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Consumptive Hypothyroidism due to Hepatic Hemangiomas: A Case Series and Review of the Literature

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ABSTRACT

Introduction: Consumptive hypothyroidism (CH) is a rare and potentially overlooked complication of hepatic hemangiomas (HH) overexpressing the enzyme deiodinase, which converts thyroxine (T4) to reverse triiodothyronine (rT3).

Materials and methods: Here, we report a case series of 3 patients and a systematic review of the literature.

Results: Hypothyroidism (mean serum TSH 52.03 mIU/L) was detected at a mean age of 4.6 months (range 3–6) in 3 infants with infantile hepatic hemangiomas, treated with thyroxine (mean dose 12 µg/kg/day). All received treatment with propranolol (1–3 mg/kg/day) from the mean age of 4 months. Hormonal treatment was stopped at a mean age of 20 months (range 12–30). Hypothyroidism reoccurred in a patient concurrently with the increase of liver lesions, requiring liver transplantation (LT) at age 39 months.

Literature review retrieved 42 studies (48 patients): HH (n = 43) were isolated in 24 infants and associated with cutaneous hemangiomas in 19. Hemangiomas were only cutaneous in 5.

In the first 43 patients, hypothyroidism was detected at a mean age of 1 month; 21 of 43 patients were prescribed propranolol alone (n = 8) or associated with other medicaments (n = 13); 2 of 43 patients underwent LT. Hormonal treatment consisted of T4 in 35 of 43 patients and T3 in 10.

CH associated with only cutaneous and extrahepatic visceral hemangiomas (n = 5), detected at a mean age of 7 months (TSH mean levels at diagnosis of 150.3 mIU/L). Three of 5 patients received treatment with propranolol ± other medicaments. All 5 patients were treated with T4.

Conclusions: Periodical thyroid function assessment is necessary in patients with hepatic hemangiomas, particularly when lesions' size and number increase rapidly.

Key Words: hepatic hemangiomas, cutaneous hemangiomas, consumptive hypothiroidsm

INTRODUCTION

Hepatic hemangiomas (infantile and congenital) are benign vascular tumors affecting 4% to 5% of Caucasian infants (1). These are classified into unifocal, multifocal, and diffuse (2). Infantile hepatic hemangiomas (IHH), characterized by glucose transporter 1 (glut-1) cytoplasmic immunostaining positivity, proliferate after birth from newborn period until 6–12 months of age with gradual involution until 3–9 years of age (3). Possible complications are high-output cardiac failure, liver failure, abdominal compartment syndrome, failure to thrive, and acquired consumptive hypothyroidism (CH). CH is a rare form of hypothyroidism resulting from overexpression of Thyroid Hormone Inactivating Enzyme type 3 (deiodinase) by vascular endothelium, resulting in conversion of thyroxine (T4) to reverse triiodothyronine (rT3) and T3 to diiodothyronine. CH is mainly associated with hepatic, rarely cutaneous hemangiomas, and some other tumors. It was first described in 2000 by Huang et al, in a 6-week-old infant with multiple hepatic hemangiomas (4). Afterwards, other authors described this form of hypothyroidism associated with hepatic hemangiomas, and a direct relationship between CH, tumor size, and D3 activity has been hypothesized. The expression of D3 (deiodinase type 3) in hemangioma is induced by basic fibroblast growth factor and vascular endothelial growth factor. Its activity increases paralleling the increase of tumor size regardless of its location as demonstrated by the normalization of rT3 levels after (medical or surgical) treatment of the lesion (5).

From the earlier, it follows that the gold standard for the diagnosis of CH is the demonstration of D3 activity on tumor tissue, but biopsy is rarely performed in patients with hepatic hemangiomas due to the risks associated with the procedure. CH has also been associated with extrahepatic hemangiomas, such as cutaneous and parotid hemangiomas, and benign neonatal hemangiomatosis.

Here, we report a case series of 3 patients: 2 affected by multifocal IHH and 1 with diffuse IHH, all complicated with CH. We also systematically reviewed previous pediatric cases reported in the literature.

