Endocrine Journal 2017, **64** (6), 639-643

NOTE

Use of liothyronine without levothyroxine in the treatment of mild consumptive hypothyroidism caused by hepatic hemangiomas

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Abstract. There have been reports of the use of levothyroxine or levothyroxine plus liothyronine for consumptive hypothyroidism caused by hepatic hemangiomas. Administration of levothyroxine without liothyronine can be inadequate to maintain normal levels of both free T3 and free T4 in some patients. However, there is no report of treatment with liothyronine plus propranolol. We herein present a case in which we used liothyronine therapy for multifocal hepatic hemangiomas in a Japanese patient with low free T3 and normal free T4 levels. A 2-month-old Japanese male was referred to our hospital because of jaundice. Abdominal computed tomography showed multifocal hemangiomas in both lobes of the liver. TSH level was elevated, free T3 level was low, free T4 level was normal, and hypothyroidism due to hepatic hemangiomas was diagnosed. In addition to propranolol, liothyronine was started. We used liothyronine without levothyroxine for hypothyroidism because only free T3 level had decreased, whereas free T4 level remained in the normal range. The TSH and free T3 levels normalized in this patient in less than 1 month. The liothyronine dose was gradually reduced with regression of the hemangiomas, and liothyronine administration was discontinued at the age of 5 months. At the age of 11 months, growth and neurological development of the patient met age-specific norms, and he was euthyroid at that time. This is the first report demonstrating the use of liothyronine with propranolol for treatment of this type of consumptive hypothyroidism.

Key words: Consumptive hypothyroidism, Hemangioma, Liothyronine, Type 3 deiodinase

THE ASSOCIATION between consumptive hypothyroidism and hepatic hemangiomas was first described in 2000 [1]. Treatment of consumptive hypothyroidism using thyroid hormone therapy has been demonstrated by several studies [1-14]. Diffuse or multifocal hepatic hemangiomas overexpress type 3 deiodinase in the vascular endothelium. Because this enzyme converts T4 and T3 to reverse T3 and diiodothyronine (T2), respectively, administration of levothyroxine without liothyronine for hypothyroidism may be insufficient to maintain normal levels of both free T3 and free T4 in some patients [2-5, 8-12, 14]. However, there is no report regarding treatment with liothyronine plus propranolol. We herein present a case of multifocal hepatic hemangiomas in a Japanese patient with low free T3 and normal free T4 levels and demonstrate the use of liothyronine plus propranolol therapy. The TSH and free T3 levels in this patient improved with the administration of liothyronine plus propranolol within a month.

Submitted Nov. 20, 2016; Accepted Feb. 17, 2017 as EJ16-0559
Released online in J-STAGE as advance publication Apr. 18, 2017
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Case Report

The patient was an 11-month-old Japanese male who was born at 38 weeks of gestation after an uncomplicated pregnancy and delivery. At birth, his height was 49.0 cm (0.0 SD) and his weight was 3.2 kg (+0.5 SD). His TSH and free T4 levels at the time of neonatal screening were normal. He was referred to our hospital because of jaundice at the age of 2 months. He showed no signs of hypothyroidism except jaundice. On physical examination, the liver was palpable 3 cm below the

right costal margin. Abdominal computed tomography showed multifocal hemangiomas in both lobes of the liver (Fig. 1). Blood tests at this time yielded the following values: serum total bilirubin, 6.4 mg/dL; serum direct bilirubin, 0.2 mg/dL; aspartate transaminase, 49 IU/L; alanine transaminase, 26 IU/L; γ-glutamyl transpeptidase, 226 IU/L; TSH, 17.7 μIU/mL (normal 0.65–6.6 μIU/mL); free T3, 1.96 pg/mL (normal 1.74–5.5 pg/mL); and free T4, 1.48 ng/dL (normal 0.90–2.0 ng/dL). To measure thyroid hormones, we used the Lumipulse® kit (Fujirebio, Tokyo, Japan). The clinical and laboratory data and the biggest tumor size of the patient are shown in Table 1. Hypothyroidism due to hepatic hemangiomas was diagnosed. In addition to propranolol (2 mg/kg/day in 3 divided doses), which is the standard treatment regimen for infantile hemangiomas [15], liothyronine (1 μg/kg/day in 3 divided doses) was started. We used liothyronine without levothyroxine for hypothyroidism because only the free T3 level had decreased; the free T4 level remained in the normal range. The TSH and free T3 levels normalized in this patient in less than 1 month of treatment. The liothyronine dose was gradually reduced, and liothyronine administration was discontinued at the age of 5 months since the tumors gradually disappeared as observed on the abdominal ultrasonography images obtained at the age of 2, 3, and 5 months (Fig. 2). At the age of 11 months, the growth and neurological development of the patient were normal for this age. His height was 73.5 cm (−0.2 SD), his weight was 10.6 kg (+1.6 SD), and he was euthyroid at this time. Tumor recurrence was not observed.

