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Original Article

Dose Adjustments of Hydrocortisone and L-thyroxine in Hypopituitarism Associated with Cholestasis

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Abstract. A patient with congenital hypopituitarism associated with cholestasis is reported here. Large doses of fat-soluble hormones (hydrocortisone (20 mg/m^2/day) and L-thyroxine (14 μg/kg/day)) were needed to resolve hypoglycemia and hypothyroidism during cholestasis. The doses could be reduced to 10 mg/m^2/day and 3.5 μg/kg/day, respectively, after improvement of cholestasis. Sodium valproate, which is a water-soluble drug, did not need any dose adjustments during cholestasis. Adjustment of fat-soluble hormone doses during cholestasis should be considered in patients with cholestasis.

Key words: hypopituitarism, cholestasis, fat-soluble hormone, dose adjustments

Introduction

Congenital hypopituitarism can be associated with liver dysfunction and cholestasis (1). Malabsorption of fat-soluble vitamins is known during cholestasis, while that of fat-soluble hormones has not been reported. We report a case of congenital hypopituitarism with cholestasis whose hypoglycemia and hypothyroidism were not improved by conventional doses of hydrocortisone and L-thyroxine. Difficulty in absorption of hydrocortisone and L-thyroxine in cholestasis is described.

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Case Report

The patient, a male infant, was born to unrelated healthy parents by emergency Caesarean section because of a low level of estriol (data not available) in maternal urine at 39 wk of gestation. He had no asphyxia (Apgar score 9 at 1 min). His birth weight and height were 3.3 kg (+0.5 SD) and 48.8 cm (–0.7 SD), respectively. Testes were descended. The length of phallus was 3.5 cm (+0.5 SD).

Severe apnea with hypoglycemia persisted 3 h after birth. Hypoglycemia disappeared with a continuous infusion of glucose (4 mg/kg/min). Conjugated hyperbilirubinemia, liver dysfunction and hepatomegaly were found at one and a half months of age. At three and a half months of age he had convulsions with hypoglycemia (5 mg/dl) after a six-hour fasting. He was diagnosed as having ACTH, TSH and GH deficiency at four months of age from the laboratory findings shown in Table 1. Sept-optic-dysplasia was suspected because of nystagmus and bilateral optic nerve

Table 1 Laboratory findings when hypopituitarism was diagnosed

cortisol	7 μg/dl	
fT_4	0.64 ng/dl	
fT_3	1.9 pg/ml	
TSH	2.0 mIU/ml	(basal level)
	24.3 mIU/ml	(peak level in TRH stimulation test at 120 min)
GH	5 ng/ml	(peak level in arginine stimulation test)
IGF-1	9 ng/ml	

Table 2 Laboratory findings and doses of therapy

mo		4	4.5	5	5.5	6	6.5	7	8	9
blood glucose level*	(mg/dl)	26	28	29	62	74	78	76	91	83
total bilirubin	(mg/dl)	11.6	10.6	9.3	7.1	4.5	5.2	1.4	0.9	0.3
direct bilirubin	(mg/dl)	7.7	7	6	4.7	3.1	3.7	0.9	0.5	0.1
GOT	(IU/l)	440	363	383	168	142	184	138	111	41
GPT	(IU/l)	204	184	205	115	64	99	100	114	44
bile acid	(μmol/l)			299		287		85	15	
Sodium valproate	(μg/ml)					65		49	55	
fT_3	(pg/ml)	1.4	3.2	3	2.9	2.6	3.6	4.2	5.7	4.3
fT_4	(ng/dl)	0.64	0.79	0.75	0.89	0.81	0.9	1.32	1.7	1.27
I-thyroxine	(μg/kg/day)		(6.5)	(8)	(10)		(14)	(10)	(5)	(3.5)
hydrocortisone	(mg/m²/day)		(10)		(20)			(10)		
Growth hormone	(mg/kg/wk)						(0.17)			

*Six-hour fasting.

hypoplasia. Pituitary stalk was not visible and septum pellucidum was detected on MRI.

Hydrocortisone (10 mg/m²/day) and L-thyroxine (6.5 μg/kg/day) were started at four months of age. In spite of replacement therapy, hypoglycemia and the hypothyroid state persisted at five months of age, when fat-soluble vitamins were relatively low with cholestasis: serum vitamin E level, 2.3 mg/l (normal 3–9 mg/l); serum 25 hydroxyvitamin D level, 15 ng/ml (normal 15–80 ng/ml). The doses of hydrocortisone and L-thyroxine needed to be increased to a maximum of 20 mg/m²/day and 14 μg/kg/day, respectively, to keep normal blood glucose levels and normal thyroxine levels (Table 2). In contrast sodium valproate (20 mg/kg/day), which was started due to seizure without hypoglycemia, was not increased to keep the appropriate level (around 50 μg/ml).

Blood glucose levels after six-hour fasting rose above 60 mg/dl with hydrocortisone (20 mg/m²/day) at five and a half months of age, one month before start of growth hormone treatment (see below). Serum cortisol levels (2 h after taking hydrocortisone orally, when the levels are supposed to be in the highest range) were not extremely high (around 8 μg/dl) and obesity was not noted at five and a half months of age. Similarly, a euthyroid state was eventually attained with L-thyroxine (14 μg/kg/day) at seven

months of age. Height had been –2 SD since one month of age. At six and a half months of age growth hormone treatment (0.17 mg/kg/week) was started.

Serum cortisol level (2 h after taking hydrocortisone orally) increased up to 15 μg/dl without change of dose (20 mg/m^2/day) at seven months of age, when cholestasis had improved: direct bilirubin level, 0.9 mg/dl; bile acid level, 85 μmol/l. The dose of hydrocortisone could be reduced to 10 mg/m^2/day at seven months of age. Hypoglycemia was not noted even after decreasing the dose. The dose of L-thyroxine could be decreased similarly at seven months of age (Table 2). The dose of L-thyroxine was 3.5 μg/kg/day at nine months of age when cholestasis was completely resolved.

Discussion

Fat-soluble hormones such as hydrocortisone and L-thyroxine were monitored during cholestasis in a patient with congenital hypopituitarism. The dose of these hormones had to be changed according to the condition of cholestasis.

Congenital hypopituitarism is known to be associated with cholestasis in the early infancy. At least thirty-two cases of congenital hypopituitarism with cholestasis have been reported (2–15). The doses of replacement therapy were mentioned in 11 cases (3, 5, 7, 8, 10, 11). Relatively high doses of L-thyroxine (8 to 10 μg/kg/day) were needed until six months of age in five cases. In these cases the doses of hydrocortisone tended to be high (10 to 20 mg/m^2/day). The dose adjustment after resolving cholestasis has not been reported for any patients.

One of the reasons why hydrocortisone and L-thyroxine should be increased in cholestasis is because supplements of fat-soluble vitamins are needed. Insufficiency of bile acids secretion in the intestine causes difficulty for the absorption of fat-soluble substances. Serum bile acid levels, an established marker for cholestasis (16), were roughly correlated with the dose of hydrocortisone and L-thyroxine in our case.

In conclusion, the dose of hydrocortisone and L-thyroxine should be increased during cholestasis in patients with hypopituitarism.

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