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CASE REPORT

Severe Graves' disease presenting with hepatic dysfunction in a 2-year-old child

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Hyperthyroidism is rare in children with an incidence of 2.91/100 000 patient-years for those under 15 years of age.[1] About 99% of cases are due to Graves' disease. Severe clinical presentation at diagnosis occurs more frequently in children than in adults and can be misattributed to more common paediatric conditions. Here, we describe a case of hyperthyroidism in a young child presenting with acute hepatitis and discuss its management.

Case Report

A previously well 2-year-old child of Caucasian descent presented to the emergency department with a 1-week history of diarrhoea and was noted to have scleral icterus (Fig. 1) and hepatomegaly on examination. Over the following 48 h, she developed lethargy, decreased oral intake and increased jaundice. There was no history of foreign travel, medication or complementary or alternative therapy use, or recent seafood ingestion. She had received routine immunisations appropriate to age. There was no family history of liver disease. She was admitted to hospital for investigation of hepatitis. Initial investigations showed ALT 1414 U/L (reference interval: 11–30 U/L), AST 1055 U/L (5–57 U/L), GGT 334 U/L (<15 U/L), bilirubin 87 umol/L (3–20 umol/L) and ALP 841 U/L (120–370 U/L). Plasma ammonia and coagulation screen were normal. Abdominal ultrasound revealed gallbladder thickening and oedema without evidence of hepatobiliary obstruction. The liver parenchyma was sonographically normal. Serology was negative for hepatitis A/B/C/E viruses, Epstein–Barr virus, CMV and HHV-6. Parvovirus B-19 serology was suggestive of past infection. Blood PCR testing for HSV1, HSV2, varicella zoster virus, enterovirus and adenovirus was negative. Autoimmune hepatitis serology, including ANA, smooth muscle antibody and liver-kidney microsomal antibodies, was also negative.

She was found to be persistently hypertensive, with systolic blood pressure 120–132 mmHg and diastolic blood pressure 68–72 mmHg and was tachycardic with heart rate 130–165 beats per minute. She had bounding pulses, a systolic murmur and hyperdynamic inferiorly displaced apex beat. Notably, she was taller than her 4-year-old brother (Fig. 1) with a height 3.5 cm above the 97th centile for her age, and a weight on the 75th centile. Further examination revealed a smooth goitre with 4-cm lobes and hyperreflexia. Pemberton sign to assess for venous obstruction was negative. She had prominent eyes with scleral icterus. Her liver and spleen were both palpable below the costal margins. ECG showed sinus tachycardia with possible evidence of left ventricular hypertrophy. Chest x-ray showed a normal cardiac silhouette and no increased pulmonary or vascular markings. Echocardiogram was not performed.

Further testing confirmed hyperthyroidism with TSH < 0.00 mIU/L, T3 30 pmol/L (4–7 pmol/L) and T4 > 64.4 pmol/L (10–20 pmol/L). Thyroid receptor antibody (TRAb) was 34.7 IU/L (<1.8 IU/L), thyroid peroxidase (TPO) antibody > 1000 kIU/L (<5.6 kIU/L) and thyroglobulin antibody 84.1 kIU/L (<4.0 kIU/L) consistent with autoimmune hyperthyroidism. The bone age was advanced at 5 years 1 month (chronological age 2 years 9 months). Full blood count showed a

Key points

1. Hyperthyroidism is a rare occurrence in young children. Tachycardia, hypertension and the presence of a goitre are suggestive of hyperthyroidism and should prompt initial investigation with TSH and free T4/T3.
2. Thyrotoxicosis-associated liver injury can be safely treated with anti-thyroid drugs despite the very small risk of drug-induced hepatotoxicity.
3. In cases where thyroid function is improving but liver function is worsening, other causes of hepatic injury should be considered, including drug-induced hepatotoxicity and autoimmune hepatitis.
4. The dose of MMI/CBZ required to control thyrotoxicosis in young children may be above the recommended starting range of 0.4–0.8 mg/kg.

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significant microcytic hypochromic anaemia with Hb of 82 (105–138 g/L) with MCV 49 (70–88 fL) and MCH 14 (22–30 g/L).

Treatment was initiated with carbimazole at 1 mg/kg/day, Lugol's iodide 0.1 mL daily and propranolol 5 mg TDS. Lugol's iodide was ceased on day 7 of treatment. The dose of carbimazole was uptitrated over 3 weeks to 2 mg/kg/day. T4 returned to the normal range 4 weeks after commencing therapy and T3 returned to normal range 6 weeks after commencing therapy (Fig. 2). Symptomatic control was achieved with propranolol and this dose was weaned from 1 month after initiation of treatment. Liver function began improving with commencement of antithyroid therapy and returned to normal levels after 8 weeks (Fig. 3). Synthetic function of the liver remained normal throughout the illness with normal albumin and coagulation profile. Liver biopsy was not performed.

