A case of an infant with extremely low birth weight and hypothyroidism associated with massive cutaneous infantile hemangioma.

Category: Case Report

Title: A case of an infant with extremely low-birth-weight and hypothyroidism associated with massive cutaneous infantile hemangioma

Short title: Hypothyroidism in cutaneous hemangioma

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Abstract

Although hepatic infantile hemangioma may correlate with consumptive hypothyroidism consequent to the overexpression of thyroid hormone inactivating enzyme by hemangioma cells, hypothyroidism has been rarely recognized in infants with cutaneous hemangioma. Here, we describe a male infant born at 28 weeks of gestational age with an extremely low birth weight (775 g) who developed a massive cutaneous hemangioma on his neck and severe abdominal distension. Imaging examinations detected a small mass lesion in the brain but no hepatic hemangioma. Laboratory findings at an age of 26 days revealed hypothyroidism. Although high-dose levothyroxine therapy failed to normalize the thyroid function, the hypothyroidism improved and cutaneous hemangioma regressed after initiating propranolol therapy. Our findings suggest that consumptive hypothyroidism should be considered as a critical comorbidity in patients with massive cutaneous infantile hemangioma. Propranolol therapy can effectively normalize thyroid function and cause hemangioma regression.

Keywords: hypothyroidism; cutaneous infantile hemangioma; propranolol

Introduction

Infantile hemangioma (IH) is a common type of benign tumor that ordinarily appears on the skin during the first few weeks of life and proliferates during the first year of life. Most cutaneous IHs are uncomplicated and involute spontaneously. However, a few cases involve complications such as ulceration, visual compromise, and airway obstruction. IHs also arise at non-cutaneous sites, such as the gastrointestinal tract, liver, and central nervous system, where they tend to cause complications. Particularly, hepatic IH has been associated with critical conditions such as cardiac failure, respiratory impairment, and hypothyroidism (1). However, only a few reports have described the association between hypothyroidism and non-hepatic IH. In this report, we present a case of an extremely low-birth-weight infant with massive cutaneous IH complicated with hypothyroidism, and review previously published pediatric cases of hypothyroidism associated with non-hepatic IH.

Case presentation

A male infant with a birth weight of 775 g was born at 28 weeks of gestational age consequent to maternal preeclampsia. At birth, he exhibited neither major anomalies nor abnormal ultrasonographic findings. He was given a surfactant for respiratory distress syndrome and was placed on mechanical ventilation during the first day of life. Although a gastrografin enema resolved his meconium-related ileus, the related abdominal distension persisted. Further examinations revealed

no evidence of organic lesions except for a cutaneous IH that had appeared on the neck at the age of 5 days and gradually enlarged to 44 mm X 22 mm X 7 mm (Figure 1A).

Newborn screening at 5 days of age revealed a normal blood level of thyroid-stimulating hormone (TSH). At 26 days of age, however, serum thyroid function tests revealed a high TSH level [15.329 μIU/mL (normal range, 0.350–4.940)] and a normal free thyroxine (fT4) level [0.88 ng/dL (normal range, 0.70–1.48)]. Consequently, 10 μg/kg/day levothyroxine (LT4) therapy was initiated for hypothyroidism, consistent with the recommended dose for infants with congenital hypothyroidism (5 to 10 μg/kg/day). Two weeks later, the TSH level had decreased to 6.947 μIU/mL but the free triiodothyronine (fT3) level remained low [1.51 pg/mL (normal range, 1.71–3.71)]. Subsequently, the patient's TSH level increased to 10.803 μIU/mL at 62 days of age, and the LT4 dose was increased to 12.5 μg/kg/day (Figure 1D). Whole- body computed tomography and abdominal magnetic resonance imaging (MRI) did not detect any visceral IHs, including diffuse hepatic hemangioma.

To prevent permanent disfigurement caused by the IH on the patient's neck, oral propranolol was initiated at a dose of 1 mg/kg/day when the patient was 69 days of age, and was later increased to 3mg/kg/day. Soon after initiating propranolol therapy, the patient's abdominal distension resolved gradually as the TSH level decreased and fT3 level increased. Subsequently, the LT4 dose was decreased to 5

μg/kg/day and maintained without further increases, despite increases in the patient's body weight. The cutaneous IH regressed remarkably with propranolol and laser therapy (Figure 1B), and both propranolol and LT4 therapy were withdrawn at 11 months of age. At 15 months of age, the patient exhibited a normal TSH response to intravenously administered thyrotropin-releasing hormone.

