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Case Report Open Access

A Girl with Yellow Eyes- An Enlightening Experience

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Background

Crigler Najjar Syndrome type 2 (CNS-2) is a very rare diagnosis [1]. Diagnosis is reached by detecting Uridine diphosphate-glucuronyl transferase (UGT) activity level in liver biopsy [1]. But this test is sophisticated, expensive and not available in all centers [2]. We assembled various interventions, mentioned in medical literature, in a systematic manner to form a unique pathway to arrive at the diagnosis of CNS-2 which can be used in set ups lacking advanced diagnostic tools.

Case Presentation

An 18 year old female health worker, resident of Birbhum, West Bengal, India married for last one year presented with a history of dysuria for 3 days and increased yellowish discoloration of eyes for 3 days. (Figure 1) She was having history of recurrent jaundice since 6 months of age and increased during menstruation, ill health and examinations. She was born of consanguineous marriage.

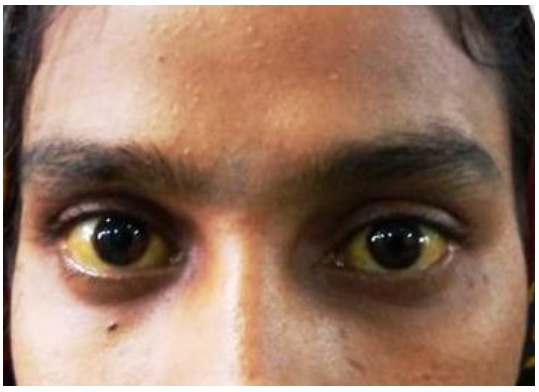

Figure 1: Showing deeply icteric sclera at the time of presentation.

There was no history of fever, clay coloured stool, loss of appetite, pruritus, abdominal pain, bleeding manifestation, upper gastrointestinal bleed, any chronic drug intake, blood transfusion. She had a normal menstrual history. On examination the patient was deeply icteric, not pale. Vitals were stable. Abdominal examination did not reveal palpable liver or spleen. No abnormality was detected in cardiovascular, respiratory and nervous system examinations.

An outside report of urine 2 days back revealed plenty of pus cells, pH 6.1, albumin +. Reports done under our care revealed haemoglobin 11.9 g/dl, total count 10500/dl, differential count neutrophil 70% lymphocyte 24% eosinophil 3% monocyte 3%, platelet 3.11 lakh/dl, ESR 30mm in first hour, fasting blood glucose 87 mg/dl, urea 40 mg/dl, creatinine 0.8 mg/dl, urine pus cells 2-4/hpf, urinary ph 6.2, urinary albumin absent. Urine culture showed no growth. Malarial parasite dual antigen was negative. Total bilirubin was 26.7 mg/dl with indirect bilirubin of 25.7 mg/dl. ALT was 51 U/L, AST was 33 U/L, ALP was 183 U/L.INR was 1.25. Ultrasonography of whole abdomen did not reveal any abnormality. Red cell indices are within normal limit. Haemoglobin electrophoresis was normal, DCT negative, reticulocyte count 1.6%. Serum LDH was 198 U/L. Serologic markers for hepatitis B, C were negative. In liver biopsy hepatocytes showed microvesicular granular cytoplasm with centrally placed normal appearing nuclei. No necrosis, inflammation, fibrosis or bile plugs were seen. Our differentials were Gilbert's syndrome and CNS-2 but UGT1A1 level detection in liver biopsy specimen is not yet available in our set up.

The patient was put on antibiotics and serial monitoring of total bilirubin level was done. During hospital stay with patient's consent we performed interventions like fasting, adding Phenobarbitone, Rifampicin to arrive at the diagnosis of CNS-2. (Figure 2) Serum PCR sequencing revealed UGT1A1 gene polymorphism with TA repeats 7/7 and UGT1A1 28/28.

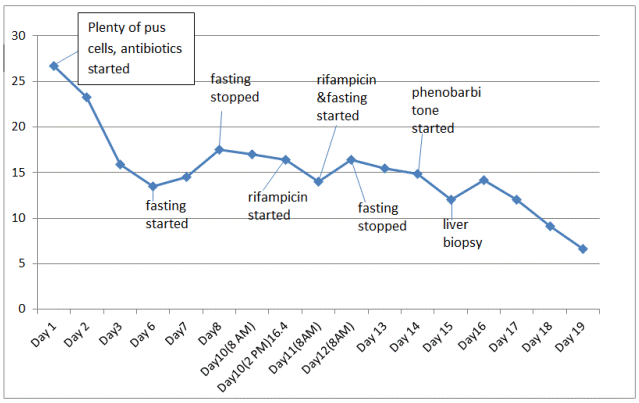

Figure 2: Pattern of change of serum bilirubin with different interventions.

