Consumptive Hypothyroidism: Case Report of Hepatic Hemangioendotheliomas Successfully Treated with Vincristine and Systematic Review of the Syndrome

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Keywords

Type 3 deiodinase · Vincristine · Consumptive hypothyroidism · Infantile hypothyroidism · Hepatic hemangioendothelioma

Abstract

Objectives: To provide a comprehensive description of consumptive hypothyroidism syndrome (CHS), a severe form of hypothyroidism that occurs due to the high expression levels of thyroid hormone inactivation enzyme type 3 deiodinase (D3) in tumors. **Study Design:** Case report and systematic review. **Results:** A 7-month-old girl with a diagnosis of massive hepatic hemangioendotheliomas was treated with high doses of thyroid hormones and tumor-directed chemotherapy with vincristine. The tumor displayed excellent response, and euthyroid status was regained. A systematic review on the databases PubMed/Medline and Embase was performed, using the term “Consumptive AND “Hypothyroidism.” From the 33 selected references, we extracted 42 case reports of CHS: 36 children and 6 adults. The laboratory profile at diagnosis displayed high TSH and low T_4 and T_3 serum levels. The serum reverse T_3 and D3 activity levels were high in all patients tested. In children, 97% had vascular tu-

mors, whereas in adults 33% were vascular tumors, 33% fibrous tumors, and 33% gastrointestinal stromal tumors. The conservative treatment was predominant in children, while in adults all cases were treated with surgery. Death occurred in 16% of children and 33% of adults. **Conclusions:** CHS is a rare form of hypothyroidism that occurs in children and adults, usually linked to hepatic vascular tumors. The condition is associated with high lethality. Prompt diagnosis, followed by high-dose thyroid hormone replacement and tumor-directed therapy are the keys to optimize outcomes.

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Introduction

Thyroid hormones play an essential role in regulating metabolic functions in humans. The fine-tuning of thyroid hormone metabolism at tissue level is made by the widely expressed iodothyronine deiodinase enzymes, which activate and inactivate thyroid hormones. Whereas type 1 and type 2 deiodinase (D1 and D2) convert thyroxine (T_4) into the active hormone triiodothyronine (T_3), type 3 deiodinase (D3) turns T_4 and T_3 into its inac-

tive products reverse T_3 (rT_3) and diiodothyronine (T_2), respectively [1].

Consumptive hypothyroidism syndrome (CHS) is an uncommon and severe form of hypothyroidism that occurs due to high levels of D3 expression by neoplastic tissues, resulting in high rates of thyroid hormone inactivation. It was first described by Huang et al. [2], with several other CHS cases reported thereafter. Although CHS has been initially noted in neonates and children with vascular tumors, it is not restricted to this age group or type of tumor. The CHS clinical course is variable, as well as the treatment modalities and the therapeutic strategies employed. Briefly, treatment has 2 aims: (1) to restore thyroid hormone levels, which is achieved with the administration of high doses of levothyroxine (LT_4) in association or not with liothyronine (LT_3), and (2) direct treatment of the tumor that expresses high D3 activity [3]. Due to the rarity of the syndrome, the treatment strategies described are quite variable.

In this study, we report a case of CHS cured after treatment of the tumor with chemotherapy. We also made a systematic literature review, with a summarized description of the clinical characteristics, treatments, and outcomes of this rare syndrome.

Case Report

A 7-month-old female patient was referred to our institution (Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil), with a diagnosis of massive hepatic hemangioendotheliomas, extensive pneumonia in the right lung, heart failure, cholestasis, and clinical hypothyroidism. Her 33-year-old mother had 2 previous pregnancies and attended scheduled prenatal consultations. The patient was delivered by a cesarean section at 32 weeks of gestation due to preeclampsia. Her birth weight was 1,830 g, with an Apgar score of 7 and 9 at the first and fifth minute, respectively. After birth, the baby presented bacterial meningitis and sepsis, with prolonged neonatal intensive care unit (NICU) hospitalization. During the NICU stay, she had a diagnosis of hypothyroidism, which required high doses of LT_4 (up to 500 μ g per day) to normalize serum TSH levels. The patient developed liver failure and was then transferred to our institution, a reference center for liver transplantation. At admission to our hospital, her weight was 4,500 g. The physical examination showed a distended abdomen, with collateral circulation, jaundice, and hepatomegaly. Due to continued ventilatory support during the NICU stay, a tracheostomy was performed, and she was being fed by tube feeding. The initial laboratory evaluation showed elevated liver enzymes, aspartate aminotransferase of 4.39 μ kat/L (reference value [RV], 0.17–0.51), alanine aminotransferase of 4.41 μ kat/L (RV 0.17–0.68), γ -glutamyl transferase of 9.57 μ kat/L (RV 0.03–0.51), total bilirubin of 124.9 μ mol/L (RV 5.0–21.0), direct bilirubin of 85.5 μ mol/L (RV 1.7–5.1), and indirect bilirubin of 39.3 μ mol/L (RV 1.7–12.0). For further evaluation of the hepatic disease, the patient

