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Coexistence of Ebstein Anomaly and Neonatal Dubin-Johnson Syndrome with Rare ABCC2 Double Heterozygous Mutations: A Case Report

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Abstract

Ebstein anomaly is a rare congenital heart defect characterized by apical displacement of the tricuspid valve, while Dubin-Johnson syndrome (DJS) is a benign hepatic condition caused by ABCC2 mutations, leading to impaired biliary excretion of conjugated bilirubin. Although each disorder is uncommon on its own, their coexistence in a neonate has never been reported in the literature. We present a novel case of a preterm infant with persistent direct hyperbilirubinemia and incidentally diagnosed Ebstein anomaly, raising significant diagnostic challenges in the neonatal period. The coexistence of these two unrelated conditions in a neonate is extremely rare and, to our knowledge, has not been previously reported.

We report the case of preterm male neonate at 31 weeks' gestation with intrauterine growth restriction, developed progressive conjugated hyperbilirubinemia with elevated transaminases and normal gamma-glutamyl transferase (GGT), yet preserved synthetic liver function. Echocardiography revealed mild Ebstein anomaly, a secundum atrial septal defect, and partial anomalous pulmonary venous drainage. Comprehensive metabolic and infectious workups were unremarkable. Whole exome sequencing identified two rare compound heterozygous variants of uncertain significance (VUS) in the ABCC2 gene, which had been previously associated with impaired MRP2 transporter function and were consistent with the clinical picture of neonatal-onset DJS.

This case illustrates the importance of considering dual diagnoses in neonates presenting with persistent cholestasis alongside incidental cardiac anomalies. The use of early genetic testing helped avoid invasive procedures like liver biopsy and unnecessary surgical intervention for suspected biliary atresia. Furthermore, the case highlights the value of multidisciplinary collaboration and a high index of suspicion when managing complex neonatal presentations. By reporting this rare cardio-hepatic association, we aim to expand clinical awareness and emphasize the evolving role of genomics in neonatal diagnostics.

Keywords: Rare Case Report; Neonatal Cardiac Anomaly; Compound Heterozygous Mutation; Neonatal Cholestasis Dubin-Johnson Syndrome; Ebstein's Anomaly.

Introduction

Ebstein anomaly is a rare congenital heart condition that affects only about 0.005% of live births and is responsible for between 0.3 to 0.6% of all congenital heart disease [1]. The defect is characterized by malformation and downward displacement of the tricuspid valve [2]. This malformation results in the right ventricle being smaller than normal while the right atrium is larger than normal [2]. Tricuspid regurgitation is detected in almost all cases of Ebstein's anomaly, exposing patients to a high possibility of cardiac hypertrophy and heart failure [3]. Causes and risk factors of Ebstein's anomaly are largely unknown, but genetics and environmental factors are believed to be involved [4]. For instance, maternal exposure to some medication and cigarette smoke are believed to increase the possibility of the condition. The clinical presentation can vary, with some cases being asymptomatic, in which case it is detected incidentally. In neonates, it often presents through cyanosis, in infants through heart failure, and in children though murmur [1].

On the other hand, the Dubin-Johnson Syndrome (DJS) is a rare autosomal recessive liver disorder characterized by prolonged or intermittent jaundice and liver pigmentation [5]. The prevalence of DJS is estimated to be less than 1 in 100,000 globally [6], but it tends to be more common in certain ethnic groups, such as among Sephardic Jews, where incidence rates of up to 1 in 3000 have been reported [7]. Many of the symptoms of DJS are shared with other diseases, which increases the likelihood of misdiagnosis. Pathogenic mutations in the adenosine triphosphate-binding cassette subfamily C member 2(ABCC2) gene were first observed and described in 1997 [8]. Since then, more than 50 different mutations of the ABCC2 that cause significant have been confirmed in different DJS patients [5]. The mutations lead to the formation of a dysfunctional MRP2 protein or accelerate mRNA degradation, which then results in diminished glycosylation and impaired sorting [9]. Although most cases of DJS present during adolescence, they also occur among new-borns.

