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Case Report

Neonatal Hyperbilirubinemia: A Case of Complex Management Involving ABO Incompatibility, Sepsis, and Suspected G6PD Deficiency treated with Methyl Prednisolone.

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Abstract

Newborn jaundice (NNJ), especially due to ABO incompatibility, is a major global health concern. Phototherapy is standard treatment, with exchange transfusions reserved for severe cases. However, in some babies these therapies may be ineffective, requiring additional immunomodulatory treatments. Limited access to these treatments in developing countries creates a critical gap, worsening jaundice severity. A 22-hour old term neonate presented with rapidly progressive severe neonatal hyperbilirubinemia (NNJ) within 15 hours of life, consistent with ABO incompatibility based on discordant maternal and infant's blood types (mother: O, baby: B-positive). Despite aggressive initial management with phototherapy and exchange transfusions, the NNJ exhibited limited improvement. Sepsis and G6PD deficiency were considered as potential contributing factors, although confirmatory testing for G6PD deficiency was deferred due to unavailability of the diagnostic test in our setting. Given a sibling's documented successful response to methylprednisolone for a similar presentation, a brief course of low-dose intravenous methylprednisolone (1mg/kg/day in 2 divided doses) (off-label use) was cautiously initiated. This resulted in a rapid and significant improvement in the neonate's hyperbilirubinemia. Methylprednisolone was prescribed for 3 days after which it was discontinued. Following close observation for 3 days and confirmation of no neurological sequelae, the neonate was discharged home in stable condition. Managing severe, worsening NNJ, especially with multiple aetiologies, is complex. Standard therapies may be inadequate. While promising, immunomodulatory therapies like IVIG may be limited in resource-poor settings. Methylprednisolone shows potential but lacks strong clinical evidence. Well-designed studies are essential to explore its safety and efficacy, particularly in developing countries with limited treatment options.

Keywords: Neonatal Jaundice; Hyperbilirubinemia; Management; Methylprednisolone.

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Introduction

Neonatal jaundice (NNJ) is the yellowish discoloration of the skin, sclera, and mucosa caused by excess accumulation of bilirubin (hyperbilirubinemia) in the tissue and plasma (serum bilirubin level should be in excess of 5mg/dl).[1][2] It is classified into direct (conjugated) and indirect (unconjugated) hyperbilirubinemia based on the bilirubin that is accumulated in excess.[3] Unconjugated bilirubin in neonates presents a multifaceted challenge. While it demonstrably functions as an antioxidant at low concentrations, it can also exert neurotoxic effects on the developing brain. The safe threshold for bilirubin levels remains a subject of ongoing debate, particularly in preterm and low birth weight infants. Additionally, the degree of vulnerability to bilirubin toxicity varies significantly among individuals, with even a single newborn showing varying tolerance levels based on their specific clinical circumstances..[3] NNJ is a common condition occurring in about 60% of term and 80% of preterm infants in the first week of life.[4] It has different aetiologies, some related to genetic traits and geographical location.[4] In developed countries, feto-maternal blood group incompatibilities are the leading causes of NNJ, while in developing countries, the case is different; as it is mostly prematurity, glucose 6 phosphate dehydrogenase deficiency (G6PD), infections as well as effects of herbal medications in pregnancy, application of dusting powder on babies and use of naphthalene balls to store baby's clothes.[1] ABO incompatibility occurs in approximately 15% of all pregnancies, but hemolytic disease of the newborn develops in only 4%.[5] It is a congenital, inherent mismatch between maternal (usually blood type O) and fetal blood types(either A,B or AB).[6] It is more common and often more severe in infants of African descent. While most increases in bilirubin are benign, about 10% of term and 25% of preterm infants may develop severe hyperbilirubinaemia, leading to acute bilirubin encephalopathy and kernicterus.[1][4] These complications are preventable if jaundice is identified early and treated promptly.[4] In severe presentations of NNJ, a therapeutic strategy often encompasses a multifaceted approach, including phototherapy, exchange transfusion (EBT), and potentially, adjunctive therapies like intravenous immunoglobulin, D-penicillamine, metalloporphyrin, phenobarbital, zinc sulfate and clofibrate and methylprednisolone.[3] The primary goal for the management of NNJ is to avoid bilirubin- induced mortality and neurotoxicity in otherwise healthy newborn babies by preventing serum bilirubin from reaching potentially neurotoxic concentrations.[1][7] Phototherapy serves as the mainstay of treatment, facilitating the conversion of unconjugated bilirubin into water-soluble forms readily excreted by the body.[1][8] It is always the first line of treatment, regardless of side-effects including interference with mother–child bonding, imbalance of thermal environment, and water loss. However, in scenarios characterized by severe jaundice refractory to phototherapy or concerns regarding bilirubin-induced neurotoxicity, exchange blood transfusion (EBT) with or without adjuvants may be warranted.[1]