underwent an abdominal CT that showed massive hepatomegaly, with many hypoechoic nodules diffusely distributed, highly suggestive of hepatic hemangioendotheliomas.

She was receiving LT_4 at a dose of 100 μ g per day, and thyroid function evaluation showed high TSH (24.01 mIU/L, RV 0.27–4.20), low total and free T_4 (60.5 nmol/L [RV 65.6–181.5] and 5.9 pmol/L [RV 12.0–21.9], respectively), and low total T_3 levels (0.29 nmol/L, RV 1.23–3.08). Based on these results, the LT_4 dose was increased to 500 μ g/day (this being the highest dose) and LT_3 to 40 μ g/day to achieve a euthyroid state during hospitalization. Thyroid ultrasound displayed a topical and homogeneous gland, with regular contours and increased age-related size (total volume of 2.4 mL, RV 0.2–2.7). Thyroid scintigraphy also showed a functional and topical gland. Based on clinical and laboratory contexts, and reaffirmed by an elevated rT_3 serum level of 2.72 nmol/L (RV 0.17–0.35), a diagnosis of consumptive hypothyroidism secondary to hepatic hemangioendotheliomas was established.

Hepatic hemangioendotheliomas treatment with vincristine was instituted. The patient received infusions of vincristine once a week, for 6 weeks, that resulted in involution of the tumor. She was discharged after 1 month of hospitalization, weighing 5,600 g, with a resolution of jaundice; she had no ventilatory support and was eating orally with no tube feeding. Thyroid function tests (under LT_4 replacement) were as follows: TSH of 5.32 mIU/mL, total T_4 of 171.2 nmol/L, free T_4 of 28.4 nmol/L, and total T_3 of 0.97 nmol/L. The patient had an excellent response to therapy, with a full resolution of the hepatic hemangioendotheliomas. She is now a healthy 9-year-old child, and no longer requires LT_4 treatment.

The parents of the patient provided written informed consent to this case report, and the reporting was approved by our institutional Ethics Committee.

Systematic Review

A search on the databases PubMed/Medline and Embase, using the term “Consumptive AND Hypothyroidism”, with no language filters, on April 6, 2017, retrieved 31 and 39 results, respectively. Based on title and abstract content, we selected 25 case reports of CHS. We also searched the references of all selected articles and identified 7 additional case reports and 1 meeting abstract of interest. Finally, from the 33 selected references, we extracted 41 case reports of CHS. After the inclusion of the present case, a total of 42 cases (36 children and 6 adults) were included in the literature review. A summarized description of the clinical characteristics, treatments, and outcomes of this rare syndrome is provided.

The planning and reporting of this systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [4].

Consumptive Hypothyroidism in Children

The clinical characteristics of CHS in children are depicted in Table 1. In this group of patients, 56% (17/30) were female (missing data of age in 6 cases), with a median age at diagnosis of 1.6 months (P25–P75: 1.0–2.9). The laboratory profile displayed high TSH levels at diagnosis (median of 62 mIU/L, P25–P75: 22–134) and low T_4 and T_3 serum levels. The serum rT_3 levels were high in all patients tested. Interestingly, 32% (7/22) of the children screened for neonatal hypothyroidism displayed a positive result.

