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Case Report

A case of an infant with congenital combined pituitary hormone deficiency and normalized liver histology of infantile cholestasis after hormone replacement therapy

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Abstract. Congenital combined pituitary hormone deficiency (CPHD) may present with cholestasis in the neonate or during early infancy. However, its precise mechanism is unknown. A 3-mo-old boy presented with cryptorchidism and hypoplastic scrotum after birth. Neonatal jaundice was noted but temporarily improved with phototherapy. Jaundice recurred at 2 mo of age. Elevated direct bilirubin (D-Bil) and liver dysfunction were found but cholangiography showed no signs of biliary atresia (BA). Liver biopsy findings showed giant cell formation of hepatocytes with hypoplastic bile ducts. Subsequent magnetic resonance imaging (MRI) of the head revealed a hypoplastic pituitary gland with an ectopic posterior lobe, and the patient was diagnosed with congenital CPHD based on decreased secretion of cortisol and GH by the pituitary anterior lobe load test. D-Bil levels promptly improved after hydrocortisone (HDC) replacement. We subsequently began replacement with levothyroxine ($L\text{-}T_4$) and GH, and liver histology showed normal interlobular bile ducts at 8 mo old. This is the first case report of proven histological improvement after hormone replacement therapy. This suggested that pituitary-mediated hormones, especially cortisol, might be involved in the development of the bile ducts.

Key words: congenital combined pituitary hormone deficiency, neonatal cholestasis, giant cell hepatitis, biliary atresia, hydrocortisone

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Introduction

Combined pituitary hormone deficiency (CPHD) is characterized by deficiency of GH, PRL, thyroid-stimulating hormone (TSH), ACTH, LH, or FSH, kinds and severity of which vary according to each case (1). There are both congenital and acquired CPHD; the latter may

consist of brain tumor and head injury. The origin of congenital CPHD is mainly unknown, but it may be partly influenced by pelvic position during delivery, newborn asphyxia, or a genetic abnormality related to transcription factors involved in the development and differentiation of the pituitary and hypothalamus. The incidence of congenital CPHD is 1 in approximately 50,000 births, of which about 10 to 35% present with comorbid cholestasis during the neonatal period and infancy (2). Distinguishing cholestasis related to congenital CPHD from biliary atresia (BA) is a key issue, as cholestasis related to congenital CPHD often develops after about one month of birth. One or more defects of ACTH, GH, and TSH have been reported as being responsible for cholestasis (2), but there are also reports that only cortisol is responsible for cholestasis, and no consensus has been achieved on the matter (3, 4). It is suspected that pituitary hormone deficiency causes a decrease in bile acid synthesis, a delay in the development of the bile acid transport pathway, and structural and functional aberrations of the cholangioles (5). Liver histology images of CPHD are characterized by signs of giant cell formation of hepatocytes with hypoplastic bile ducts (6). There are no reports comparing liver tissue findings before and after hormone replacement therapy. Here, we report an infant boy with congenital CPHD and comorbid cholestasis caused by intrahepatic bile duct hypogenesis, and confirm that his bile ducts normalized reversibly by hormone replacement including hydrocortisone (HDC).

Case Report

A boy was born via normal vaginal delivery at the gestational age of 38 wk and 5 d. His body weight was 3,154 g and his height was 49.5 cm. His Apgar score after 1 min and 5 min was 9 points, respectively. Family history did not involve hepatobiliary disease or endocrine disorder. He was a fully breastfed child. Hepatosplenomegaly was not found on physical examination. External malformation, cryptorchidism, scrotum collapse, and swelling of the sacrum were recognized. Neonatal jaundice was found (day 7: total bilirubin [T-Bil] 21.6 mg/dL, direct bilirubin [D-Bil] 0.6 mg/dL) and it recovered with phototherapy within 2 wk after birth. He always produced cream-colored stool from birth, but elevation of D-Bil and liver enzymes was not seen (day 21: T-Bil 18.6 mg/dL, D-Bil 0.2 mg/dL, aspartate transaminase [AST] 49 IU/L, alanine transaminase [ALT] 19 IU/L). Gamma glutamyl transpeptidase (γGTP), which showed high levels (1,084 IU/L) at birth, gradually decreased. Newborn mass screening was normal.

At one month old, a slight increase in D-Bil (1.1 mg/dL) was noted when the boy suffered from a urinary tract infection (UTI) with accompanying vesicoureteral reflux and his cream-colored feces persisted. Slow biliary excretion to the duodenum was found by hepatobiliary scintigraphy, suggesting that BA was not the diagnosis. Subsequently, the color of his feces became white and jaundice worsened after he was infected with respiratory syncytial virus (RSV) at 2 mo old. Elevated D-Bil (10.6 mg/dL) and liver dysfunction (AST 1,903 IU/L, ALT 907 IU/L) were found, and BA was suspected. The patient was referred to our hospital at 3 mo old.

