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Unusual association of diseases/symptoms

Intractable neonatal jaundice due to hereditary spherocytosis and Gilbert's syndrome

Abdul Qader Tahir Ismail, Anjum Gandhi, Nagui El-Shimy

Paediatrics Department, Good Hope Hospital, Birmingham, West Midlands, UK

Correspondence to Dr Abdul Qader Tahir Ismail, aqt.ismail@bnc.oxon.org

Summary

In this article the authors present a case of pathological neonatal jaundice resistant to phototherapy in a baby with a family history of Gilbert's syndrome and hereditary spherocytosis. Her presentation was ultimately explained with a diagnosis of both conditions, and required treatment with phenobarbitone. The authors discuss the mechanism by which Gilbert's syndrome results in hyperbilirubinaemia and its similarities with Crigler–Najjar syndrome. The presentation of hereditary spherocystosis in the neonatal period is also explored, as is the mechanism of exaggerated hyperbilirubinaemia when the two conditions co-exist.

BACKGROUND

Jaundice develops in 60% of term, and 80% of preterm babies; it is the most common neonatal condition requiring medical attention. High haemoglobin load at birth, decreased red blood cell (RBC) lifespan and immaturity of hepatic conjugating enzymes are contributing physiological factors. Several aetiologies, from infection, fluid intake levels, inherited hepatic and red cell enzyme defects to endocrine, can cause pathological presentation within the first 24 hours of life and increase unconjugated hyperbilirubinaemia towards threatening kernicterus levels. Therefore pathological jaundice requires aggressive treatment with concurrent identification of the underlying cause.

CASE PRESENTATION

A 3.35 kg baby girl was born at 38+2 weeks gestation by vaginal delivery, with appearance pulse grimace (reflex) activity respiration scores of 9 at 1 and 5 min. There was history of prolonged pre-labour rupture of membranes, but no other risk factors for infection. Due to jaundice within the first 24 h, the baby was reviewed by the neonatal team.

INVESTIGATIONS

Clinical examination was normal; investigations revealed a raised white cell count of 19.7×10^9/l, C reactive protein of 9 mg/l, serum bilirubin (SBR) of 239 µmols/l, haemoglobin (Hb) of 17.3 g/dl, direct Coombs test was negative, and both baby and mother were O+. Double phototherapy, intravenous infusion (IVI) of 60 ml/kg/day 10% dextrose, and intravenous benzyl penicillin and gentamicin were commenced.

The next day, bilirubin levels continued to increase (250, 284 and 336 µmols/l) despite ongoing double phototherapy, so triple phototherapy was commenced. The SBR remained elevated, and 2 days later it was 386 µmols/l (direct 37) with the baby breastfeeding and on 120 ml/kg/day IVI. Glucose-6-phosphate dehydrogenase deficiency screen and blood cultures returned negative.

DIFFERENTIAL DIAGNOSIS

Due to the presence of a family history of Gilbert's syndrome (GC) (father) and hereditary spherocytosis (HS) (grandmother), we consulted the hepatology and haematology teams. They agreed with us that, intractable jaundice is not a classical presentation of Gilbert's syndrome. We were advised to send blood for Crigler–Najjar (CN) DNA test and start giving phenobarbitone, while continuing triple phototherapy. They also considered HS unlikely due to current Hb levels and lack of spherocytes on the blood film.

TREATMENT

Once, on phenobarbitone, the SBR began falling, with subsequent measurements of 318 and 227 µmols/l and phototherapy was gradually stopped. As the feeding and growth were well, she was discharged.

OUTCOME AND FOLLOW-UP

The genetic test returned negative for CN (no pathogenic UDP-glucoronysyltransferase 1 enzyme (UGT1A1)) mutations were detected), but positive for Gilbert's (homozygous for allele 7). We did not believe that this diagnosis alone explained her hyperbilirubinaemia, so further tests were arranged, which revealed an Hb of 8.0 g/dl, mean cell volume of 89 fl, 4.9% reticulocyte count and this second blood film contained spherocytes and pincer cells in band 3 spectrin deficiency 'highly suggestive of hereditary spherocytosis'; diagnosis was confirmed by dye reduction testing.