What Is Known

- Consumptive hypothyroidism (CH) is a rare form of hypothyroidism due to thyroid hormone inactivating enzyme type 3 (Deiodinase) overexpressed by hepatic/hepatic and cutaneous hemangiomas, and occasionally by some otherextrahepatic visceral hemangiomas.
- Early recognition and substitutive hormonal treatment are important in terms of neurocognitive outcome.
- Medical treatment for the hemangiomas and reduction in tumor burden leads to CH resolution in most cases.

What Is New

- Pediatric hepatologists should recognize the importance of periodicalassessments of thyroid function in patients with hepatic hemangiomas

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CASE SERIES

Patient 1

A full-term female infant presented at 3 months of age with abdominal distension and poor feeding. Extended neonatal screening (ENS) was reported normal. A little cutaneous hemangioma was present on the forehead. Abdominal distension was noted on examination, with the liver edge palpable 2 to 3 cm below the costal margin. Ultrasound revealed an enlarged liver with multiple contextual pseudonodular macro areas (maximum diameter = 3 cm). Magnetic resonance imaging (MRI) was indicative of hepatic multifocal hemangiomas. Liver function tests (LFTs) were normal. Thyroid US was normal. Thyroid-stimulating hormone (TSH) values were markedly elevated at 58.7 mIU/L. She was therefore treated with good clinical response for severe hypothyroidism with levothyroxine (10 μg/kg/day) suspended at the 13th month of life, and propranolol (1–3 mg/kg/day), stopped at 22 months. At 4 years of age, she had normal development; control MRI, after 19 months of treatment with propranolol and after 10 months of treatment with levothyroxine, showed absent liver hemangiomas (Fig. 1A,B).

Patient 2

M. is a preterm male infant, born at 26 weeks after twin pregnancy. During the hospitalization in the Neonatal Intensive Care Unit (NICU), multiple cutaneous hemangiomas appeared (n = 6, of which 3 on the trunk and 3 in the lower limbs; the largest in the right thigh measuring 1 × 2 cm). Extended neonatal screening (ENS) and LFTs was reported normal. He was diagnosed with hypothyroidism (TSH: 36,700 mIU/ml) and started treatment with levothyroxine (12 μg/kg/day) at 1 month of life. He was evaluated at 5 months in a dermatology clinic for his cutaneous hemangiomas, and abdominal ultrasound revealed an enlarged liver with hepatic multifocal hemangiomas. Thyroid US was normal. He started propranolol therapy (1–2 mg/kg/day) until the hepatic picture was normalized after 7 months (control US). He was weaned off levothyroxine progressively with reduction to 5 μg/kg/day until discontinuation at the age of 1 year and 9 months and is currently on no medications since 3 years, with normal neurological development.