At discharge, routine brain MRI screening for extremely low-birth-weight infants revealed a mass with a 1-cm diameter in the left internal acoustic meatus (Figure 1C). The mass exhibited iso-intensity on both T1- and T2-weighted images, and uniform contrast enhancement. The patient had a normal auditory brain stem response; normal serum levels of soluble interleukin-2 receptor, carcinoembryonic antigen, human chorionic gonadotropin, and neuron-specific enolase; and normal urinary concentrations of homovanillic acid and vanillylmandelic acid. An MRI scan at 10 months of age revealed that the mass in the left internal acoustic meatus had diminished in size. Accordingly, the mass was assumed to be an intracranial IH.

The patient is now 18 months of age and healthy, with no signs or symptoms of thyroid dysfunction. He has exhibited catch-up growth in both body length and weight and normal neurological development.

Discussion

In a study of 92 patients with IH, Huang *et al.* reported that 10% (9/92) had high TSH levels; of these, two with apparent acquired hypothyroidism harbored massive hepatic hemangiomas (1). Kulungoaski *et al.* reviewed 121 patients with hepatic IH and observed that hypothyroidism was recorded in 100% (16/16) of patients with diffuse hepatic IH and 21.4% (9/42) of patients with multifocal hepatic IH, but not in patients (0/17) with focal hepatic IH (2). However, only a few pediatric cases of hypothyroidism associated with non-hepatic IH have been reported. To the best of our knowledge, hypothyroidism was comorbid with a large IH in the parotid gland in two cases, a large cutaneous IH in two cases, including ours, and multiple small cutaneous IH in one case (Table 1).

Hypothyroidism associated with hepatic IH is attributed to the overexpression of type 3 iodothyronine deiodinase (DIO3) within the hemangioma (1). DIO3 deiodinates thyroxine and triiodothyronine (T3) into the respective biologically inactive forms of reverse T3 (rT3) and diiodothyronine (T2). Consequently, the decreases in biologically active thyroid hormone levels lead to consumptive hypothyroidism. Notably, as DIO3 activity has been detected in both cutaneous and hepatic IH, large-sized non-hepatic IHs can also cause consumptive hypothyroidism.

A resistance to thyroid replacement therapy is a characteristic manifestation of consumptive hypothyroidism. Higher doses of LT4 are required to normalize TSH levels in patients with consumptive hypothyroidism relative to congenital

hypothyroidism; however, the doses can be reduced with involution of the hemangioma (7). Laboratory findings of low fT3 and high TSH levels without a remarkably low fT4 level, as well as high rT3 level, can help to indicate consumptive hypothyroidism (8). Although we were unable to measure this patient's DIO3, rT3 and T2 levels, we consider his condition to have indicated consumptive hypothyroidism, given the refractoriness to the replacement therapy and the improvement in thyroid function after propranolol therapy.

Overexposure to iodine through topical iodine-containing antiseptics and iodinated contrast media have been reported to cause transient hypothyroidism in low birth weight infants (9, 10). However, most of the cases of iodine overexposure-induced hypothyroidism showed predominantly low fT4 levels without remarkable low fT3 levels, and immediate normalization of thyroid function after commencement of LT4. Although we did not measure the urinary excretion of the iodine to evaluate the iodine overexposure, the gastrografin enema is unlikely to cause the hypothyroidism in this patient.

Generally, LT4 monotherapy is recommended as the treatment for hypothyroidism. A case of consumptive hypothyroidism with low fT3 and normal fT4 levels were successfully treated with liothyronine (LT3) monotherapy (11). Thus, administration of LT3 could be indicated in patients with consumptive hypothyroidism.

Corticosteroid or propranolol therapy is indicated for cases wherein an IH

disturbs a patient's physiological functions. Recently, propranolol has been shown to be noninferior to corticosteroids for the treatment of ulcerated IH (12). Thus, propranolol is currently considered the first-line treatment because of its risk-benefit profile. In this case, we closely monitored vital signs and laboratory results while administering propranolol, which ensured that we could avoid side effects such as hypotension, hypoglycemia, and bronchospasm.

In conclusion, consumptive hypothyroidism could be a critical complication in patients with not only hepatic IH but also massive cutaneous IH. In such cases, thyroid replacement therapy is essential for the prevention of mental and growth retardation. IH involvement should be considered in patients exhibiting refractoriness to thyroid replacement therapy.

Learning Points:

Consumptive hypothyroidism should be considered as a critical comorbidity in patients with massive cutaneous infantile hemangioma.

IH involvement should be considered in patients exhibiting refractoriness to thyroid replacement therapy.

Laboratory hallmark of consumptive hypothyroidism is low fT3 and high TSH levels without a remarkably low fT4 level.

