A full-term baby boy underwent an ultrasound scan of the abdomen at 6 weeks of age for the follow-up of an antenatal diagnosis of left-sided hydronephrosis. Although there was no hydronephrosis, the abdominal ultrasound revealed an enlarged liver with multiple hypoechoic lesions measuring up to 25 mm in diameter. He was admitted to the hospital for further evaluation of the hepatic lesions.

Examination revealed multiple small external hemangiomas on the scalp and both wrists and axilla. The infant’s abdomen was distended with hepatomegaly 6–7 cm below the costal margin. There was no evidence of cardiac failure, an observation that was confirmed by a cardiology consult. His electrolytes, creatinine, urine catecholamine metabolites, γ-hydroxybutyric acid, α-fetoprotein, and liver enzymes were all within reference intervals, except for an increased γ-glutamyl transferase of 257 IU/L (reference interval, 7–64 IU/L). Thyroid function tests (TFT) revealed an increased thyroid-stimulating hormone (TSH) concentration of 37.7 mU/L (age-specific reference interval, 0.30–5.00 mU/L), free thyroxine (fT4) within the reference interval at 17.9 pmol/L (age-specific reference interval, 12.0–30.0 pmol/L), and low free triiodothyronine (fT3) of 3.3 pmol/L (age-specific reference interval, 3.8–6.0 pmol/L) (Beckman DxI, Beckman Coulter). Thyroid peroxidase and thyroglobulin antibodies were negative. The newborn TSH screening test results were within reference intervals. MRI scan of the abdomen showed multiple liver lesions consistent with hemangioendothelioma.

DISCUSSION

DISCREPANCY IN THYROID FUNCTION TESTS AND FURTHER INVESTIGATIONS

Analytical interference in TSH or fT4 immunoassay, congenital hypothyroidism secondary to dysmorphogenesis, and consumptive hypothyroidism due to hemangioendothelioma are the possible causes for discrepant TSH and fT4 results in this patient.

We excluded possible TFT assay interferences by reanalyzing the TFT after using heterophile antibody blocking tubes (Scantibodies Laboratories) and by re-checking TFT results with different analyzers (Siemens Centaur and Roche E602).

A Technetium-99m thyroid uptake scan showed normal thyroid location, size, and uptake. The reverse T3 (rT3) concentration was 20.95 nmol/L (adult reference interval, 0.17–0.45 nmol/L). The rT3 was measured using an RIA (RADIM). The rT3 concentrations are highest immediately after birth in umbilical cord blood (0.3–5.51 nmol/L); however, these concentrations gradually decrease during infancy and childhood (1).

PROBABLE DIAGNOSIS AND FOLLOW-UP

A diagnosis of consumptive hypothyroidism associated with hepatic hemangioendothelioma (HHE) was considered the most probable explanation of abnormal thyroid function in this baby.

T3 replacement was commenced at 25 μg/day (4.2 μg/kg per day), which is a standard dose (range 2.5–5 μg/kg per day). This dose was increased to 100 μg/day (16 μg/kg per day) over the next 4 weeks. The patient’s hemangioendothelioma was treated with prednisolone and propranolol.

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QUESTIONS TO CONSIDER

1. What are the possible causes for discrepant TSH and fT4 results?
2. What additional biochemical testing would be helpful to elucidate the cause of the discrepancy in the TSH and fT4?
3. What is the most probable diagnosis?
A repeat abdominal ultrasound after 6 months of treatment revealed regression of the hemangioendothelioma compared to previous scans. T4 requirements decreased as the hemangioendothelioma resolved. Repeat TFT revealed TSH of 2.59 mIU/L (reference interval, 0.5–4.0), fT4 of 26.2 pmol/L (reference interval, 10.0–19.0 pmol/L), and fT3 of 3.9 pmol/L (reference interval, 3.5–6.5 pmol/L). The L-T4 dose was reduced to 50 μg/day and TFT results were maintained within reference intervals. The patient continues to wean off T4, and at the most recent review (9 months after commencement of treatment) he was on 50 μg for 5 days and 25 μg for 2 days, equivalent to 43 μg/day, or 4.4 μg/kg per day.

