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CASE REPORT

Neonatal isolated ACTH deficiency (IAD): a potentially life-threatening but treatable cause of neonatal cholestasis

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SUMMARY

Isolated ACTH deficiency (IAD) is a rare cause of neonatal cholestasis and hypoglycaemia. This diagnosis has a 20% mortality potential if unrecognised. We describe a case of an infant presenting with cholestatic jaundice and hypoglycaemia. The patient had laboratory findings suggestive of IAD, which was later confirmed with molecular genetic testing. One of the mutations this patient had is a new finding. The patient was started on glucocorticoid replacement therapy after which his bilirubin and glucose levels normalised.

BACKGROUND

Isolated ACTH deficiency (IAD) is a rare disorder, characterised by secondary adrenocortical insufficiency with low or absent cortisol production, normal secretion of pituitary hormones other than adrenocorticotropic hormone (ACTH) and the absence of structural pituitary defects. This diagnosis can result in 20% mortality in the neonatal period if unrecognised. Early and lifelong treatment with glucocorticoid usually reverses the signs and symptoms associated with this condition. We describe a case of a newborn presenting with hypoglycaemia and cholestatic jaundice, who was found to have low cortisol and ACTH levels. A suspected diagnosis of IAD was confirmed with targeted molecular genetic testing of the TBX19 gene, which came back confirming the diagnosis. One of the mutations that the patient had is a new finding.

CASE PRESENTATION

The infant was a term baby boy born to a 28-year-old mother who received regular prenatal care. Maternal prenatal laboratories and ultrasound imaging were within normal limits. The infant's birth weight was 3.8 kg. He was referred to our hospital for further evaluation and management because of signs of jaundice, hypoglycaemia, one episode of apnoea lasting about 20 s and poor feeding at day 11 of life. Initial physical examination revealed a hypoactive neonate with yellowish discolouration of his body, with normal vital signs (axillary temperature of 37.2°C, heart rate 130 bpm, blood pressure 75/40 mm Hg, respiratory rate of 40/min). Weight on admission was 3.9 kg and head circumference was 36 cm. Neither hepatosplenomegaly nor facial dysmorphism was noted. Genital examination was within normal limits.

INVESTIGATIONS

Laboratory findings including complete blood panel with differential count and electrolytes were within normal limits. Sepsis work up came back negative. Total and direct bilirubin were 18 and 2.4 mg/dL, respectively. Alanine aminotransferase was 32 units/L (normal 12–78 units/L), aspartate aminotransferase was 62 units/L (normal <48 units/L), alkaline phosphatase was 255 units/L (normal 55–176 units/L) and λ-glutamyl transpeptidase was 300 units/L (normal 8–78 units/L). Investigations were started for hypoglycaemia and cholestatic jaundice.

The apnoea episode was associated with low blood glucose level of 19 mg/dL; the infant was given 2 mL/kg bolus of dextrose 10% water solution. His blood glucose level improved to 80 mg/dL thereafter.

During work up for hypoglycaemia, the cortisol level was found to be low. Following an ACTH stimulation test the cortisol level increased from <0.2 μg/dL before the ACTH dose to 0.5 μg/dL thereafter. The serum ACTH level was also found to be low. The other hormone levels (luteinising hormone, follicle stimulating hormone, growth hormone, insulin-like growth factor 1, testosterone, thyroid-stimulating hormone, T4, T3) were within normal limits. Urine and serum for amino and organic acids screens were normal. Urine-reducing substances, toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus and herpes viral serology, newborn screen and α 1-antitrypsin were within normal limits. MRI of the brain was obtained to look for pituitary abnormalities, and was normal. Ultrasonography of the abdomen demonstrated a normal gall bladder and normal appearing adrenal glands. Hepatobiliary iminodiacetic acid scan of the liver was normal, ruling out biliary obstructive lesions.

Given the high suspicion for IAD, targeted *TBX19* mutation analysis by PCR and automated sequencing was obtained and confirmed the diagnosis of IAD, showing two sequence variants in the *TBX19* gene, associated with the IAD (table 1).

The first mutation was a heterozygous deletion of two bases in the exon, which causes a reading frame-shift mutation beginning with arginine at codon 53. The second was a heterozygous C to T base change that converts the arginine at codon 179 into a termination signal. The first sequence variant has not been previously identified in the

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Table 1 TBX19 gene analysis results confirming the diagnosis of IAD

TBX19 region	Base change	Codon change	Mutation type	Interpretation
Exon 1	C.158_159 delGA heterozygous	p.Arg53fs	Frame-shift deletion	Unlisted*
Exon 3	C.535C>T heterozygous	p.Arg179	Non-sense	ACTH deficiency
Exon 2, 4–8	No abnormalities	No abnormalities	Not applicable	Negative

*Likely to be pathogenic, based on the effects of similar small frame-shift deletions.
ACTH, adrenocorticotropic hormone; IAD, isolated adrenocorticotropic hormone deficiency.

common databases, but is likely to be pathogenic, based on the effects of similar small frame shift deletions. The second sequence variant has been previously identified in at least one other patient with IAD.[1]

DIFFERENTIAL DIAGNOSIS

Other causes of neonatal cholestasis should be considered in the differential diagnosis (box 1).

TREATMENT

The patient was started on hydrocortisone supplementation with total daily dose of 15 mg/m^2/day given three times a day. He was discharged home with maternal instructions for frequent feeding every 3 hours, and with the plan to continue the life-long treatment of hydrocortisone replacement therapy.

