IHH Complicated Consumptive Hypothyroidism: A Case Report and Literature Review

Conflict of Interest Disclosures: The authors have no conflicts of interest relevant to this article to disclose.
Funding: No funding was provided for our project.

Abbreviations:
CTX, cyclophosphamide;
D3, type 3 iodothyronine deiodinase;
IFN, interferon;
IHH, Infantile hepatic hemangioma;
MRI, magnetic resonance imaging;
PFO, patent foramen ovale;
TSH, thyroid-stimulating hormone;
US, ultrasonography;
VCR, vincristine.

Article Summary:
Through a case of IHH complicated consumptive hypothyroidism and literature review, this study highlight better treatment protocol for these rare patients.

Contributors' Statement Page:
Dr Qianlong Liu conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.
Drs Xin He and Na Liu conceptualized and designed the study, collected data, carried out the initial analyses, and reviewed and revised the manuscript.
Drs Shi and Geng conceptualized and designed the study, carried out the initial analyses, and reviewed and revised the manuscript.
Dr Guo designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT:
Infantile hepatic hemangioma(IHH) is the most common benign liver tumor in infancy, some life-threatening complications like abdominal compartment syndrome, consumptive hypothyroidism and cardiac failure may occur in these patients. Hypothyroidism should be focused and managed earlier to prevent intellectual and growth retardation. We described a 4 months old infant complaint of progressive abdominal distention, who was diagnosed diffuse hepatic hemangiomas by ultrasonography and MRI, treated successfully with propranolol and levothyroxine for consumptive hypothyroidism. At 8 months old levothyroxine was stopped, she grew up with a normal growth trajectory and neurodevelopment at her last follow-up at the

age of 13 months. Literature review and our case suggest that thyroid function should be evaluated even though negative neonatal screen and propranolol should be first-line agent for diffuse IHH. It is helpful that simultaneous anti-tumor and thyroid replacement make diffuse IHH patients with consumptive hypothyroidism recovery better.

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

Introduction

Infantile hepatic hemangioma(IHH) is the most common benign liver tumor in infancy, which was categorized into three patterns: focal, multifocal and diffuse. Most focal IHHs are similar to rapidly involuting congenital hemangiomas, while the multifocal and diffuse patterns are true infantile hemangiomas and may be associated with life-threatening complications like abdominal compartment syndrome, consumptive hypothyroidism and cardiac failure.[1,2] Consumptive hypothyroidism complicates only in 5.3% of all IHH cases but timely treatment is crucial for the patients to prevent intellectual and growth retardation.[3] Here, we report a 4-month-old boy with diffuse hepatic infantile hemangiomas complicating consumptive hypothyroidism, which was managed successfully by combination therapy of propranolol and levothyroxine.

Case report

A 4-month-old female infant complaint of progressive abdominal distention due to hepatic hemangiomas. She was an unexpected baby of her mother aged 40 years old. Routine examination was performed and nothing abnormal was found during pregnancy. She was full-term and healthy at birth. At 3 months of age, she was

admitted to emergency department of a Children's hospital because of abdominal distension and edema of both feet. Abdominal ultrasonography(US) revealed multiple hemangiomas of liver, and laboratory test showed hyponatremia and anemia. 2-day treatment was ineffective on the abdominal distension and edema of lower extremities. Her parents declined to further treatment and went home, for which the Spring Festival was around the near, the lower extremities returned spontaneously to normal 3 days later.

The infant had a good diet without constipation or difficult defecation, but her parents felt that her abdomen appeared more distended when she was 4 months old. Again she admitted to emergency department of previous Children's hospital, laboratory test, US and enhanced computed tomography were performed, which showed that *hepatic hemangioendotheliomas* have complicated hyponatremia, coagulation abnormality, hypoproteinemia and anemia. Due to nothing better regimen for the treatment of *hepatic hemangioendotheliomas*, the infant was asked to transfer.