PERIPHERAL METABOLISM OF THYROID HORMONES

Thyroid hormone is derived from the amino acid tyrosine. Iodination of tyrosine residues on thyroglobulin ultimately produces T4 and T3.

T4 contains 4 iodine atoms (3, 5 positions on inner ring and 3’, 5’ positions on the outer ring of the thyronine molecule). Almost all T4 is synthesized by the thyroid gland. Biologically active T3 contains 3 iodine atoms at the 3, 5, and 3’ positions. Only 20% of T3 is synthesized by the thyroid gland and the remaining 80% is produced by the outer-ring deiodination (5’) of T4 in peripheral tissues. Biologically inactive reverse T3 (rT3) has 2 iodine atoms on the outer ring but only 1 iodine atom on the inner ring (3, 3’, 5’ T3). Almost all rT3 is formed by peripheral conversion of T4 (2).

The peripheral metabolism of thyroid hormones is catalyzed by deiodinase enzymes. There are 3 main types of deiodinases: type 1, type 2, and type 3. Type 1 iodothyronine deiodinase (D1) has inner- and outer-ring deiodinase activity and is mainly expressed in liver, kidney, and thyroid. Type 2 iodothyronine deiodinase (D2) is mainly expressed in the central nervous system (CNS), anterior pituitary, brown fat, cardiac and skeletal muscle, placenta, and thyroid. D2 is responsible for outer-ring deiodination and has a higher affinity for T4 than does D1. D2-generated T3 is required for feedback regulation of TSH secretion (2).

Type 3 iodothyronine deiodinase (D3), which has inner-ring deiodination activity, inactivates thyroid hormones by converting T4 to rT3 and T3 to diiodothyronine (T2). D3 is mainly found in the placenta, uterus, CNS, and skin and is the most important source of rT3 (2) (Fig. 1).

In the euthyroid state, D1 is the minor source of serum T3. However, in the setting of hyperthyroidism, about 50% of serum T3 production is attributed to D1. Therapeutically, D1 is inhibited by propylthiouracil,
which is used to treat hyperthyroidism. In contrast, D2 is insensitive to inhibition by propylthiouracil. D1 activity is decreased in acute illness, causing low serum T3 and high rT3 (due to low clearance of rT3 to T2 by D1 and reactivation of D3 in the liver and skeletal muscle) (2). The high expression of D3 in the uteroplacental unit and developing fetus limits the transfer of maternal thyroid hormones to the fetus. D3 expression falls and becomes undetectable in most tissues other than the CNS and skin after birth. However, it remains the major path of thyroid hormone inactivation (2).

**INFANTILE HHE**

Infantile HHE is the most common vascular tumor of the liver in children, accounting for 12% of all hepatic tumors. Most patients are diagnosed during the first 6 months of life, with a female predominance (3). Patients usually present with an abdominal mass, but other symptoms and signs can include hepatomegaly, high-output cardiac failure, skin hemangiomas, thrombocytopenia, hemolytic anemia, and peritoneal bleeding. Although asymptomatic lesions may spontaneously regress within a year, those patients with symptomatic lesions require aggressive management. Medical treatment options include corticosteroids, interferon-α, and oral propranolol (4). Intervventional treatments include embolization and ligation of the hepatic artery, resectional surgery, and liver transplantation (3).

**CONSUMPTIVE HYPOTHYROIDISM**

The association between consumptive hypothyroidism and infantile HHE was first described in 2000 (5). The majority of consumptive hypothyroidism cases have been described in children with hemangioendotheliomas, but cases have also been reported in adults with massive vascular and fibrous tumors (6–8).

