Treatment of juvenile Graves’ disease and its ophthalmic complication: the ‘European way’

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Abstract

Three treatment modalities are available for Graves’ disease: antithyroid drugs, surgery and radioactive iodine (RAI). None has been shown to be ideal or superior to the others. There are wide differences between individual physicians and between the physicians in different countries on the optional treatment for childhood hyperthyroidism. While antithyroid drugs remain the initial treatment of choice in almost all the medical centers in Europe, with surgery being used mainly to deal with antithyroid failures, radiiodine is preferred by only a small percentage of physicians for this group of patients. In the USA, on the contrary, radiiodine treatment of thyrotoxicosis in children has strong advocates, who emphasize the safety, simplicity and economic advantages of iodine-131 ablation, which should be considered more commonly in children. Until now, the available data have shown no significant increase in thyroid neoplasia, gonadal injury or congenital abnormalities in the offspring of older children and adults receiving RAI for thyrotoxicosis. Given the considerable increase in the risk of thyroid cancer in young children exposed to external radiation, it has been hypothesized that there may be a small increase in the risk of thyroid cancer in young children treated with RAI. Until long-term data on safety are available, specifically for young children, differences between the physicians in different countries will remain.

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Introduction

The association of goiter and exophthalmos was first recorded in a Byzantine legal text from the third century, in which a ‘man with bulging eyes and a great walnut round the neck’ was described (1). The recognition of the disease known as exophthalmic goiter is attributed, however, to Parry, who, in 1786, observed the first patient. However, his record of six cases was not published until 1825, 3 years after his death (2, 3). Similar patients were reported in 1835 by Graves and in 1840 by Von Basedow (2, 4). Graves’ disease (GD) is the most common cause of juvenile thyrotoxicosis in children and adolescents (5). In Denmark, about 95% of children with thyrotoxicosis have GD (5, 6). In Iceland, the incidence of GD as a cause of thyrotoxicosis is 8.3% (7). Other causes of hyperthyroidism in this age group include thyroiditis (8), functioning thyroid adenoma or multinodular goiter (9), carcinoma (10), iodine-induced hyperthyroidism (11), thyrotropin-dependent hyperthyroidism (12) and excess ingestion of thyroid hormone (13). Overall, pediatric contribution to the incidence of thyrotoxicosis is small, the age group 0–15 years contributing only 5–6% of the total number of patients (14). Most children with GD have a family history of some type of autoimmune thyroid disease (14), and some have other autoimmune endocrine diseases, such as diabetes mellitus and Addison’s disease (15). Systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, vitiligo, idiopathic thrombocytopenic purpura and pernicious anemia also have been described in these children (15). In addition, GD is more common in children with Down’s syndrome than in normal children (15, 16).

Clinical manifestations

The main clinical features of thyrotoxicosis in children and adolescents, which are similar to those in adults, are shown in Table 1 (14, 17–19). Regarding ophthalmopathy, it appears that manifestations of thyroid eye disease in childhood thyrotoxicosis are more common but less severe, and more likely spontaneously to remit completely than in adults (20–24). Most children have stare and wide palpebral fissures, which are signs of thyrotoxicosis; 50–75% have exophthalmos (25),...
which is occasionally asymmetric (23) but is rarely the presenting complaint (26). Eye pain, diplopia, chemosis and ophthalmoplegia are rare. The stare and wide palpebral fissures improve with treatment of thyrotoxicosis. As adolescence approaches, the manifestations of thyroid eye disease (TED) begin to simulate more closely the adult findings (23). Thyrotoxicosis associated with activating mutations of the thyroid-stimulating hormone (TSH) receptor has been associated with mild stare, lid retraction and the appearance of proptosis. It is presumed that these eye findings are the direct consequence of excessive thyroid hormone action, and that they are not immunologically mediated. The findings remit when the thyrotoxicosis is controlled (27–31).

Table 1 Clinical features of thyrotoxicosis in children and adolescents (14, 17–19).

<table>
<thead>
<tr>
<th>Percentage</th>
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<tbody>
<tr>
<td>Goiter 99</td>
</tr>
<tr>
<td>Tachycardia 83</td>
</tr>
<tr>
<td>Nervousness 80</td>
</tr>
<tr>
<td>Increased pulse pressure 77</td>
</tr>
<tr>
<td>Hypertension 71</td>
</tr>
<tr>
<td>Exophthalmos 66</td>
</tr>
<tr>
<td>Tremor 61</td>
</tr>
<tr>
<td>Increased appetite 60</td>
</tr>
<tr>
<td>Weight loss 54</td>
</tr>
<tr>
<td>Thyroid bruit 53</td>
</tr>
<tr>
<td>Increased perspiration 49</td>
</tr>
<tr>
<td>Hyperactivity 44</td>
</tr>
<tr>
<td>Heart murmur 43</td>
</tr>
<tr>
<td>Palpitations 34</td>
</tr>
<tr>
<td>Heat intolerance 33</td>
</tr>
<tr>
<td>Fatigue 16</td>
</tr>
<tr>
<td>Headache 15</td>
</tr>
<tr>
<td>Diarrhea 13</td>
</tr>
</tbody>
</table>

Treatment

The ideal treatment of Graves’ thyrotoxicosis in childhood remains controversial. None of the three available treatment modalities, antithyroid drugs (ATD), surgery and radioactive iodine (RAI), has been shown to be ideal or clearly superior to the others.

