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Delayed Diagnosis of Crigler-Najjar Disease: A Case Report of a 17-Year-Old Man with Progressive Jaundice

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ABSTRACT

Crigler-Najjar syndrome type II is a metabolic disorder stemming from mutations in the UGT1A1 gene, resulting in heightened levels of unconjugated bilirubin. Here is a case report of a 17-year-old male patient with minor thalassemia and G6PD deficiency who was referred due to worsening jaundice. He has had a history of lifelong jaundice, which has intensified over the past year and a half. Subsequently, the patient was diagnosed with Crigler-Najjar type II based on his medical history, clinical examination, and laboratory findings. Furthermore, the patient's positive response to phenobarbital treatment confirmed the diagnosis. Consequently, it is imperative to consider Crigler-Najjar syndrome in cases of unexplained unconjugated hyperbilirubinemia.

Introduction

Crigler-Najjar syndrome type II (OMIN: 606785) is a rare genetic disorder inherited in an autosomal recessive manner. The prevalence of Crigler-Najjar syndrome (CN-II) is approximately 0.6 to 1 case per million births [1]. Due to the mutation in the UGT1A1 gene, the natural function of the bilirubin-uridine (UDP)-glucuronosyltransferase enzyme is impaired, leading to the accumulation of unconjugated bilirubin and the clinical presentation of this syndrome. The UDP-glucuronosyltransferase enzyme is required for the glucuronidation of unconjugated bilirubin in the liver, converting it to a more soluble product that can be easily eliminated by the kidneys [2].

In cases where there is a complete absence of UGT1A1 enzyme activity, the condition is classified as type I, which does not respond to phenobarbital. Conversely, a partial loss of UGT1A1 activity results in type II, which can be responsive to phenobarbital treatment [3]. In CNS type II or mild CNS, the unconjugated bilirubin (UCB) level is between 102 and 340 µmol/L (6-20 mg/dL) [4]. Consequently, type II is less severe

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and demonstrates a more favorable prognosis, with patients presenting persistent jaundice. The bilirubin level in CN II may be elevated with stress, fatigue, infection, pregnancy, or certain specific drugs.

Among clinical presentations, prolonged neonatal jaundice lasting longer than 14 days in term infants and 21 days in preterm infants is the most frequent phenomenon. Physical examination in these patients is essentially normal, apart from icterus. The outlook for Crigler-Najjar syndrome type II (CN-II) is favorable. During the neonatal phase, infants diagnosed with CN-II should undergo phototherapy and exchange transfusion, similar to the approach for CN-I, due to their tendency to experience neonatal hyperbilirubinemia and prolonged unconjugated hyperbilirubinemia linked to breastfeeding (known as breast milk jaundice) [5]. At this stage, the expression of UGT1A1 in the liver is only 1% of that observed in adults.

In the case report below, we present a young male patient with progressive jaundice since early childhood. Further examinations revealed unconjugated hyperbilirubinemia with normal liver enzymes, a negative hemolytic panel, and mild splenomegaly. The patient exhibited a UGT1A1 gene defect and demonstrated a highly favorable response to phenobarbital treatment, leading to a significant reduction in serum bilirubin levels. The purpose of this report is to raise awareness among physicians about this benign condition and emphasize the importance of avoiding unnecessary investigations.

Case presentation

A 17-year-old male patient with minor thalassemia and G6PD deficiency was referred to the hepatology department for further investigation due to exacerbated jaundice. The patient has a history of jaundice throughout his life but reported an increase in intensity over the last year and a half. The patient did not mention symptoms such as weakness, itching, changes in urine or feces color, arthralgia, myalgia, weight loss, loss of appetite, fever, or abdominal pain. Furthermore, he denied any recent intravenous drug use, contact with chemicals, recent travel, or contact with a person suffering from jaundice.

His medical history includes minor thalassemia, gastroesophageal reflux, urinary tract stricture surgery, and a history of phototherapy in infancy due to jaundice. The patient also provided details of his current medications and family medical history. His drug history included propranolol, sertraline, fluconazole, and antifungal topical ointment. His family history revealed minor thalassemia, hyperthyroidism, and hypertension in his father; minor thalassemia in his sister; and a history of intrauterine fetal demise (IUFD) in one of his siblings without any known chromosomal disorder.

