

## REVIEW

## Juvenile thyrotoxicosis; can we do better?

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Thyrotoxicosis remains a frustrating condition for the young person, family, and health professionals involved. The associated symptoms do not always suggest thyroid disease and patients can be unwell for many months before the diagnosis is made. The antithyroid drug regimen used to treat children and adolescents with thyrotoxicosis varies from one unit to another and yet the potentially life threatening side effects and remission rates post-treatment may be related to the regimen used. Most patients with thyrotoxicosis will need many years of drug therapy if the thyroid gland is not removed surgically or destroyed by radioiodine. Even "definitive" treatment will typically necessitate thyroxine replacement for life.

This review will discuss some of these issues and highlight areas of management that require further study.

## AETIOLOGY

Most paediatric patients with thyrotoxicosis have autoimmune thyroid disease. Around 95% of patients will have Graves' disease in which case excess thyroid hormone is the result of thyrotropin (TSH) receptor stimulation by autoantibodies.<sup>1</sup> In Graves' disease the thyroid develops a lymphocytic infiltrate as well as follicular hyperplasia. Activated T cells initiate B cell proliferation and TSH receptor antibody production. Hashimoto's disease is an autoimmune thyroiditis which may also result in hyperthyroidism, although in this setting the excess thyroid hormone is discharged from an inflamed gland and is not the result of TSH receptor stimulation (see below). Rare causes of thyrotoxicosis include McCune-Albright syndrome<sup>2</sup> and germline as well as somatic gain of function mutations of the TSH receptor which are associated with the presence of diffuse hyperplasia and toxic "hot" nodules, respectively.<sup>3 4</sup> TSH secreting tumours and thyroid hormone resistance are exceedingly rare causes of thyrotoxicosis.

## THE GENETICS OF AUTOIMMUNE THYROID DISEASE

About 80% of the susceptibility to autoimmune thyroid disease may be determined by genetic factors.<sup>5</sup> A number of susceptibility loci are linked to the development of autoimmune thyroid disease. Two loci are unequivocally associated with the development of Graves' disease, namely the MHC (chromosome 6p21) and CTLA4 (2q33). Together these loci account for about 50% of the inherited susceptibility to

Graves' disease. Further putative Graves' disease loci have been identified by linkage studies on chromosomes 5q31-q33, 14q31, 18q21, 20q11, Xp11, and Xq21.<sup>6</sup>

## INCIDENCE

The incidence of thyrotoxicosis in young people is around 1 per 100 000 person-years. The incidence rises from around 0.1 per 100 000 in young children to 3 per 100 000 in adolescence.<sup>1</sup> The incidence appears to be rising in some parts of the world, with rates up to 14.1/100 000/year reported from Hong Kong.<sup>7</sup> There is a higher prevalence in females (6-8 times) and a family history of autoimmune disease is often present. Incidence has been linked to dietary iodine intake, with supplementation associated with both a rise and a fall in the number of cases of Graves' disease.<sup>8 9</sup> Thyrotoxicosis is more common in children with other autoimmune conditions; in our regional centre four children with type 1 diabetes have developed Graves' disease in recent years.

## PRESENTATION

Young people have frequently experienced symptoms for some time before a diagnosis is reached. This delay may be in the order of eight months in prepubertal children compared to five months in pubertal children.<sup>10</sup> Prepubertal children tend to present with weight loss and frequent stools in contrast to features such as irritability, heat intolerance, and neck swelling seen in pubertal individuals.<sup>11</sup> If the diagnosis is not suspected referral can be to one of many subspecialists. In the past few years children with undiagnosed thyrotoxicosis in the northern region of England have initially been referred to cardiologists with a heart murmur, gastroenterologists with diarrhoea and failure to thrive, as well as to psychiatric/psychology services because of challenging behaviour and school refusal. Autoimmune thyroid disease can develop during the first three years of life and may have a deleterious impact on short and long term neurodevelopment.<sup>12</sup> The thyroid gland in Graves' disease is usually (but not always) increased in size, and thyroid gland examination may be overlooked as it does not fall neatly into one of the recognised systems. Graves' disease is a multi-system disease, although involvement of extra-thyroidal sites like skin is uncommon in childhood and involvement of the eyes (ophthalmopathy) tends to be less severe. By the time the diagnosis is made height is usually significantly

**Abbreviations:** PTU, propylthiouracil; RI, radioiodine; TBII, thyroid binding inhibiting immunoglobulin; TSH, thyrotropin