The ATD, methimazole (MMI), carbimazole (CMZ) and propylthiouracil (PTU), inhibit thyroid hormone biosynthesis (32). PTU has the additional property of inhibiting the extrathyroidal conversion of T4 to T3. CMZ is not available in the USA, but it is used extensively in Europe. MMI (and CMZ) has a longer serum half-life (12–16 h) (33, 34), and therefore single daily doses are adequate in most patients. In contrast, PTU has a short half-life (4–6 h) and requires administration several times each day. However, it should be mentioned that all of the thionamide drugs are concentrated by the thyroid gland and therefore have a longer biologic half-life within the thyroid than in the blood. Moreover, some studies indicate that under certain circumstances PTU may be given once daily without losing control of hyperthyroidism (35). The recommended initial dose of MMI or CMZ is 0.5–1.0 mg/kg daily, given once or twice daily, and that of PTU is 5–10 mg/kg daily, given three times daily. Children who are older, with longer duration of symptoms, large goiters, or higher serum T4 and T3 concentrations, should be given the higher doses. Once the patient becomes euthyroid, the dose and frequency should be decreased. Occasionally, the dose needs to be increased because the initial dose was too small or the thyrotoxicosis has worsened. MMI (or CMZ) is preferable to PTU because single daily doses are effective in most patients, and fewer tablets per day are needed. The maximal clinical response to medications occurs after about 4–6 weeks of therapy. Before that time, the symptoms of hyperthyroidism may be controlled with beta-blockers such as propranolol (32–34). When clinical improvement occurs, the dose may be tapered in an attempt to maintain thyroxine levels in the normal range. Two general methods are used. One method is to reduce the dose to achieve levels of T4 and TSH in the normal range. The advantage of this method is that the dosage, and therefore the side effects, may be minimized. Another method is to block and replace. This method may give more stable hormonal levels and optimize the probability of remission (36), although some authors dispute this proposition (37). Medical therapy has a high risk of failure in children with large goiters, a history of previous relapse, high thyroxine (>20 µg/dl) and thyroglobulin (>50 µg/ml) levels, or ophthalmopathy (38). Remission rates range from 34% to 64% (Table 2) (39). Indicators of possible remission include a smaller size of the thyroid gland, a decreased T3 to T4 ratio, a
The incidence of recurrent hyperthyroidism correlates with the size of the thyroid remnant. Experience has shown that when the thyroid remnant is less than 4 g, the likelihood of recurrent thyrotoxicosis is small (47, 48). The likelihood of recurrence is even smaller after total thyroidectomy, but the morbidity rate is considerably higher. Preoperative therapy consists of Lugol’s solution 10–14 days prior to surgery and beta-adrenergic blockers for the purpose of preventing thyroid storm. Like many others, it is our practice to employ ATD preoperatively. Postoperative complications in more than 2000 children and adolescents are summarized in Table 4 (49–55).

Radioiodine therapy
The thyroid gland is one of the most sensitive organs to the carcinogenic effects of radiation during childhood. While a number of studies have indicated a dose–response effect, no clear threshold dose has been identified. Young age is a major factor for sensitivity to radiation. In the pooled analysis of seven studies, the risk of developing thyroid carcinoma after irradiation below the age of 5 years is twofold higher than in children treated with irradiation between 5 and 9 years of age, and fivefold higher than in children treated between 10 and 14 years of age (56). The high susceptibility of young children to the carcinogenic effects of radiation to the thyroid thus contrasts with the very low susceptibility of adults. This is consistent with experimental studies on animals and suggests greater radiation effects during periods of rapid cell proliferation, as observed during the development of the thyroid gland. The risk of thyroid cancer is not significant when individuals are over 15 or 20 years of age at exposure (57). RAI therapy for GD was introduced at Massachusetts General Hospital nearly 60 years ago (58, 59). It is estimated that more than 2 million patients of all ages have received RAI for GD, making this therapy one of the most widespread therapeutic uses of a systemically administered radionuclide (49). It has been proved to be an effective therapy for childhood thyrotoxicosis due to GD. It is the preferred treatment in some centers, especially in the USA, and in most others it is recommended for any patient who

