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Misdiagnosis of Cholestasis in a Neonate with Dubin-Johnson Syndrome: A Pre- and Postmortem Report

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Abstract

Dubin–Johnson syndrome (DJS) that commonly known as "black liver disease, is a hereditary disease," DJS affects individuals of all around the world. This case report explores the challenges involved in diagnosing neonatal cholestasis and emphasizes the importance of considering rare genetic disorders in the differential diagnosis. It describes the clinical experience of a newborn with cholestasis who was initially misdiagnosed with common causes, which unfortunately led to a fatal outcome. Postmortem analysis confirmed Dubin-Johnson syndrome (DJS), a rare hereditary cause of conjugated hyperbilirubinemia. The report highlights the subtle presentation of DJS, atypical hematological disturbances, and the severe systemic impact. This case underscores the need for early genetic testing and a thorough diagnostic approach that considers rare disorders like DJS to improve neonatal outcomes.

Keywords: Dubin-Johnson syndrome, Forensic, neonatal cholestasis, death, case report

Introduction:

In the intricate field of neonatal medicine, accurate diagnosis is paramount to ensure appropriate treatment and management. Cholestasis in neonates presents a diagnostic challenge due to its varied etiology, ranging from common transient conditions to rare genetic disorders (1, 2). Neonatal cholestasis, characterized by conjugated hyperbilirubinemia, can result in liver damage and impaired bile flow, necessitating prompt management to prevent adverse outcomes (3). Additionally, cases of severe cholestasis in neonates with hemolytic anemia, like pyruvate kinase deficiency, have been reported, underlining the complexity and potential fatality of cholestatic conditions (4). The mortality rate associated with cholestasis varies depending on the underlying causes and patient populations. In very preterm infants, cholestasis was linked to increased mortality, with a rate of 13.5% in cholestatic infants compared to 2.7% in controls (5). Predictors of mortality in neonates with cholestasis included higher total bilirubin levels and lower albumin levels, with ursodeoxycholic acid potentially impacting survival

rates (6). Timely recognition is crucial for improving outcomes in neonatal cholestasis, as it may indicate correctable surgical conditions or genetic/metabolic disorders that require prompt medical attention (2, 7). The early genetic testing is crucial for accurate differential diagnosis in neonates (1).

Among the causes of cholestasis, Dubin-Johnson syndrome, an autosomal recessive liver disorder, stands out as a rare hereditary cause of conjugated hyperbilirubinemia, often overshadowed by more prevalent diseases (8, 9). It mainly manifests as long-term fluctuation jaundice (10). This syndrome occurs in all nationalities (11).

This case report delves into the clinical journey of a neonate initially misdiagnosed with common causes of cholestasis, unraveling the complexities that led to the eventual postmortem confirmation of Dubin-Johnson syndrome. Through a detailed pre- and postmortem analysis, we aim to shed light on the diagnostic pitfalls and underscore the significance of considering rare disorders in differential diagnoses to foster better clinical outcomes.

Case Report

A 14-day-old baby boy was admitted to the hospital with tachypnea. The prenatal and birth history were unremarkable, and the family had no known history of liver disorders. Upon physical examination, no definitive abnormalities were noted. However, laboratory tests revealed significant hematological disturbances: an elevated white cell count (69,800), thrombocytopenia with a platelet count of 70,000, and markedly prolonged prothrombin time (PT 41 seconds, INR=6). The total bilirubin level was significantly elevated at 18 mg/dL with a direct bilirubin level of 2.31 mg/dL. Direct Coombs test was negative. The neonate received supportive care during hospitalization; however, his condition deteriorated over 14 days, developing edema and ecchymosis, particularly on the abdomen. Tragically, the baby succumbed to his condition.

The autopsy revealed an enlarged liver with darker coloration than normal. No cardiac anomalies were detected, but there was evidence of cerebral hemorrhage in the occipital region. Histopathological examination of the liver showed diffuse deposition of coarse granular dark pigment within hepatocytes on hematoxylin and eosin (H&E) staining.

The cause of death was determined to be acute respiratory distress secondary to Hydrops fetalis, which followed an inherited liver disorder—Dubin-Johnson syndrome.