Table 1. Clinical characteristics of children and adults with consumptive hypothyroidism syndrome

	Children	Adults
Patients	36	6
Female sex ^a	17 (56)	3 (50)
Age	1.6 months (1.0–2.9)	50 years (41–58)
Tumor histology		
Hepatic hemangioma	13 (36)	1 (17)
Hepatic hemangioendothelioma	10 (27)	1 (17)
Diffuse infantile hepatic hemangioma	8 (22)	–
Parotid hemangioma	2 (5)	–
Hepatic hemangioma/hemangioendothelioma	1 (2)	–
Cutaneous hemangiomatosis	1 (2)	–
Fibrosarcoma	1 (2)	–
Gastrointestinal stromal tumor	–	2 (33)
Fibrous tumor	–	2 (33)
Positive neonatal screening	7 (32)	NA
Baseline TSH, mIU/L	62 (22–134)	64 (26–82)
High levels of rT ₃ ^b	18 (100)	3 (100)
High D3 tumor activity	3 (100)	6 (100)
Use of LT ₄ ^c	32 (94)	5 (83)
Maximum LT ₄ dose, µg	69 (42–122)	300 (150–300)
Use of LT ₃ ^c	13 (38)	1 (17)
Maximum LT ₃ dose, µg	30 (11–84)	20
Outcome		
Alive	30 (83)	4 (66)
Death	6 (16)	2 (33)

Data are shown as *n* (%) or median (P25–P75). rT₃, reverse T₃; LT₄, levothyroxine; LT₃, liothyronine; NA, not applicable. ^a Data available for 30 children. ^b Data available for 18 children and 3 adults. ^c Data available for 34 children.

In the group of CHS children, 97% (35/36) had vascular tumors, with hepatic vascular tumors representing 88% (32/36) of cases, parotid hemangiomas 5% (2/36), cutaneous hemangiomatosis 2% (1/36), and fibrosarcoma 2% (1/36). Of the hepatic tumors, 15 were hemangiomas, 10 were hemangioendotheliomas, 1 was hepatic hemangioma/hemangioendothelioma, and 5 were diffuse infantile hemangiomas. Because there is a high risk of bleeding associated with vascular tumor biopsy, only 3 patients underwent tissue sampling. High D3 activity was confirmed in all tumor specimens.

We observed considerable variation in tumor treatment strategies, with medical treatment being the predominant one. Medications used for tumor-directed therapy consisted of corticosteroids, propranolol, interferon, vincristine, Cytosan, and cyclophosphamide (Table 2).

Surgical treatment was performed in 25% (8/32) of cases. Three patients had missing information about tumor treatment, and 1 patient died before transplantation and received no medications but LT₄ replacement. The modalities of surgical treatment consisted of 2 liver transplantations, 2 resections (hepatic hemangioma and fibrosarcoma), 2 embolizations (hepatic hemangioma and hepatic hemangioendothelioma), and 2 hepatic artery ligations. Radiotherapy was employed in 1 case of hepatic hemangioma. Two patients had spontaneous tumor resolution (hepatic heman-

gioma and cutaneous hemangiomatosis). The frequency of the different tumor-directed treatment modalities employed in children with CHS is summarized in Figure 1.

The treatment of hypothyroidism consisted of LT₄ administration in 94% (32/34) of patients, with 38% (13/34) requiring it in association with LT₃. In 1 case only LT₃ was used. There were missing data about hormone replacement of 2 patients. The median maximum dose of LT₄ was 69 µg/day (P25–P75: 42–122) and of LT₃ 30 µg/day (P25–P75: 11–84). Sixteen percent (6/36) of patients died: 4 cases of hemangioendotheliomas, 1 case of hemangioma, and 1 case of hemangioma/hemangioendothelioma.

Consumptive Hypothyroidism in Adults

Adult patients comprise 14% (6/42) of all reported CHS cases. The clinical characteristics of the group of adults with CHS are depicted in Table 1. In this group of patients, 50% (3/6) were female, with a median age of 50 years (P25–P75: 41–58). As in the children's group, the laboratory profile showed high TSH levels at diagnosis (median of 64 mIU/L, P25–P75: 26–82), low T₄ and T₃, and elevated levels of rT₃.