New treatments for neonatal jaundice help clear bilirubin faster, reduce phototherapy time and lower the need for exchange transfusions.[4] To be considered for routine clinical use, an alternative treatment strategy should be less invasive and at least as effective and safe as phototherapy. The best drug for adjuvant pharmacotherapy, for NNJ has not been identified. Methylprednisolone, a corticosteroid, may be implemented as an adjunct in specific cases of severe jaundice, particularly when underlying etiologies such as hemolysis or inflammation contribute to the condition.[9] Its mechanism of action involves suppression of red blood cell breakdown and modulation of the immune response, ultimately leading to a reduction in bilirubin production.

We present a unique case of severe NNJ occurring in the setting of ABO incompatibility, sepsis, family history of G6PD deficiency and the role of methyl prednisolone in the management.

Case Presentation

A 22 hour-old, 3kg term male neonate was brought to the special care baby unit (SCBU) of Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH), Bauchi, Nigeria with yellowness of the body noticed at the 15th hour of life. He was delivered via elective cesarean section to a 30-year-old para 4 +0 = 3 alive at 37-week gestation, indication being 3 previous scars. APGAR scores were 7 and 9 in the first and fifth minutes respectively. Pregnancy was booked and uneventful. Mother's prenatal tests were said to be normal. The mother's blood type was O rhesus D antigen positive while father was blood type B rhesus D antigen positive. No maternal risk for sepsis, no use of icterogenic substances like naphthalene balls or henna. Both parents are medical practitioners. There was a positive family history of neonatal jaundice in all 3 siblings within the first week of life. The first sibling (male) had jaundice which resolved with phototherapy but at one year of age, jaundice reoccurred warranting investigation for G6PD deficiency (qualitative) which was found to be reactive. The second sibling died following jaundice-related complication. The third sibling (female) had severe jaundice necessitating several EBTs and use of methyl prednisolone before resolution. She is alive and healthy.

Physical examination of the index case revealed temperature of 37.2^{o}C and generalized jaundice (Kramer 5). He was not pale nor dehydrated. No dysmorphic features were appreciated. BIND score was zero.

A diagnosis of severe NNJ 2^{o} to ABO incompatibility was made. Admitting serum bilirubin (SB) was total SB (TSB) of 25mg/dL (425umol/L), direct Coombs test (DCT) was positive; baby's blood group was B positive. The baby immediately commenced intensive phototherapy and had double volume EBT with a compatible blood within 5hrs of admission. Despite ongoing phototherapy, total bilirubin levels rose significantly 29.7 mg/dL (504.9umol/L), with a predominant indirect fraction 26.9 mg/dL (457.3umol/L), suggesting continued hemolysis. Three additional exchange transfusions with supplemental blood transfusions were performed over the next three days due to persistently high unconjugated hyperbilirubinemia and pallor. Additionally, fever was noted. Given the refractory severe NNJ despite treatment, the presence of fever, and the family history of G6PD deficiency, a differential diagnosis of ABO incompatibility with superimposed sepsis and G6PD deficiency was entertained. While CBC was suggestive of sepsis, G6PD assay was deferred due to recent blood transfusions and non-availability in the centre. To address the refractory jaundice, a multidisciplinary approach was adopted, involving consultations with clinical hematology and chemical pathology specialists, the treatment strategy was escalated as follows by day four: 1) No more EBT 2) Empiric intravenous ceftazidime was initiated to address potential sepsis. 3) Due to intravenous immunoglobulin IVIG unavailability, methylprednisolone (1mg/kg/day in two divided doses) was used as an alternative immunomodulator, following the sibling's successful response to the same treatment for a similar condition. 4) An additional phototherapy unit with white reflective linens was employed to maximize its efficacy (irradiance of 80uw/nm/cm) Figure 2.

