Clin Pediatr Endocrinol 2019; 28(1), 9–14

Case Report

Combination therapy of propranolol, levothyroxine, and liothyronine was effective in a case of severe consumptive hypothyroidism associated with infantile hepatic hemangioma

Asami Osada[1, 2], Eriko Araki[1], Yukio Yamashita[1], and Tomohiro Ishii[2]

[1]*Department of Pediatrics, Yokohama Municipal Citizen's Hospital, Yokohama, Japan*

[2]*Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan*

Abstract. Infantile hepatic hemangioma (IHH) can be accompanied by consumptive hypothyroidism. We report the case of a 4-mo-old boy who showed massive hepatomegaly, peripheral coldness, lethargy, and failure to thrive. An enhanced computed tomography scans demonstrated multiple hemangiomas in both lobes of the liver, and a thyroid function tests showed severe hypothyroidism: TSH 561.5 μIU/mL, free triiodothyronine (fT_3) 1.0 pg/mL, and free thyroxine (fT_4) < 0.7 ng/dL. IHH gradually regressed following propranolol treatment and fT_4 increased to a low normal level (1.0 ng/dL) by high dose replacement of levothyroxine, while fT_3 remained very low (< 1.0 pg/mL), even following high doses of levothyroxine; fT_3 eventually normalized following the administration of liothyronine. We suggest that treatment strategies should be individualized based on thyroid function, and that the combination therapy of propranolol for anti-tumor treatment and levothyroxine and liothyronine for respective thyroid hormone replacement is effective, particularly in cases of severe consumptive hypothyroidism due to multiple IHHs.

Key words: infantile hepatic hemangioma, consumptive hypothyroidism, propranolol, levothyroxine, liothyronine

Introduction

Infantile hepatic hemangioma (IHH) is a benign tumor, with around 5–10 cases occurring per year in Japan (1). The pathological features of IHH have not been fully elucidated, but are likely caused by neoplastic proliferation of endocapillary cells or vascular anomalies (2). IHH often undergoes spontaneous gradual involution; however, in some cases of IHH, intervention is mandatory because of serious complications including heart failure, respiratory distress, coagulation abnormality (Kasabach-Merritt syndrome), or compartment syndrome. Consumptive hypothyroidism is one such complication of IHH, occurring in 5.3% of all IHH cases (1). Iodothyronine deiodinase is highly expressed in hepatic hemangioma cells and

Received: August 28, 2018
Accepted: November 1, 2018
Corresponding author: Tomohiro Ishii, M.D., Ph.D., Department of Pediatrics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
E-mail: tishii@1992.jukuin.keio.ac.jp

inactivates both triiodothyronine and thyroxine (3). While the traditional treatment for IHH was systemic steroid or interferon administration, propranolol is the currently recommended treatment choice (4, 5). Here, we report the case of a 4-mo-old boy with severe IHH-mediated consumptive hypothyroidism that was improved by propranolol-containing combination therapy administration, and review previous cases that were treated with propranolol.

Case Report

The patient was a 4-mo-old boy with abdominal distension, which had been present for 2 mon. He was delivered at 38 wk of gestation with no asphyxia, weighing 3432 g. His mother was diagnosed with mild hypothyroidism (TSH 7.339 μIU/mL, fT_4 1.10 ng/dL, fT_3 3.12 pg/mL) during fertility treatment and was prescribed a 3-mo course of levothyroxine; she became pregnant 8 mo later and displayed normal thyroid function throughout the pregnancy. The patient's newborn screening tests were all normal, including thyroid function (TSH 3.6 μIU/mL, fT_4 2.71 ng/dL), although at birth he had a 2 cm diameter subcutaneous hemangioma on his forehead that was successfully treated by laser ablation. Other than the subcutaneous hemangioma, he did not show any abnormal growth, development, or physical examination findings at his routine checkup at 1 mo of age.