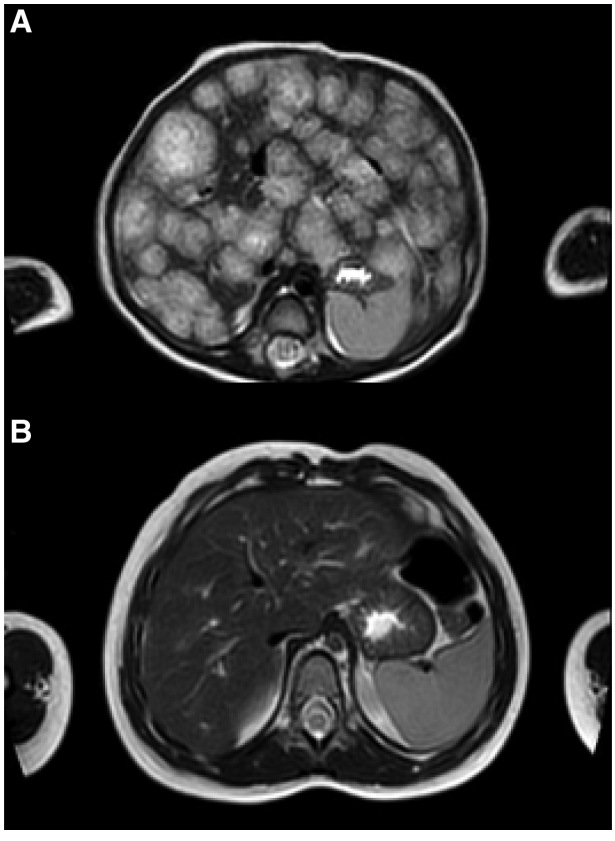

FIGURE 1. MRI of the abdomen in one of our patients (patient 1), before (A) and after (B) 19 months of treatment with propranolol/10 months of treatment with levothyroxine. The T2-weighted axial MRI images shows the regression of a diffuse infantile hepatichemangioma with innumerable T2 hyperintense masses throughout the liver with central hypointense central regions. MRI = magnetic resonance imaging.

Patient 3

Second child, born at term from normal pregnancy, ENS reported normal, was hospitalized at the age of 6 months for evidence of pallor and abdominal distension, referable to massive hepatomegaly, associated with thrombocytopenia and coagulopathy (Kasabath-Merritt syndrome). The ultrasound examination revealed multiple expansive nodules located in the II–III, VII–VIII, and VI segments, subsequently diagnosed as IHH at liver biopsy. Thyroid US was normal. Liver mass was first treated with steroids, vincristine, with tendency to regression. At that time, TSH was found markedly high at 60.7 mIU/L, requiring treatment for severe hypothyroidism with levothyroxine (15 μg/kg/day). After clinical improvement, he was switched to propranolol at the age of 9 months (3 mg/kg/day). The good clinical response allowed to stop hormone therapy at age 24 months. However, hypothyroidism reoccurred at the age of 32 months together with the enlargement of 2 liver nodules and no longer responsive to medical treatment. A new laparoscopic biopsy of the liver confirmed the diagnosis of Glut-1 positive IHH. However, because of the risk of malignancy reported in previous cases of IHH relapsing (6, 7), we referred the child to a Liver Transplant Center. At the age 3 years, the patient underwent liver transplantation (LT), having considered the risk of developing hepatic angiosarcoma (8). Liver histology confirmed the diagnosis of IHH but revealed some foci of Kaposiform hemangioendotelioma. After LT, he stopped levothyroxine therapy due to the complete normalization of the thyroid profile. He presented mild developmental delay, probably related to spectrum autism disorder.

LITERATURE REVIEW

We searched within the PubMed academic medical database. Search strategy was formulated around terms for "Consumptive hypothyroidism" and "Hemangioma AND Hypothyroidism." Systematic search of the databases of literature was performed with no language or data restrictions. To be eligible for inclusion, studies had to describe a case of consumptive hypothyroidism associated with hemangioma in children. Study details and quality characteristics were independently extracted by two of the authors for all the articles and in a stepwise approach, first by reading the title, then by reviewing the abstract, and finally by revising the full text, where appropriate (Figure S1 http://links.lww.com/PG9/A96). At the end of revision, 42 studies were selected including 48 patients.

CH was found in infants with "multifocal/diffuse hepatic hemangiomas" (24 cases), and "hepatic and cutaneous hemangiomas" (19 cases). Hypothyroidism was detected at a mean age of 1 month. Mean levels of TSH at diagnosis were in the range 15–475 mIU/L. Neonatal screening, showed CH in 7 cases, normal results in 13, in the remaining cases, it was not reported. Among these 43 patients, 8 patients received treatment with propranolol, 13 propranolol in combination with other medicaments, and 21 did not received propranolol. Two patients underwent liver transplantation; 35 of 43 patients were treated with T4 and 10 with T3 (Table 1).