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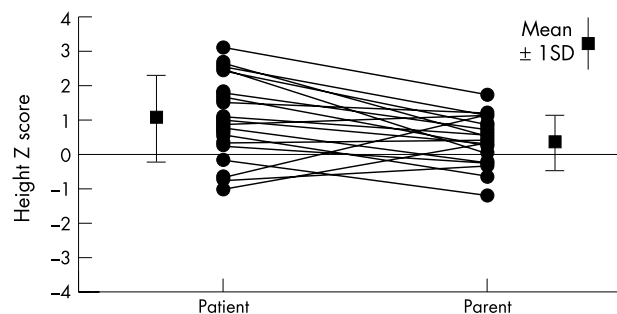
above the mid-parental target (fig 1) although patients are not necessarily thin.<sup>13</sup> The growth acceleration in thyrotoxicosis probably reflects increased growth hormone secretion coupled with the direct effects of thyroid hormone on the epiphysis.<sup>14 15</sup> Children can have signs of mitral valve disease at diagnosis, and although this may be due to thyroid hormone excess it has also been described in patients with hypothyroidism and may be an autoimmune phenomenon.<sup>16</sup> Suppressed TSH values are associated with increased cardiovascular mortality in the elderly,<sup>17</sup> and the true impact of a lengthy period of hyperthyroidism in childhood and adolescence on the heart and other systems is uncertain.

### THYROID EYE DISEASE

Graves' ophthalmopathy is an organ specific autoimmune process that is strongly linked to Graves' hyperthyroidism. It does not always occur at the same time as the hyperthyroidism and does not necessarily correlate with biochemical severity. Ocular manifestations of thyrotoxicosis commonly reflect thyroid hormone excess rather than autoimmune infiltration of the orbital tissues. This is illustrated by the "staring eyes" seen in infants with thyrotoxicosis secondary to gain of function mutations of the TSH receptor. Eye signs may be seen in 25–63% of young patients although severe, autoimmune infiltrative eye disease is uncommon.<sup>18 19</sup> Thyroid eye signs are particularly distressing for the young person affected and all patients with significant ocular disease such as chemosis, proptosis, or impaired motility require early review by an ophthalmologist.

### INVESTIGATIONS

TSH levels are suppressed with raised thyroxine concentrations (either free thyroxine, triiodothyronine, or both). A suppressed TSH with normal thyroid hormone levels can reflect euthyroid sickness as well as evolving thyrotoxicosis. Distinguishing between Graves' disease and Hashimoto's thyroiditis is important because of the different prognoses. A radio-isotope uptake scan of the thyroid gland (<sup>123</sup>I or <sup>99m</sup>Tc) will show diffusely increased uptake in Graves' disease but decreased uptake in Hashimoto's disease. Ultrasound scanning by an appropriately skilled and experienced operator can determine the size of the goitre, and the echogenicity of the thyroid tissue may suggest either Graves' or Hashimoto's disease. Ultrasonography can also be used to investigate a nodule or nodular goitre. An isolated thyroid nodule on examination or on isotope scanning in the thyrotoxic child raises the possibility of McCune-Albright syndrome. Fine needle biopsy and the involvement of a thyroid surgeon at an early stage is advisable because of the small possibility of thyroid neoplasia. Young people with thyrotoxicosis have



**Figure 1** Height SDS of patients with Graves' disease diagnosed in northeast England in recent years compared to mid-parental height SDS. Patients are significantly taller than would be expected based on parental size ( $p=0.02$ ).

increased bone turnover and reduced bone mineral density, both of which return to normal with treatment.<sup>20</sup>

### THYROID ANTIBODIES

The principal autoantigens in Graves' disease are the TSH receptor, thyroid peroxidase, and thyroglobulin. Antibodies to one of these autoantigens can be detected in more than 90% of patients with autoimmune thyroid disease. Thyroid binding inhibiting immunoglobulin (TBII; autoantibodies to the TSH receptor) are present in approximately 75–90% of patients with Graves' disease,<sup>21</sup> while thyroid peroxidase antibodies or thyroglobulin antibodies are present in approximately 68% of paediatric patients.<sup>10</sup> TBII are disease specific and so are not found in the euthyroid population, in contrast to antibodies to thyroid peroxidase and thyroglobulin. The autoimmune process in Hashimoto's disease does not target the TSH receptor and is usually more destructive to thyroid tissue. This is why patients with Hashimoto's disease who are hyperthyroid can become euthyroid and then hypothyroid in the short to medium term. There are obvious similarities between Graves' and Hashimoto's disease, and the presence of a lymphocytic infiltration and antibodies to antigens other than the TSH receptor in Graves' disease explains why they too can become hypothyroid in the long term. The TBII titre in pregnant patients with Graves' disease can be used to predict the risk of hyperthyroidism in the fetus.