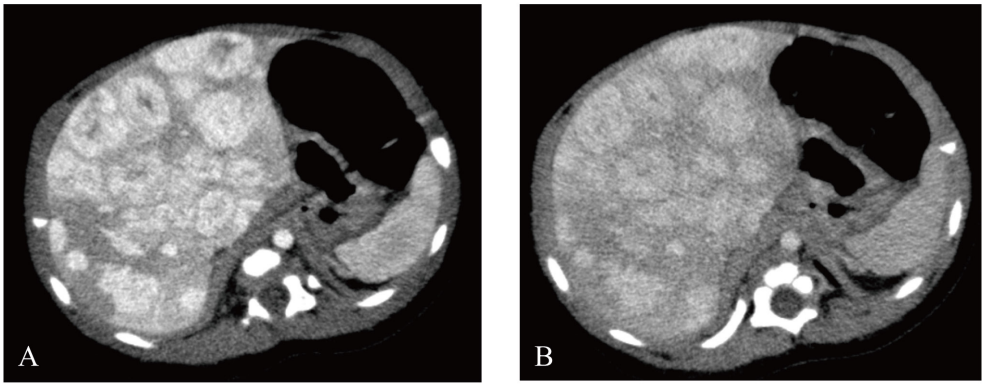

Fig. 1 Pretreatment contrast-enhanced computed tomography (CT) of the liver
Multifocal hepatic hemangiomas were gradually enhanced from the surroundings in the arterial phase (**A**). The tumors remained enhanced in the equilibrium phase (**B**). There were 71 tumors. The tumors were 1.0 cm to 4.0 cm in size.

Table 1 Clinical and laboratory data of the patient

Age	Weight (kg)	Length (cm)	Thyroid function test			Liver function test			Tumor		Treatment	
			TSH (μIU/mL)	free T3 (pg/mL)	free T4 (ng/dL)	T-Bil (mg/dL)	AST (IU/L)	ALT (IU/L)	Number	Size (cm)	L-T3 (μg/kg/day)	Propranolol (mg/kg/day)
1 day	3.208	49.0										
5 days			5.9		2.19							
2 mo 10 d	6.286	56.5	17.73	1.96	1.48	6.4	49	26	71	4.0×2.5	1	1
2 mo 22 d	6.461	61.0	8.384	4.36	1.26	3.2	64	36	23	3.0×1.5	1	2
3 mo 4 d	6.745	62.0	1.956	4.95	0.98	1.3	57	46	6	1.8×1.2	1	2
4 mo 5 d	7.865	63.0	2.571	4.52	0.86	0.7	59	55			1	2
4 mo 26 d	8.455	65.4									0.7	2
5 mo 22 d	9.030	66.6	0.980	3.91	1.04	0.5	35	26	0	Disappeared	Cessation	2
6 mo 12 d	9.185	67.8	1.789	4.29	1.13	0.6	45	35				2
8 mo 13 d	9.815	71.3	1.436	4.41	1.12	0.6	41	23	0	-		2
11 mo 8 d	10.57	73.5	1.515	4.60	1.23	0.6	34	12	0	-		2

mo, months; T-Bil, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; L-T3, L-triiodothyronine.
Reference ranges [16]: TSH 0.65-6.6 μIU/mL, free T3 1.74-5.5 pg/mL, free T4 0.90-2.0 ng/dL.