When admitted to our pediatric surgery, abdominal distension was obvious and the inferior edge of the liver was palpable at the level of anterior superior iliac spine by physical examination, which was in consistent with followed US and magnetic resonance imaging(MRI). Abdominal US showed multiple hypoechoic nodular lesions in liver parenchyma with increased vascularity, which was confirmed using liver MRI as diffuse hepatic hemangiomas(Fig. 1). Laboratory examinations revealed anemia(76 g/L), hypoproteinemia(album 29.5g/L), hyponatremia(118 mmol/L) and normal range of liver enzyme levels. AFP was 11239 ng/ml. Coagulation test

suggested very low fibrogen(55 ng/mL) and normal D-Dimer. Cardiac function was evaluated by echocardiography with patent ductus arteriosus, atrial septal defect, patent foramen ovale(PFO), pulmonary hypertension(56 mmHg), little regurgitation of tricuspid valve and bicuspid valve.

Hypothyroidism was diagnosed with elevated thyroid-stimulating hormone(TSH) level(45.9 μIU/mL; normal range, 0.27–4.2 μIU/mL), low free T3(fT3) level (0.87 pmol/L; normal range, 3.1–6.8 pmol/L), low total T3 level(0.45 nmol/L; normal range, 1.15-3.1 nmol/L), very high rT3(>500 ng/dl; normal range, 35-95 ng/dL) but normal T4. US demonstrated normal thyroid in size and echogenicity. Her weight was 4.7 kilogram and treated with oral propranolol 5 mg twice a day. Thyroid function was rechecked 3 days later and TSH was lower(27.1 μIU/mL) than before. And consumptive hypothyroidism was confirmed when her parents denied any bad results during neonate. Levothyroxine was administered orally 16.7 μg once a day. Other support treatment such as cryoprecipitate, suspension red blood cells and nutrient guidance were given to improve her general condition.

Hyponatremia, hypoproteinemia, and anemia returned to normal after 3-day treatment. And coagulation abnormality was improved significantly. With 2-week medical treatment, only patent foramen ovale(PFO) still did exist by echocardiography, while TSH rebounded slightly to 24.9 μIU/mL after gradual decrease to the lowest point 17.20 μIU/mL on the seventh day(Fig. 2). Therefore, levothyroxine was adjusted to 25 μg per day after consultation with endocrinologist. Hepatomegaly recovered to the level of umbilicus on the lower margin. The parents

were satisfactory with the effect and discharged with propranolol(5 mg, twice a day) and levothyroxine(25 μg/day).

With close follow-up, her thyroid function normalized completely and the levothyroxine was gradually reduced to 12.5 μg once every other day then stopped by 8 months of age. At the same time, abdominal US showed a reduction in the size of the hepatic hemangiomas and the liver edge was 2cm below the right costal margin. Propranolol was increased to 15 mg/day(approximately 2 mg/kg/day) according to her weight 7.35kg. At the age of 12 months, MRI showed her liver was much better than before. In addition, she grew up as well as other normal infants without any neurodevelopment abnormalities.

Literature review

46 patients with consumptive hypothyroidism secondary to hepatic hemangiomas or hemangioendotheliomas were retrieved from 38 English articles, which was searched by PubMed with term “hepatic hemangioma”, “hepatic hemangioendothelioma” and “hypothyroidism” from the publications up to October, 2020. Given significant response of propranolol for hepatic hemangioma from Mazereeuw-Hautier’s report in 2010[4], patients were summarized and divided into group A(from 2011 to 2020) and group B(from 2000 to 2010) in Table 1. Steroids were the most frequent agents for hepatic hemangiomas or hemangioendotheliomas before 2011, but propranolol has been used most widely for the next decade according to Figure 3.

