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A Case Report of a Suspected Neonatal Alloimmune Thrombocytopenia in a Tertiary Health Institution

Odunayo Afolayan [a], Samson Ojedokun [b], Oluwakayode Ashaolu [a], Esther Kosoko [a], Temitope Oyelami [a] and Michael Onigbinde [a++*]

[a] Department of Paediatrics and Child Health, LAUTECH Teaching Hospital Ogbomoso, Oyo State, Nigeria.
[b] Department of Chemical Pathology, LAUTECH Teaching Hospital Ogbomoso, Oyo State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Author OA and MO designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors EK and OA managed the analyses of the study. Author SO and TO managed the literature searches. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Fetal and neonatal alloimmune thrombocytopenia FNAIT is the leading cause of severe thrombocytopenia in the fetus and neonate leading to serious bleeding, intracranial haemorrhage and death and also intracranial haemorrhage in full-term infants.

[++] Consultant Paediatrics/Lecturer;
**Corresponding author: E-mail: moonigbinde@lautech.edu.ng;*

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We reported a case of a 33-year-old woman who was delivered of a male neonate via Emergency lower segment Cesarean section CS on account of premature rupture of the membrane with oligo hydramnios at an estimated gestational age EGA of 29 weeks 3 days. Her blood group is O Rhesus D positive, and Genotype HbAA. No known premorbid illness. Her last confinement was of a male child delivered via CS and died within 12 hours of birth.
This reported case of suspected FNAIT was a baby received alive after CS with birthweight of 1,060g and APGAR score of $7^{1}8^{5}$ transiently, and was noticed to be bleeding from the mouth and anus shortly after birth. Thereafter, he had thrombocytopenia, persistent anaemia, several apneic attacks, seizures, desaturation and died after 42 hours of life despite all prompt clinical interventions. Autopsy summary includes anaemia, central cyanosis, petechial hemorrhage, diffuse alveolar damage, cerebral edema, acute tubular necrosis, small for gestational age and placental vasculopathy.
Conclusion: Fetal and neonatal alloimmune thrombocytopenia is a rare disorder and yet poses a challenging diagnosis and treatment plan in resource-limited centres especially in developing countries. Although the clinical findings of the reported suspected case were not classical as previously reported by other studies, they're pointers to our curiosity and open to further criticism.

Keywords: Fetal and neonatal alloimmune thrombocytopenia FNAIT; Case report; Nigeria.

1. INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia FNAIT is a rare condition with a significant risk of severe neonatal morbidity and has been identified as the major cause of primary hemorrhagic morbidity and mortality in neonates [1]. The mechanisms leading to such loss are not clearly cut and little is known about the appropriate preventive protocol for this devastating event [2].

The condition is caused by maternal alloantibodies against the human platelet antigens 1a or 5b of the fetus leading to severe hemorrhage. Anti-HPA-1a-mediated event shows a severe clinical outcome more often than anti-HPA-5b-mediated [2]. Several large prospective studies of women negative for HPA-1a, showed that between one in 1000 and one in 2000 HPA-1a-positive infants had neonatal thrombocytopenia caused by maternal antibodies [1].

The incidence of the HPA-1a-negative phenotype in Caucasian populations is about 2.5%. One-third of these individuals are positive for the HLA-DR antigen B3*0101 and are at high risk of becoming immunized against HPA-1a when they carry an HPA-1a-positive fetus. This occurs in about 35% of cases. Of these, about one in three will deliver an HPA-1a-positive child with significant thrombocytopenia ($<50 \times 10^{9}$ platelets/l) [1].

In contrast to maternal immunization against fetal red cell antigens, it is common for immunization against platelet alloantigens to occur during a first pregnancy and for a firstborn infant to be affected by FNAIT. However, most instances of maternal immunization may be triggered by exposure to fetal blood at the time of delivery, setting the stage for an infant to be born subsequently with thrombocytopenia [2].

FNAIT is the leading cause of severe thrombocytopenia in the fetus and neonate [3] leading to serious bleeding, intracranial haemorrhage and death and it is the leading cause of intracranial haemorrhage in full-term infants [4-6]. A severely affected infant will present with florid petechial haemorrhages and purpura and a profoundly low platelet count. Typically, no other explanation for thrombocytopenia is discovered after evaluation for bacterial and viral infection, disseminated intravascular coagulation and other congenital conditions associated with thrombocytopenia [7].

A similar, but usually less serious condition can be caused by passive transfer of platelet autoantibodies; in such cases, the mother will usually have a low platelet count and/or a history of autoimmune thrombocytopenia [1].