Breastfeeding was discontinued, and the neonate was transitioned to intravenous fluids to optimize bilirubin clearance via adequate hydration and uninterrupted light exposure. By day 5, hyperbilirubinemia demonstrated signs of improvement, with complete resolution by day 7. The unconjugated bilirubin level at that time was 7.0 mg/dL (119umol/L). Notably, no evidence of neurological deficits was observed during admission or at any subsequent follow-up visits. A G6PD enzyme assay to evaluate for the deficiency remains outstanding due to logistical constraints. While urinalysis revealed the presence of bilirubin (+2), blood (+3), and urobilinogen (+), with a urine pH of 7, it is noteworthy that both liver function tests and abdominal ultrasound performed during admission were unremarkable.
Figure 1 shows the serum bilirubin distribution during the period of admission.

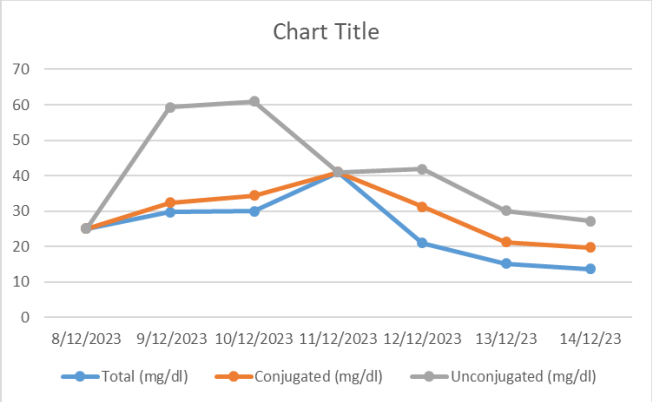

Figure 1. Line graph illustrating the distribution of serum bilirubin over time during admission

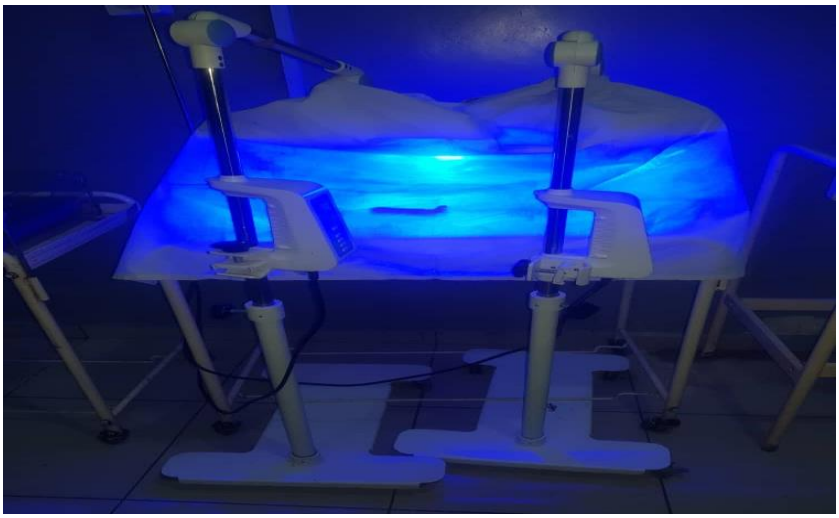

Figure 2. Phototherapy optimization

Ethics Approval and consent

Ethics approval and consent to participate was obtained from the health research ethics committee of the Abubakar Tafawa Balewa University Teaching Hospital. Informed consent from the parents of neonates was obtained. Additionally, the confidentiality of information was assured, and this study was conducted following the declaration of Helsinki. The patient provided written informed consent for the publication of this case report and accompanying images.

Discussion

NNJ remains an important cause of morbidity and mortality in neonates. Among the conditions leading to unconjugated hyperbilirubinemia are increased hemolysis due to infections or immunologic causes like Rhesus, ABO, and other blood group incompatibilities, or hemolytic anemias resulting from inherent defects and enzyme abnormalities like G6PD deficiency.[10] ABO incompatibility occurs almost exclusively in the offspring of women of blood group O; it rarely develops in group A mothers with high titre anti- IgG. Haemolysis due to anti-A is more common (1 in 150 births) than that to anti- B immune antibodies. [6] This case exhibited a classic presentation indicative of ABO incompatibility as the primary etiology of hemolysis. This constellation of findings included a blood group discrepancy (mother O+,

infant B+) and a positive direct Coombs test. The onset of jaundice within the first 24 hours of life aligns with the expected presentation in ABO incompatibility. However, unlike the typically mild and isolated presentation of jaundice with minimal or absent anemia, this case demonstrated a marked deviation from this pattern exhibiting rapidly progressing severe jaundice reaching significant values of 25mg/dl within 7 hours of it being noticed accompanied by severe anemia.