Discussion

The presented case highlights the diagnostic challenges and clinical implications of neonatal cholestasis, particularly when associated with rare genetic disorders like Dubin-Johnson syndrome (DJS). Dubin-Johnson syndrome was described in 1954(12). DJs is a very rare disease and reports are distributed around the world(10). There are a few case reports on neonatal-onset Dubin-Johnson syndrome (DJS), particularly from Iranian, Far-East Asia and Moroccan Jews, and Europe (13). A study of Jewish descent from Moroccan and Iranian revealed that Dubin-Johnson syndrome is common in these populations (prevalence of one per one thousand and three hundred individuals) (8). This syndrome is characterized by fluctuating conjugated hyper-bilirubinemia without hemolysis, and patients may suffer from nonspecific symptoms, such as abdominal discomfiture(11). Normal Alanine transaminase (ALT)-cholestasis in a well-looking neonate should trigger evaluation for DJs (13). Some children might have different degrees of hepatic function abnormality and cholestasis (14). DJs, as one cause of cholestasis, should be considered when the common causes for conjugated hyperbilirubinemia have been excluded, and patient has an increased percentage of direct bilirubin concentration relative to total bilirubin concentration (15).

The initial presentation of tachypnea and lack of definitive physical abnormalities underscore the subtlety with which DJS can manifest, often leading to misdiagnosis or delayed diagnosis. The significant hematological disturbances observed in this case, including elevated white cell count, thrombocytopenia, and prolonged prothrombin time, are not typical for DJS, which primarily presents with conjugated hyperbilirubinemia without overt hemolysis (16). This condition is often caused by defects in the ABCC2 gene, which encodes the multidrug resistance protein 2 (MRP2) (16). DJS is distinct from other forms of hyperbilirubinemia, such as Gilbert's syndrome and Rotor's syndrome, which are associated with unconjugated hyperbilirubinemia (17). This atypical presentation may have contributed to the initial misdiagnosis. The absence of hemolysis was further supported by a negative Direct Coombs test, ruling out immune-mediated hemolytic anemia as a cause of jaundice (18). However, it is important to note that a negative Direct Coombs test does not completely rule out the possibility of immune-mediated hemolytic anemia, as seen in a case of Coombs-negative severe hemolysis associated with hepatitis A (19).

The progression to edema and ecchymosis, along with autopsy findings of an enlarged liver with darker coloration and cerebral hemorrhage, indicates a severe systemic impact beyond the liver's dysfunction. These findings suggest that while DJS is often considered benign, its manifestations can be severe and life-threatening, as seen in this neonate who developed Hydrops fetalis—a condition often associated with fetal anemia but not commonly linked to DJS (20).

This case underscores the importance of considering inherited causes early in the differential diagnosis of neonatal cholestasis. While common conditions should not be overlooked, rare disorders like DJS should remain part of the differential, especially when clinical findings do not align with more prevalent diseases. Early genetic testing could facilitate timely diagnosis and management, potentially altering the clinical course (21, 22).

Conclusion:

In conclusion, this tragic case serves as a poignant reminder of the complexities surrounding neonatal cholestasis and the need for heightened awareness of rare genetic disorders like Dubin-Johnson syndrome. It calls for a more nuanced approach to diagnosis and management that balances consideration of both common and rare etiologies to improve outcomes for affected neonates.

Limitation:

It is important to note that this case report has a limitation, which is the retrospective nature of the diagnosis. The diagnosis relied on postmortem findings to confirm Dubin-Johnson syndrome. This limitation underscores the challenge of diagnosing rare genetic disorders in neonates. Symptoms of these disorders may overlap with more common conditions, potentially leading to misdiagnosis or delayed diagnosis during the patient's life.

Suggestions

To help with difficult diagnoses, it is recommended that newborns with cholestasis and unusual blood problems should have thorough genetic testing early on in their evaluation. This could help in identifying rare disorders like Dubin-Johnson syndrome promptly, leading to better management and potentially improving their clinical outcomes.

Ethical Considerations

Ethical Considerations: All ethical principles were considered in this article.

Funding: No finding

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