

Panhypopituitarism - a rare cause of neonatal cholestatic jaundice

Cecil Vella, Bettina Gauci, John Torpiano

Abstract

Although not uncommon, neonatal cholestatic jaundice is usually caused by congenital anatomical defects of the biliary tree or intrinsic liver pathology. We describe a case of persistent cholestatic jaundice in a six week old female infant caused by panhypopituitarism.

To our knowledge this is the first report of hypopituitarism presenting with cholestatic jaundice in Malta. Prolonged obstructive jaundice in the neonatal period should be urgently investigated until a cause is found.

Keywords

neonatal cholestasis, panhypopituitarism

Introduction

Neonatal jaundice is most frequently caused by unconjugated hyperbilirubinemia. However, conjugated hyperbilirubinemia is always a concern as it may be attributable to genetic, metabolic, infectious, and obstructive causes.¹ Panhypopituitarism is a rare condition in childhood and does not usually present in the neonatal period. Congenital hypopituitarism may be caused by one of a number of genetic disorders (such as POU1F1 or PROP1 gene mutations, etc)² or be part of a developmental defect involving the hypothalamus and/or pituitary gland (such as holoprosencephaly, interrupted pituitary stalk, septo-optic dysplasia, etc). Both causes of congenital hypopituitarism may very rarely present as cholestatic jaundice in the neonatal period.

Cholestatic jaundice in the neonate should be promptly and energetically investigated in an effort to exclude any underlying anatomical problem of the biliary tree which requires surgical correction before irreversible damage to the liver occurs. In the absence of any positive investigations suggesting a structural biliary problem or intrinsic liver pathology, further investigations should be performed to exclude an endocrine problem, such as hypothyroidism, cortisol insufficiency or growth hormone insufficiency. A combination of more than one such hormone insufficiency should alert the physician to the possibility of an underlying pituitary problem.

Case report

A six week old female infant presented to out patients with a history of prolonged jaundice. She was born at term by normal vaginal delivery following a normal uneventful pregnancy.

The infant was seen at a well baby clinic the week before and following a suggestion that the jaundice might be of breast milk origin, the mother decided to stop breast feeding and changed to formula milk. At presentation weight gain was noted to be slow but sustained. The infant was moderately jaundiced and direct questioning to the colour of the stools revealed

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that these were pale in colour. The liver and spleen were not enlarged. An initial bilirubin level showed a total bilirubin of 170umol/l (Normal value <17 umol/l) with a direct fraction of 130umol/l. The infant was admitted for further investigations of cholestatic jaundice.

Initial total serum bilirubin	170 umol/l (<17umol/l)
Direct bilirubin	130 umol/l
ALT (Serum)	31 (5-33 U/l)
Alkaline Phosphatase	780 (0-449 U/l)
Gamma GT	84 (5-36 U/l)
Full blood count	Normal
Free T4	9.3 (11-18 pmol/l)
TSH	3.7 (0.3-3.0 mU/l)
Lipid profile	Normal
Renal profile	Normal
Urine analysis	Normal
Urine Culture	Normal
Cortisol AM serum	<27.6 (138-690 nmol/L)
Prolactin level	Normal
Plasma amino acids (Quantitative)	Normal
Alpha 1-Antitrypsin level	Normal
Alpha 1-Antitrypsin phenotype	Normal
Galactosaemia screen	Normal
Tyrosinaemia screen	Normal
IGF-1	<30ng/ml (48-313 ng/ml)
INR	1.06
APTT	1.51
TORCH / Viral hepatitis screen	Negative

Table 1: List of initial investigations.

On the ward her stools were noted to be pale and her urine dark. She was feeding well. Liver profile showed a normal alkaline phosphatase and alanine aminotransferase level (ALT) with a slightly raised gamma-glutamyl transferase (GGT) level. Ultrasound of the abdomen showed a normal liver echogenicity, no dilated bile ducts and a gall bladder. A HIDA (Hepatobiliary Iminodiacetic Acid) scan following priming with phenobarbitone showed tracer extraction noted from the blood pool with very markedly delayed transit into the bowel (Figure 1).