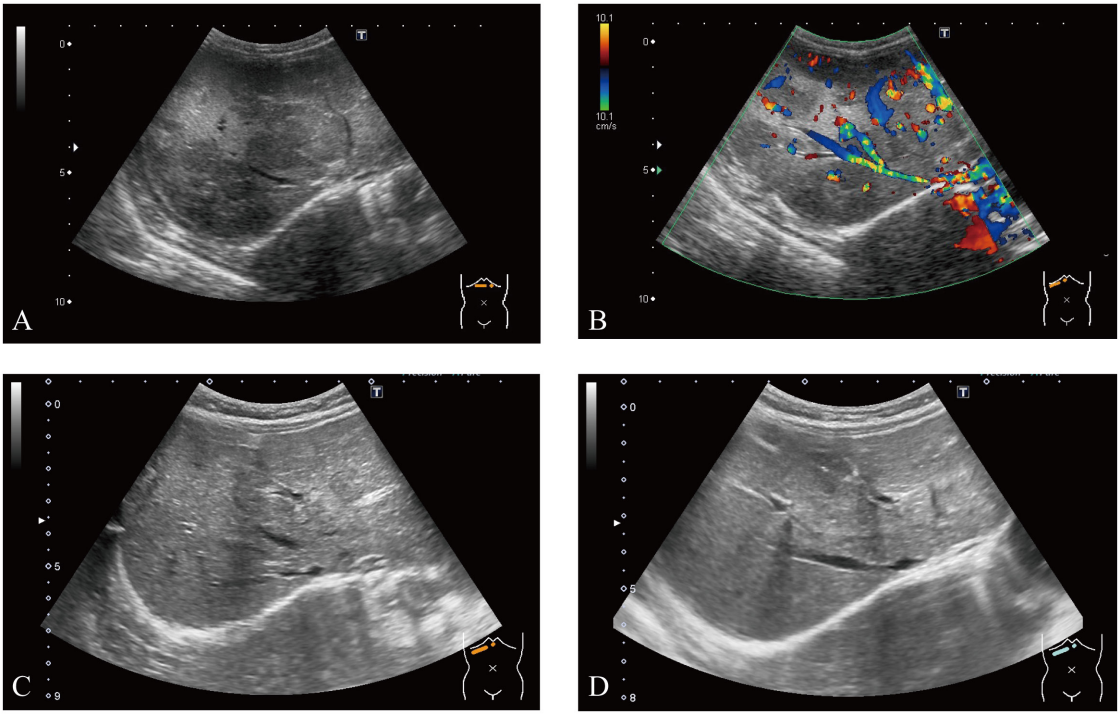

Fig. 2 Pretreatment abdominal ultrasonography showed multiple round low echoic lesions in the right hepatic lobe at the age of 2 months (**A**). Doppler study showed vessels surroundings the nodules at the age of 2 months (**B**). After starting propranolol, abdominal ultrasonography at the age of 3 months showed marked involution (**C**). Abdominal ultrasonography revealed no tumor in the liver at the age of 5 months (**D**).

Discussion

To our knowledge, this is the first report demonstrating the use of liothyronine plus propranolol for the treatment of mild consumptive hypothyroidism caused by hepatic hemangiomas. Most studies on this type of consumptive hypothyroidism report the use of levothyroxine or levothyroxine plus liothyronine for treatment [1-12, 14]; while 1 study reported the use of liothyronine plus prednisolone [13]. However, there is no report of using liothyronine plus propranolol for the treatment of consumptive hypothyroidism. Administration of levothyroxine without liothyronine can lead to an overdose, as demonstrated in patients with hypothyroidism caused by multifocal hepatic hemangiomas [3, 10-12]. Administration of levothyroxine without liothyronine can be deemed as inadequate to maintain normal levels of free T3 and free T4 in some patients. In the present case, we used liothyronine without levothyroxine for hypothyroidism because only the free T3 level had decreased; the free T4 level remained in the normal range. We considered an administration of levothyroxine, when the free T4 level were low and TSH level were high in this case. Furthermore, the thyroid function was carefully monitored during the therapy. It is possible that the patient would have done well without therapy; however, hormone therapy was required to decrease the risk of mental retardation.

Hypothyroidism in this patient was caused by hepatic hemangiomas. Thyroid function improved with regression of the hemangiomas. We cannot measure reverse T3 level in Japan. Moreover, tests for mutations for congenital hypothyroidism were not performed; however, TSH and free T4 levels measured during neonatal screening were normal, indicating that the possibility of pertinent mutations was low. Because the patient was brought to our department after enhanced computed tomography was performed, thyroglobulin and urinary iodine levels were fallacious. TSH receptor antibody level was 6.3% (normal 0.0−15.0%) at the age of 4 months, and the mother did not use any drugs.

