Novel Insights from Clinical Experience

Use of Combined Liothyronine and Thyroxine Therapy for Consumptive Hypothyroidism Associated with Hepatic Haemangiomas in Infancy

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Established Facts

- Hepatic haemangiomas may induce overactivity of type 3 deiodinase (D_3) leading to consumptive hypothyroidism.

Novel Insights

- Combined treatment with liothyronine and levothyroxine provides effective support by treating both peripheral and central hypothyroidism.
- Reverse T_3 concentrations may act as useful surrogate markers of D_3 overactivity.

Key Words

Hepatic haemangioma · Hypothyroidism · Type 3 deiodinase · Reverse T_3

Abstract

Hepatic haemiangiomas in infancy are rare. An association with hypothyroidism has been previously reported and is believed to be secondary to the conversion of thyroxine (fT_4) to biologically inactive reverse triiodothyronine (rT_3) by type 3 iodothyronine deiodinase (D_3). We report a case that responded well to the combined use of liothyronine and thyroxine therapy.

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Introduction

Infantile haemangiomas are common with an incidence of up to 10% in Caucasian infants and the majority are single cutaneous lesions [1]. They generally undergo a proliferative phase in the first year of life with subsequent involution [1]. The association between hepatic haemangiomas and hypothyroidism is rare but well documented [2, 3]. In these cases, the development and course of hypothyroidism appears to be linked to the natural history of the hepatic lesions with resolution of the hypothyroidism associated with regression of the haemangiomas.
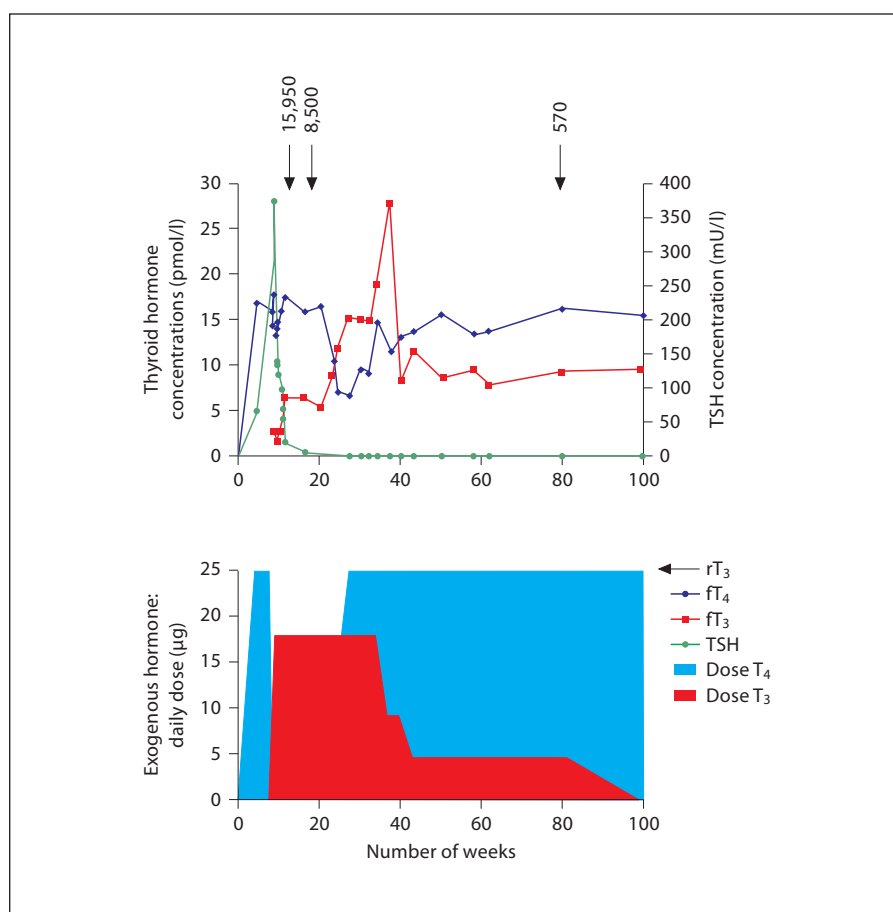
Fig. 1. Change in concentrations of fT_3, fT_4 and TSH over time and in response to treatment with levothyroxine and liothyronine. Normal range: TSH <6 mU/l, fT_3 14–41 pmol/l, fT_4, 10–23 pmol/l, rT_3 120–540 pmol/l.