The tumor expression of D3 enzyme activity in hepatic and cutaneous hemangioma lesions is believed to cause the consumptive hypothyroidism (5, 8, 9). High expression of D3 activity has been described in a patient with a large malignant solitary tumor and hypothyroidism (7). D3 inactivates thyroid hormones by converting T4 to rT3 and T3 to T2. Excessive degradation of thyroid hormones due to high expression of D3 by tumor tissue is also supported by the increased concentrations of rT3, the requirement for extremely high doses of thyroid hormone replacement, and improvement of hypothyroidism after liver transplantation or involution of HHE (5, 6, 8, 9).

Patients with consumptive hypothyroidism usually present with features of the underlying tumor but can also present with severe hypothyroidism refractory to usual doses of thyroid hormone replacement. Biochemically, these patients have increased TSH with fT4 concentrations that are low or within reference intervals. The fT3 concentration is usually low with increased concentrations of rT3 and T2. Frequent TFT monitoring is important in patient management because the rate of T4 degradation (and hence the concentrations of TSH, fT4, and fT3) is dependent on the mass of the HHE. The rate of T4 degradation is highest during the proliferative phase of HHE (5). Diagnosis of consumptive hypothyroidism requires clinical suspicion because biopsy and demonstration of D3 activity in HHE tissue is not routinely done due to risk of bleeding. TFT should be ordered for a patient with HHE, and this is more important in infants because hypothyroidism can have detrimental effects on child development.

Our patient had subclinical hypothyroidism with increased TSH and fT4 within the reference interval, with a slightly low fT3. However, he required high doses of T4 to maintain euthyroid status during the early phase of the disease. This high dose requirement has been shown in previous cases, and some patients require combined T4 and T3 replacement or intravenous T3 replacement (10). However, the thyroid hormone requirement decreases with the involution of the tumor.

**POINTS TO REMEMBER**

- Consumptive hypothyroidism is a rare but important associated condition in patients with HHE.
- A high index of suspicion is required to diagnose consumptive hypothyroidism.
- Refractory hypothyroidism can be a clue to asymptomatic vascular tumors.
- Regular monitoring of thyroid function tests is important for the management of consumptive hypothyroidism since thyroid hormone degradation is dependent on tumor mass.

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**References**

Commentary

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Consumptive hypothyroidism is a rare endocrinopathy caused by the accelerated inactivation of circulating thyroid hormones at rates that exceed the synthetic capacity of the thyroid gland. This condition is characterized by the accelerated inactivation of circulating thyroid hormones at rates that exceed the synthetic capacity of the thyroid gland. This condition is characterized by increased thyroid hormone inactivation by documenta
tion of either supernormal requirements for exogenous thyroid hormone or increases in serum rT3 (the product of T4 inner-ring deiodination). Both of these features were present in the current case.

Whereas type 3 deiodinase (D3) is highly expressed in virtually all proliferating hemangiomas, both high specific enzyme activity and large tumor burden are required to cause systemic hypothyroidism. This is illustrated by recent studies of the Liver Hemangioma Registry (1), which show a direct relationship between tumor burden and hypothyroidism risk and have documented a 100% incidence of consumptive hypothyroidism in infants with massive tumor burden from diffuse hepatic hemangiomas (defined as innumerable tumors with nearly complete hepatic parenchymal replacement). By maintaining an appropriate index of suspicion, healthcare providers can readily diagnose and treat consumptive hypothyroidism in this at-risk population to reverse its deleterious effects on fluid balance and cardiac function and to prevent the permanent neurologic injury caused by infantile hypothyroidism.

This case illustrates the benefits of timely diagnosis and therapy in the care of infants with consumptive hypothyroidism. As noted by the authors, there have been 3 reports of adults with consumptive hypothyroidism from D3-expressing fibroblastic or vascular tumors. Although rare, these isolated cases illustrate that the pathophysiology of consumptive hypothyroidism extends beyond infants with hemangiomas and suggest that future research may identify additional populations that are susceptible to this rare endocrine disease and could benefit from screening and early treatment.

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