TABLE 1. Summary of the systematic review of the literature with studies reporting CH in patients with hepatic hemangiomas

		Hemangioma					Treatment			
References	**Sex, age**	**Type**	**Size (cm)**	**Description**	**TSH onset mU/L**	**Neonatal screening congenital hypot.**	**Lev.**	**Lio.**	**Propr.**	**Other**
Joshi et al (9)	F, 3 m	HH	N.R.	Diffuse	75	N.R.	Yes	Yes	Yes	Prednisolone + IFNα
Kim et al (10)	M, 1 m	IHH	N.R.	Diffuse	100	Normal	Yes	No	Yes	Prednisolone
Macchiaiolo et al (11)	F, 2 m	HH+ CuH	N.R.	Diffuse	15	N.R.	No	No	Yes	No
Verma et al (12)	F, 4 m	HH+1CuH	2.6×4.8	Multiple	17.5	CH	Yes	No	Yes	No
Osada et al (13)	M, 4 m	IHH+ 1sub-CuH	N.R., 2	Multiple	561	Normal	Yes	Yes	Yes	No
Acharya et al (14)	F, 20 d	HHE+ CuH	1- 3,N.R.	Multiple	100	N.R.	Yes	No	Yes	Prednisolone
Simsek et al (15)	M, 4 m	IHH+ 1 CuH	N.R., <0.5	Multiple	177	Normal	Yes	No	Yes	Methyl-pr.
Al-Ghamdi et al (16)	M, 2 m	HH	N.R.	Multiple	281	N.R.	Yes	No	Yes	No
Campbell et al (17)	F, 11 d	HH+3 CuH	N.R.	Multiple	115.4	N.R.	Yes	No	Yes	No
Takai et al (18)	M, 6 d	HHE	N.R.	Diffuse	54.7	N.R.	N.R	No	Yes	Prednisolone
Weber P. et al (19)	F, 7 m	HHE	N.R.	Diffuse	24	N.R.	Yes	Yes	No	VCR + Steroids
Nguyen et al (20)	M, 2 m	HH + 5 CuH	N.R.	Multiple	54	Normal	No	No	Yes	No
Higuchi et al (21)	M, 11 m	HH	4×2.5	Multifocal	17.7	Normal	No	Yes	Yes	No
Al Tasseh et al (22)	M, 3.5 m	HH+1CuH	0.5-0.42, 1.5×1.5	Diffuse	220	N.R.	Yes	No	Yes	No
Varrasso et al (23)	F, 4 m	HH	N.R.	Diffuse	69.96	N.R.	Yes	No	Yes	Predn.
Wasserman et al (24)	F, 49 d	HH+1CuH	N.R., 0.15	Diffuse	123	Normal	Yes	Yes	Yes	Predn. +VCR
Wijeratne et al, 2014(25)	F, 36 d	HHE+ CuH	>0.25	Multiple	37.6	Normal	Yes	No	Yes	Prednisolone
Sun et al (26)	F, 21 d	HH+ CuH	N.R.	Multiple	nr	N.R.	Yes	No	Yes	Steroids
Vergine et al (27)	F, 2 m	HH + subCuH	N.R.	Multiple	21	Normal	Yes	No	Yes	Predn. + VCR+ Cycloph.
Imteyaz et al (28)	F, 4 m	HH	N.R	Multiple	14.2	N.R	N.R.	No	No	Prednisone
Emir et al (29)	F, 15 d	HH+ 1 CuH	3×3.5 2×1	Multiple	74.2	CH	Yes	No	Yes	Methyl-pr.
Jassam et al (30)	M, 56 d	HHE	N.R.	Multiple	138	Normal	Yes	No	No	Prednisolone + IFNα + HA ligation
Yeh et al (31)	F, 42 d	HH+ CuH	N.R.	Diffuse	68	N.R.	Yes	No	No	Methyl-pr.+ pred. +VCR
	M, 21 d		N.R.		19.8	N.R.	No	No	No	Prednisolone +VCR + Cycloph.
	M, 35 d		N.R.		31.4	N.R.	Yes	No	Yes	Methyl-pr.
	F, 14 d		N.R.		55.8	N.R.	Yes	No	Yes	Methyl-pr.+Prednisolone +VCR
Bessho et al (32)	F, 4 m	HH	N.R.	Diffuse	42.5	CH	Yes	No	No	Prednisolone + IFNα+SG
Çetinkaya et al (33)	M, 28 d	HH	3	Multiple	150	CH	Yes	Yes	No	Methyl-pr. + IFN α
Peters et al (34)	M, 28 d	HH+3CuH	N.R.	Multiple	66.2	CH	Yes	Yes	No	VCR+Dexa.
Mouat et al (35)	F, 21 d	HHE	N.R.	Massive	17	Normal	Yes	No	No	Predn.
Cho et al (36)	M, 10m	HH	N.R.	Multiple	18.98	Normal	Yes	No	No	Prednisolone
Kalpatthi et al, 2007(37)	M, 4 m	HH+ CuH	N.R.	Multiple	53.3	Normal	Yes	No	No	Prednisolone
Lee et al (38) **Balazas et al** (39)	F, 42 d	HHE	N.R.	Multiple	182	Normal	Yes	Yes	No	Predn.+ IFNα +Hydroc. +VCR +Cytoxan+ LT
Güven et al (40)	F, 3 m	HHE	N.R.	Multiple	100	N.R.	Yes	Yes	No	Methyl-pr.
Ho et al (41)	F, 3 m	HHE	N.R.	Multiple	90	N.R.	Yes	Yes	No	Predn.