Initial ophthalmic assessment showed normal visual acuity, mild bilateral proptosis with inferior scleral show (see figure 1) and full range of eye movements. Proptosis resolved at 6-month review.

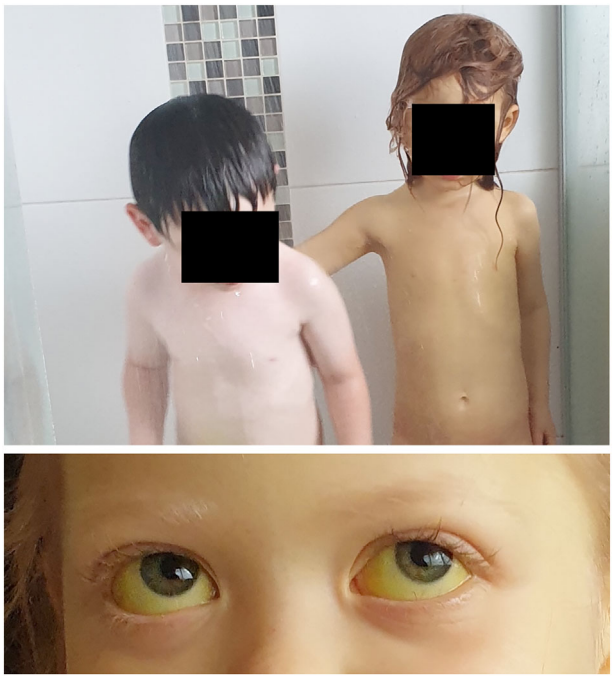

Fig. 1 Home photography prior to treatment showing tall, jaundiced child with scleral icterus.

Discussion

Thyroid hormone is essential to normal function of the liver and severe hyperthyroidism can rarely be associated with hepatobiliary dysfunction.[2] Antithyroid drugs such as propylthiouracil (PTU), methamethiazole (MMI) and its derivative carbimazole (CBZ) are also associated with hepatoxicity, and as such the management of thyrotoxicosis presenting with hepatitis is challenging. We believe our patient to be the youngest published case of Graves' disease presenting with cholestasis and hepatitis.

Abnormal liver function tests are common at the onset of Graves' disease, with 37–78% having at least one elevated liver enzyme.[3] ALP most commonly elevated, but GGT, AST, ALT and bilirubin may all also be raised.[2] Liver injury is thought to be due to relative hypoxia in the perivenular regions, with an increase in oxygen demand without increase in hepatic blood flow.[4] Consistent with this, liver biopsies have shown centrilobular necrosis, glycogen depletion and increased mitochondria numbers.[4,5] Our patient did not undergo liver biopsy but it is interesting to note the much greater elevation in AST than ALT. With a normal CK and no evidence of haemolysis, it is likely the excess AST was due to mitochondrial proliferation in injured hepatocytes. Fulminant hepatic failure has rarely been described in adult patients with severe thyrotoxicosis and is more common in those with