In the review of systems, he reported recent weight loss and periodic weakness. His skin examination revealed a rash, itching in fungal areas, and skin discoloration (worsening jaundice) (Figure 1, Figure 2). His vital signs were within normal limits (blood pressure: 125/95 mmHg, pulse rate: 85/min, respiratory rate: 19/min, temperature: 37°C, O2 saturation: 98%). The physical examination revealed pale conjunctiva, icteric sclera, and obvious jaundice on the trunk (Figure 3). In the abdominal examination, the spleen was found about two centimeters below the edge of the rib, and the liver about one centimeter below the edge of the rib.

In the medical history of the patient, at the age of two days, he was admitted to the hospital due to jaundice and underwent phototherapy. In the laboratory tests at 29 days old, the G6PD level was sufficient (total bilirubin: 3.6, direct bilirubin: 0.2). At the age of four, an ultrasound showed that the liver, bile ducts, gall bladder, kidneys, pancreas, and spleen were normal. From this date, due to laboratory data revealing G6PD deficiency, caution was observed regarding drug and food care, especially beans. Follow-up lab data illustrated (total bilirubin: 2, direct bilirubin: 0.2) at six years old and (total bilirubin: 3.1, direct bilirubin: 0.2) at ten years old. Following the exacerbation of jaundice at the age of 16, he was referred to an

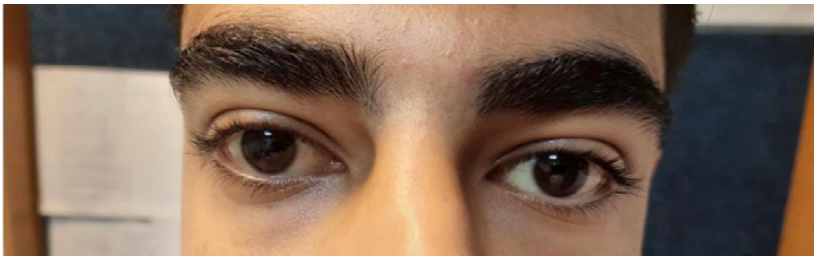

Fig. 1. Yellowish discoloration of patients' sclera and skin

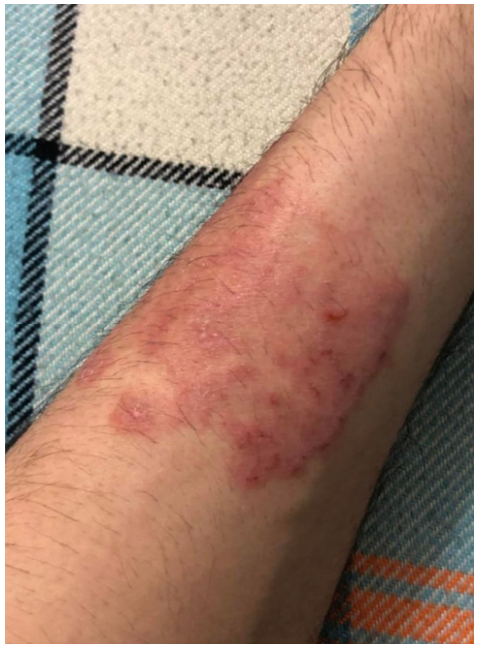

Fig. 2. Fungal lesions in patients' forearm

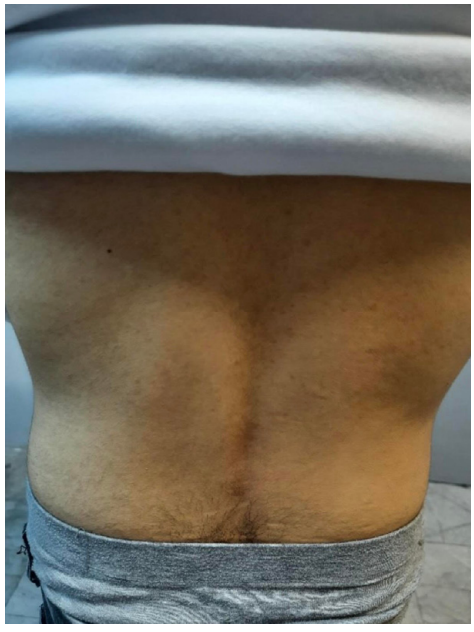

Fig. 3. Jaundice is apparent in patients' body

Table 1. Laboratory findings.