Follow-up in clinic showed that, the baby was feeding well and thriving, not visibly jaundiced although a little pale. Phenobarbitone was gradually tapered and stopped and folic acid was commenced.

DISCUSSION

Was it reasonable to test for CN syndrome in this baby with a family history of GC and hereditary spherocytosis?

The majority of bilirubin is conjugated in the liver UGT1A1, which makes it water soluble and excretable in bile into the gastrointestinal tract.

In GS, there is extra base pair insertion within the TATA box sequence promoter region of the UGT1A1 gene; normal is $A(TA)_{6/6}TAA$, patients may be heterozygous ($A(TA)_{6/7}TAA$) or homozygous ($A(TA)_{7/7}TAA$). In homozygotes the longer promoter region results in reduced gene expression and enzyme production to ~30% of normal levels, resulting in Gilbert's syndrome's clinical manifestation of mild hyperbilirubinaemia when stressed, which does not require treatment.

There are two types of CN syndrome, type I patients are homozygous for UGT1A1 gene mutations resulting in complete loss of conjugating enzyme activity, giving the clinical picture of severe non-haemolytic jaundice resulting in kernicterus and death within the first couple of years of life. The only effective treatment is liver transplantation, with phototherapy and exchange transfusions as temporary emergency measures. CN type II patients are heterozygous for UGT1A1 mutations resulting in ~10% normal activity. Phenobarbitone (enzyme inducer) effectively treats their moderate hyperbilirubinaemia.

These classical models present GS and CN as distinct genotypes; current understanding is that, phenotypic similarities between GS and CN type II can be explained by considering the two as on a spectrum. Some CN type II patients are also homozygous for $TA_{7/7}$ in the UGT1A1 promoter region[1] just as some GS patients are heterozygous for mutations within UGT1A1's coding region.[2] The interaction between the longer promoter region and coding region mutations gives the range of hyperbilirubinaemia phenotypes of GS and CN type II patients and explains the ongoing debate about mode of inheritance. It also explains why it is possible and not entirely unlikely both conditions present in one family.

So in theory, GS could have caused this baby's hyperbilirubinaemia if genetic testing hadn't ruled out UGT1A1 mutations, homozygosity for $TA_{7/7}$ alone could not be responsible.

Could the combination of GC and HS explain this presentation of jaundice?

HS is the most common hereditary haemolytic disease in people of North European descent, with incidence in the US estimated at 1 in 2000 births.[3] Partially spherical RBCs have increased osmotic fragility due to mutational defects in membrane proteins and are trapped by an enlarged spleen. HS presents in the neonatal period with varying degrees of haemolysis and jaundice.

Regarding a combination of HS with GS, Iolascon *et al*[4] found that of the 178 neonates with HS, 97% which had $TA_{7/7}$ homozygosity, required phototherapy for their jaundice compared to 63% of the 178 with $TA_{6/6}$ or $TA_{6/7}$. It appears therefore, that in HS hyperbilirubinaemia is exacerbated when combined with GS since a greater proportion of the increased bilirubin load remains unconjugated.

Learning points

- Although these two hereditary conditions (GC and HS) are relatively common, case reports of their concurrent presence in one neonate is rare.
- Since the clinical presentation is not typical to either, diagnosis and treatment can be difficult which increases the risks of prolonged hyperbilirubinaemia.
- This article highlights the importance of family history and an understanding of bilirubin metabolism when considering aetiology of neonatal jaundice.
- This will prevent underdiagnosis of these conditions, and in rare cases such as this, prevent one condition masking another.

Competing interests None.

Patient consent Obtained.

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