Prospective studies [4,8] have shown that the degree of thrombocytopenia in neonates at risk (mother immunized against HPA-1a) can be quite variable. A report that severe thrombocytopenia is more than twice as common in infants born to a blood group A mother than in those born to a blood group O mother requires further confirmation [9]. An infant born to a mother who previously gave birth to an infant

with neonatal alloimmune thrombocytopenia NAIT tends to have a more severe disease than its older sibling [4].

The most serious complication of NAIT is intracranial hemorrhage, which occurs in 10–20% of symptomatic infants and up to 80% of these bleeds occur prenatally. After delivery, the greatest risk of bleeding is in the first 96 hours of life.[1] This case report was on findings based on recurrent incidents of neonatal death of the same mother with similar bleeding within the first few hours of life.

2. METHODS

The report was conducted at the Ladoke Akintola University of Technology Teaching Hospital Ogbomoso Oyo State Nigeria.

The Case file of the patient was retrieved and necessary information was obtained for the write-up. Other background notes were obtained from the search engine using important keywords such as NAIT, FNAIT, severe thrombocytopaenia, and Neonatal death. All data were summarized with utmost level of confidentiality.

3. CASE SUMMARY

3.1 Maternal History

The mother is a 33-year-old P_1^{+1} woman who was delivered via Emergency lower segment Cesarean section CS on account of preterm premature rupture of the membrane with oligo hydramnios at an estimated gestational age EGA of 29 weeks 3 days. Her blood group is O Rhesus D positive, and Genotype is HbAA. Not a known patient with diabetes mellitus or hypertension. No history suggestive of preeclampsia or eclampsia.

3.2 Past Confinement

Her first confinement is a male child alive and well. She had a right salpingectomy on account of ruptured right tubal ectopic gestation. Her last confinement was of a male child delivered via CS and died within 12 hours of birth. The cause of death was inconclusive but the child was reported to have some petechia hemorrhages distributed around his body.

3.3 Index Pregnancy History

Pregnancy was spontaneously conceived and booked in a private hospital at an estimated gestational age EGA of 4 weeks. She was regular with antenatal visits and routine medications. There was no history of peripartal rash or fever during the first trimester. However, she was treated for malaria with oral medications at EGA of 21 weeks. She received one dose of tetanus toxoid TT, but received no dose of intermittent preventive therapy IPT for malaria.

Detailed history dated back to one week before delivery when mother noticed drainage of fluid per vagina suspected by mother to be liquor on account of which she presented and was admitted for care at a private hospital. After 24 hours into this admission, she was observed to have started bleeding through the vagina. She was administered dexamethasone 12mg intramuscularly 12 hourly for 24 hours, magnesium sulphate $MgSO_4$ and antibiotics intravenously without any significant improvement.

She was brought from the private hospital after one week of admission to this hospital on the day of delivery. At presentation, she was not in any distress, not pale. The abdomen was uniformly enlarged with SFH 24cm, Right occipitoanterior, Cephalic presentation, no palpable contractions FHR 152bpm. She had obstetric ultrasounds done just prior to CS which revealed a singleton fetus in cephalic presentation with fundo-posterior placenta. Deepest vertical pool of liquor 1.1cm, EFW- 1268.60g EGA 28 weeks 2 days, EDD 16-10-2023 FHR 142bpm. An assessment of a 33 year old unbooked G_3 P_1^{+1} 1A with previous scar at EGA 29weeks 3days with prolonged preterm rupture of membrane PROM + Anhydraminous was made. On this account, she subsequently had emergency CS and was delivered of a male neonate. The mother was adequately taken care of and transferred to the recovery unit.

3.4 Neonate History

The Paediatrics team was invited to be on ground during the CS. A preterm very low birth weight male neonate was delivered to the team. The baby was received alive with cries and tended to under a radiant warmer. He was thoroughly assessed, had a birthweight of 1,060g (1.06kg), Head Circumference HC 26cm, Chest Circumference CC 24cm, Femur Length FL 32cm, an APGAR score of $7^{1}8^{5}$ transiently, and was noticed to be bleeding from the mouth and anus after a few minutes of life.

Subsequently, the baby had an apnea episode for which he was resuscitated via airway

sanctioning and AMBU bagging for about 30 minutes before he regained spontaneous respiration. An initial dosage of intravenous vitamin K 5mg and intravenous caffeine citrates was administered. However, bleeding continued moderately from the mouth and anus.