Activity as seen in the transverse colon on the 20-hour image making a diagnosis of biliary atresia unlikely. Further investigations are listed in Table 1. Over the next week her total and direct bilirubin levels remained raised. Repeat thyroid testing was performed in view of the persistently low serum concentration of FT4 associated with a non-significant elevation of serum TSH concentration. Serum cortisol and IGF-I concentrations were also found to be very low. A glucagon stimulation test was performed to further assess anterior pituitary function. The stimulation test showed a very flat response in both growth hormone (peak concentration of 2.3 ug/l, normal values > 7ug/ml) and cortisol secretion (peak concentration of 97 nmol/l), confirming a diagnosis of panhypopituitarism. The patient was started on oral

hydrocortisone replacement (15 mg/m²/day) followed by oral thyroxine (25ug/day) and subcutaneous growth hormone (0.6mg/m²/day). Her jaundice improved and subsided following three full weeks of treatment. Liver profile returned to normal and stools became fully pigmented. An MRI scan showed a very small anterior pituitary gland, an undescended posterior pituitary and a very thin stalk consistent with pituitary hypoplasia. The optic chiasm was normal.

Follow up at five months of age showed she is thriving well with increase in her growth parameters from the 3rd percentile to the 50th percentile for weight and height.

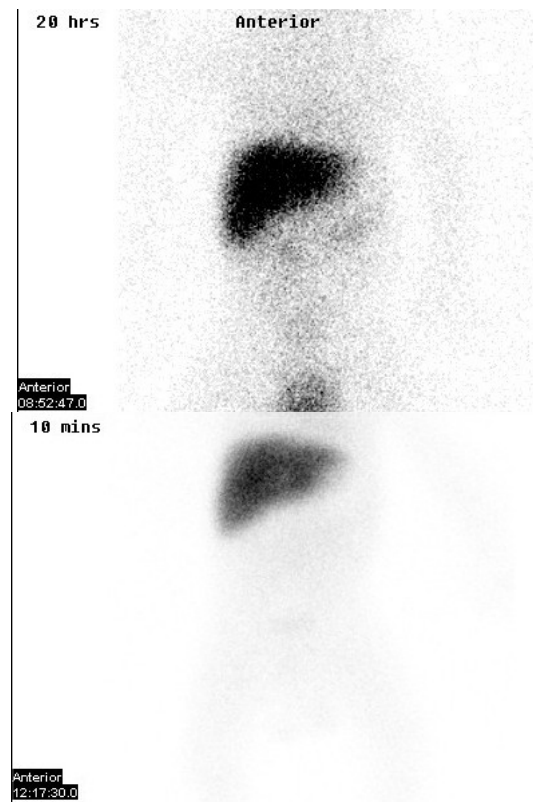


Figure 1. HIDA scan at 10 minute and 20 hours showing delayed but definitive gastrointestinal activity

Discussion

The aetiology of neonatal cholestasis is vast. Intra and extra hepatic pathology may be responsible and urgency in investigation is important in order to identify pathologies, such as biliary atresia, that require surgical intervention within a limited time frame. The association of liver dysfunction with hypopituitarism was first suggested in 1956.¹ Cholestasis associated with hypopituitarism may occur at birth, together with or following physiological jaundice.³ The mechanisms of the development of jaundice in pituitary hormone insufficiency are unclear,

but it is known that thyroid hormone and cortisol affect the bile acid-independent bile flow.⁴ Cortisol can influence bile formation, reduce bile flow as has been observed in rat studies following adrenalectomy.⁵ Growth hormone has also been shown to modulate bile acid synthesis both in rats and humans^{6,7} and that GH is important for bile acid formation. All three hormones are important independently in bile acid formation and excretion. Although jaundice usually improves and disappears following a month of treatment with hormone replacement, it may follow a protracted course.^{7, 8} Ocular manifestations or seizures should suggest the possible association of septo-optic dysplasia.

Delay in the resolution of jaundice has been previously reported and raised transaminase levels may take up to several months to return to normal.⁷ With hormone replacement patients normalize growth and liver function have an excellent quality of life but will require life long treatment.

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