

Case Report

Isolated Cortisol Deficiency: A Rare Cause of Neonatal Cholestasis

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ABSTRACT

For decades, congenital panhypopituitarism has been recognized to cause infantile cholestasis. However, the identity of the hormone whose deficiency causes such derangement of the liver is not clear. Here, we report four cases of isolated severe cortisol deficiency presenting with neonatal cholestasis and hypoglycemia, of whom two had familial primary glucocorticoid deficiency and the other two had isolated adrenocorticotropin deficiency. The resolution of cholestasis by hydrocortisone replacement therapy suggests a causal relationship between cortisol deficiency and the development of neonatal cholestasis. In conclusion, the presentation of a young infant with cholestasis and hypoglycemia should alert pediatricians to the possibility of cortisol deficiency and prompt investigation of adrenal function should be undertaken.

Key Words: Endocrine, familial glucocorticoid deficiency, hypoglycemia, infant, liver disease

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During the neonatal and early infancy period, the liver is vulnerable to injury by different mechanisms because of the relative immaturity of the synthetic and excretory functions of bile acid and bilirubin.^[1] As a result, injury to the neonatal liver by infectious, metabolic, endocrine, storage, or hypoxic/ischemic diseases results ultimately in cholestatic hepatitis.^[2] Multiple hormonal deficiencies (cortisol, growth hormone, thyroxin), associated with congenital panhypopituitarism, caused around 50 cases of cholestasis in neonates and young infants, as reported in the literature.^[3-13] The identity of the hormone whose deficiency causes such derangement of the liver is not clear. Some authors suggested that growth hormone deficiency is the major cause of cholestasis.^[13-16] Only a handful of cases have been reported about the possible role of isolated cortisol deficiency in inducing neonatal cholestasis.^[3,10,17-19]

Here, we report four cases of severe cortisol deficiency presenting with neonatal cholestasis, of whom two had familial primary glucocorticoid deficiency and the other two had isolated adrenocorticotropin hormone (ACTH) deficiency.

The resolution of cholestasis by hydrocortisone replacement therapy suggests a causal relationship between cortisol deficiency and the development of neonatal cholestasis.

PATIENTS

Four male infants with a median age of 10 weeks (range 6-12 weeks) presented at our hospital between 2007 and 2011 for investigation of prolonged neonatal jaundice [Table 1]. All were full-term babies of consanguineous parents with normal birth weights. Two were delivered normally (cases 3 and 4), and the other two were delivered by cesarean section due to fetal distress. The postnatal period was uneventful apart from jaundice that started during the first week. At admission, two (cases 1 and 2) developed recurrent tonic hypoglycemic convulsions (glucose <2.4 mmol/L) and other two were noticed to develop recurrent asymptomatic hypoglycemia documented by repeated prick tests for glucose prior to feeding. The older sibling of case 1 died at age one month because of undiagnosed liver disease and hypoglycemic convulsions. On physical examination, cases 1 and 2 had generalized hyperpigmented skin. All the infants had normal male genitalia and none had dysmorphic features. Mild hepatomegaly was observed in all the infants.

Biochemical evidence of cholestatic hepatitis was observed in all the cases [Table 1]. The level of serum bile acid (normal 0–8.1 $\mu\text{mol/L}$) was elevated in three patients (cases 2, 3, 4) and normal in patient 1. Synthetic function tests

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Table 1: Liver enzymes in neonates with isolated adrenal insufficiency presenting with cholestasis

Case	Age at diagnosis (weeks)	TSB/D (<17/<5 µmol/L)	ALT (30-60 U/L)	GGT (11 - 60U/L)	Serum bile acid (0-10 umol/L)
1	12	95/76	81	70	9.8
2	6	141/100	71	35	78
3	12	210/160	321	49	144
4	8	166/137	109	122	171

ALT= Alanine aminotransferase, GGT= Gamma-glutamyl transferase, TSB/D= Total bilirubin/direct bilirubin

of the liver were normal in all the patients. Ultrasound of the abdomen revealed mild hepatomegaly and normal adrenal glands in all the infants. Extensive workup excluded infectious, metabolic, and structural causes of neonatal cholestasis. Urine for bile acid analysis in infants with normal serum bile acid level excluded primary bile acid synthetic disorders. Results of extensive endocrine investigations during the episodes of hypoglycemia are shown in Table 2. All the infants had severe cortisol deficiency with very high ACTH in patients 1 and 2 and very low ACTH in patients 3 and 4. Plasma growth hormone, thyroid function tests, rennin, aldosterone, and 17-hydroxy progesterone levels were all normal. Magnetic resonance imaging of the brain in case 3 showed a normal pituitary gland and in case 4 showed a loss of the normal hyperintense signal of the adenohypophysis. No midline brain defects could be seen in both the cases. On the basis of the above findings, cases 1 and 2 were diagnosed as familial glucocorticoid deficiency, and cases 3 and 4 were diagnosed as isolated ACTH deficiency. Hydrocortisone was commenced immediately in cases 1 and 2 at a dose of 5 mg IV every six hours for two days before shifting to an oral dose of 2.5 mg three times a day. In cases 3 and 4, hydrocortisone was initiated at 2.5 mg three times a day.