### INITIAL MANAGEMENT—SYMPTOM CONTROL

Initial management will depend on the patient's symptoms and signs. This is related to both the amount of circulating thyroxine in the bloodstream and the levels of the more active T3 in the tissues. The use of  $\beta$  blockers will help to alleviate most symptoms in the initial phase after presentation. This can be given orally as propranolol at a dose of 250–750  $\mu$ g/kg/dose three times per day. Atenolol can also be used and compliance may be better as it is a once daily medication. These can be weaned and stopped as the patient becomes euthyroid. Beta blockade should be avoided in patients with asthma and cardiac failure, even if the thyrotoxicosis is the cause of the cardiac failure.

### ANTITHYROID DRUGS—THIONAMIDES<sup>22 23</sup>

The antithyroid drugs used most commonly in the UK are carbimazole and propylthiouracil (PTU). Methimazole (which is produced from carbimazole *in vivo*) is used in North America and Japan. These drugs prevent the synthesis of thyroid hormone by acting as preferential substrates for thyroid peroxidase. They inhibit the oxidation and organic binding of iodide *in vitro*, but this is not a significant action *in vivo*. PTU but not carbimazole or methimazole, decreases T4 to T3 conversion (deiodination) in the periphery. These drugs do not affect the release of preformed thyroid hormone which is why it can take weeks to establish a euthyroid state. There is evidence that these agents have a direct immunosuppressive effect. The obvious advantage of carbimazole over PTU is that it can be administered once daily (although many doctors choose to administer the drug twice daily initially); also, the incidence of major side effects may be lower (see below).<sup>23</sup>

There are two main approaches when treating patients with antithyroid drugs:<sup>24</sup>

- "Block and replace" (combined) therapy—where thyroid hormone production is prevented by antithyroid drugs and thyroxine is then added in a replacement dose.
- "Dose titration" (adaptive) therapy—where the dose of antithyroid drug is adjusted so that thyroid hormone production is normalised.

There are established as well as theoretical reasons why maintaining a clinically and biochemically euthyroid state is highly desirable. Both strategies are used by paediatric endocrinologists but it is unclear which of these approaches is the most appropriate. Potential advantages of the “block and replace” regimen include:

- Improved stability with fewer episodes of hyperthyroidism or hypothyroidism.
- A reduced number of venepunctures and visits to hospital.<sup>25</sup>
- The possibility of improved remission rates following a larger antithyroid drug dose.<sup>26</sup>

Potential advantages of the dose titration approach include:

- Fewer side effects with a lower antithyroid drug dose.<sup>27</sup>
- Improved compliance on one, rather than two medications.

In some patients, often inadvertently in our experience, thyroid gland function is partially blocked and thyroxine added in a dose that is below replacement levels. The initial dose of carbimazole used to block thyroid hormone production is around 0.75–1 mg/kg/day and for propylthiouracil, 5–10 mg/kg/day. These doses are then reduced by up to 50% if dose titration is used. Carbimazole has a longer half life than PTU and can be administered once daily, while PTU needs to be given 8–12 hourly. The child treated with a blocking dose of carbimazole or PTU will typically require thyroid hormone replacement after 6–12 weeks. Larger doses establish a euthyroid or hypothyroid state more quickly than smaller doses. Persistent hyperthyroidism beyond 3–4 months suggests that the dose needs to be increased although compliance should also be reviewed. Serum TSH levels can remain suppressed for months in patients who have been thyrotoxic for a long time and need to be interpreted cautiously.