On general clinical examination baby appeared dusky, and he was in respiratory distress, no dysmorphic features or peripheral edema was observed. Anterior fontanelle was patent and normotensive, tone was normal for age. He was dyspneic evident by intercostal and subcostal recessions, respiratory rate was 62cpm, he had bronchovesicular breath sounds, SPO_2 was 51% while on improvised bubble continuous positive airway pressure CPAP @ 3L/m. Heart Rate was 160b/m, 1st and 2nd heart sounds present without murmur. The abdomen was flat, the umbilical stump dressing was clean and dry, anus was patent, a preterm external male genital was observed, and the testis was not descended bilaterally. The report of laboratory investigation requested are presented on Table 1.

An assessment of preterm very low birth weight male neonate with severe sepsis complicated by disseminated intravascular coagulopathy DIC and Vitamin K dependent bleeding were made.

The following medications and fluid were administered: I.V Ceftazidine 50mg/kg/dose, I.V Gentamicin 2.5mg/kg/dose, I.V Caffeine citrate 20mg/kg stat then 10mg/kg daily, I.V Vit K 5mg stat then 1mg/kg/day, I.V.F 80mls/kg/day of 10% Dextrose Water.

At 4 hours of life, the baby was noticed to be bleeding from the umbilical stump inclusive of earlier noted bleeding sites. Urgent PCV done was 36%. A session of simple transfusion with fresh whole blood at 20 ml/kg was done.

At 12 hours of life, bloody vomitus was observed. A repeat PCV was 35%. Another simple transfusion at 20mls/kg and a post-transfusion PCV done was 32%. A 3rd transfusion was done at the 24hr of life, post transfusion vitals include: HR 148bpm, $SP0_2$ 92% on intranal oxygen INO_2, RR 58cpm and Temperature was 36.8°C.

At 28 hours of life baby was noticed to have seizures; generalized clonic tonic movement of the body and upward rolling of the eye. I.V diazepam 0.3 mg per kg was given. I.V Phenobarbital 15mg per kg and 5 mg per kg 12 hourly. A lumbar puncture for cerebrospinal fluid CSF analysis and exchange blood transfusion was planned.

About 30 minutes later, the baby was noticed to be vomiting coffee-brown effluent as well as passing melena followed by an apnea episode of which cardiopulmonary resuscitation CPR via AMBU bagging and chest compression was immediately commenced. He regained spontaneous respiration after 15 minutes of resuscitation, SPO_2 72% on 100% RR 60cpm.

At 42hrs of life, the baby was noticed to be having recurrent episodes of apneic attacks, cardiopulmonary resuscitation was done at every instance with AMBU bagging and chest compressions. The last resuscitation effort lasted about 1 hour 30 minutes during which the baby did not regain spontaneous breathing even with 0.1mg of adrenaline administered with continued resuscitation to no avail. The baby had no cardiac activity and no respiratory effort he was thereafter certified dead.

3.5 Gross Autopsy Findings

A fresh body of a male neonate was received. The crown heel length, crown-rump length, head circumference, abdominal circumference and chest circumference measure 50cm, 32cm,30cm, 23cm and 26cm respectively. Inner canthus, outer canthus, and philtrum lengths measure 2cm, 8.5cm, and 5cm respectively. The umbilical stump is clean.

He is pale and anicteric. There is central cyanosis.

There are areas of petechial hemorrhage in epicardial and pleural surfaces.

The left and right lungs weigh 51gm. Cut surfaces are grossly normal. The heart is flabby and measures 15 grams. There are no septal defects. The liver weighs 64 grams. The capsule is shiny. The cut surface is grossly normal. The esophagus was patent, with no defect. The stomach and intestine are patent and grossly normal. The kidneys weigh 21 grams and show normal fetal lobulation. The capsule strips with easy to reveal a smooth sub-capsular surface. The cut surface shows marked corticomedullary differentiation. The spleen and thymus weigh 8gm each and cut surfaces are grossly normal. The brain weighs 246 grams and bilaterally symmetrical. It is edematous with flattened gyri and narrowed sulci. No gross anomalies are seen in the cerebrum, cerebellum and brain stem. Also, the received placenta measures 13x12x3cm. The external and cut surface is not remarkable.

Table 1. Investigations at admission

Parameters	PCV	RGB	microESR	WBC	Neutrophils	Lymphocytes	Platelets
Results	47%	5.0mmol/L	3.0mm/hr	17,000c/mm	40%	60%	90,000c/mm

PCV: Packed cell volume. RBG: Random blood glucose. WBC: White blood cell counts ESR: Erythrocyte sedimentation rate.

3.6 Autopsy Histology

Lungs show congestion of alveolar capillaries, interstitial edema, areas of hemorrhage and infiltration by neutrophils. There is alveolar collapse. Features are in keeping with diffuse alveolar damage.

Kidneys show vascular congestion, interstitial edema, tubular necrosis, and areas of hemorrhage. Features are in keeping with acute tubular necrosis.