Genetic analysis in case 1 revealed a homozygous mutation in the coding region of the ACTH receptor (MC2R) gene consisting of one base protein insertion in exon 1 of the gene, leading to a premature stop codon after 94 amino acids, confirming the diagnosis of type 1 familial glucocorticoid deficiency. Genetic analysis in case 2 was negative for any mutation in the MC2R gene or the melanocortin 2 receptor accessory protein (MRAP)-encoding gene. Following commencement of hydrocortisone, the hypoglycemia did not recur and hyperpigmentation of the skin reduced markedly. Cholestasis resolved within three months and liver aminotransferase enzymes normalized after 6–12 months of starting hydrocortisone.

DISCUSSION

Data from our case series strongly support the hypothesis

of other researchers^[2,9,16-18] that cortisol deficiency might have a major role in the pathogenesis of cholestasis in young infants. The pathophysiologic mechanism, however, remains ill defined. In animal models, cortisol has been shown to influence bile formation. Bile flow was reduced in adrenalectomized rats,^[20] and hydrocortisone infusion has been observed to enhance bile flow in a dog and rat.^[21,22] Bile acids are the major determinant and driving force for bile flow in biliary canaliculi and any alteration in bile acid synthesis or secretion leads to reduced bile flow and cholestasis.^[23] Three of our patients had very high serum bile acid level which suggests that cortisol deficiency might have altered the hepatic transport of bile acids across bile canaliculus, thereby diminishing bile acid concentration in bile and promoting accumulation of bile acids in hepatocytes and blood. The level of serum bile acid was normal in case 1 and mass spectroscopy analysis of urine showed no abnormal metabolites indicative of bile acid synthesis defect which suggests that cortisol deficiency might also cause cholestasis through a mechanism other than alteration of transport or synthesis of bile acids.

It is noteworthy that the presentation of adrenal insufficiency with cholestasis is limited only to the early infantile period; hepatic manifestations beyond infancy include hypertransaminasemia^[24] but not cholestasis. This observation could be attributed to the relative immaturity of the synthetic and excretory functions of bile acid and bilirubin during early infancy.^[1] During the study period, around 350 infants presented at our unit with cholestasis due to various etiologies; four of which (1%) was due to isolated cortisol deficiency. The presentation with hypoglycemia with or without convulsion, in addition to cholestasis was constant in all four cases and characteristic of the cases of isolated cortisol deficiency reported in the literature.^[3,10,17-19] The pattern of liver enzymes and biochemical indices of cholestasis were not specific to isolated cortisol deficiency and could occur with other causes of cholestasis. Previous reports of isolated cortisol deficiency-associated cholestasis in young infants showed that gamma-glutamyl transferase was elevated.^[10,7] In contrast, data from our study showed that isolated cortisol deficiency could cause normal gamma-glutamyl transferase cholestasis, similar to progressive familial intrahepatic cholestasis type 1 and 2 and primary bile acid synthetic defects.^[2] None of our patients had liver biopsy; however, data from the literature indicate that hepatic histological changes were not specific and showed giant cell transformation, canalicular bile stasis, Kupffer cell hyperplasia, and mononuclear cell infiltration and minimal fibrosis in portal tracts^[3,17] Therefore, given the availability of noninvasive hormonal tests and in the right clinical setting of cholestasis and hypoglycemia, liver biopsy is not necessary for the diagnosis of suspected cortisol deficiency in young infants.

Table 2: Endocrine investigations during episodes of hypoglycemia

Case	Cortisol (83-580 nmol/L)	ACTH (0-13.3 pmol/L)	GH (0-2.6 mIU/L)	Free T4 (12-22 pmol/L)	TSH (1.36-8.8 mIU/L)	Diagnosis
1	2.21	427	6.77	12.1	6.47	FGD
2	4.5	391	12.5	16	10.8	FGD
3	2.7	0.22	9.9	15.3	8.11	ACTH deficiency
4	3.8	2.5	10.3	19.2	10.3	ACTH deficiency

ACTH: Adrenocorticotropin hormone, FGD: Familial glucocorticoid deficiency, T4: Thyroxine, TSH: Thyroid stimulating hormone, GH: Growth hormone

Although isolated cortisol deficiency is a treatable cause of neonatal cholestasis when diagnosed early, if left untreated, it may be fatal or lead to liver failure^[18] or neurodevelopmental disability as a result of severe recurrent hypoglycemia. Late diagnosis and initiation of hydrocortisone leads to liver cirrhosis and the need for liver transplantation during early childhood.^[9]

In conclusion, the presentation of a young infant with cholestasis and hypoglycemia should alert pediatricians to the possibility of cortisol deficiency and prompt investigation of adrenal function. Isolated cortisol deficiency should be considered among the differential diagnosis of normal gamma-glutamyl transferase cholestasis in neonates and young infants.

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