.8
, 5	12.0	42.5	**10.0**	32.6	63.5
, 7	14.5	48.0	**12.0**	37.9	58.0

DISCUSSION

The most significant manifestation of neonatal thrombocytopenia is bleeding and it can involve vital organs as seen in the first infant. Cutaneous bleeding is common in severe neonatal thrombocytopenia.[7] Baer *et al*[2] reported that 30% of cases of severe thrombocytopenia in a large series presented in the first 3 days of life and cutaneous bleeding was more common in infants with platelet counts of <20000/µl, consistent with the findings in this report. They found no significant correlation between platelet counts and pulmonary, gastrointestinal, or intraventricular bleeding.[2] Likewise, Stanworth *et al* reported that one third of neonates enrolled in their series developed thrombocytopenia of <20000/µl, but only 9% developed major hemorrhage.[1] Hence, the threshold for spontaneous major bleed is variable in

affected neonates and may be influenced by co-morbidities.

The diagnostic criteria of NATP include the presence of symptomatic thrombocytopenia as in our patient and serological evidence of maternal antiplatelet antibodies against paternally derived neonatal platelet antigens.[7,9]Parental platelet antigen genotypes can be identified on DNA sequencing. These were not achieved in our patients due to the lack of relevant laboratory capacity. Infants with NATP are often otherwise well. The initial presence of non-specific symptoms in our patient could be due to co-existing sepsis following thepossibly unhygienic delivery environment. However, the persistent severe thrombocytopenia in this infant could not be attributed to sepsis alone. Although bleeding diathesis can occur in severe sepsis, the repeated isolated depletion of platelet following EBTs with freshly-donated blood was consistent with the presence of transferred platelet antibodies in the infant.[8,9] This culminated in the likely CNS bleed and his demise. The elder sibling was not affected by the condition apparently due to her non-inheritance of the offending paternal platelet antigen.[7]

In a recent cohort study evaluating 5000 births to women with viral hepatitis, HBV exposurewas not significantly associated with anadverse neonatal outcome.[13] This does not preclude the risk of perinatal transmission of HBV. Maternal antenatal screening for HBVsAg and prompt administration of HBV vaccine and immumogloblin in the first 24hours of life reduce the risk of neonatal HBV infection and chronic complications.[14]The maternal HBV status was known post-delivery in this patient because the pregnancy was not booked. Nonetheless, the infant received hepatitis immunoglobulin on the 5th day of life partly due to financial constraints; ideally, it should be administered within the first 12 hours of birth in HBV-exposed infants with acceptable efficacy by the 48th hour of life.[14]Neutrophil predominance is typicalof early neonatal period. As seen in our patients, other full blood count parameters may be normal in neonatal purpura.[11]

The management of thrombocytopenic purpura comprises treatment of the underlying causes and platelet transfusions. NATP requires administration of antenatal intravenous gamma-globulin(IVIG) to the mother. Delivery by cesarean section is recommended.[8]Transfusion of platelet concentrate (especially washed maternal platelets) is indicated in this case but not available in our free healthcare facility and the parents could not comply with referral for tertiary care.As attempted in this patient, EBTs with freshly donated blood could behelpful, removingsome anti-platelet antibodies from the neonatal circulation. However, treatment with IVIG is necessary in some cases of NATP and rarely intravenous methylprednisolone.[8] The outcome of neonatal thrombocytopenic purpura is variable depending on the underlying cause and associated systemic complications, especially vital organ haemorrhages. A limitation of this reportis the non-availability of serology andHumanPlatelet Antigen genotyping at our centre to confirm NATP. Also, referral feedback on the HBsAg-status of thesecond infant at six weeks of age is desirable.[14]

In conclusion, the differential diagnoses of neonatal thrombocytopenic purpura arebeyond bacterial sepsis.Frontline clinicians should think laterally when assessing neonates with persistent severe thrombocytopenia. Prompt supportive care is pertinent to good outcome. Specialized testingcould enable definitive diagnosis.

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