Abdominal distension was noticed in the patient at 2 mo of age, which progressively worsened. When medical attention was sought at 4 mo of age, his liver was palpable 5 cm below the right costal margin on the right midclavicular line; he also had several features suggestive of hypothyroidism including peripheral coldness, lethargy, and failure to thrive (Fig. 1). His length was 59.6 cm (< 3rd percentile, –2.1 SD), weight was 5980 g (10th percentile, –1.3 SD), and head circumference was 40.0 cm (90–97th percentile, –0.4 SD). Thyroid ultrasonography revealed the maximum transverse diameter was 28.7 mm (+ 0.2 SD), and an enhanced abdominal computed tomography scans showed multiple tumors unevenly occupying both lobes of the liver (Fig. 2) and replacing most of the normal hepatic architecture. The findings of peripheral rim contrast enhancement in the arterial phase led to a diagnosis of IHH. The tumor marker alpha-fetoprotein (AFP) was 23900 ng/mL (with low serum L3 isozyme, 1.9%), excluding the possibility of hepatoblastoma or hepatocellular carcinoma. Head magnetic resonance imaging and abdominal ultrasonography did not show hemangioma in any other organs. A blood test revealed severe hypothyroidism (TSH 561.5 μIU/mL, fT_3 1.0 pg/mL, and fT_4 < 0.7 ng/dL), with negligible anti-thyroid autoantibodies (anti-thyroglobulin antibody 15.6 IU/mL and anti-thyroid peroxidase antibody 9.7 IU/mL). The patient also had cardiomegaly (cardiothoracic ratio 61% on chest X-ray); however, ejection fraction did not decrease (63.2%). He did not have any other complications such as respiratory failure, coagulation disorder, or compartment syndrome. The patient was diagnosed with IHH and consumptive hypothyroidism.

Due to the size of the IHH and the severity of the hypothyroidism, we simultaneously started propranolol treatment and levothyroxine replacement. Propranolol was started at 0.25 mg/kg/d, and gradually increased to 2.0 mg/kg/d for 3 wk in the absence of adverse events such as hypoglycemia or bradycardia (Fig. 3); no adverse events were observed in our patient during the period of propranolol treatment. Levothyroxine was initiated at 50 μg/d (8.3 μg/kg/d) and increased to 80 μg/d (13 μg/kg/d). After 2 wk of 80 μg/d (13 μg/kg/d) levothyroxine treatment, fT_4 increased to a low-normal level (1.0 ng/dL) but fT_3 remained very low (< 1.0 pg/mL). Liothyronine was then added at a dose of 20 μg/d (3.3 μg/kg/d), and TSH gradually normalized over the following month. To avoid the risk of overtreatment, liothyronine replacement was continued for 4 wk until the patient became euthyroid. The IHH decreased in diameter to 6

