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CASE REPORT

An interesting case of prolonged jaundice

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In this case report we describe the investigation and management of an 8 week old girl who presented with prolonged jaundice. She was born at term, was breast fed since birth and thriving. The investigation of her jaundice led to a diagnosis that is considered a rarity, namely progressive intrahepatic cholestasis type 2.

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CASE PRESENTATION

The patient was born at term to non-consanguineous parents of Eastern European descent *via* an elective caesarean section, weighing appropriately for age with a normal newborn examination. On the third day of life the newborn was noted to be jaundiced. As per routine investigation a transcutaneous bilirubin measurement was taken which resulted to be 219 µmol/L. The cutoff for initiating phototherapy on day 3 of life was 300 µmol/L. The transcutaneous bilirubin was repeated the following day and it had decreased to a value of 183 µmol/L which was within normal limits for her gestational age and in keeping with physiological jaundice in an exclusively breast fed infant. The baby continued to have normal routine visits till 2 months of age.

During a routine check up at the age of two months she was noted to be visibly icteric. On examination there was an absence of hepatosplenomegaly and the baby was otherwise thriving. A transcutaneous bilirubin was taken; 381 µmol/L, indicating the presence of prolonged jaundice. A thorough history was taken from the parents who reported that the stools were pale and the urine was dark in colour.

A set of first line investigations to determine the cause of the jaundice were done including: a complete blood count, liver profile with direct bilirubin, electrolytes, C- reactive protein, direct antibody test and International Normalised Ratio (INR). The results suggested a diagnosis of a conjugated hyperbilirubinemia with a serum bilirubin of 105 µmol/L, direct bilirubin of 91 µmol/L, ALP of 1128 IU/L, ALT of 380 µmol/L and a normal GGT of 42 µmol/L. The INR was within normal limits and the direct antibody test was negative. In view of the conjugated hyperbilirubinemia she was started on a galactose-free formula pending exclusion of galactosemia.

Second line tests were conducted including: thyroid function test, venous blood gases, cortisol, alpha-1-antitrypsin, galactose 1-phosphate uridylytransferase level, urine organic acids, CMV PCR and hepatitis screen. The blood tests ruled out a metabolic cause such as galactosemia. The virology was negative except for positive CMV in serum and urine. The rest of the tests were within normal limits.

After excluding an infectious and metabolic cause the baby underwent an ultrasound of the abdomen that showed a hyperechoic liver, no evidence of biliary atresia or bile duct dilatation, a normal gallbladder morphology and a slightly enlarged spleen. She was subsequently referred to a tertiary paediatric liver centre for assessment and liver biopsy. The liver biopsy showed mild portal fibrosis, giant cell hepatitis and no evidence CMV infection.

In addition to blood investigations and imaging, a genetic conjugated jaundice panel was conducted. The patient was confirmed to have a compound heterozygote mutation in the *ABCB11* gene in keeping with bile salt export pump deficiency (BSEP), a hereditary cholestatic condition also referred to as progressive familial intrahepatic cholestasis (PIFC) type 2. Parental testing confirmed both parents to be carriers of this mutation but her elder sibling was not a carrier. As part of the work up an auditory response brainstem test was performed which was within normal limits for her age. An ophthalmological follow up confirmed the absence of CMV ocular involvement and was within normal limits, therefore excluding the possibility of congenital CMV infection.

She was started on Multivitamin supplements, ursodeoxycholic acid, phytomenadione, cholecalciferol, alpha tocopheryl and rifampicin (due to progressive pruritus). Her liver function tests progressively improved as can be appreciated in

Table 1. The infant received the vaccinations are per usual immunisation schedule and continued to thrive appropriately. She is currently receiving odevixibat a non-systemic ileal bile acid transport inhibitor as part of a Phase 3 trial of a novel medical treatment for the condition with the aim to limit disease progression and the need for surgical intervention. As delineated in Table 2, she is responding well with a significant reduction in serum bile acid levels and pruritus with regular 3 monthly reviews.

Table 1 Trend in liver function tests as child grew and underwent treatment

	2 months		3 months	4 months	9 months
Bilirubin (µmol/L)	106.5	113.9	90.9	74.7	38.6
Direct bilirubin ((µmol/L))	91	88	66	51	36
Alkaline phosphatase (U/L)	1128	1073	705	610	601
Alkaline transaminase (U/L)	380	550	821	683	434
Gamma Glutamyl-Transferase (U/L)	42	56	63	51	36

Table 2 Trend in serum bile acids as child got older and underwent treatment

	5 months	6 months	8 months	9 months
Serum bile acids (µmol/L)	564	540	519	399

Discussion

Prolonged jaundice is frequently encountered by paediatricians and midwives and the causes are broad, ranging from physiological to pathological. Conjugated hyperbilirubinemia is never benign and a thorough investigation is necessary. The diagnosis of PFIC is a rare condition that should be thought of when metabolic, infectious and other main causes of cholestasis such as biliary atresia are excluded.[1] PFIC type 2 is an autosomal recessive disease caused by mutations in the ABCB11 gene that encodes bile salt export pump (BSEP).[1] This pump deficiency causes ineffective secretion of bile salts which accumulate in the canaliculi and cause hepatocellular injury.[2] The resultant injury manifests as cholestasis, jaundice, malabsorption and pruritus with the risk of hepatocellular carcinoma before one year of age.[1] Ultrasonography of the liver usually shows a normal appearance with a possibly enlarged gallbladder. Liver histology with immunostaining aids diagnosis by revealing canalicular cholestasis, enlarged portal tracts, absence of true ductular proliferation and periportal biliary metaplasia of hepatocytes.[1]

Ursodeoxycholic acid is the first step in treatment, it is a non-toxic hydrophilic bile acid that helps to protect the liver cells by replacing endogenous cytotoxic bile salts.[3] Pruritus can be a severe and is thought to be caused by accumulation of bile acids. Rifampicin improves pruritus and induces conjugation as well as excretion of bilirubin. Enriched formulas with medium chain triglycerides and fat soluble vitamins are preferred as these babies suffer from malabsorption which can affect their growth.[4]

Besides the above treatment the other option is surgical management. This involves biliary diversion procedures and liver transplants for those who do not respond well to medical therapy. Ideally such procedures are offered before cirrhosis and end stage liver disease has developed. Novel therapies may avert the need for surgery and eventual liver transplant.[4]

Conclusion

In conclusion, prolonged jaundice can be due to a multitude of causes and rarities such as progressive intrahepatic cholestasis type 2 are part of a long list of differential diagnoses. It is important to keep in mind these rarities in order to be able to properly diagnose and initiate treatment before complications such as cirrhosis occur.

References

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