At the time of hospitalization, his height was 60.8 cm (–0.25 standard deviation [SD]), weight was 4,845 g (–1.89 SD), and he presented with conjunctival icterus and jaundice of the skin. There was no hepatosplenomegaly on physical examination. Laboratory findings (Table 1) revealed marked elevation of serum liver enzymes (AST 2,367 IU/L, ALT 1,175 IU/L) and D-Bil (9.9 mg/dL). The serum level of alkaline phosphatase (ALP) was high (2,983 IU/L), while that of γGTP was within the normal range (54 IU/L). Plasma blood glucose level was low (46 mg/dL). Thyroid function tests showed free triiodothyronine (free T_3) 1.9 pg/mL, free thyroxin (free T_4) 0.5 ng/dL, and TSH 2.69 μU/mL. Amino acid and bile acid analyses showed no abnormalities. Tests screening for

Table 1 Laboratory data at the age of 3 mo

WBC	10,700	/μL	Alb	4.3	g/dL	CMV IgM	(+)
RBC	357×10^4	/μL	T-Bil	15.1	mg/dL	CMV IgG	(+)
Hb	9.8	g/dL	D-Bil	9.9	mg/dL	EBV VCA IgM	< 10
Plt	42.3×10^4	/μL	AST	2,367	IU/L	EBV VCA IgG	< 20
PT-INR	1.05		ALT	1,175	IU/L	EBV EBNA	< 10
APTT	39.3	sec	LDH	974	IU/L	HBs-Ag	(–)
HPT	71.6	%	ALP	2,983	IU/L	HCV-Ab	(–)
			γGTP	54	IU/L		
			CK	105	IU/L		
			T-Chol	174	mg/dL		
			BUN	18.5	mg/dL		
			Cr	0.27	mg/dL		
			Na	135	mEq/L		
			K	5.5	mEq/L		
			Cl	107	mEq/L		
			Ca	10.0	mg/dL		
			NH_3	59	μg/dL		
			CRP	0.26	mg/dL		
			Glucose	46	mg/dL		

hepatitis viruses were all negative, but serum anti-cytomegalovirus (CMV) immunoglobulin M (IgM) was positive. By immunostaining of the CMV pp65 antigen in white blood cells (CMV antigenemia assay), 5 out of 50,000 cells were positive. Abdominal ultrasonography showed no hepatosplenomegaly and a normal gallbladder. There was no triangular cord sign.

Transcystic cholangiography performed under general anesthesia showed normal extrahepatic bile ducts, ruling out the possibility of BA. Intraoperative liver biopsy showed bile duct hypogenesis with giant cell formation, feathery degeneration of hepatocytes, and hemosiderin deposition, but neither steatosis nor inflammatory cell infiltration was observed. (Figs. 1a and b). In liver tissues, CMV-positive cells did not present using immunohistochemistry with anti-CMV antibody and owl's eye inclusion bodies were not observed. In addition, the expression level of bile transporters such as the bile salt export pump (BSEP), multidrug resistance protein 3 (MDR3), and multidrug resistance-associated protein 2 (MRP2) varied in liver tissues, suggesting that the diagnosis of progressive familial intrahepatic cholestasis was denied. We suspected CMV-induced cholestasis, therefore ganciclovir was administered for 22 d until CMV-antigenemia-positive cells disappeared. Jaundice and liver dysfunction improved temporarily, but serum transaminase levels reascended and D-Bil did not normalize, although a slight decline of D-Bil before the administration of HDC might have reflected improvement of CMV-induced cholestasis. At this point, we performed a stimulating test with L-arginine, CRH, and thyrotropin-releasing hormone to differentiate from congenital hypopituitarism. GH and cortisol showed an under-response, while ACTH and TSH showed an over-response as well as a delayed response (Table 2). An MRI of the head revealed a hypoplastic pituitary with formation of an ectopic posterior lobe (Fig. 2). These results clarified the diagnosis of congenital CPHD. We immediately administered HDC (12.5 mg/m^2/d) at five months old and his D-Bil levels rapidly decreased. Subsequently, levothyroxine (L-T_4) (2.6 μg/kg/d) and GH (0.175 mg/kg/wk) were started at 6 and 7 mo old, respectively. Prior to GH replacement, D-Bil and hepatic enzyme levels were considerably improved. The second liver biopsy, performed at 8 mo old, showed

