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A rare manifestation of a common disease - Thyrotoxicosis

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Background

Hyperthyroidism is a rare hypermetabolic status in children 1. Most common cause is the Graves' disease with an incidence of 1 to 3 per 100,000 and it is common in girls aged 10-15 years1,2. Male: female ratio in this disease is 5-10:1 11. Thyroid stimulating hormone (TSH) receptor antibodies (TRAb), and thyroid peroxidase (TPO) antibodies are common in this disease and TRAb cause hyperstimulation of the gland and enhances follicular growth1-3. Other causes of hyperthyroidism in this age group include Hashitoxicosis, McCune-Albright tri-iodothyronine (T3) toxicosis, thyroid adenoma, hyper-functioning thyroid carcinoma, congenital hyperthyroidism such as TSH receptor activation mutation, thyroid receptor beta subunit resistance and pituitary TSH producing tumour2.

Case Presentation

A thirteen-year-old male child was transferred from the local hospital due to severe hypertension, anemia, fever and diarrhea. He had fatiguability, insomnia and weight loss for the past four months. He had presented with a fracture involving the distal tibia and the radius about two months before this presentation, following a minor trauma and this needed internal fixation. There was no family history of thyroid disease or other autoimmune disease. On examination, he was a thin built child with an average height with mild exophthalmos and diffusely enlarged smooth goiter. He had fine tremors, tachycardia of 150-160bpm and the blood pressure was well above the 99th centile. Apex was not deviated and on auscultation he had a flow murmur. On investigation, he had normochromic normocytic anemia, hypokalaemia (serum potassium 2.5 mmol/L), hypercalcaemia (serum calcium 3.57mmol/l) with suppressed parathormone (PTH) values. Electrocardiogram showed evidence of sinus tachycardia. Echocardiogram and the renal Doppler did not show any aetiology for the hypertension. He had a high free thyroxine (T4) level of 128mU/L with suppressed thyroid stimulating hormone (TSH) <0.001mU/L. Thyroperoxidase (TPO) antibodies were positive with 998 IU/ml. TSH receptor antibodies (TRAb) could not be done in this patient as it was not available in the state sector. X-ray revealed healing fractures but there was no osteopenia or evidence of fibro-osseous dysplasia. Ultrasound scan of the thyroid showed a diffusely enlarged thyroid gland with no nodules or lymphadenopathy. Table 1 is a summary of the laboratory investigations.

Child was started on carbimazole and propranolol maximum doses. He needed three antihypertensives to control his blood pressure. Hypokalaemia was managed with oral supplements. We managed the hypercalcaemia with hyperhydration and diuretics but he did not respond until his thyroxinaemia was controlled. After three weeks of antithyroid drugs free T4 normalized together with normokalaemia and normocalcaemia. His exophthalmos was less comparatively and antihypertensives were tailed off over 2 weeks. His general condition improved with weight gain and he was no longer having insomnia, or fatiguability.

Discussion

Graves' disease is an autoimmune disease, where the thyroid hormone levels are raised giving rise to a

Table 1: Laboratory investigations

Investigation	Day 1	Day 5	Day 25 (2 weeks after therapy)
Thyroid stimulating hormone (mIU/L)	0.001	<0.001	0.01
Thyroxine (mIU/L)	40	128	10.9
Haemoglobin (g/dL)	8.1	8.0	10.2
Serum calcium (mmol/L)	3.57	3.3	2.4
Serum sodium (mmol/L)	139	136	140
Serum potassium (mmol/L)	2.5	2.7	4

hyper-catabolic state4. Thyroid receptor antibodies, which are thyroid stimulating, are involved in the pathogenesis1,2. Apart from that, there will be lymphocytic infiltration of the gland 1. Hashitoxicosis is the differential diagnosis and it is also mediated by antibodies and it is transient, as the toxicosis is due to the destruction of follicles releasing the thyroid hormone2. Eye signs in Graves' disease are more common in adults compared to children1,2. Children present with thyrotoxicosis, weight loss, insomnia, increased sweating and hyperphagia 1,2. Altered behaviour and deterioration of school performance are also seen which may be unnoticed for months 1,2.

Mild to moderate hypercalcaemia is seen in 20% of hyperthyroid patients5. Thyroxine stimulates bone turnover, immediately causing hypercalcaemia. In this state, there is suppressed parathormone (PTH) and vitamin D levels5. Hypercalcaemia resolves once the hyperthyroidism is under control and the rapid improvement may result from hydration 5. However, in our patient, irrespective of adequate hydration and diuretics, his hypercalcemia did not improve until the thyroxinaemia settled. Hypokalaemia may also occur in hyperthyroidism and it is sometimes associated with periodic paralysis6. Thyroxine enhances activities of the sodium potassium ATPase pump causing potassium shift in to cells and hypokalemia6. Immediate management is to replace potassium. If not, it may be associated with life threatening complications such as respiratory muscle paralysis and cardiac arrhythmia3,4,6. Hypokalaemia improves when thyrotoxicosis is under control.

Hyperthyroidism and hypothyroidism both may result in hypertension7. Free triiodothyronine (T3) may increase cardiac contractility and dilation of blood vessels causing stimulation of the renin-angiotensin system7. Inhibition of atrial, brain natriuretic peptides and endothelin cause further vasodilation and leads to wide pulse pressure 7.About 6-16% of patients may develop cardiac failure 7. Cardiac failure is common among patients with pre-existing cardiac diseases and is managed with anti-thyroid drugs and anti-hypertensives 3,4,7. Anemia in Graves' disease is not well understood and is assumed to be due to multiple causes8. It is postulated that the anemia is due to autoimmune hemolysis 8, impairment of the utilization of iron, deficiencies of folate and vitamin B12, or increased plasma volume 9,10. However the red cell numbers in Graves' patients are high8 in spite of having anemia. Increase in oxygen demand with toxicosis, result in stimulation of the bone marrow leading to relative deficiency of iron, folate and B12 9,10. However, the management is symptomatic9,10.

Mainstay of management of patients with Graves' disease is the use of anti-thyroid drugs 1,2. Commonly used drugs are carbimazole and propylthiouracil. Since propylthiouracil is associated with liver failure, carbimazole is preferred in children2. Both these drugs inhibit iodination in follicles and organification 2. Propylthiouracil can block peripheral conversion of T4 to T32. For symptom relief, propranolol is also prescribed for a shorter period 2. Our patient was started on carbimazole 30 mg daily in three divided doses along with propranolol. Patients should be educated in side effects like agranulocytosis, urticaria, arthralgia and hepatitis 2. In the case of a thyroid storm, where the mortality is high, prompt, aggressive treatment is needed2,3,4. Usually it manifests with a secondary superimposed factor such as infection, trauma, surgery, diabetic ketoacidosis or myocardial infection3,4. Performing TSH antibodies and thyroid peroxidase antibodies aids in the diagnosis and the titer will give an idea of the severity of the condition2. However, as we did not have TSH antibodies, we only did thyroid peroxidase (TPO) antibodies in this child.

On follow up, he needs thyroid function tests and gradual adjustment of the doses. Once euthyroid propranolol could be withdrawn2. Anti-thyroid drugs need to be given for nearly 36 months in children2. Afterwards, gradual tapering off can be done. Factors that may predict poor remission include younger age, high thyroid hormone levels at diagnosis, persistently elevated antibody levels, larger thyroid gland and male sex 12. The remission rate in this condition is around 30% 1. However, Graves' disease has a high recurrence rate. About 50% of children may have recurrences 2. In case of failure to go into remission or recurrence they need to be treated with radioiodine or surgery 2.

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