WBC	6**000**	**AST**	17
RBC	4.82	ALT	15
Hb	10.6	ALK	316
Hct	35.8	Bill T	15.7
MCV	77	Bill D	0.6
MCH	24	Fe (Iron)	110
MCHC	31.6	TIBC	285
Platelet	153	Ferritin	98
RDW	17.9	G6PD	Deficient
Direct Coombs	Negative	Ceruloplasmin	42
Indirect Coombs	Negative	LDH	299

internal medicine ward, showing grade 1 fatty liver in ultrasound investigation and (total bilirubin: 8.5, direct bilirubin: 0.6). Due to the increase in bilirubin at the age of 16, the patient was diagnosed with Gilbert's syndrome. At the age of 17, owing to the tests (total bilirubin: 15.7, direct bilirubin: 0.6), he was referred to a hepatologist for further investigations (Table 1).

Moreover, in a current ultrasonography after the admission, the dimensions of the liver were larger than normal (164 mm). The liver parenchymal echo was normal and uniform. No space-occupying lesion was evident in the liver. The gallbladder had normal wall volume and thickness. A stone with a diameter of 10 mm was seen in the lower part of the gallbladder. The spleen was seen with normal echo and dimensions of 77x182 mm, which is larger than normal. Liver enzymes were also within the normal range.

Owing to markedly elevated bilirubin levels, diagnoses such as Gilbert's syndrome and hemolysis attributable to G6PD deficiency were deemed improbable. Consequently, a strong inclination towards Crigler-Najjar syndrome type 2 was acknowledged. In light of limited access to genetic investigation, the consideration of an exploratory intervention involving phenobarbital treatment was entertained. Phenobarbital is known to elicit the UGT1A1 enzyme, and an ensuing reduction in bilirubin levels subsequent to its administration could serve to substantiate the diagnosis.

Based on patient history, clinical examination, and laboratory findings, CN-II was diagnosed. Upon considering the diagnosis of Crigler-Najjar type 2, phenobarbital was administered to the patient. Subsequently, during the one-month follow-up, the bilirubin level decreased to 1, and the patient expressed satisfaction with the treatment received

Discussion

Crigler–Najjar syndrome (CNS) is a rare autosomal recessive inherited non-hemolytic unconjugated hyperbilirubinemia caused by UDP-glucuronosyltransferase deficiency. It is characterized by intermittent jaundice triggered by stress and is typically managed through conservative treatments. Permanent neurological damage is rare in CN2, as these patients have residual UGT1A1 enzymatic activity (less than 10%), which protects them from developing serious neurological damage. Furthermore, the need for a liver transplant is infrequent in CN2. Although symptoms of the disease often start in newborns (birth to 4 weeks) or infancy (1 to 23 months), in our case, the presentation and diagnosis of Crigler-Najjar were delayed until the patient was seventeen years old.

The treatment approach for CNS type 2 typically involves avoiding medications that may displace bilirubin from albumin, such as penicillin, sulphonamides, salicylates, ceftriaxone, and furosemide [6]. It is recommended to administer phenobarbital for a lifetime to eliminate the risk of kernicterus, despite this risk being minimal. The suggested dosage of phenobarbital ranges from 3-5 mg/kg/day, with adjustments to achieve a daily intake of 60-180 mg, either in single or divided doses [5, 7]. Typically, patients exhibit a therapeutic response within two to three weeks. Serum bilirubin levels can decrease by more than 30% after phenobarbital therapy [8]; similarly, in our study, the phenobarbital level decreased to normal after the treatment period.