Hemangioendothelioma was incorrectly used in 39% (18/46) cases, which is

actually a histologic diagnosis[5,6]. These patients were diagnosed at the mean age of 2.72 months and with no gender difference. Due to some non-available information in articles, at least 71.7%(33/46) IHH patients with consumptive hypothyroidism can be classified into diffuse type according to Christison-Lagay's subtype classification.[5] When diagnosed, the most common symptom was abdominal distension(63%), followed by cutaneous hemangioma(20%), poor feeding(17%) and jaundice(15%) (Fig. 4). Other symptoms including constipation, pallor, peripheral coldness, lethargy and respiratory distress were documented in literatures.

When we focused on the consumptive hypothyroidism caused by IHH, more than 37% consumptive hypothyroidism had to require excessive dose of levothyroxine(>10 μg/kg/d) and even in 26% patients liothyronine was combined to normalize the thyroid function.

Discussion

Multifocal and diffuse IHHs are similar to infantile hemangiomas, which proliferate disproportionately with the child's growth toward the first year of life, especially rapidly at the age of 1-3 months, and then involute slowly for a few years. Many IHHs are undetected without symptoms but some may be found accidentally or present with complicated conditions like abdominal compartment syndrome, consumptive hypothyroidism and cardiac failure.[7]

Consumptive hypothyroidism is secondary to more than 70% of diffuse IHHs, which should be detected and managed early with thyroid replacement[8], because thyroid hormone play a crucial role in neurodevelopment in the first year of life. Due

to rapid proliferation of hemangiomas in the first weeks or months of life, overproductive type 3 iodothyronine deiodinase(D3) in the tumor catabolizes active thyroid hormone, resulting in low fT3 and extremely high level of TSH and rT3, which is different from congenital hypothyroidism and may need excessive dose of thyroid replacement therapy.[9]

In our case, diffuse IHH was diagnosed clinically by enhanced CT, US and MRI. Biopsy was declined by her parents and propranolol was indicated by the clinical diagnosis with informed consent. Thyroid function was significantly improved after 5-day administration of propranolol and normalized after ended following replacement therapy, which indirectly demonstrated that hypothyroidism was caused by IHH and benefited from the treatment of IHH. During the course of IHH, rT3 decreased gradually with the reduction of hepatic hemangioma in size and numbers[3,10], which can be recommended as a marker for evaluating the effect of treatment protocol of IHH.[11,12]

Over past two decades, diffuse IHHs were managed first with medical therapy including corticosteroids, interferon(IFN), vincristine(VCR), cyclophosphamide(CTX) and propranolol; while for some more complicated patients resistant to agents, surgical approach including embolization, ligation of hepatic artery and liver transplantation may be the last ditch.[13] Propranolol has been the first-line systemic treatment for infantile hemangioma and was proved to respond well for patients with IHH[1,14] as in our case. And increasing evidence showed propranolol should be recommended firstly for IHH if indicated.[1]

However, consumptive hypothyroidism usually missed the newborn screening and occured in the first weeks or months of life when IHHs may be gradually apparent. For infants with multiple skin hemangiomas(especially more than 5) or refractory hypothyroidism, abdominal US should be screened to exclude occult IHH.[15,16] Thyroxine plays a crucial role in the prevention of neurodevelopmental retardation, even permanent injury of nervous system in the first year of life, so it is necessary to monitor closely and normalize thyroid function as soon as possible. In addition, the course of abnormal catabolism of thyroxine through D3 from the tumor would be inhibited by control of IHH. Consumptive hypothyroidism was found in 70% diffuse IHH patients[8], and as mentioned in our results more than 70% consumptive hypothyroidism was caused by diffuse IHH, So multi-disciplinary treatment was suitable for these patients. What we should pay attention to is that conventional thyroid replacement therapy doesn't maintain euthyroid status in more than 1/3 patients, even in 26% patients combination of replacement therapy required.