The patient had mild hypothyroidism compared to most case reports of consumptive hypothyroidism in the setting of hemangiomas. The severity of consumptive hypothyroidism depends on the volume of hepatic

hemangiomas. We assumed that propranolol could be involved in the involution of multifocal hepatic hemangiomas, thus leading to the early normalization of thyroid hormones. It took 1 month for this patient to have thyroid hormone levels in the normal ranges; this is shorter than most reported durations for improvement. The requirement for thyroid hormone was gradually reduced, and the treatment was discontinued at the age of 5 months. Administration of levothyroxine plus propranolol has been reported for 2 cases of mild hypothyroidism [2, 12]. Although the longitudinal data on thyroid function was unknown, the patient was euthyroid in 2 months after treatment with levothyroxine plus propranolol [2]. In the other patient, the levels of free T4 remained high for 5 months, although the TSH level normalized within 1 month of levothyroxine plus propranolol therapy [12]. Attaining normal thyroid function in patients with mild consumptive hypothyroidism treated with levothyroxine or liothyronine without propranolol has been reported to be difficult [9-11, 13]. A summary of the published cases of mild consumptive hypothyroidism is presented in Table 2. Based on the previous reports, it can be assumed that propranolol administration aided early normalization of thyroid function in this case. In most of the previous reports, the number and the size of the tumors are not described in detail, making the comparison difficult. However, based on the ultrasonography and computed tomography images, it can be estimated that the number and the size of the tumors were lower for the present case. In this case, the levels of free T4 and TSH decreased after administrating liothyronine and propranolol; however, the patient was euthyroid. In conclusion, administration of liothyronine plus propranolol can be considered in some patients with hypothyroidism caused by multifocal hepatic hemangiomas, especially when the free T3 and free T4 levels are low and in the normal range, respectively.

Disclosure

The authors have nothing to disclose.

Table 2 Summary of mild cases of consumptive hypothyroidism

Age	TSH		free T3		free T4		Treatment			Authors
	Min-Max	Time to normalize	Min-Max	Time to normalize	Min-Max	Time to normalize	L-T3 (μg/kg/day)	L-T4 (μg/kg/day)	Others	
3 wk	-17	2 mo	-	7.5 mo	-	-	0	25	PSL	Mouat *et al*. [9]
7 wk	1.2-57.4	3 mo	1.0-3.8	10 mo	1.3-2.3	5 mo	0	7.5	PSL	Bessho *et al*. [10]
10 mo	2.5-75.88	5 mo	-2.27	Not done	1.6-	Not Done	0	4.6	PSL	Cho *et al*. [11]
8 wk	2.5-39.9	8 mo	-	Normal	1.85-2.80	10 mo	0	2.0	PSL→Propranolol	Vergine *et al*. [12]
6 wk	-9.47	2 mo	-	-	-	2 mo	0	Unknown	Propranolol	Mhanna *et al*. [2]
4 mo	1.07-14.2	6 mo	0.54-1.72 (T3)	Not done	1.0-2.9	10 mo	Unknown	0	PSL	Imteyaz *et al*. [13]
2 mo	0.980-17.73	1 mo	1.96-4.95	1 mo	0.86-1.48	Normal	1.0	0	Propranolol	Higuchi *et al*. (*)

wk, weeks; mo, months; L-T3, L-triiodothyronine; L-T4, L-thyroxine; PSL, prednisolone.
Reference ranges [9]: TSH 0.4-4.0 units/mL, free T3 3.0-10.0 pmol/L, free T4 11.0-32.0 pmol/L
Reference ranges [10]: TSH 0.4-3.8 μIU/mL, free T3 3.1-6.3 pg/mL, free T4 1.1-1.7 ng/dL
Reference ranges [11]: TSH 0.4-5.0 mIU/L, free T3 2.27-3.57 pg/mL, free T4 0.8-1.6 ng/dL
Reference ranges [12]: TSH 0.6-8.0 mIU/L, free T3 0.18-0.46 ng/dL, free T4 0.8-1.8 ng/dL
Reference ranges [2]: TSH 0.4-8.2 mIU/L, free T4 0.89-1.6 ng/dL
Reference ranges [13]: TSH 0.50-4.50 μIU/mL, T3 0.80-2.00 ng/mL, free T4 0.7-1.6 ng/dL
Reference ranges* [16]: TSH 0.65-6.6 μIU/mL, free T3 1.74-5.5 pg/mL, free T4 0.90-2.0 ng/dL

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