The management approach includes providing counseling on dietary modification, ensuring adequate hydration, avoiding triggers such as stress or fasting, and recommending lifelong phenobarbital therapy. Genetic counseling, particularly concerning consanguinity, is an important aspect of management in conjunction with regular follow-up. Currently, available treatment strategies can halt the progression of complications; however, there is a need for the development of therapies targeting specific gene mutations.

Conclusion

In summary, this case report underscores the clinical importance of Crigler-Najjar syndrome type II, notably in patients who exhibit unexplained unconjugated hyperbilirubinemia. Such cases may remain undiagnosed until later in the lifespan, highlighting the imperative need for heightened clinical awareness. This report emphasizes that clinicians should include CNS2 in their differential diagnoses when encountering patients with persistent jaundice and elevated unconjugated bilirubin levels. Early diagnosis and intervention are pivotal, as they can lead to significant advancements in patient outcomes and overall quality of life. The findings advocate for ongoing education and training for healthcare providers regarding this rare but impactful condition, ensuring that symptoms are recognized promptly and managed effectively.

By improving a deeper understanding of CNS2, we can enhance patient care and mitigate the risks associated with this syndrome, ultimately contributing to better health outcomes for affected individuals. This literature also opens a new avenue in the investigations about jaundice and invites hepatologists for further research.

Ethical Considerations

Ethical Approval

The authors' institute provided ethical approval for this case study.

Patient consent

Written informed consent was obtained from patient to publish this case report and utilizing the radiological images.

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Authors' contribution

P.B: did the procedure, managed the patient and led to the ultimate diagnosis and the current study. F.F and S.R: collected the data and write the manuscript.

Conflict of Interests

The authors state that this publication process does not involve any conflicts of interest.

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None.

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References

[1] Ebrahimi A, Rahim F. Crigler-Najjar syndrome: Current perspectives and the application of clinical genetics. Endocr Metab Immune Disord Drug Targets. 2018;18(3):201-11. https://doi.org/10.2174/1871530318666171213153130

[2] Gailite L, Valenzuela-Palomo A, Sanoguera-Miralles L, Rots D, Kreile M, Velasco EA. UGT1A1 variants c. 864+ 5G> T and c. 996+ 2_996+ 5del of a Crigler-Najjar patient induce aberrant splicing in minigene assays. Front Genet. 2020;11:169. https://doi.org/10.3389/fgene.2020.00169

[3] Strassburg CP. Hyperbilirubinemia syndromes (Gilbert-Meulengracht, crigler-najjar, dubin-johnson, and rotor syndrome). Best Pract Res Clin Gastroenterol. 2010;24(5):555-71. https://doi.org/10.1016/j.bpg.2010.07.007

[4] Zheng B, Hu G, Yu J, Liu Z. Crigler-Najjar syndrome type II in a Chinese boy resulting from three mutations in the bilirubin uridine 5'-diphosphate-glucuronosyltransferase (UGT1A1) gene and a family genetic analysis. BMC Pediatr. 2014;14:1-4. https://doi.org/10.1186/1471-2431-14-267

[5] Ranjan P, Kohli S, Saxena R, Thakur S. Mutation analysis in Crigler-Najjar Syndrome type ii-case report and literature review. J Clin Exp Hepatol. 2011;1(3):204-6. https://doi.org/10.1016/S0973-6883(11)60239-9

[6] Nair KM, Lohse P, Nampoothiri S. Crigler-Najjar syndrome type 2: Novel UGT1A1 mutation. Indian J Hum Genet. 2012;18(2):233. https://doi.org/10.4103/0971-6866.100776

[7] Kumar P, Sasmal G, Gupta S, Saxena R, Kohli S. Crigler Najjar Syndrome Type 2 (CNS Type 2): An Unwonted Cause of Jaundice in Adults. J Clin Diagn Res. 2017 Jul;11(7):OD05-OD06. https://doi.org/10.7860/JCDR/2017/28195.10221

[8] Wu Y, Li G, Zhou Y, Li J, Hu Y. [Genetic analysis of a child affected with Crigler-Najjar syndrome type II]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2016 Jun;33(3):328-31. https://doi.org/10.3760/cma.j.issn.1003-9406.2016.03.011