### ANTITHYROID DRUG SIDE EFFECTS

Some of the side effects of antithyroid drugs are dose related (particularly with carbimazole) and some idiosyncratic. Minor side effects such as rashes, nausea, and headaches occur in 2–15% of patients and usually develop during the first weeks of therapy.<sup>11 28</sup> The more severe side effects include agranulocytosis, neutropenia, and hepatitis which are potentially life threatening and probably more common with PTU administration than carbimazole.<sup>23 29</sup> Drug related neutropenia occurs in approximately 0.3% of patients and typically occurs within three months of commencing treatment. A slightly greater percentage may develop a mild to moderate leucopenia. The neutropenic patient may present with features of fever and toxicity and there may be evidence of oropharyngeal infection. Thionamide induced neutropenia is an autoimmune phenomenon which, while idiosyncratic, may be more common with higher doses. Opsonic anti-neutrophil antibodies and lymphocytes sensitised to antithyroid drugs have been detected in the circulation of patients suffering from agranulocytosis secondary to antithyroid drugs. It is proposed that these antibodies lead to the destruction of granulocyte precursors within the bone marrow. If neutropenia occurs, antithyroid medication should be stopped immediately. Neutrophil function usually returns to normal spontaneously after 1–2 weeks, but GSF- $\alpha$  administration may speed the recovery. All patients should be given written information detailing the need to stop the antithyroid drug at the time of any intercurrent illness and to have an urgent full blood count performed. Although some paediatricians may measure the white cell count routinely

when checking thyroid function, the neutropenia can occur suddenly and so this is of limited value in the long term. Patients who become neutropenic should not be switched to another antithyroid drug because of the likelihood of recurrence. Hepatitis can be severe and fulminant. It is more common with PTU and families should be warned to stop therapy in the event of jaundice, dark urine, or pale stools.<sup>29</sup>

### ALTERNATIVES TO THIONAMIDES

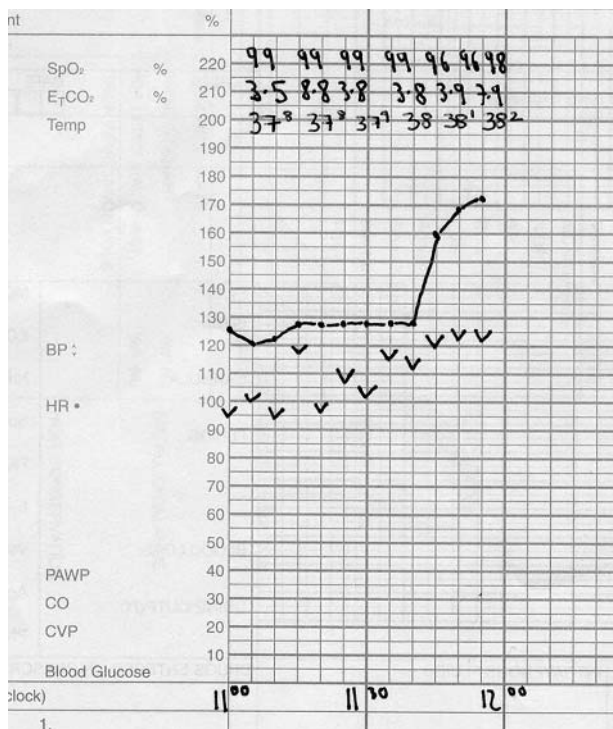
There are instances when patients cannot be given antithyroid medication because of drug side effects. Other forms of treatment are therefore required prior to definitive treatment with radio-iodine or surgery. Iodide will block thyroid hormone synthesis and release and can be administered in addition to  $\beta$  blockade. “Escape” will occur after a period of weeks and it is best reserved for severely toxic patients or for the immediate preoperative period. Iodine containing compounds such as sodium ipodate 500 mg–1 g daily have also been used to treat adults with Graves’ disease in the longer term where they have maintained remission for many months.

Adult patients awaiting definitive treatment have been treated with lithium carbonate (800 mg nocte) if  $\beta$  blockade alone is inadequate therapy. Lithium blocks thyroxine release and may therefore be a useful means of reducing the likelihood of a thyroid crisis at surgery or for rapid control following the administration of radio-iodine.<sup>30</sup> Lithium can be commenced three days before radioiodine and continued for a total of 10 days. The free T4 will start to fall by day 3. A minority of patients become nauseous by day 9 or 10 of lithium treatment, in which case the dose needs to be reduced.