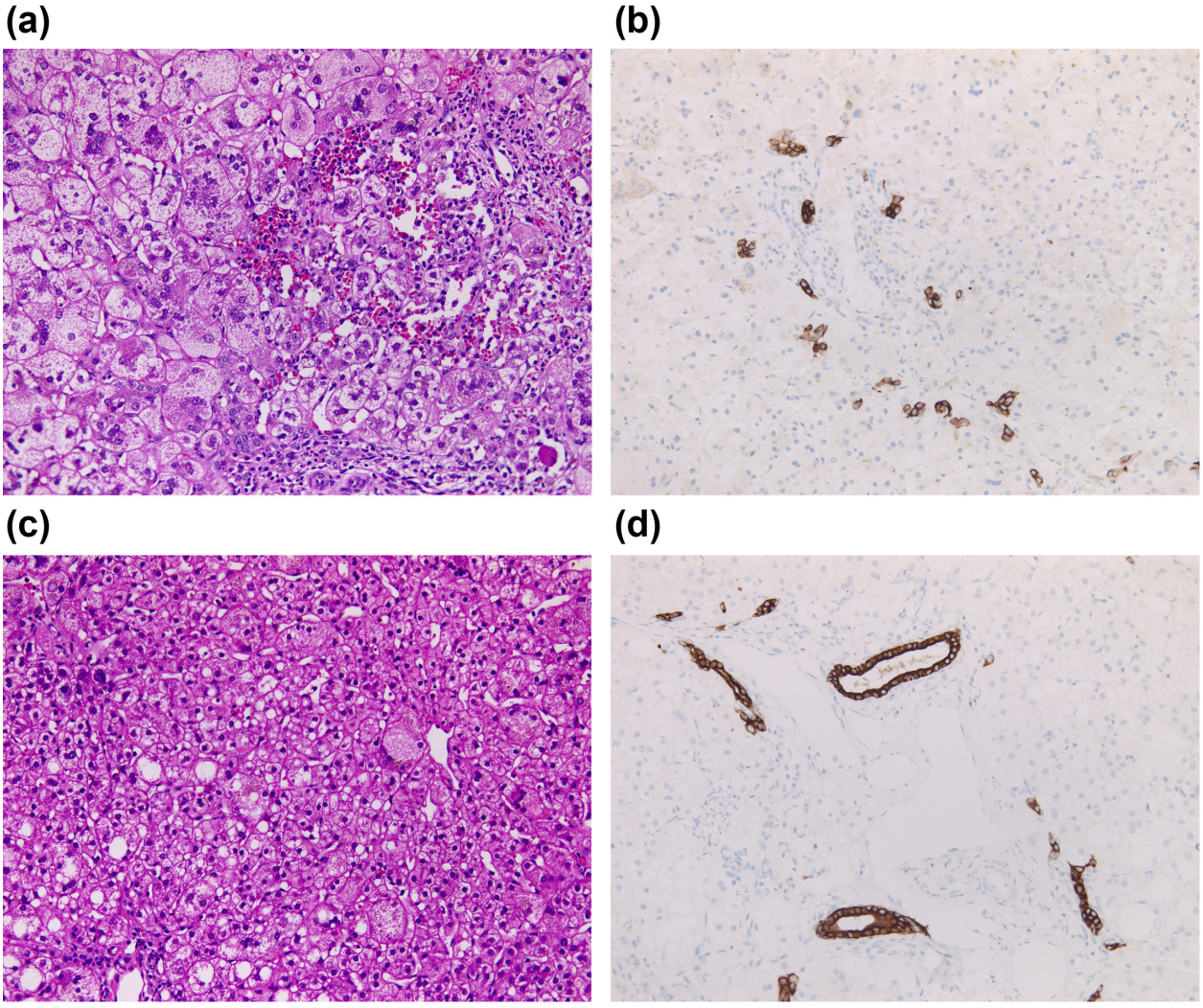

Fig. 1. Liver histology by hematoxylin-eosin (HE) staining and cytokeratin 19 (CK19) immunohistochemistry. a: before treatment (HE): giant cell formation and feathery degeneration of hepatocytes with extramedullary hematopoiesis. b: before treatment (CK19): small immature bile duct without lumen formation. c: after treatment (HE): improvement of the enlarged hepatocytes. d: after treatment (CK19): neogenesis of the bile ducts with lumen formation.