(Continued)

TABLE 1. (*Continued*)

References	Sex, age	Hemangioma Type	Size (cm)	Description	TSH onset mU/L	Neonatal screening congenital hypot.	Treatment Lev.	Lio.	Propr.	Other
Konrad et al (42)	M, 63 d	HH	N.R.	Multiple	100	Normal	Yes	No	No	No
Ayling et al (43)	F, 56 d	HHE	N.R.	Multiple	220	N.R.	No	No	No	No
	M, 10 d	HHE	N.R.	Multicentric	35	CH	Yes	No	No	LT
	M, 42 d	HHE	N.R.	N.R.	200	CH	Yes	No	No	HA ligation
	F, 4 m	HHE	N.R.	N.R	475	N.R.	Yes	No	No	HA ligation
	F, 4 m	HHE	N.R.	N.R	16	N.R.	N.R.	No	N.R.	HA ligation
Mason et al (44)	F	HH	N.R.	Multiple	155.9	N.R.	Yes	No	No	Methyl-pr.+embolization
Huang et al (4)	M, 42 d	Hepatic	N.R.	Multiple	156	N.R.	Yes	Yes	No	Prednisolone + IFNα HA ligation

CuH = cutaneous hemangioma; Cycloph. = cyclophosphamide; d. = days; Dexa. = dexamethasone; F. = female; HA = hepatic artery; HH = hepatic hemangioma; HHE = hepatic hemangio-endothelioma; IFNa = interferon alpha; Hydroc. = hydrocortisone; Hypot. = hypothyroidism; IHH = infantile hepatic hemangioma; Levo = levothyroxine; Lio. = liothyronine; LT = liver transplantation; M. = male; m. = months; Methyl-pr. = methyl-prednisolone; N.R. = not reported; Pred. = prednisone; Prop. = propranolol; SG = surgical resection; VCR = vincristine.

Literature review also found CH is associated with nonhepatic hemangiomas: parotid hemangioma (2 cases), benign neonatal hemangiomatosis (1 patient), internal acoustic meatus hemangioma and cutaneous hemangioma (1 patient), large (12 × 10 cm) cutaneous hemangioma (1 patient). CH was associated with only cutaneous and extrahepatic visceral hemangiomas, detected at a mean age of 7 months (TSH mean levels at diagnosis of 150.3 mIU/L); 3 of 5 patients received treatment with propranolol ± other medicaments, all 5 patients were treated with T4 (Table 2).

DISCUSSION

CH is a rare form of hypothyroidism (to date, more than 40 cases of CH secondary to HH have been reported). It caused by the high expression of the D3 isoenzyme by the vascular tumor, which transforms thyroid hormones into inactive form during the proliferative phase of IHH (4).