The normally functioning thyroid gland produces T_4 in response to thyroid-stimulating hormone (TSH). Extrathyroidal conversion of T_4 to the biologically active T_3 by outer ring deiodination is catalysed by the actions of type 1 and 2 iodothyronine deiodinases (D_1 and D_2). An alternative inner ring deiodination catalysed by type 3 iodothyronine deiodinase (D_3) converts T_4 to the biologically inactive reverse T_3 (rT_3) and is also able to deiodinate local T_3 to inactive T_2 [4]. It has been suggested that hepatic haemangiomas induce D_3 activity which effectively leads to a consumptive hypothyroidism [2].

Treatment of the hypothyroidism can be difficult as exogenous thyroid hormone is also converted to inactive rT_3. This has implications both for the support of the infant during management of the haemangiomas and for the long-term neurodevelopmental outcome.

Laboratory Procedures

Samples of fT_3, fT_4, and TSH were all analysed on the Immulite 2000 analyser as a chemiluminescent immuno-metric analysis (Diagnostic Products, Gwynedd, UK). rT_3 was analysed by a radioimmunoassay including a polyethylene glycol precipitation and centrifugation (Teomed AG, Greifensee, Switzerland).

Patient Report

This Caucasian male infant was referred to our regional unit at 4 weeks of age with a raised TSH detected after routine neonatal hypothyroid screening. He was the second twin from an unplanned monochorionic twin pregnancy. His parents were nonconsanguineous, with 3 older children and no family history of thyroid disorders. He was delivered by emergency caesarean section at 34 weeks after spontaneous onset of labour, with a birth weight of 1.8 kg (9th centile; –1.22 SDS). Cutaneous haemangiomas were noted at birth.

After delivery, he required a 3-week admission to his local neonatal unit to establish a feeding pattern. The initial neonatal thyroid screen was taken at 7 days of life and repeated at a corrected gestational age of 36 weeks according to UK repeat screening guidelines for premature infants. The TSH concentrations were
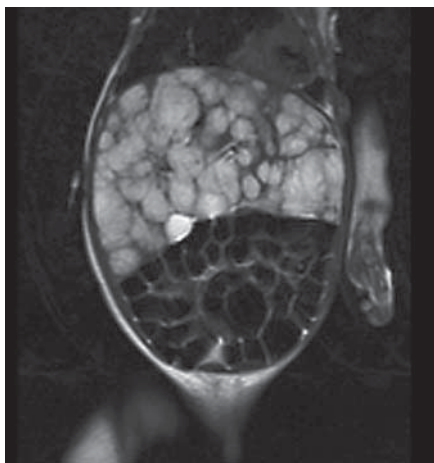
Fig. 2. Abdominal MRI scan demonstrating multiple hepatic haemangiomata.

reported as 1.8 mU/l, (normal <6) and 9.7 mU/l, respectively. The family was then contacted and asked to attend our unit for further evaluation.

On examination the child was noted to be mildly jaundiced and to have multiple haemangiomata over his chest wall, back and limbs that were reported by the parents to be increasing in size. Venous thyroid function tests at this time revealed a TSH of 66.2 mU/l (normal <6) and a fT_4 of 16.9 pmol/l (normal range [NR] 19–39 <4 weeks of age). Liver function tests were normal. A nucleotide thyroid scan demonstrated very avid uptake of isotope in the region of the normally located thyroid gland. He was commenced on oral levothyroxine 25 µg daily. Thyroid autoantibodies were negative. His twin and mother had normal thyroid function.

At 6 weeks of age the child was admitted to his local hospital following an apnoeic episode. No clear cause was identified but he was noted to have a mildly distended abdomen and multiple hepatic nodules were identified on abdominal ultrasound scan (USS). He was transferred to our unit at 7 weeks of age after a second apnoeic episode and a repeat abdominal USS demonstrated marked hepatomegaly with multiple hepatic lesions without obvious vascular flow on colour Doppler. Haematological investigation suggested anaemia with abnormal lymphocytes. During this time, there was a steady increase in TSH concentrations with a reducing fT_4 and fT_3 (fig. 1).

At 8 weeks of age, the infant deteriorated with rapidly increasing hepatomegaly, respiratory compromise and bradycardia requiring ventilatory support. Cardiac dysfunction and possible neuroblastoma stage 4S were excluded with a normal echocardiogram, bone marrow aspirate and skin biopsy. An abdominal MRI confirmed the diagnosis of neonatal haemangiomatosis (fig. 2).