Table 2 Endocrinological examination

	0 min	30 min	60 min	90 min	120 min
GH (ng/mL)	2.2	1.2	1.6	2.1	2.6
Cortisol (μg/dL)	3	6	7	7	8
ACTH (pg/mL)	18.9	100.8	83.3	77.3	91.3
PRL (ng/mL)	21.6	37.4	37.3	36.5	32.1
TSH (μU/mL)	5.38	31.18	35.71	40.90	45.37
free T_3 (pg/mL)	2.1				
free T_4 (ng/dL)	0.7				
LH (mIU/mL)	0.2				
FSH (mIU/mL)	<1.0				

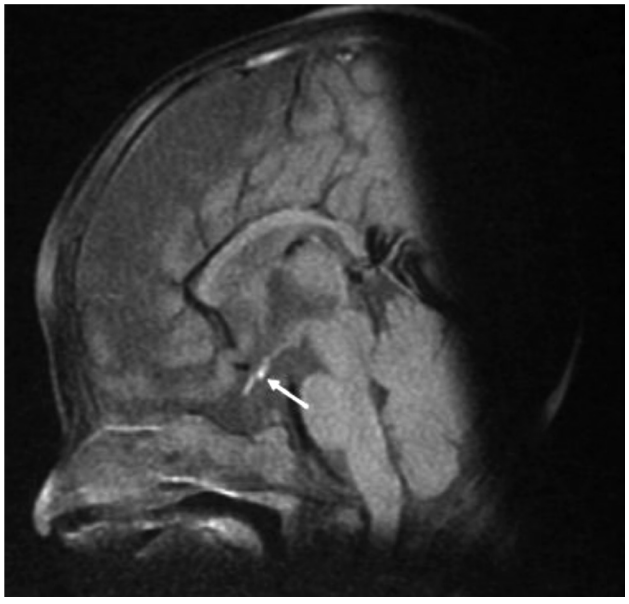

Fig. 2. MRI image of the brain (T1 weighted image). Arrow indicates ectopic posterior lobe. Pituitary hypoplasia is observed. Pituitary stalk is not interrupted.

improvement of hepatocytic degeneration and revival of normal interlobular bile ducts in portal tracts, suggesting that severe intrahepatic cholestasis had remarkably recovered (Figs. 1c and d). The patient maintained normal physical and mental development at 1 yr and 9 mo old and showed no signs of jaundice or liver dysfunction at the time of his last evaluation (Fig. 3). No genetic mutation involved in the formation of bile ducts that causes cholestasis was noted.

Discussion

Liver histology after hormone replacement with HDC, L-T_4, and GH showed improvement of the damaged hepatocytes and recovery of the intrahepatic bile ducts. Torbenson *et al*. reported that hypopituitarism accounted for 10 (16%) of 63 cases of neonatal giant cell hepatitis, placing it second to idiopathic 31 (49%) cases (6). Interestingly, portal and lobular inflammation was mild to absent in 95% of patients with neonatal giant cell hepatitis (6). The histological features of giant cell hepatitis in hypopituitarism showed a significant difference in hypoplasia of the bile ducts (6). Liver histological findings in our case were the same as those reported by Torbenson *et al*. (6). These indicated that giant cell formation of hepatocytes with hypoplastic bile ducts and no/few inflammatory cells is a characteristic of cholestasis caused by hypopituitarism. To the best of our knowledge, our case is also the first case report that showed liver histology images after hormone replacement. Hormone replacement promoted formation of bile ducts and normalization of hepatocytes, suggesting that giant cell formation of hepatocytes in hypopituitarism is reversible.

Congenital CPHD may present with cholestasis during the neonatal period and infancy. However, it is unclear which pituitary hormone deficiency causes cholestasis. In four cases of neonatal cholestasis reported by Hussaini (two cases with familial glucocorticoid deficiency and two with isolated ACTH deficiency), thyroid hormone and GH levels were normal and cholestasis improved with HDC replacement alone (3). In 16 cases of neonatal pituitary stalk interruption syndrome with or without cholestasis, the plasma cortisol level was significantly lower in the cholestasis group, while there was no significant difference with respect to GH and thyroid hormone (4). Our case found improvement in D-Bil levels after HDC replacement, suggesting that cortisol might play an important role in the amelioration of cholestasis. In animal experiments, Shiojiri *et al*. reported that immature hepatocytes failed to differentiate into intrahepatic bile duct cells without dexamethasone (7). Glucocorticoid exhibits choleretic effects by activating Cl^-/HCO_3^- exchangers via glucocorticoid receptors (8). Since cortisol is necessary for differentiation into bile ducts and for functional choleresis, we consider that cortisol is one of the most important hormones involved in cholestasis caused by congenital CPHD. However, cholestasis was improved with administration of HDC in addition