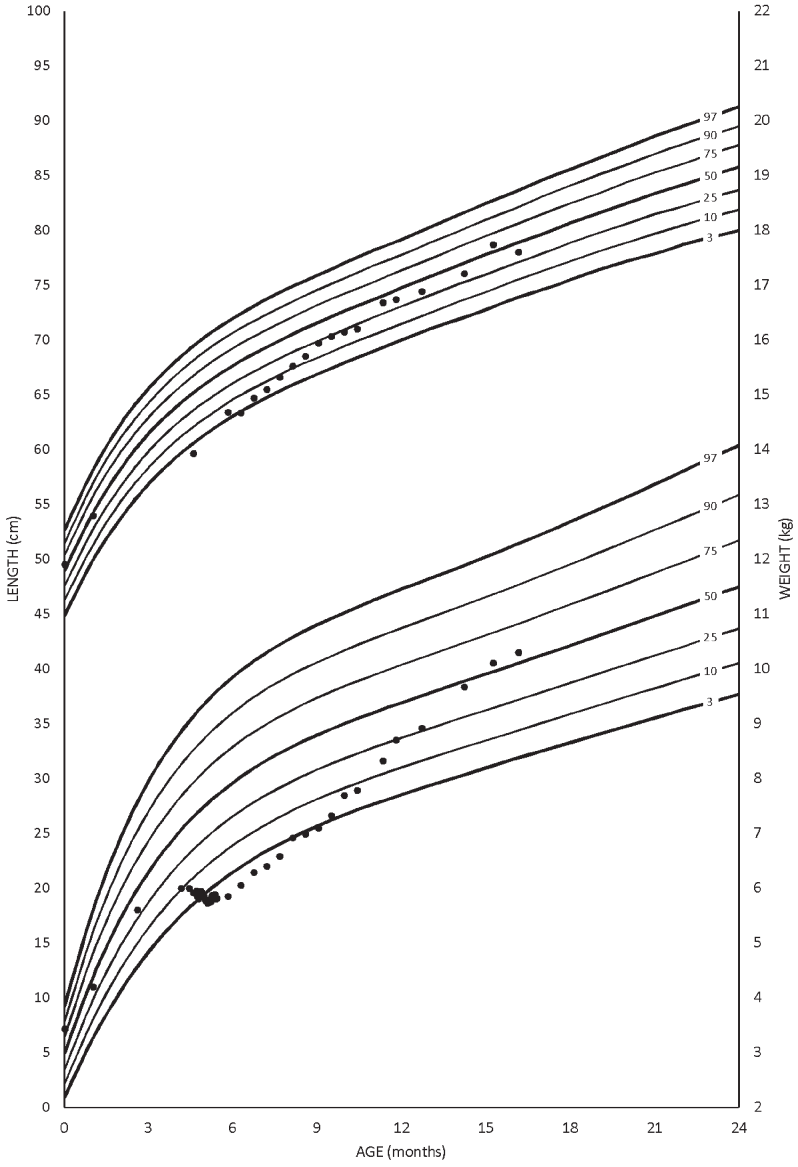


Fig. 1. Growth chart of the patient. The upper chart shows length, and the lower chart shows weight. The number on each line indicates percentile of the age- and sex-matched reference.

mm, and propranolol was stopped at 1 yr and 1 mo of age; serum AFP levels declined to within normal limits within a month of propranolol treatment initiation. At the latest visit at 1 yr and 5 mo of age, the patient acquired catch-up growth, and his psychomotor development was not delayed. No evidence of IHH regrowth was observable via ultrasonography.

Discussion

Our patient had the most severe described case of IHH-mediated consumptive hypothyroidism subsequently treated with propranolol (Table 1). As his newborn screening of thyroid function was normal, it is unlikely that he had congenital hypothyroidism. The cause of such severe hypothyroidism in our patient