OUTCOME AND FOLLOW-UP

The patient was discharged home on hydrocortisone supplementation. At the follow-up appointment 1 week after discharge, he was doing well clinically. His bilirubin level had decreased to 10 mg/dL and direct bilirubin to 1.3 mg/dL. He was seen at the genetic clinic, where parental testing for *TBX19* was recommended given the autosomal recessive inheritance pattern. Also discussed with the parents was that evaluation by endocrinology and neonatology in addition to targeted TBX19 mutation analysis would be essential in the management of future pregnancies. The patient has continued to follow-up with the paediatric endocrinology clinic, and continues to show significant improvement—his bilirubin level had decreased to 0.4 mg/dL with direct bilirubin level of 0.1 mg/dL at around 3 months; 20 months after diagnosis, the patient is thriving well on a weight-adjusted maintenance dose of cortisol. He is under the care of his local paediatric gastroenterologist and endocrinologist.

Box 1 Possible causes for neonatal cholestasis

- Obstructive/anatomical causes: biliary atresia and choledochal cysts
- Infections: toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes infections, urinary tract infection.
- Metabolic: tyrosinaemia, α1-antitrypsin, fructosaemia, galactosaemia, hypothyroidism.
- Genetic: alagille syndrome, progressive familial intrahepatic cholestasis, bile acid defects, cystic fibrosis.
- Toxic or secondary: total parenteral nutrition, medication.
- Idiopathic.

DISCUSSION

Neonatal cholestasis accounts for ~33% of paediatric hepatobiliary diseases. It is defined as prolonged elevation of conjugated bilirubin beyond 14 days of life and biochemically as a conjugated bilirubin level of ≥2 mg/dL or direct bilirubin level >20% of the total bilirubin. In general, conjugated jaundice that appears within 3 months of life is neonatal cholestasis.[2] This diagnosis requires immediate evaluation and management, as some of the causes are fatal in early life, if left untreated, whereas others can result in substantial morbidity by causing chronic liver disease progressing to cirrhosis eventually requiring liver transplantation.

There are wide and varied causes of neonatal cholestasis known so far, and the list keeps increasing with descriptions of new causes. Our case is one such uncommon cause of cholestasis. To the best of our knowledge, there have been only 11 of 17 patients with neonatal IAD presenting with neonatal cholestasis and the rest with neonatal hepatitis on biopsy carrying a T-pituitary (TPIT) mutation.[3] In that series, symptoms of adrenal insufficiency and cholestatic jaundice disappeared with cortisol replacement therapy in all cases.

Our case describes a neonate who presented with hypoglycaemia and prolonged direct hyperbilirubinaemia, with laboratory results and genetic testing confirming the diagnosis of neonatal IAD. The patient's cholestasis was present since birth until the treatment with hydrocortisone was started; following initiation of the treatment, the patient's condition improved significantly and both, his total and direct bilirubin levels started trending down, with prompt normalisation of blood glucose levels.

Our case indicates that the low level of cortisol as a result of low ACTH level was the cause of both hypoglycaemia and neonatal cholestasis, which resolved with supplementation treatment.

IAD is rare disorder that can cause life-threatening severe hypoglycaemia and prolonged cholestatic jaundice; the disease can carry a 20% mortality rate if undiagnosed during infancy.[4] It is characterised by low or absent production of ACTH hormone, which leads to decreased production of cortisol with otherwise normal secretion of other pituitary hormones and no structural defects of the pituitary gland on imaging studies.

IAD in childhood carries an autosomal recessive inheritance pattern. It has been shown to have a genetic cause in addition to other potential causes, as some patients with IAD do not have a TPIT mutation. TPIT as a T-box gene is a novel T-box transcription factor demonstrated in mice and is present exclusively in the developing corticotroph and melanotroph cells. An exclusive expression, such as this, of TPIT in pituitary proopiomelanocortin (POMC) cells suggests that a loss of TPIT function due to its mutation should produce an isolated deficiency of pituitary POMC and isolated ACTH deficiency. Based on this, it was inferred that the human homologue TBX19 (a T-box gene on chromosome 1q23-24, that encodes TPIT) could also be restricted to the same pituitary cells, and thus loss of TBX19 function might produce an isolated deficiency of pituitary POMC (ACTH).[3]

Most of the cases with TBX19 mutation have been reported to present in the early neonatal period.[5] From a review of the literature, hypoglycaemia, seizures and prolonged jaundice are

Learning points

- The presentation of a young infant with cholestasis and hypoglycaemia should alert paediatricians to the possibility of isolated adrenocorticotropic hormone deficiency (IAD), a potentially life-threatening but treatable condition and prompt investigation of adrenal function should be considered.
- IAD should be in the differential diagnosis when the rest of the pituitary hormones and brain imaging are within normal limits.
- The significance of the heterozygous deletion of two bases in the exon, which caused a reading frame-shift mutation beginning with arginine at codon 53, as found in our patient, and which has not so far been reported, needs to be clarified.

described as the most common symptoms during the neonatal period. The exact mechanism of cholestasis in IAD is still unclear, but in animal models, cortisol has been shown to play a role in bile formation and flow.[6]

The triad of recurrent severe hypoglycaemia, episodes of low cortisol level and cholestasis, is present in almost all reported cases during infancy; which indicates that the age of onset and the severity of cortisol deficiency are important predictors for development of cholestatic jaundice in childhood.[5]

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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