The patient was discharged on phenobarbitone 60 mg once daily on day 19 with total serum bilirubin level of 6.6 mg/dl. (Figure 3) The patient is on phenobarbitone and follows up in outpatient basis. On day 46 her total bilirubin was 5.4 mg/dl and on day 70 her total bilirubin was 4.6 mg/dl and indirect bilirubin was 4.1 mg/dl. Then the patient became pregnant and jaundice increased with her age of gestation. An elective lower uterine caesarean section delivery was done in the 38th week of gestation. Her baby had physiological jaundice at birth. But both mother and baby recovered from jaundice within 7 days of delivery but serum PCR of her baby could not be done as the patient didn't give consent for further testing. On her last

outpatient visit one week back the patient had mild icterus and her total bilirubin level was 4.6 mg/dl with normal enzymes.

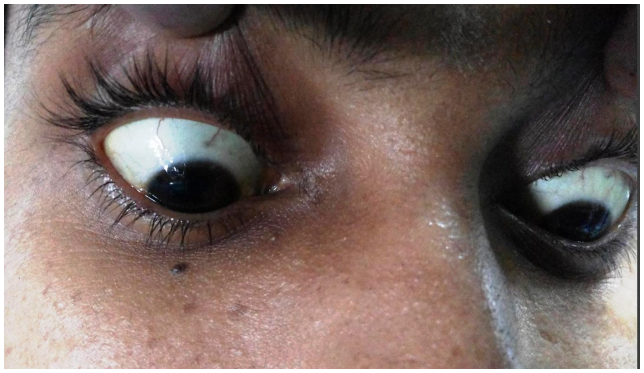

Figure 3: Minimal icterus at the time of discharge on day 19.

Discussion

Our patient had recurrent jaundice since 6 months age. According to Lidofsky SD et al jaundice may not manifest until early childhood in CNS-2. [3] In CNS-2 serum bilirubin levels can wax and wane with time and most patients respond to phenobarbitone (an agonist of constitutive androstane receptor CAR, which increases expression of UGT1A1 and thus increases bilirubin-UGT activity) treatment with a decrease of serum bilirubin of ≥25% which corroborated with our findings [1,3]. Serum bilirubin concentrations may decrease to normal levels in patients with Gilbert's syndrome with phenobarbitone treatment, but the levels in patients of CNS-2 do not reach the normal range [3,4,5]. In our case the bilirubin decreased considerably but did never come to the normal level. The Gilbert's syndrome which typically present during or after adolescence rarely produces clinical jaundice, serum bilirubin levels may rise two to threefold with fasting or dehydration but are generally below 4 mg/dl while it ranges from 0.3 to 1.0 mg/dl in normal subjects [4]. In CNS-2, serum bilirubin level ranges from 6 to 20 mg/dl and the majority of patients survive into adulthood without complications [4]. Our patient presented with a total bilirubin of 26.7 mg/dl. Such high bilirubin levels have been rarely associated with CNS-2 in studies available so far. In the nonfasting state, an increase in total bilirubin to >1.5 mg/dl, 4 to 6 hours after the administration of rifampicin, distinguishes persons with Gilbert's syndrome from those without it [6]. On the other hand rifampicin being an enzyme inducer increases bilirubin-UGT level and helps to decrease bilirubin in CNS-2 as was seen in our case. To confirm diagnosis of CNS-2, UGT enzyme activity in liver biopsy and analysis of bile pigments for bilirubin conjugates by chromatographic method can be measured [1,7]. We could not perform both investigations in the patient because of unavailable technical conditions in our center. Thus we devised our own diagnostic algorithm comprising of history, simple laboratory investigations, and different interventions like fasting, rifampicin and phenobarbitone.(Figure 1) after taking proper consent from patient and intuitional ethical committee. The results were in favour of CNS-2 as we found that there is significant decrease in serum bilirubin level on rifampicin and phenobarbitone and serum bilirubin increases on fasting, which corroborated with other studies but has never been put into a complete diagnostic pathway before [4,6]. From historical point of view we can see that patient had recurrent episodes of jaundice since childhood which is unlikely in Gilbert syndrome, also history of consanguinity is an important associated risk factor for CNS type 2 [1]. Serum PCR sequencing revealed UGT1A1 gene mutation which is found both in Gilbert's syndrome and CNS-2 [4]. Although common belief leans towards no need to treat CNS type II patients, risk of neurological problems in severe hyperbilirubinemia warrants consideration. In addition many adults are concerned about the physical appearance in their social life. Treatment with low dose phenobarbitone (60 to 120 mg/day) is suggested in these patients [3].

Conclusion

CNS-2 can present with isolated unconjugated hyperbilirubinemia as high as 25 mg/dl which has rarely been reported. Consanguineous marriage may have some association with CNS-2. Rifampicin decreases bilirubin in CNS-2 in contrast to Gilbert's syndrome and low dose phenobarbitone can drastically decrease bilirubin in CNS-2 but fails to bring it down to normal range. In resource poor countries like India, CNS-2 can be diagnosed on the basis of pattern of laboratory parameters, response to fasting and drugs in combination with UGT1A1 gene mutation and an uneventful liver morphology.

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