The current study reports the case of a neonate patient who presented with persistent conjugated hyperbilirubinemia and was subsequently found to have mild Ebstein's anomaly as well as DJS variants. Prior to this case, there was no any other known case of the two conditions coexisting in a single patient

Case Presentation

We present the case of a male neonate born to a 38-year-old gravida 4, para 3 mother who experienced premature prolonged rupture of membranes (PPROM) for 24 hours at 31 weeks' gestation. The pregnancy had been otherwise uneventful, and the mother had no significant medical history. She had previously delivered three children vaginally without complications. Due to the presence of fetal distress and meconium-stained amniotic fluid (MSAF), an emergency cesarean section was performed.

At birth, the infant was non-vigorous, covered in thick MSAF, and had Apgar scores of 5 and 8 at 1 and 5 minutes, respectively. Initial resuscitation included one cycle of positive pressure ventilation followed by endotracheal intubation. He weighed 1.56 kg, indicating intrauterine growth restriction (IUGR), and was clinically estimated to be 33-34 weeks gestational age. The neonate was transferred to the neonatal intensive care unit (NICU) for further management.

On initial physical examination, the baby appeared active, pink, and non-dysmorphic. He had no apparent major anomalies except for right-sided talipes. Cardiovascular examination was unremarkable, with normal heart sounds and no audible murmur. Respiratory examination showed equal air entry through the endotracheal tube. Neurological reflexes were intact, and the musculoskeletal and abdominal exams were within normal limits, with a patent anus and palpable testes.

The infant was managed in the NICU with a dose of intratracheal surfactant (Survanta), empiric antibiotics ampicillin and gentamicin, caffeine citrate, and supportive care. He was initially kept NPO and later transitioned to enteral feeding with expressed breast milk. Phototherapy was initiated for neonatal jaundice. He was extubated successfully within the first 24 hours of life, and respiratory status improved steadily with non-invasive ventilation.

In the second week of life, laboratory evaluation revealed persistently elevated bilirubin levels, with a total bilirubin peaking at 20.5 mg/dL and a direct conjugated component of 10.2 mg/dL. Liver function tests showed elevated Alanine Transaminase (130-199 IU/L) and Aspartate aminotransferase (300-525 IU/L), while gamma-glutamyl transferase (GGT) remained within normal range (60 - 64 IU/L) as detailed in (Table 1), which presents a chronological summary of key laboratory parameters including bilirubin levels and liver enzymes, organized by postnatal day. Albumin and INR levels were stable, and synthetic liver function was preserved. The infant had pigmented stools, though they were occasionally lighter than expected. Abdominal ultrasound revealed a normal hepatobiliary anatomy with no signs of obstruction or biliary atresia. Cranial imaging was unremarkable.

Liver function test	Lab values	Normal values*
Day 3 of Admission		
Total Bilirubin	15.2 mg/dL**	0.2 – 1.2 mg/dL
Direct Bilirubin	7.6 mg/dL	0.0 – 0.50 mg/dL
Alanine Transaminase	130 U/L***	5 – 55 U/L
Aspartate aminotransferase	130 U/L	5 – 34 U/L
Gamma-Glutamyl Transferase	62 U/L	12 – 64 U/L
Day 7 of Admission		
Total Bilirubin	20.5 mg/dL	0.2 – 1.2 mg/dL
Direct Bilirubin	10.2 mg/dL	0.0 – 0.50 mg/dL
Alanine Transaminase	150 U/L	5 – 55 U/L
Aspartate aminotransferase	480 U/L	5 – 34 U/L
Gamma-Glutamyl Transferase	60 U/L	12 – 64 U/L
Day 14 of Admission		
Total Bilirubin		
	22.6 mg/dL	0.2 – 1.2 mg/dL
Direct Bilirubin	11.6 mg/dL	0.0 – 0.50 mg/dL
Alanine Transaminase	199 U/L	5 – 55 U/L
Aspartate aminotransferase	525 U/L	5 – 34 U/L
Gamma-Glutamyl Transferase	64 U/L	12 – 64 U/L
Day 30 of Admission		
Total Bilirubin	16.1 mg/dL	0.2 – 1.2 mg/dL
	8.2 mg/dL	
Direct Bilirubin	102 U/L,	0.0 – 0.50 mg/dL
Alanine Transaminase	310 U/L	5 – 55 U/L
Aspartate aminotransferase	64 U/L	5 – 34 U/L
Gamma-Glutamyl Transferase		12 – 64 U/L