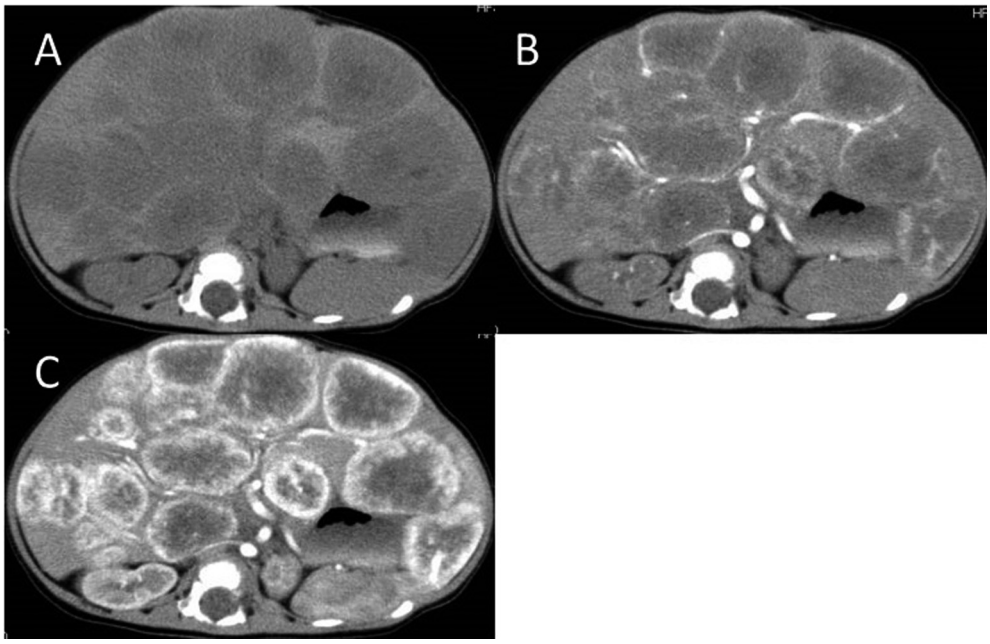
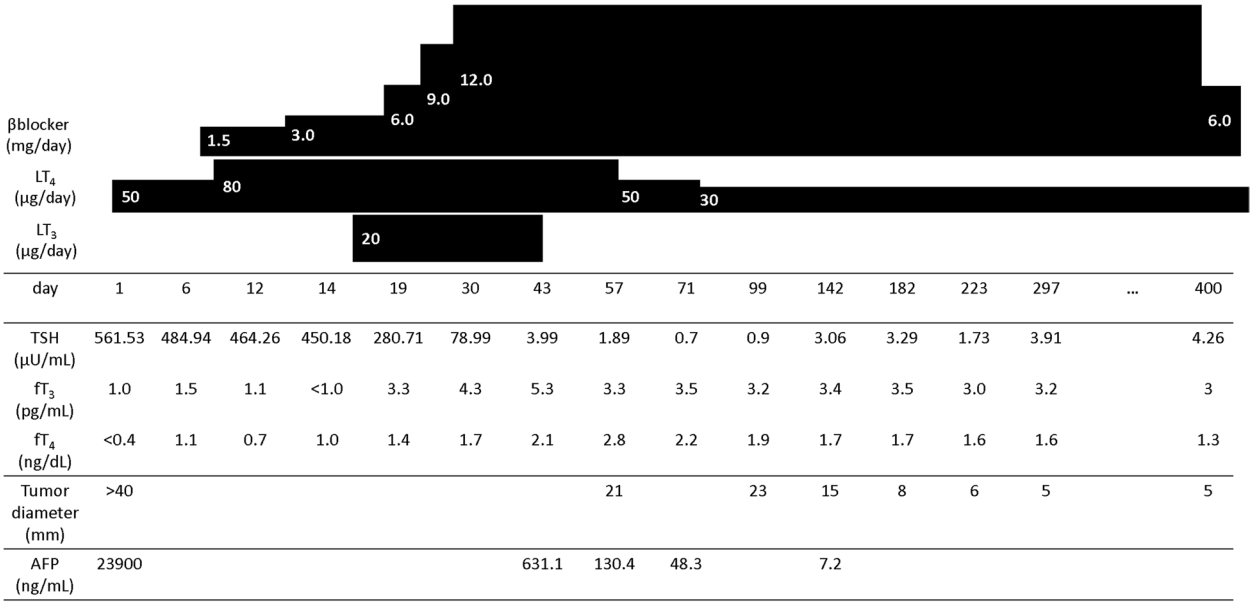


Fig. 2. Abdominal computed tomography scan following initial presentation. Unenhanced (A) and enhanced abdominal computed tomography scans (B, early arterial phase, and C, late phase).



day	1	6	12	14	19	30	43	57	71	99	142	182	223	297	...	400
TSH (μU/mL)	561.53	484.94	464.26	450.18	280.71	78.99	3.99	1.89	0.7	0.9	3.06	3.29	1.73	3.91		4.26
fT_3 (pg/mL)	1.0	1.5	1.1	<1.0	3.3	4.3	5.3	3.3	3.5	3.2	3.4	3.5	3.0	3.2		3
fT_4 (ng/dL)	<0.4	1.1	0.7	1.0	1.4	1.7	2.1	2.8	2.2	1.9	1.7	1.7	1.6	1.6		1.3
Tumor diameter (mm)	>40							21		23	15	8	6	5		5
AFP (ng/mL)	23900						631.1	130.4	48.3		7.2					

Fig. 3. Treatment course and thyroid function profile. LT4: levothyroxine, LT3: liothyronine.

is unclear; however, we hypothesized that the large IHH tumor mass was likely associated with high activity of type 3 iodothyronine deiodinase, although tumor volumetry data were not available in our patient. Consistent with this assumption, and based on an evaluation of all previous cases, Luongo *et al.* (6) speculated that the severity of hypothyroidism is proportional

Table 1. Previously reported cases of infantile hepatic hemangioma with hypothyroidism treated by propranorol