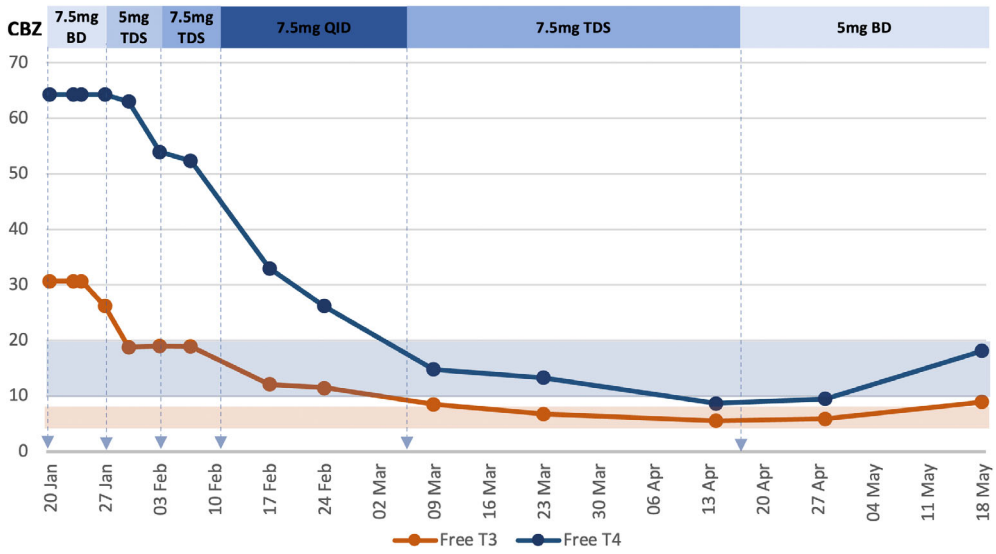

Fig. 2 Thyroid function tests and carbimazole (CBZ) from weeks 1 to 16 of treatment. Shaded bars indicate normal range for T3 (orange) and T4 (blue).

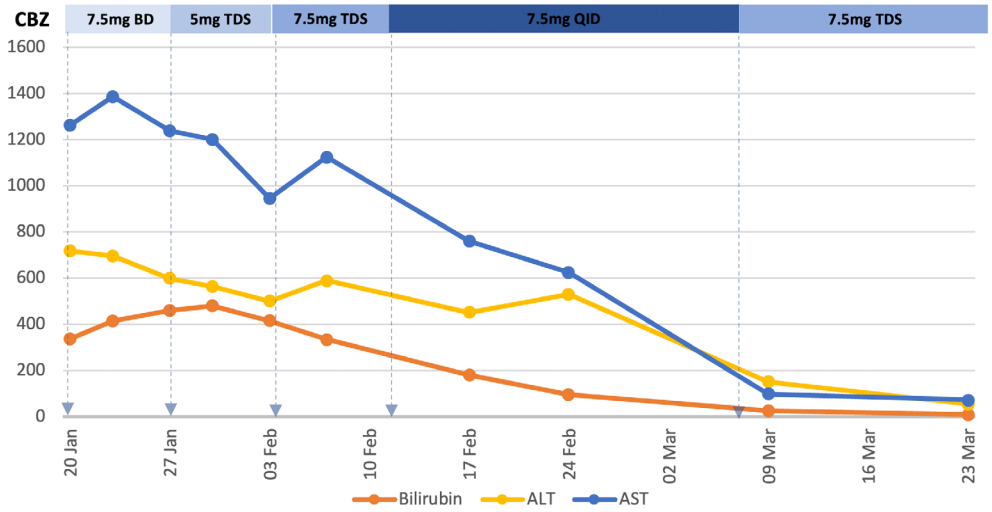

Fig. 3 Liver function tests and carbimazole (CBZ) dose from weeks 1 to 9 of treatment. Bilirubin normalised after 6 weeks, ALT and AST normalised after 12 and 14 weeks, respectively. GGT and ALP remained unchanged.

cardiac failure.[2] Literature in the paediatric population is limited to case reports. When present at diagnosis, hepatitis and cholestasis tend to resolve following antithyroid therapy.[6]

Autoimmune hepatitis has an increased prevalence in Graves' disease and has rarely been described at disease onset.[7] Serology and liver biopsy may be required to differentiate the two conditions if abnormal liver function continues despite improving thyroid function. In our case, the diagnosis of autoimmune hepatitis was considered, however given the lack of autoantibody elevation and improvement in liver enzymes with antithyroid treatment, liver biopsy was not performed.

Antithyroid treatment is the first-line treatment in Graves' disease in children. PTU treatment can cause hepatoxicity which occurs more frequently in children. For this reason, PTU is not recommended for use in children. MMI/CBZ may be associated with a cholestatic pattern of hepatic injury. MMI-induced hepatotoxicity is rare, with less than 30 described cases in the literature.[2] While this is usually mild, cases of severe hepatic injury have rarely been described with MMI/CBZ treatment and are thought to be due to a hypersensitivity reaction.[2]

The recommended starting dose of MMI/CBZ is 0.4–0.8 mg/kg/day, with 0.4 mg/kg recommended in milder disease and 0.8 mg/kg recommended in more severe disease.[8] In our patient, improvement in thyroid function was not seen until the dose was increased to 1.3 mg/kg/day, and normalisation of thyroid function was achieved with 2 mg/kg/day. No side effects of treatment were seen. In a case report of a 3-year-old with thyrotoxicosis, 1.8 mg/kg/day was required to normalise thyroid function, indicating that higher doses of CBZ may be required in young children.[9] As increased hepatic mitochondrial activity has been seen on liver biopsy with thyrotoxicosis, we hypothesise that this may lead to increased inactivation of CBZ. Further study would be required to determine the true mechanism.

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