Of note, tumor histology in the adult population differed somewhat from pediatric patients. Hepatic vascular tumors represented only 33% (2/6) of cases (1 hemangioma and 1 hemangioendothelioma). Gastrointestinal stromal tumors (GIST) and fibrous tumors

Table 2. Treatment of children and adults with consumptive hypothyroidism syndrome^a

Patient No.		Age, months	Sex	Treatment	Outcome	Reference
<i>Children</i>						
1	HmH	1.5	M	C, Inf, Eb, LT ₄ , LT ₃	Death	Huang [2], 2000
2	HeH	2	F	Tx	Alive	Ayling [8], 2001
3	HeH	0.3	M	LT ₄	Death	Ayling [8], 2001
4	HeH	MD	M	HAL	Alive	Ayling [8], 2001
5	HeH	4	F	HAL	Alive	Ayling [8], 2001
6	HmH	2.25	MD	SR, LT ₄	Alive	Konrad [9], 2003
7	HmH	0.01	F	C, LT ₄ , LT ₃	Alive	Guen [10], 2005
8	HmH	2.5	F	C, LT ₄ , LT ₃	Alive	Ho [11], 2005
9	HeH	1.5	F	C, V, Inf, Cyt, Tx, LT ₄ , LT ₃	Alive	Lee [12], 2006 and Balazs [13], 2007
10	HeH	7	M	C, LT ₄	Alive	Kalpatthi [14], 2007
11	HmH	10	M	C, LT ₄	Alive	Cho [15], 2008
12	HeH	0.75	F	C, LT ₄	Alive	Mouat [16], 2008
13	HeH	1	M	C, Inf, LT ₄ , LT ₃	Alive	Çetinkaya [17], 2010
14	IDHmH	1	M	C, V, LT ₄ , LT ₃	Alive	Peters [3], 2010
15	HmH	1.5	F	C, Inf, Rsc, LT ₄	Alive	Bessho [18], 2010
16	IDHmH	1.5	F	Missing Data ^b , LT ₄	Alive	Forrester [19], 2010
17	HeH	2	M	C, Inf, Eb, LT ₄	Death	Jassam [20], 2011
18	HmH	2.5	MD	C, Pro, LT ₄	Alive	Emerick [21], 2011
19	IDHmH	1.5	F	C, V, LT ₄ , LT ₃	Alive	Yeh [22], 2011
20	IDHmH	0.06	M	C, V, Clf	Alive	Yeh [22], 2011
21	IDHmH	1.25	M	C, Pro, LT ₄	Alive	Yeh [22], 2011
22	IDHmH	0.5	F	C, V, Pro, LT ₄ , LT ₃	Alive	Yeh [22], 2011
23	HmH	4	F	C, LT ₄ , LT ₃	Alive	Imteyaz [23], 2012
24	PHmH	0.1	F	C, Pro, LT ₄	Alive	Vigone [24], 2012
25	IDHmH	2	F	C, V, Pro, Clf, LT ₄	Alive	Vergine [25], 2012
26	CH	8	M	SR, LT ₄	Alive	Metwalley [6], 2013
27	HmH/HeH	0.5	F	C, Pro, LT ₄	Death	Emir [26], 2016
28	FS	0.06	MD	Rsc, LT ₄	Alive	Connelly [27], 2014
29	PHmH	1.5	M	Pro, LT ₄	Alive	De Corti [5], 2015
30	IDHmH	1.75	F	C, V, Pro, LT ₄ , LT ₃	Alive	Wasserman [28], 2015
31	HmH	2	M	Pro, LT ₃	Alive	Higuchi [29], 2015
32	HmH	MD	MD	Rdt, LT ₄ , LT ₃	Alive	Bramswig [30], 2001
33	HmH	4	F	C, Pro, LT ₄	Alive	Varrasso [31], 2017
34	HeH	3	F	C, V, LT ₄ , LT ₃	Alive	Weber Pasa, this study
<i>Adults</i>						
35	HeH	21	F	Tx, LT ₄	Alive	Huang [32], 2002
36	FT	54	M	Rsc, LT ₄	Alive	Ruppe [33], 2005
37	HmH	38	F	Rsc, LT ₄	Alive	Howard [34], 2011
38	FT	76	F	Rsc, LT ₄ , LT ₃	Alive	Aw [35], 2014
39	GIST	51	M	Rsc, Imt, Srf, LT ₄	Death	Maynard [36], 2014
40	GIST	60	M	Rsc, Snt	Death	Yan [37], 2015

C, corticosteroid; Inf, interferon; Eb, embolization; HAL, hepatic artery ligation; Tx, transplantation; Rdt, radiotherapy; Rsc, resection; V, vincristine; Cyt, Cytosan; Pro, propranolol; Clf, cyclophosphamide; SR, spontaneous resolution; Imt, imatinib; Srf, sorafenib; Snt, sunitinib; LT₄, levothyroxine; LT₃, liothyronine; HmH, hepatic hemangioma; HeH, hepatic hemangioendothelioma; IDHmH, infantile diffuse hepatic hemangioma; GIST, gastrointestinal stromal tumor; FT, fibrous tumor; PHmH, parotid hemangioma; CH, cutaneous hemangiomatosis; FS, fibrosarcoma; M, male; F, female; MD, missing data. ^a Treatment data not available for 2 children. ^b No specific tumor-directed treatment described.