### MANAGEMENT OF THYROTOXIC CRISIS<sup>31</sup>

Thyroid storm or “crisis” is rare in childhood. When it does occur it is precipitated by surgery (see fig 2), infections, withdrawal, or non-compliance with antithyroid treatment and radioiodine therapy.<sup>32</sup> Typically it presents with fever, sweating, widened pulse pressure, and hypertension although patients can also have seizures. Tachycardia occurs and can lead to high output cardiac failure. Management should centre around the following areas:

- Correcting hyperthyroidism. Antithyroid medication can be used to prevent thyroid hormone synthesis. Large doses of propylthiouracil may reduce the generation of T3 in the periphery. Iodide can be used in conjunction with thionamides to further decrease hormone synthesis. It can be given orally or via a nasogastric tube as Lugol’s iodine or potassium iodide. Intravenous iodide can be given using the radiographic contrast dyes ipodate and iopanoate.
- Restoring homeostasis. It is essential to restore fluid balance to normal and to correct electrolyte disturbances. This may need to take place on a paediatric intensive care unit where invasive monitoring and inotropic support can be utilised. Beta blockers can help to minimise the adrenergic effects. Hyperthermia should be treated aggressively. Dexamethasone is often given as there is concern that thyroid storm may lead to relative adrenal insufficiency, and because it is a deiodinase inhibitor.
- Treating decompensating factors. It is important to seek out and treat the factor that led to decompensation. Broad spectrum antibiotics should be used once the appropriate investigations have been done.
- Excluding co-morbidity such as Addison’s disease.



**Figure 2** Perioperative record of patient undergoing abdominal surgery who had unrecognised Graves' disease. A steady rise in temperature during the procedure and sudden rise in pulse rate can clearly be seen.

### PREDICTING THE DISEASE COURSE

Patients are often treated with antithyroid drugs for two to three years before therapy is stopped in the hope that the disease will remit. Younger, male patients are more resistant to drug therapy and are less likely to remit when therapy is stopped. Long term remission rates are lower than in adult patients<sup>33</sup> and appear to be falling.<sup>34</sup> Studies conducted solely in children and adolescents have shown that pubertal rather than prepubertal patients, and those with a small goitre and a relatively high BMI at presentation are more likely to remit if medical therapy is stopped after two years.<sup>11, 35</sup> Although the study by Lippe and colleagues<sup>36</sup> suggested that 25% of children with thyrotoxicosis remit after each two year period of medical therapy, many paediatric endocrinologists suspect that current remission rates are more disappointing than this. In our own clinic population just one child in 20 with Graves' disease achieved remission without relapse after two years of medical treatment. Hence the family needs to be aware of the likely disease course and of the treatment options once antithyroid drug therapy is stopped. There is a strong argument for tailoring therapy according to the clinical, biochemical, and immune characteristics at presentation.<sup>35</sup>

### DEFINITIVE TREATMENT

There is a longstanding debate about the management of patients who relapse and do not want to return to antithyroid drug treatment, who cannot tolerate antithyroid drugs, or who are poorly compliant. In our unit the adolescent who relapses after medical treatment or who is requesting definitive treatment is encouraged to meet with both the surgical and radiotherapy teams. This review will not discuss the relative merits of surgery and radioiodine (RI) in detail, but simply highlight some of the key factors that figure in more comprehensive discussions (table 1).

### Surgery

Subtotal thyroidectomy has the potential to render the patient euthyroid off therapy<sup>37</sup> although the likelihood of recurrence or of hypothyroidism has resulted in many surgeons recommending total thyroidectomy. Complications such as long term hypoparathyroidism and vocal cord palsy are uncommon when the operation is conducted by an experienced surgeon and the risk of death is likely to be no greater than 1 in 1000.<sup>38</sup> There may be particular advantages with this treatment option in those with a large goitre or with ophthalmopathy.

### Radioiodine<sup>39</sup>

RI is the simplest and cheapest option, although there is initial inconvenience because of the need to avoid close contact with others, particularly young children. If RI is administered, it is important to select the correct dosage. The aim should be to ablate the thyroid gland and render the patient hypothyroid. Prior treatment with carbimazole and particularly PTU may have a detrimental impact on RI efficacy.<sup>40</sup> Antithyroid medication (other than lithium) should be stopped 3–7 days prior to RI therapy and be recommenced, if necessary, one week afterwards. It should be restarted earlier in the patient thought to be at risk of a thyroid storm, although this may also compromise the efficacy of RI therapy. Titrating the RI dose according to gland size requires a tracer dose of <sup>131</sup>I, and many recent reports have used a predetermined amount between 300 and 550 MBq during adolescence. Following RI therapy patients should be reviewed within the first few days because of the small possibility of a thyroid "crisis", and then every six weeks so that thyroxine replacement can be initiated before the patient becomes profoundly hypothyroid. A minority of patients will require a second dose of RI and this is more likely if lower doses are used.<sup>41</sup> In a recent study of children and adolescents receiving RI in an average dose of 14.7 mCi (~540 MBq), hypothyroidism developed between 40 and 90 days in 75% of patients.<sup>42</sup> Male patients and those with more active disease (reflected by factors such as gland size, antibody titres, and thyroid hormone levels) are more likely to remain hyperthyroid,<sup>33, 40</sup> and it can be argued that this should be taken into consideration when deciding on an RI dose. Studies in adults have suggested that thyroid volume is reduced by up to 90% in most patients 12 months post-therapy.<sup>43</sup>