*Pediatrics normal laboratory values, department of pediatrics, Abha maternity and children hospital, Kingdome of Saudi Arabia.
** Milligrams per Deciliter
*** Units per liter

Table 1: liver function test reports

Given the direct hyperbilirubinemia with normal GGT and preserved liver function, a differential diagnosis including progressive familial intrahepatic cholestasis (PFIC), Dubin-Johnson syndrome (DJS), bile acid synthesis defects, and neonatal metabolic or mitochondrial hepatopathies was considered. Comprehensive metabolic screening, including GALT, biotinidase, and carnitine levels, returned normal. Urinalysis was negative for reducing substances and tyrosinemia screening was also unremarkable.

During the course of evaluation, echocardiography revealed a mild form of Ebstein anomaly characterized by apical displacement of the tricuspid valve. Additionally, a small secundum atrial septal defect with left-to-right shunt and partial anomalous pulmonary venous drainage (PAPVD) of the left upper pulmonary vein to the innominate vein were identified. Computer Tomography chest angiography confirmed these findings, and left ventricular function was preserved. As Shown in (Figure 1), Electrocardiography showed bradycardia and a prolonged QT interval. No arrhythmias or signs of heart failure were observed.

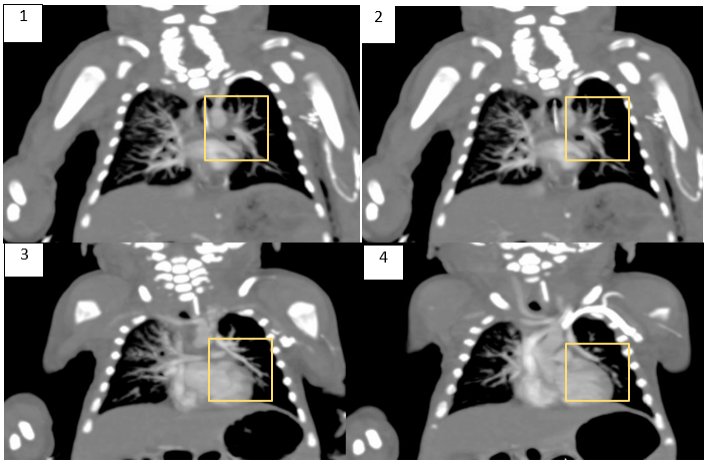

Figure 1: Computer Tomography chest angiography

Due to the unusual combination of clinical findings and persistent cholestasis, whole exome sequencing was (WES) performed and revealed two heterozygous variants of uncertain significance (VUS) as shown in (Table 2). These findings were interpreted as being consistent with Dubin-Johnson syndrome in the appropriate clinical context, as both variants have been previously reported in association with impaired MRP2 function.

Gene &transcript	cDNA	Amino acid change	Zygosity	MAF*	Classification & (CADD** score)	OMIM phenotype & (inheritance)
ABCC2	c.908A>G	p.Lys303Arg	Heterozygous	0.00%	VUS (<10)	Dubin–Johnson syndrome (AR)
(NM_000392.5)	c.4179G>T	p.Met1393Il	Heterozygous	0.00%	VUS (23.6)	
*MAF (minor allele frequency) based on gnome data. **[Deleterious: >= 20, Likely Deleterious: 10 to 19, Unlikely Deleterious: <10]						

Table 2: Whole Exome Sequences (WES) have identified two heterozygous variants in the ABCC2 gene.