Fig. 1. Frequency of the different tumor-directed treatment modalities employed in children with consumptive hypothyroidism syndrome.

accounted for 33% (2/6) of cases each. All adult patients underwent liver biopsy, and functional assays confirmed high D3 activity levels.

All adult patients underwent tumor surgery: 1 partial hepatectomy and 1 transplantation in the vascular tumors, 1 partial gastrectomy and transverse colectomy en bloc resection and 1 laparoscopic abdominal resection for the GISTs. The type of resection for the fibrous tumors is not specified. Hypothyroidism treatment was comprised of LT₄ administration in 83% (5/6) of patients, and only 1 (16%) patient received LT₃ in association with LT₄. The median maximum dose of LT₄ was 300 µg/day (P25–P75: 150–300). Thirty-three percent (2/6) of patients died from tumor progression, both with GIST diagnosis (Table 2).

Discussion

We described an infant with CHS-related hemangioendothelioma successfully treated with vincristine. CHS is an uncommon and severe form of hypothyroidism that occurs due to increased activity of D3, resulting in high rates of inactivation of thyroid hormones. The laboratory hallmark of this condition is high TSH levels and low serum T₄ and T₃ levels, accompanied by high rT₃ serum levels. High doses of LT₄ and/or LT₃ are required to normalize serum thyroid hormone levels. Usually, after successful tumor treatment, a euthyroid state is achieved. The CHS case reported here presented all characteristic features of the condition.

A systematic review showed that 97% of CHS in children were due to vascular tumors, with only 1 case of a solid tumor – a congenital fibrosarcoma. Conversely, in adults, with only 6 cases reported, vascular tumors, fi-

brous tumors, and GIST each accounted for 33% of the occurrences. Direct tumor therapy is an essential component of CHS treatment. The modalities employed are multiple, and the treatment strategies used vary according to tumor histology, patient characteristics, center experience, and available resources [5]. In children, the conservative treatment was preferred due to the favorable response of vascular tumors to medical treatment. Tumor resection was needed in only 2 cases: one case of fibrosarcoma and 1 hypervascularized vascular tumor where malignancy was suspected. While in adults the surgical treatment was predominant since most tumors were of non-vascular histology, in children the optimal tumor-directed treatment needs to be individualized according to specific patient and tumor characteristics, along with center experience and available resources.

The diagnosis of CHS requires a high suspicion index in patients with positive neonatal screening for hypothyroidism [6]. Of note, in our review, neonatal screening identified 32% (7/22) of CHS cases in children as congenital hypothyroidism. Some characteristics can help to differentiate CHS from other forms of congenital hypothyroidism, namely, normal thyroid morphology and iodine incorporation, high levels of rT₃ and the requirement of high doses of LT₄/LT₃ to restore serum TSH normal levels [6]. Notwithstanding, since hemangiomas are the most common vascular tumors in children, occurring in approximately 5–10% of 1-year-old children [7], it is reasonable to speculate that the actual prevalence of CHS may be underestimated. In this regard, further studies are warrant-

ed to explore the association of hemangiomas and clinical/subclinical thyroid dysfunction. From now on, it would be adequate to include serum TSH screening in the evaluation of patients with hemangiomas, particularly the larger ones.

In summary, we provide a summarized description of the 42 cases of CHS reported to date, highlighting the importance of an aggressive high-dose replacement of thyroid hormones along with early effective tumor-directed treatment approaches. Further efforts to support the development of treatment protocols to optimize thyroid hormone replacement and direct tumor treatments are warranted and should be the focus of future studies. Due to the high prevalence of vascular tumors in neonates, one should be aware of the necessity to include CHS in the differential diagnosis of congenital hypothyroidism.

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The authors declare that there is no conflict of interest that would impair the impartiality of this scientific study.

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