The etiology of elevated D3 activity in IHH is not fully known. It was assumed that endothelial cells in infantile hemangiomas and placenta share some immunohistochemical markers (50), including GLUT1, specific marker of IHH (51), and it has been proposed that IH could be derived from placental angioblasts sharing similar characteristics such as high D3 activity and self-limited growth (31). Generally, CH has poor response to the usual doses of levothyroxine(10-15/kg/day in infants with congenital hypothyroidism) (52). T3 is useful in case of severe consumptive hypothyroidism. When hypothyroidism is very severe, large doses of thyroid hormone are necessary to normalize the T4 level. Since T4 is rapidly converted to the inactive rT3 form, combined therapy with T3 may be necessary (53).

Our cases of hepatic hemangiomas complicated by CH were multifocal in two and diffuse in one of three patients. In the first two infants early medical management led to good hepatic outcomes, while in the third a liver transplant was required. Noteworthy, differently from the first 2 cases, patient 3 had not cutaneous hemangiomas.

Current guidelines recommend screening with abdominal ultrasonography in the presence of 5 or more cutaneous hemangiomas because risk of IHH increases along with increasing numbers of cutaneous lesions (54). However, IHH can also be found in the presence of one or no cutaneous hemangioma as seen in our patients 1 and 3, suggesting the importance of abdominal US for all children with any cutaneous lesions and systemic compromise. In this regard, difficulties in feeding and abdominal distension can be red flags and require further investigation.

Although neonatal screening was normal in all three patients and congenital hypothyroidism was excluded; however, a severe form of hypothyroidism was detected on thyroid function test assessment. The level of rT3 could be useful in cases nonresponder to T4 treatment; however, it is not always feasible in clinical practice. We did not measure the level of rT3 nor the activity of tissue D3 (due to the risk of bleeding from biopsy), but the diagnosis of consumption hypothyroidism associated with the presence of IHH was inferred from the high TSH presenting values, the poor response to the usual doses of levothyroxine and the gradual normalization of the thyroid profile concomitant with the reduction of the hemangiomatous mass. This is consistent with the first cases described by Huang et al. (4) and also with data of our systematic review (Table 1). Literature search also found that CH may be occasionally observed in some patients with cutaneous hemangiomas only and extrahepatic visceral hemangiomas (Table 2).

CONCLUSIONS

CH should be investigated in all patients with IHH and possibly also in those with large-sized cutaneous hemangiomas and extrahepatic visceral hemangiomas. Thyroid function should be periodically assessed particularly when the size and number of hemangiomas increase rapidly. Early substitutive hormone treatment may avoid lower neurocognitive outcome, which is likely in those infants with more severe hypothyroidism. In addition, future studies should investigate the incidence and effects of propranolol treatment on thyroid dysfunction. On the other hand, an acquired infantile hypothyroidism, not recalled at neonatal screening, can hide an unrecognized hepatic hemangioma. So, unexplained hypothyroidism could represent a red flag for an underlying IHH. This hypothesis requires other studies to be supported.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of

TABLE 2. Summary of the systematic review of the literature with studies reporting CH in patients with extra-hepatic hemangiomas

References	Sex, age	Hemangioma		TSH onset mU/L	Neonatal screening	Treatment			
		Type	Size (cm)			Lev.	Lio.	Propr.	Other
Igarashi et al (45)	M, 26 d	I.A.M. + CuH	1 cm 44 × 22 × 7 mm	15.32	Normal	Yes	No	Yes	Laser-therapy
Chakraborty et al (46)	M, 2.5 y	CuH	12 × 10 cm	76	N.R.	Yes	N.R.	N.R.	N.R.
De corti et al (47)	M, 48 d	Parotid IH	4cm	8.28	Normal	Yes	No	Yes	No
Metwalley et al (48)	M, 8 m	BNH	5- 10 mm	176	Normal	Yes	No	No	No
Vigone et al (49)	F, 7 d	Parotid IH	N.R.	476	+ for CH	Yes	No	Yes	Corticosteroid

+ = positive; BNH = Benign neonatal hemangiomatosis; CH = congenital hypothyroidism; CuH = cutaneous hemangioma; d. = days; F. = female; I.A.M. = internal acoustic meatus; Levo = levothyroxine; Lio. = liothyronine; M. = male; m. = months; N.R. = not reported; Prop. = propranolol.

kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

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