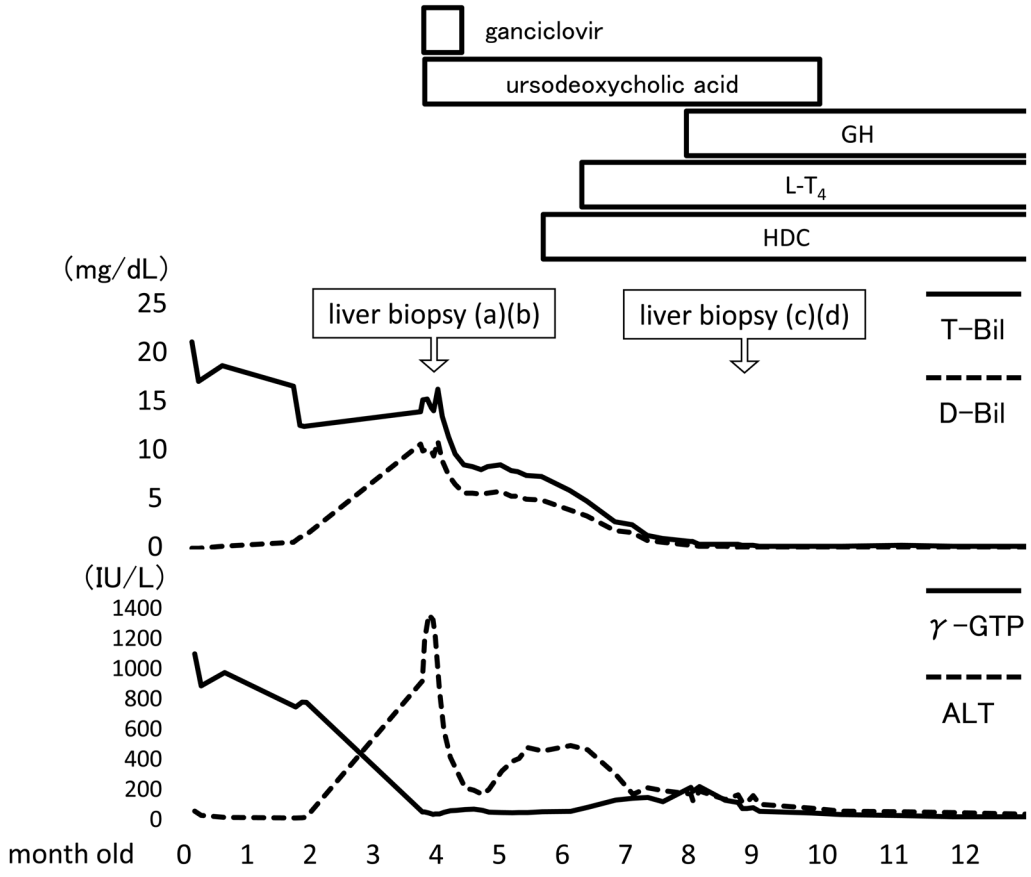

Fig. 3. Clinical course. HDC supplementation was started at 5 mo old. Direct bilirubin began to decline soon after treatment and normalized at the age of 12 mo.

to L-T_4 and GH. In rat studies, thyroid hormone has an effect on bile flow (9) and IGF I has a protective effect on experimental liver cirrhosis (10, 11). These studies demonstrated that thyroid hormone and GH might also be important for improvement of cholestasis. Further research is needed for pathological elucidation of cholestasis associated with hypopituitarism.

We might have been able to diagnose our case as CPHD at an earlier stage because cryptorchidism and hypoplastic scrotum in addition to hypoglycemia and hypothyroidism were present. Examinations should be performed, keeping the possibility of CPHD in mind, when the patient presents with neonatal cholestasis and hypopituitarism features including prolonged hypoglycemia, electrolyte abnormality, cryptorchidism, or microphallus.

Not all congenital CPHD patients present with cholestasis. In our case, CMV infection was serologically and cytologically proved although histologically, it was not. Jaundice was temporarily improved with ganciclovir. Previous reports showed that CMV is associated with hepatitis and BA (12, 13). These suggested that not only CPHD but also CMV might have contributed to cholestasis in our case. In addition, urinary tract and RSV infections might have partly led to aggravation of liver dysfunction. Although these infections may have affected cholestasis, this case is a valuable case in which improvement could be confirmed clinically and histologically after hormone replacement.

We presented an abstract of this manuscript at the 50th annual meeting of the Japanese Society for Pediatric Endocrinology.

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