At the time of his respiratory deterioration, oral levothyroxine therapy was discontinued and parenteral liothyronine (T_3) commenced. Once stable, the liothyronine was administered enterally. On this treatment, his TSH returned to the normal range and his fT_3 concentrations improved. rT_3 was measured at a concentration of 15,950 pmol/l (NR 120–540 pmol/l).

The child was commenced on treatment with weekly vincristine for 6 weeks and 3 months of dexamethasone to reduce the hepatic haemangiomas. At 3.5 months, after 5 weeks of treatment, the rT_3 fell to 8,500 pmol/l with a TSH of 7.42 mU/l, fT_3 4.28 pmol/l (NR 14–41 pmol/l) and a fT_4 of 14.99 pmol/l (NR 10–20 pmol/l) on a total daily dose of 18 µg liothyronine.

There was a gradual clinical improvement of the severe abdominal distension that correlated with a reduction in the size of the hepatic lesions on serial abdominal USS. At 6 months of age, the fT_4 fell to 6.9 pmol/l with a TSH of 1.17 mU/l (fig. 1). Levothyroxine was restarted at 12.5 µg, increasing to 25 µg. The rise in fT_3 after the introduction of levothyroxine reflected the increase in total exogenous hormones received and a likely concurrent functional reduction of the hepatic haemiangiomas and D_3 activity. Liothyronine was gradually reduced and fT_3 concentrations were maintained, paralleling the dropping rT_3 concentrations (570 pmol/l at 1.5 years of age) with treatment of the haemangiomas. The cutaneous haemangiomas regressed in parallel with the hepatic lesions.

Neurodevelopmental follow-up is ongoing and the presence of an unaffected identical twin is likely to highlight any future developmental difficulties. Despite some delay in motor milestones during his first year of life, which were attributed to physical barriers such as his grossly distended abdomen, his current global development appears normal and in keeping with his sibling.

In this case, the hypothyroidism was detected early because the UK screening guidelines recommend a second TSH measurement at 3 weeks of age in premature infants. Without this screen, it is unlikely that the hypothyroidism would have been recognised before presentation with respiratory compromise and this may have had further consequences for the intellectual development.

Discussion

This case highlights the difficulty in the management of the consumptive hypothyroidism associated with hepatic haemangiomas and overactivity of D_3. The raised TSH and the avid uptake of isotope in a normally placed thyroid gland on technetium scan demonstrated that the thyroid gland functioned appropriately.

Treatment with exogenous levothyroxine alone may be ineffective, as it too is rapidly converted to inactive rT_3. In addition, our case demonstrates that the overactivity of D_3 can lead to concentrations of rT_3 much greater than those previously reported. The rT_3 served as a useful surrogate marker for D_3 activity and we found that this decreased in proportion to the involution and resolution of the hepatic haemangiomas.

Hepatic haemangiomas can cause massive abdominal distension, secondary respiratory failure and inability to feed. This condition may be further complicated by severe hypothyroidism by exacerbating electrolyte distur-

bances and reducing cardiac contractility. We found that administration of T_3, initially intravenously and subsequently orally, improved the systemic effects of the hypothyroidism. Although the haemangiomas responded well to treatment with vincristine and corticosteroids, supportive therapy during these months was crucial. The outcomes of previously described similar cases have been more variable with reports of hepatic artery ligation, liver transplantation and death [5].

T_3 concentrations and the peripheral hypothyroidism stabilised on oral administration of liothyronine and fT_4 concentrations were initially maintained without exogenous supplementation. This may have been in part due to competition between the liothyronine and fT_4 for conversion by D_3. However, we restarted levothyroxine as soon as the fT_4 dropped with the aim of protecting the long-term intellectual development of the child. The recognition of the role of thyroid hormone transporters including MCT8 and OATP1C1 support the view that T_4 is the primary thyroid hormone to cross the blood-brain barrier [4, 6]. It is subsequently converted by D_2 to T_3 in astrocytes and this locally produced T_3 is taken up into neurons. These neurons also control the deactivation of thyroid hormones by D_3 [6]. Neurological development is therefore dependent on ensuring adequate circulating fT_4 concentrations.

In conclusion, treatment of this condition depends on the effectiveness of therapy to reduce the haemangiomas and appropriate support of the thyroid hormone axis during this time. Treatment with T_4 alone may be insufficient and this report demonstrates that a combination of exogenous T_3 and T_4 may be the optimal management for improving both systemic and central hypothyroidism and preserving neurological development. In addition, the rT_3 concentrations may be useful indicators of D_3 overactivity, the severity of the condition and the response to treatment.

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