In conclusion, evaluation of thyroid function is mandatory for infants with diffuse IHH.[17] Combination of levothyroxine and liothyronine, and even unusually high dose of thyroxine replacement would be indicated in some IHH cases with consumptive hypothyroidism. Treatment of IHH resulting in regression of hemangiomas, in which propranolol can be recommended for the first option, helps to manage consumptive hypothyroidism.[2,18] Simultaneous management of consumptive hypothyroidism and IHH is important for the patients with IHH complicated hypothyroidism.[2]

References:

1. Yang K, Peng S, Chen L, Chen S, Ji Y. Efficacy of propranolol treatment in infantile hepatic haemangioma. *J Paediatr Child Health*. 2019;55(10):1194-1200. doi:10.1111/jpc.14375

2. Kim YH, Lee YA, Shin CH, et al. A Case of Consumptive Hypothyroidism in a 1-Month-Old Boy with Diffuse Infantile Hepatic Hemangiomas. *J Korean Med Sci*. 2020;35(22):e180. doi:10.3346/jkms.2020.35.e180

3. Osada A, Araki E, Yamashita Y, Ishii T. Combination therapy of propranolol, levothyroxine, and liothyronine was effective in a case of severe consumptive hypothyroidism associated with infantile hepatic hemangioma. *Clin Pediatr Endocrinol Case Rep Clin Investig Off J Jpn Soc Pediatr Endocrinol*. 2019;28(1):9-14. doi:10.1297/cpe.28.9

4. Mazereeuw-Hautier J, Hoeger PH, Benlahrech S, et al. Efficacy of propranolol in hepatic infantile hemangiomas with diffuse neonatal hemangiomatosis. *J Pediatr*. 2010;157(2):340-342. doi:10.1016/j.jpeds.2010.04.003

5. Christison-Lagay ER, Burrows PE, Alomari A, et al. Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. *J Pediatr Surg*. 2007;42(1):62-68. doi:10.1016/j.jpedsurg.2006.09.041

6. Iacobas I, Phung TL, Adams DM, et al. Guidance Document for Hepatic Hemangioma (Infantile and Congenital) Evaluation and Monitoring. *J Pediatr*. 2018;203:294-300.e2. doi:10.1016/j.jpeds.2018.08.012

7. Mhanna A, Franklin WH, Mancini AJ. Hepatic infantile hemangiomas treated with oral propranolol--a case series. *Pediatr Dermatol*. 2011;28(1):39-45. doi:10.1111/j.1525-1470.2010.01355.x

8. Yeh I, Bruckner AL, Sanchez R, Jeng MR, Newell BD, Frieden IJ. Diffuse infantile hepatic hemangiomas: a report of four cases successfully managed with medical therapy. *Pediatr Dermatol*. 2011;28(3):267-275. doi:10.1111/j.1525-1470.2011.01421.x

9. Simsek E, Demiral M, Gundoğdu E. Severe consumptive hypothyroidism caused by multiple infantile hepatic haemangiomas. *J Pediatr Endocrinol Metab JPEM*. 2018;31(7):823-827. doi:10.1515/jpem-2018-0055

10. Acharya S, Giri PP, Das D, Ghosh A. Hepatic Hemangioendothelioma: A Rare Cause of Congenital Hypothyroidism. *Indian J Pediatr*. 2019;86(3):306-307. doi:10.1007/s12098-018-2806-x

11. Çetinkaya S, Kendirci HNP, Ağladioğlu SY, et al. Hypothyroidism due to hepatic hemangioendothelioma: a case report. *J Clin Res Pediatr Endocrinol*. 2010;2(3):126-130. doi:10.4274/jcrpe.v2i3.126

12. Peters C, Langham S, Mullis PE, Dattani MT. Use of combined liothyronine and thyroxine therapy for consumptive hypothyroidism associated with hepatic haemangiomas in infancy. *Horm Res Paediatr*. 2010;74(2):149-152. doi:10.1159/000281884

13. Varrasso G, Schiavetti A, Lanciotti S, et al. Propranolol as first-line treatment for life-threatening diffuse infantile hepatic hemangioma: A case report. *Hepatology*. 2017;66(1):283-285. doi:10.1002/hep.29028