The case was reviewed by a multidisciplinary team including pediatric gastroenterology, cardiology, and genetics. Based on the available data, the final impression was a rare co- occurrence of Ebstein anomaly and Dubin–Johnson syndrome. The preserved synthetic liver function, normal GGT, pigmented stools, and lack of hepatomegaly strongly argued against PFIC or other progressive hepatobiliary conditions. The patient was discharged in stable condition on ursodeoxycholic acid and scheduled for follow-up in pediatric gastroenterology and cardiology clinics. Genetic counselling was provided to the family.

This case highlights the importance of considering multiple concurrent rare diagnoses in neonates with complex presentations. To our knowledge, this is the first reported case of Dubin–Johnson syndrome occurring concurrently with Ebstein anomaly in a single patient.

Discussion

The current case is an extremely rare occurrence in which a preterm neonate presents with both Ebstein anomaly and DJS. Early examination revealed the presence of fetal distress and meconium-stained amniotic fluid (MSAF). The presence of direct hyperbilirubinemia with normal GGT and preserved liver function, diagnosis pointed to intrahepatic cholestatic disorders, such as DJS, which was confirmed by the confirmation of two heterozygous ABCC2 variants of uncertain significance. The advancement of sequencing technology has significantly improved research of complex disorders like DJS, evidenced by the detection of multiple ABCC2 mutations in DJS patients [5]. Some of the ABCC2 mutations that have previously been established in DJS patients include gene deletions, missense mutations, nonsense mutations, and splice site mutation [5]. In our case, whole exome sequencing

(WES) identified two variants of uncertain significance (VUS) in the ABCC2 gene (c.908A>G (p.Lys303Arg) and c.4179G>T (p.Met1393Ile)). Although the mutations are classified as VUS, their presence in compound heterozygosity coupled with other clinical features supported the diagnosis of DJS.

The complexity of our case was increased by the presence of Ebstein anomaly. Ordinarily, this condition can range from minimal to severe, with extreme deformity of the tricuspid valve exposing the patient to congestive heart failure and death [1]. In our case, however, Ebstein anomaly was mild, marked by apical displacement of the tricuspid valve, a small secundum atrial septal defect with left-to-right shunt, and PAPVD of the left upper pulmonary vein to the innominate vein.

The co-occurrence of Ebstein anomaly with DJS not only increased complexity in the management of the case but also opened the door for future research. Although the chances of coincidental occurrence are high given that there is no reported link between ABCC2 mutations and cardiac malfunctions, the possibility of shared developmental pathways should not be ruled out.

In cases where DJS has occurred independently, the management of the disease has mostly been effective [10]. Elsewhere, mild forms of Ebstein anomaly, such as in our case where there was no significant tricuspid regurgitation or arrhythmias ordinarily remain stable [1]. However, co-existence of the two conditions, even in mild form, increases risk of poor prognosis, especially given that it is the first known case of co-existence. Management of the current case focused heavily on stabilization, nutritional optimization, and phototherapy, which stabilized the patient. Ursodeoxycholic acid for was issued on discharge for cholestasis, while genetic counselling to the family not only informed appropriate management of the current case but also educated them regarding future reproductive decisions. However, long-term follow-up is still necessary to monitor potential unknown complications. Moreover, the documentation of such rare cases is critical for the development of medical literature regarding the two conditions as well as forming the basis for additional research on the potential genetic or developmental links between the two conditions

Conclusion

This case illustrates the importance of multidisciplinary collaboration and genetic investigation in neonates with complex presentations. The coexistence of two rare conditions-Ebstein anomaly and neonatal Dubin-Johnson syndrome-demonstrates that comprehensive evaluation can reveal dual diagnoses that, if overlooked, may lead to suboptimal care. The presence of a double heterozygous ABCC2 mutation, including a variant of uncertain significance, underscores the diagnostic value of early genetic analysis. Recognition of such dual presentations can prevent unnecessary interventions and optimize patient outcomes. Reporting such rare associations contributes to the collective understanding of neonatal pathology and emphasizes the evolving role of genetics in modern neonatal medicine.

Declarations

Contributors: All authors contributed to planning, literature review and conduct of the review article. All authors have reviewed and agreed on the final manuscript.

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