Long term follow up studies of cancer risk (thyroid and extra-thyroid) in patients treated with RI have largely been reassuring.<sup>44</sup> Children receiving RI have developed thyroid tumours, but most were treated with low doses of RI, and thyroid malignancy is more common in patients with Graves' disease who have not received RI compared to the normal population.<sup>39, 45</sup> If a relatively high dose of RI is used, and the thyroid gland ablated, the risk of thyroid malignancy should be very low. It is, nevertheless, important to recognise that carefully collected long term safety data are not available in large numbers of treated children given the RI doses now recommended. Many endocrinologists therefore feel that RI should be avoided where possible in the very young child because of an increased neoplastic potential of a growing and developing thyroid gland.<sup>39, 46</sup> We have recently treated a 3 year old who became neutropenic on antithyroid drugs with RI.<sup>47</sup> There were no immediate complications although we intend to monitor her closely with regular clinical examination and annual ultrasonography. We also intend to administer thyroxine replacement in a dose that maintains the TSH in the low to normal range. Long term follow up of all young patients receiving RI therapy is essential if the future management of patients with thyrotoxicosis is to be refined.

**Table 1** Treatment of thyrotoxicosis in young people

	Advantages	Disadvantages
Medical	Relatively simple Relatively cheap Non-invasive	Potentially life threatening side effects Most appropriate regimen unknown Compliance issues Low remission rates Surgical expertise required
Surgical (total thyroidectomy)	Definitive Removes an unsightly goitre	Anaesthetic risk Surgical complications Specific complications: hypoparathyroidism laryngeal nerve palsy visible scar (+/- keloid) Risk of thyroid "crisis" Thyroxine replacement required
Radioiodine	Usually definitive Cheap  Non-invasive	Initial inconvenience after RI administration Short term side effects, e.g. neck discomfort, transient hypoparathyroidism May precipitate thyroid crisis Second dose may be needed Ophthalmopathy may deteriorate Thyroxine replacement required Relative lack of long term safety data in the young

Thyroid eye disease can deteriorate significantly following RI therapy in a small number of patients, although the risk can be reduced by ensuring that patients do not become significantly hypothyroid.<sup>48-49</sup> Some endocrinologists feel that RI should be avoided in all people with severe ophthalmopathy.

**NEW THERAPEUTIC APPROACHES**

In 2002 Xiao and colleagues<sup>50</sup> reported a series of mostly young adult patients with Graves' disease managed by selective arterial embolisation of the thyroid gland. Twelve of the 22 patients treated became euthyroid off therapy during the subsequent period of review (around 27 months). Six required subtotal thyroidectomy because of a persisting large gland and a continuing need for antithyroid drugs. Two patients required a maintenance dose of chemotherapy. The authors of this study suggest that embolisation could be offered to patients who are unable to receive one of the other standard therapies, although this treatment should be regarded as experimental at this moment in time.

**SUMMARY**

Patients with thyrotoxicosis may be symptomatic for many months before the diagnosis is made. This can have significant implications for school performance and, potentially, skeletal and cardiovascular health. General paediatricians and subspecialists therefore need to be aware of the broad spectrum of symptoms in this disorder and have a low threshold for examining the thyroid gland and checking thyroid function tests. It should be possible to predict the likelihood of relapse in a young person on the basis of the clinical, biochemical, immune, and possibly genetic indices at presentation. Treatment can then be tailored to the individual. We need to know more about the advantages and disadvantages of the two main antithyroid drug regimens in the growing child and adolescent. RI therapy remains an attractive option for many young people with thyrotoxicosis. Some young people simply do not want surgery, and if the side effects of anti thyroid drugs are troublesome or if compliance is a major issue, the family should be encouraged to meet the radiotherapist. We need to monitor all young people who have received RI therapy in the long term so that we can be more certain about the risks and benefits in pubertal and prepubertal children.

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