G6PD deficiency is an X-linked recessive disorder characterized by a mutation in the gene responsible for G6PD enzyme production. This enzyme plays a critical role in protecting red blood cells from oxidative stress.[11] Its deficiency can lead to a spectrum of clinical presentations, including neonatal jaundice that may be rapidly progressive and accompanied by anemia,[11] as observed in this case. The rapid hemolytic course, male gender, and positive family history for G6PD deficiency raised clinical suspicion for this condition. Though blood film was normal, the unavailability of diagnostic testing at our facility and recent blood transfusions unfortunately precluded definitive confirmation.

Sepsis is known to cause severe neonatal jaundice solely or in combination through a dual mechanism - increased red blood cell destruction (hemolysis) and hepatocellular dysfunction, including intrahepatic cholestasis.[1] In this case, the neonate developed fever during admission, and a complete blood count (CBC) suggested the presence of sepsis. This suggests that sepsis may have played a significant role in the development of severe jaundice.

Neonatal hyperbilirubinemia, though frequent (60% of term neonates), is usually seen within the first week of life and often self-limiting. While some research suggests a potential antioxidant role for bilirubin, our case highlights the complexities that can arise when multiple factors contribute to severe hyperbilirubinemia.

The treatment of severe NNJ is usually with phototherapy with or without EBT, in our case despite initial interventions including intensive phototherapy, exchange transfusion, and broad-spectrum antibiotics, serum bilirubin levels continued to rise with worsening anemia of which, use of immunomodulative therapy was considered. Intravenous immunoglobulin (IVIG) is a well-established treatment for severe jaundice associated with sepsis, ABO isoimmunization, and G6PD deficiency.[12] Its effectiveness in reducing the need for repeated exchange blood transfusions (EBTs) is well-documented[12] Unfortunately, in this case, despite recognizing the potential benefit of IVIG, its unavailability necessitated exploration of alternative treatment strategies. While no prior studies have definitively proven the efficacy of methylprednisolone in NNJ, its successful use in the patient's sibling with similar ABO isoimmunization and a history of three EBTs presented a compelling rationale for its consideration. Also, optimizing phototherapy efficiency was paramount to minimize the need for further EBTs, as the neonate had already undergone four procedures with persistent significant hyperbilirubinemia. Our primary concern was to prevent neurological complications associated with severe jaundice, while simultaneously mitigating the potential risks of repeated EBTs, for which a definitive safety threshold regarding the number of procedures is not established. This scenario presented a significant treatment dilemma, requiring a careful balance between the potential benefits and risks of various treatment options, particularly the off-label use of methylprednisolone. While the efficacy of methylprednisolone use in sepsis remains controversial, with some studies reporting adverse effects or lack of benefit,[13] its potent anti-inflammatory and immunomodulatory properties offered a potential therapeutic approach for this patient.[14] The decision to administer methylprednisolone was informed by the hypothesis that its core properties/effects could help mitigate ongoing inflammation, modulate the immune response, reduce hemolysis, and enhance hepatic bilirubin uptake and clearance.[11][15][16] Although the risks associated with corticosteroid use in neonates cannot be ignored, the therapeutic strategy ultimately proved successful, as jaundice improved within hours. To the best of our knowledge, this case report describes a unique application of methylprednisolone in the management of severe NNJ.

Following clinical improvement, the neonate was discharged home with a structured follow-up plan at the neonatal clinic. The child is currently developing well with no evidence of neurologic deficit.

Conclusion

This case highlights the complexities associated with managing severe, rapidly progressive neonatal hyperbilirubinemia. Optimal outcomes in neonates with jaundice arising from a combination of causes necessitate a multidisciplinary approach in management. In select cases like ours, alternative therapies beyond phototherapy and exchange transfusion, such as methylprednisolone, may be considered especially in resource poor setting where IVIG is not readily accessible either due to unavailability or cost constraint factors. Timely intervention and meticulous serial monitoring are essential to mitigate potential complications and improve the overall prognosis for these vulnerable neonates.

Recommendations

Further research is warranted to elucidate the broader role of methylprednisolone in managing severe neonatal hyperbilirubinemia associated with this specific combination of etiological factors. Routine G6PD screening for all neonates with jaundice should be made readily available.

Limitation

Definitive diagnosis of G6PD deficiency was hampered by non-availability of the definitive test and prior blood transfusions.

Declarations

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Conflict of interest statement

The authors affirm that they have no competing financial interests or personal

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