

## Cholestatic hepatitis as a result of severe cortisol deficiency in early infancy: report of two cases and review of literature

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Cholestatic hepatitis is identified as one of the features of hypopituitarism in the newborn, but the exact etiology of cholestasis in these cases has not been well established yet. We report here two infants, one with isolated glucocorticoid deficiency and the other with multiple pituitary hormone deficiency, indicating primary and central adrenal insufficiency, respectively, who presented with recurrent hypoglycemic seizures and cholestatic hepatitis. Severe cortisol deficiency in these cases was suggested to be the cause of cholestatic hepatitis. Review of the literature and our cases showed that the cortisol deficiency in both primary and central adrenal insufficiency occurring only during neonatal and early infancy period cause cholestatic hepatitis. The severity and the age of onset of cortisol deficiency are suggested to be the important predictors of cholestatic hepatitis in childhood.

**Key words:** cholestatic hepatitis, cholestasis, isolated glucocorticoid deficiency, hypopituitarism, glucocorticoid insufficiency, adrenal insufficiency.

Cholestasis is regarded as one of the findings of hypopituitarism during the neonatal period. The etiology of cholestasis in these cases is unclear. Isolated growth hormone deficiency and multiple pituitary hormone deficiency have been considered as the causes of cholestatic hepatitis in the neonatal and early infancy period<sup>1-4</sup>. Which hormone deficiency causes such metabolic derangement is an open question. The role of cortisol deficiency in the etiology of cholestatic hepatitis has not been well established yet.

We herein present two infants with cholestatic hepatitis, one of whom had isolated glucocorticoid deficiency and the other panhypopituitarism. Both had had jaundice since birth and recurrent hypoglycemic convulsions. The findings of cholestatic hepatitis resolved by hydrocortisone replacement therapy suggested the role of severe cortisol deficiency as a cause of cholestasis.

### Case Reports

#### Case 1

A three-month-old male infant was admitted to the hospital with recurrent generalized convulsions. It was noted that he had had

jaundice since his first day of life. Phototherapy had been initiated at the third day of life but jaundice did not resolve. The patient was the second child of nonconsanguineous parents. The first child had died of an unknown cause within 24 hours after birth.

On physical examination, the infant was hypotonic and had generalized jaundice. The liver was palpated 1 cm below the costal margin, and spleen was not palpable. Chest examination was normal. No hyperpigmentation was noted. The penile stretch length was 3.5 cm and bilateral testes were palpable at scrotum.

Laboratory examination revealed serum Na level: 135 mEq/L, K: 4.9 mEq/L, Cl: 110 mEq/L, ALT: 124 U/L (0-41), AST: 243 U/L (0-37), GGT: 471 U/L (11-49), LDH: 783 U/L (240-480), ALP: 1857 U/L (250-1000), total bilirubin: 5.6 mg/dl, conjugated bilirubin: 4.78 mg/dl, Ca: 10.3 mg/dl, and P: 5.9 mg/dl. When glucose level was 29 mg/dl, ACTH level was >1250 pg/ml (9-46 pg/ml), cortisol level <1 µg/dl, insulin level 0.4 µU/ml, and active renin: 37.6 pg/ml (3.5-65.6). Thyroid hormone levels were normal. The laboratory assessment for metabolic disorders including tandem

mass spectrometry (MS), urinary organic acid profile and  $\text{NH}_3$  levels were all normal. The markers for hepatitis and TORCH infections were also negative.

Low plasma cortisol level despite elevated ACTH in the absence of mineralocorticoid deficiency indicated the diagnosis of isolated glucocorticoid deficiency, and hydrocortisone replacement therapy was instituted. After one month, bilirubin levels were in normal range and after four months all of the liver function tests returned to normal. During 30 months of follow-up, ACTH levels remained high despite hydrocortisone replacement therapy and mineralocorticoid function was normal. No hypoglycemic attacks were noticed during this period.

### Case 2

A six-month-old female infant was admitted to the hospital with jaundice appearing on the first day of life. Phototherapy had been applied for 10 days but jaundice had persisted. She had been hospitalized several times due to recurrent hypoglycemic attacks during infections. The patient was born by an uncomplicated cesarean delivery with a birth weight of 3000 g. She was the second offspring of a consanguineous marriage. Two pregnancies of the mother were complicated with spontaneous abortions. The family had a four-year-old healthy boy.

On physical examination, she had pallor and decreased subcutaneous fat. The liver was 1 cm palpable below the costal margin. The chest and genital examinations were normal.