Case	Age (mo)	TSH (μIU/mL)	fT_4 (ng/dL)	fT_3 (pg/mL)	Propranolol (mg/kg/d)	LT4 (μg/kg/d)	LT3 (μg/kg/d)	Reference
1	3	NA	NA	NA	1.5	NA	0	4
2	2	9.47	1.22	NA	2.0	NA	0	4
3	2	115	0.5	1.9	NA	15	0	4
4	2	102.5	< 0.39	2.3	2.0	9.6	0	3
5	3	220	1.1	3.1	2.0	25	0	5
6	1	67	1.08	1.26	2.0	10	4.0	4
7	2	17.7	1.48	1.96	2.0	0	1.0	7
This case	4	561.53	< 0.4	1.0	2.0	14	3.3	

NA: not available.

to the size of the tumor and its specific activity. However, further investigation is required to fully evaluate the relationship between IHH tumor volume and deiodinase enzymatic activity.

Immediate normalization of thyroid function, as well as tumor regression, is mandatory for avoiding irreversible developmental delay in these patients. Our patient was successfully treated by the combination of propranolol and thyroid hormone supplementation, avoiding such complications. As described above, levothyroxine was initially started as a monotherapy; however, subsequent addition of liothyronine was required. This was surprising as levothyroxine monotherapy was effective in the majority of previously reported cases of consumptive hypothyroidism, except for case 6 in Table 1 – this patient required co-administration of liothyronine and levothyroxine to normalize thyroid function. Considering the possibly high consumption rate of T_3 and T_4 in large tumors, the combined replacement of levothyroxine and liothyronine could be more beneficial than high dose levothyroxine monotherapy; combination therapy may also be a better option for initial treatment in cases such as ours. However, when serum fT_4 is normal and fT_3 is reduced, we may use liothyronine supplementation alone, as reported by Higuchi *et al.* (7). Based on these data, we suggest that treatment strategies should be individualized based on thyroid function, and that the combination of propranolol for anti-tumor treatment and levothyroxine and liothyronine for thyroid supplementation is an effective treatment option, particularly in cases of severe consumptive hypothyroidism due to multiple IHHs and probable high activity type 3 iodothyronine deiodinase activity.

Conclusion

We successfully managed severe hypothyroidism due to multiple IHHs in a pediatric patient using the combination therapy of propranolol for anti-tumor treatment and levothyroxine and liothyronine for thyroid hormone replacement. We suggest that treatment strategies should be individualized depending on thyroid function, and that this combination therapy is particularly effective in cases of severe consumptive hypothyroidism due to multiple IHHs and probable high type 3 iodothyronine deiodinase activity.

References

1. Kuroda T, Hoshino K, Nosaka S, Shiota Y, Nakazawa A, Takimoto T. Critical hepatic hemangioma in infants: recent nationwide survey in Japan. Pediatr Int 2014;56: 304–8.

[Medline] [CrossRef]
2. Christison-Lagay ER, Burrows PE, Alomari A, Dubois J, Kozakewich HP, Lane TS, *et al*. Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. J Pediatr Surg 2007;42: 62–7, discussion 67–8. [Medline] [CrossRef]
3. Campbell V, Beckett R, Abid N, Hoey S. Resolution of consumptive hypothyroidism secondary to infantile hepatic hemangiomatosis with combination propranolol and levothyroxine. J Clin Res Pediatr Endocrinol 2018;10: 294–8. [Medline] [CrossRef]
4. Otani G, Goto M, Nogi A, Yanagihara S, Hataya H, Sakakibara H, *et al*. Liothyronine was effective in two cases of consumptive hypothyroidism associated with multiple hepatic hemangiomas. J Jap Pediatr Soc. 2017;121: 610–5 (In Japanese).
5. Al Tasseh F, El-Khansa M, Abd O, Abdel Khalek A, El-Rifai N. Diffuse hepatic hemangioma with single cutaneous hemangioma: an alerting occurrence. Clin Case Rep 2017;5: 887–90. [Medline] [CrossRef]
6. Luongo C, Trivisano L, Alfano F, Salvatore D. Type 3 deiodinase and consumptive hypothyroidism: a common mechanism for a rare disease. Front Endocrinol (Lausanne) 2013;4: 115. [Medline]
7. Higuchi S, Takagi M, Hasegawa Y. Use of liothyronine without levothyroxine in the treatment of mild consumptive hypothyroidism caused by hepatic hemangiomas. Endocr J 2017;64: 639–43. [Medline] [CrossRef]