14. 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(6):887-890. doi:10.1002/ccr3.963

15. Cho YH, Taplin C, Mansour A, et al. Case report: consumptive hypothyroidism consequent to multiple infantile hepatic haemangiomas. *Curr Opin Pediatr*. 2008;20(2):213-215. doi:10.1097/MOP.0b013e3282f409c3

16. Rialon KL, Murillo R, Fevurly RD, et al. Impact of Screening for Hepatic Hemangiomas in Patients with Multiple Cutaneous Infantile Hemangiomas. *Pediatr Dermatol*. 2015;32(6):808-812. doi:10.1111/pde.12656

17. Campbell V, Beckett R, Abid N, Hoey S. Resolution of Consumptive Hypothyroidism Secondary to Infantile Hepatic Hemangiomatosis with a Combination of Propranolol and Levothyroxine. *J Clin Res Pediatr Endocrinol*. 2018;10(3):294-298. doi:10.4274/jcrpe.4865

18. Takai A, Iehara T, Miyachi M, et al. Successful treatment of a hepatic-hemangioendothelioma infant presenting with hypothyroidism and tetralogy of Fallot. *Pediatr Neonatol*. 2018;59(2):216-218. doi:10.1016/j.pedneo.2017.08.002

Legend of figures:

FIGURE 1

A. T1WI and (B) T2WI in axial MRI of the liver show diffuse nodules. C. A T1WI in coronal MRI abdomen shows enlarged liver with multiple conglomerated hyperintense lesions extensively involving all the lobes of liver with non-visibility of the intervening parenchyma. D. Abdominal US shows multiple hypoechoic nodular lesions in liver parenchyma.

FIGURE 2

Changes of thyroid function over time after treatment.

↓stands for start, ↑stands for remove; the area between the dotted lines stand for normal range of fT4.

fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid-stimulating hormone;

LT4, levothyroxine

FIGURE 3
Treatment choice for diffuse or multifocal IHHs complicated consumptive hypothyroidism.
VCR, vincristine; IFN, interferon; CTX, cyclophosphamide

FIGURE 4
Symptoms of IHH complicated consumptive hypothyroidism.

Table 1. Summary of previously reported IHH patients with hypothyroidism

Group	Group A (2011-2020)	Group B (2000-2010)	total
number of patients	28	18	46
gender(M/F)	13/15	9/9	22/24
age(month)	2.96(0.2-26)	2.34(0.2-10)	2.72(0.2-26)
diagnosis(n)			
HHE（diffuse）	7(6)	11(6)	18(12)
HH(diffuse)	21(17)	7(4)	28(21)
symptoms			
abdominal distension	20	9	29
cutaneous hemangiomas	8	1	9
jaundice	5	2	7
poor feeding	5	3	8
other symptoms	6	7	13
asymptomatic	0	4	4
therapy protocols(hemangioma)			
Pro	11	0	11
Pro+/steroids+/VCR+/CTX*	12	0	12
Pred	1	4	5
Pred+/MP/+IFN**	1	2	3
VCR(+DXM)[#]	1	1	2
MP(+IFN)[##]	0	2	2
Spontaneous involution	0	2	2
Surgical ligation	1	3	4
Embolization	1	2	3
Liver transplantation	0	2	2
therapy protocols (hypothyroidism)			
LT4	18	12	30
LT4+T3	4	6	10
T3	2	0	2
Spontaneous involution	3	0	3

NA	1	0	1

CTX, cyclophosphamide; DXM, dexamethasone; HH, hepatic hemangioma; HHE, hepatic hemangioendothelioma; IFN, interferon; LT4, levothyroxine; MP, methylprednisolone; NA, not available; Pred, prednisonlone; Pro, propranolol; T3, liothyronine; VCR, vincristine.

*treatment regimen included propranolol and one of other agents.

**treatment regimen included Pred and one of other agents except propranolol.

[#]treatment regimen included VCR only or VCR and DXM.