Laboratory examination revealed ALT: 159 U/L, AST: 273 U/L, ALP: 417 U/L, GGT: 471 U/L, total bilirubin: 3.92 mg/dl, conjugated bilirubin: 1.75 mg/dl, and glucose: 78 mg/dl. The serology for hepatitis and TORCH viruses were negative. Sweat chloride test,  $\alpha_1$  antitrypsin, profile of urinary organic acids, and tandem MS were normal. Basal cortisol level at 08.00 a.m. was 4.65  $\mu\text{g}/\text{dl}$ , and ACTH level was 6.39 pg/ml (9-46 pg/ml). Low dose and standard dose ACTH tests showed peak cortisol levels of 12.2 and 15.8  $\mu\text{g}/\text{dl}$ , respectively. Free  $\text{T}_4$  level was at lower normal range ( $\text{FT}_4$ : 10.35 ng/ml, normal range: 9 – 19.04 ng/ml) and TSH level was normal, whereas prolactin level was 85.6 ng/ml (1-25 ng/ml). IGF-1 and IGFBP-3 levels were low according to her

age and sex (IGF-1 level: 18 ng/ml, IGFBP-3: 1422 ng/ml). Magnetic resonance imaging of pituitary gland revealed pituitary hypoplasia, ectopic neurohypophysis and absent pituitary stalk. Hydrocortisone replacement therapy was started. After two months, bilirubin as well as ALT and AST levels were normalized. As thyroid hormone levels were found to decrease to subnormal levels, L-thyroxin was also instituted. Growth hormone stimulation test was performed after the patient became euthyroid and a peak growth hormone level of 4.2 ng/ml was obtained. During 18 months of follow-up, hypoglycemic attacks ceased.

### Discussion

Few infants with cholestatic hepatitis have been reported to be associated with hypopituitarism. Most of these cases had multiple pituitary hormone deficiency<sup>1-3,5</sup>. Review of the literature in 1992 revealed 24 out of 223 cases with neonatal hypopituitarism had evidence of cholestasis<sup>5</sup>. Which hormone deficiency causes cholestasis is unknown. Some authors suggested that growth hormone deficiency was the major factor yielding cholestasis<sup>1</sup>. Drop et al.<sup>2</sup> supported this hypothesis by observing that cholestasis did not resolve with thyroxin and hydrocortisone therapies in two infants with hypopituitarism. Lanes et al.<sup>3</sup> reported two patients whose abnormal liver function tests improved after growth hormone and glucocorticoid substitution. Steiner et al.<sup>6</sup> showed that cholestasis was unresponsive to thyroxin but resolved with hydrocortisone therapy. Recently, one patient with isolated ACTH deficiency was reported to die of cholestasis at the age of seven months<sup>7</sup>. In our report, the presence of cholestasis in both primary and central adrenal insufficiency implied that the main hormone in charge of cholestasis is indeed cortisol deficiency. There are very few cases in the literature who have had primary adrenal insufficiency presenting with cholestasis. In 1981, Leblanc et al.<sup>8</sup> postulated that cortisol deficiency might have a role in neonatal cholestasis. One patient with congenital adrenal hyperplasia due to 11 hydroxylase deficiency and two patients with adrenal hypoplasia were shown to have neonatal cholestasis. Contrary to this finding, in another report none of the patients with congenital adrenal hypoplasia, presenting in

the neonatal and early infancy period, had the signs of cholestasis<sup>9</sup>. All these patients presented with salt-losing crises within their first month and many of them had normal basal cortisol levels at presentation, reflecting active glucocorticoid production in the fetocortex in the neonatal period. Thus, glucocorticoid deficiency did not exist in these patients in the neonatal period. Therefore, we can assume that glucocorticoid deficiency appearing only in the neonatal and early infancy period causes cholestatic hepatitis.

Finally, as one of our patients had isolated glucocorticoid deficiency, we also reviewed the data of these cases in the literature. These patients are generally diagnosed beyond the neonatal period<sup>10,11</sup>. The patients who have signs and symptoms of adrenal insufficiency in the neonatal period are very few in number. Four of the cases with isolated glucocorticoid deficiency, who had presented in the neonatal period, were also associated with cholestatic hepatitis<sup>12-15</sup>. Five of our six patients with isolated glucocorticoid deficiency, who were reported previously<sup>16</sup>, presented beyond the period of early infancy and did not have any findings of cholestatic hepatitis. The sixth, unreported case was diagnosed and treated within the second day of life before any sign or symptom other than hyperpigmentation had emerged.

Both of our cases reported here had a prominent finding of cholestatic hepatitis. They had been jaundiced since birth with no spontaneous resolution up until the time of presentation, at three and six months of age, respectively. Following hydrocortisone administration, cholestasis resolved and liver enzymes decreased to normal levels in a few months in both infants. Data in the literature and our findings strongly suggest that neither ACTH nor any other pituitary hormone deficiency is responsible for the development of cholestasis, but cortisol deficiency seems to be the primary factor as a cause of cholestatic hepatitis. However, not all infants with cortisol deficiency develop cholestatic hepatitis. The important association of recurrent hypoglycemic episodes with cholestasis is present virtually in all patients in the literature, including ours. It is well known that sustained and recurrent hypoglycemic seizures indicate severe cortisol deficiency. Thus, it may be suggested that

the severity and the age of onset of cortisol deficiency are the important predictors of cholestatic hepatitis in childhood.

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