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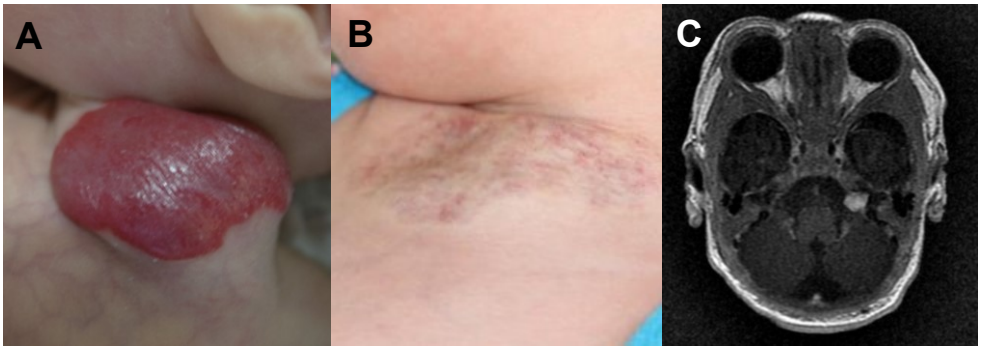
Figure legends

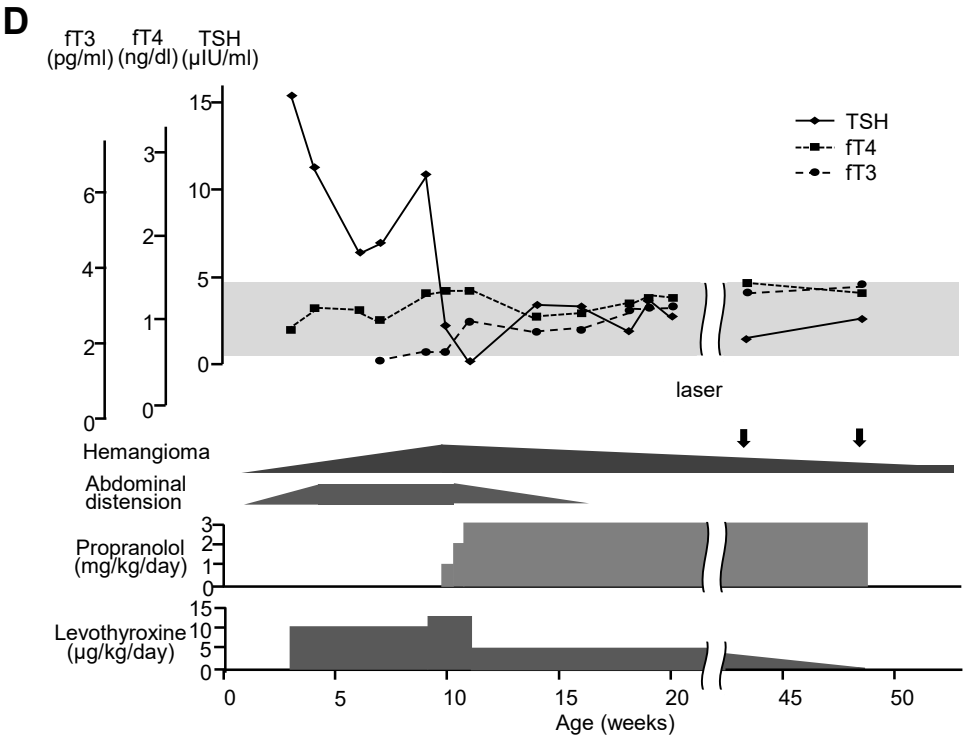
Figure 1. Cutaneous infantile hemangioma on the neck of a premature, extremely low-birth-weight infant before (A) and after (B) treatment. A mass in the left internal acoustic meatus is visible on an axial contrast-enhanced T1-weighted magnetic resonance image obtained at 4 months of age (C). Clinical and laboratory course during follow-up (D). The shaded region indicates the normal ranges of thyroid stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3).

Table 1. Cases of consumptive hypothyroidism associated with non-hepatic infantile hemangioma

Age	Sex	IH		LT4 therapy		Therapy for IH	Reference
		Location	Size / Number	Maximum dose (μg/kg/day)	Duration		
7 d	F	Parotid gland	Extension to eye, nostril, cheek, mouth, auricle, and thyroid lodge / 1	13.2	3.7 y	Corticosteroid -> Propranolol	(3)
1.5 m	M	Parotid gland	4 cm in diameter / 1	3	13.5 m	Propranolol	(4)
8 m	M	Cutis	5–10 mm in diameter / more than 100	15	nd	−	(5)
1.5 y	M	Cutis	12 cm X 10 cm / 1	40	nd	−	(6)
26 d	M	Cutis	44 mm X 22 mm X 7 mm / 1	12.5	10 m	Propranolol	Present case

d, days; m, months; y, years; F, female; M, male; IH, infantile hemangioma; LT4, levothyroxine; nd, not described


A
B
C


D
fT3 (pg/ml)
fT4 (ng/dl)
TSH (µIU/ml)
TSH
fT4
fT3
laser
Hemangioma
Abdominal distension
Propranolol (mg/kg/day)
Levothyroxine (µg/kg/day)
Age (weeks)