The liver shows congested blood vessels and areas of hemorrhage.

The placenta and umbilical cord show chorionic villi of various sizes. Some of the villi are hyalinized. There is fibrosis. The umbilical veins show areas of thrombosis. The features are in keeping with a placental vasculopathy.

3.7 Summary of Autopsy Diagnosis

Anaemia, Central cyanosis, Petechial hemorrhage, Diffuse alveolar damage, Cerebral edema, Acute tubular necrosis, Small for gestational age and Placental vasculopathy.

3.8 Pathologist Remarks

The cause of placental vasculopathy could not be determined. The mother should be screened for cytomegalovirus and thrombophilia for possible cause.

4. DISCUSSION

The key findings from this case included a recurrent neonatal death of unknown cause, small for gestational age, PROM, significant anhydranminous, uncontrolled hemorrhage, thrombocytopenia, persistent anemia, recurrent apnea and seizures. Although the first child of this woman was unaffected however the cause of sudden death in the two subsequent babies raised an index of suspicion of an alloimmune disease having ruled out rhesus incompatibility in this case. Also, the factors [10] responsible for intrauterine growth restriction were ruled out in this patient and anemia was not present at birth except for thrombocytopenia and early neonatal bleeding.

Evaluation of hemolytic anemia in the neonatal period should include comparing blood types of both the mother and the neonate, Coombs testing, serum bilirubin, and evaluation of the peripheral blood smear. The presence of mismatched ABO or Rh red blood cell antigens can be a clue that maternal antibodies directed against neonatal red blood cells are the culprit and can be confirmed by a positive direct or indirect Coombs test that evaluates for the presence of such antibodies which were not done in this case report.

Feto-maternal ABO blood group mis-match is a rare cause of neonatal thrombocytopenia. It has been documented that platelet carries small quantity of A and B antigen on its surface, so infants of blood group O mothers with heavy expression of A or B antigen on their platelet could present with thrombocytopenia because of ABO incompatibility [9]. In this instance one will expect a concomitant reduction in the heamatocrit, this contradict the finding in the case where PCV was within normal limit despite moderately severe thrombocytopenia.

The recurrence of early neonatal death under similar condition of neonatal bleeding and thrombocytopenia experienced by this mother, as well as thrombocytopenia occurring within 72 hours of life heightens the suspicion of neonatal alloimmune thrombocytopenia. Early onset neonatal thrombocytopenia occurs within the first 72 hours of life and results mostly from maternal antibody directed against fetal platelet alloantigen.[2] Another important cause of early onset neonatal thrombocytopenia is maternal pre-eclampsia which is effectively ruled out in this case, other causes such as congenital infection and perinatal infection are not in keeping clinical findings in this case.

The severe bleeding which necessitated repeated blood transfusion and exchange blood transfusion in this neonate as well autopsy findings of widespread petechial hemorrhages involving the lungs, liver and the heart are consistent with this suspicion. Also, the

generalized seizure developed at 28 hours of life was initially thought to have resulted from intracranial hemorrhage, however findings at autopsy were not in keeping with intracranial hemorrhage. Intracranial hemorrhage is the most serious complication of fetal and neonatal autoimmune thrombocytopenia affecting 10-20% of symptomatic infants, majority of bleeding occurs prenatally and the first 96 hours of life [1,2,11]. The placenta findings of hyalinized villi, fibrosis and umbilical venous thrombosis in this baby are similar to that observed by De Tar et al [12] in a reported case of neonatal alloimmune thrombocytopenia with HLA alloimmunization.

Other diagnostic considerations in this case includes vitamin K deficiency bleeding of the newborn particularly the early onset subtype, factor xiii deficiency bleeding, cytomegalovirus infection and disseminated intravascular coagulopathy. Early onset vitamin K deficiency bleeding is a known cause of severe hemorrhage in the newborn however there's no history of maternal usage of warfarin, anti-convulsant and anti-epileptic drugs in pregnancy in this case. Thrombocytopenia which is a prominent feature in this case is not a clinical manifestation of either vitamin K deficiency bleeding or factor xiii deficiency bleeding. Platelets count in disseminated coagulopathy intravascular DIC, may be low but other parameters in this case are not in support of a diagnosis of DIC due to the fact that this pattern of early neonatal bleeding was experienced in two previous pregnancies.

5. CONCLUSION

Fetal and neonatal alloimmune thrombocytopenia is a rare disorder and yet pose a challenging diagnosis and treatment in resources limited centres especially in developing countries. Although the clinical findings of the reported suspected case were not classical as previously reported by other studies, yet they're pointers to our curiosity and open to further critics to forestall future occurrences.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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