Table 3 Complications of antithyroid drug treatment of children and adolescents with Graves’ thyrotoxicosis (adopted from 39).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Poor compliance (%)</th>
<th>Overall toxicity (%)</th>
<th>Major toxicity* (%)</th>
<th>Minor toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaidya et al. (18)</td>
<td>17</td>
<td>5</td>
<td>0</td>
<td>1 3 8</td>
</tr>
<tr>
<td>Barnes et al. (17)</td>
<td>16</td>
<td>14</td>
<td>6</td>
<td>8 1 NR</td>
</tr>
<tr>
<td>Shiroozu et al. (97)</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>1.5 1.5 0</td>
</tr>
<tr>
<td>Buckingham et al. (94)</td>
<td>7</td>
<td>32</td>
<td>14</td>
<td>7.5 9 6</td>
</tr>
<tr>
<td>Hamburger (73)</td>
<td>9</td>
<td>17</td>
<td>6</td>
<td>8 3 5</td>
</tr>
<tr>
<td>Lippe et al. (95)</td>
<td>2</td>
<td>NR</td>
<td>2</td>
<td>NR NR NR</td>
</tr>
<tr>
<td>Gorton et al. (96)</td>
<td>13</td>
<td>11</td>
<td>4</td>
<td>7 2 11</td>
</tr>
</tbody>
</table>

*Mainly severe polyarthritis, agranulocytosis, aplastic anemia, severe hepatitis and cholestasis. NR, non-reported.
Table 4 Postoperative complications of thyroidectomy in more than 2000 children (49–55).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>100</td>
</tr>
<tr>
<td>Transient hypocalcemia (1–7 days)</td>
<td>10</td>
</tr>
<tr>
<td>Keloid</td>
<td>2.8</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism</td>
<td>2</td>
</tr>
<tr>
<td>Vocal cord paralysis</td>
<td>2</td>
</tr>
<tr>
<td>Transient hoarseness</td>
<td>1</td>
</tr>
<tr>
<td>Temporary tracheostomy</td>
<td>0.7</td>
</tr>
<tr>
<td>Hemorrhage/haematoma</td>
<td>0.2</td>
</tr>
<tr>
<td>Death</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Younger children with smaller goiters usually are given lower doses, and those with larger goiters, higher doses. It is better to give more rather than less, because the likelihood of persistent thyrotoxicosis is lower. For example, in children treated with 50–200 μCi/g (1.85–7.4 MBq) radioiodine per gram of thyroid tissue, estimated according to the following formula (60):

\[
\text{estimated thyroid weight (g) (by palpation or U/S)} \times 50 \text{ to } 200 \mu\text{Ci}^{131}\text{I}
\]

has a serious side effect or tires of ATD therapy. The dose in children, which is given orally, usually is calculated to deliver from 50 to 200 μCi (1.85–7.4 MBq) radioiodine per gram of thyroid tissue, estimated by GD are more likely to be totally destroyed by iodine-131 than would large multinodular thyroid glands. The remaining irradiated tissue would then be at risk of subsequent neoplastic transformation. Although none of the thyroid cancer deaths occurred in individuals who where treated as children, the number of treated children was very small, and the thyroid cancer incidence in this group is unknown (71). In general, outcomes after iodine-131 treatment for juvenile hyperthyroidism have been reported so far for approximately 1000 individuals in different reports (19, 62, 63, 72–76). The duration of follow-up in those studies ranged from less than 5 years to 15 years, with only some subjects followed for more than 20 years. These studies have not revealed an increased risk of thyroid malignancy, as stated by Rivkees et al. (49). Only four cases of thyroid malignancy in children previously treated with iodine-131 have been reported so far (19, 61, 77, 78). Three of these individuals were treated with low doses of iodine-131, and one patient with a moderate one. As discussed above, low doses of iodine-131 are associated with an increased incidence of thyroid nodules and neoplasms (78). A significant relationship between the number of iodine-131 treatments and thyroid cancer was also reported by Ron et al. (71), in a study which mainly concerns adult patients with thyrotoxicosis. This finding justifies those who advocate that when RAI is used in children, it is important that a higher dose of iodine-131 is given. The goal of RAI therapy from the beginning in such cases should be to ablate the thyroid gland and achieve hypothyroidism. If no thyroid tissue remains, the risk of thyroid cancer will be very small, if present at all. To achieve this goal, Rivkees used doses of iodine-131 of 250–300 μCi/g thyroid tissue (79). Another potential adverse effect of RAI therapy is the development or worsening of ophthalmopathy, as has been observed in adults (80, 81). However, no such data have been reported so far in a pediatric group.
Thyroid eye disease in childhood

In contrast to adults, as stated above, ophthalmopathy in childhood thyrotoxicosis is more common but less severe, and more likely to remit completely. It is well known that exophthalmometry varies in different population studies and is age-related. A study conducted by Gerber et al. (82) to determine the normal standards for exophthalmometry in children 10–14 years of age, in relation to age, height, weight and sexual maturation, found that the mean measurement for boys is of the order of 17.0 and ranges from 16.3 to 18.0 mm, while for girls it is 16.8 and ranges from 16.7 to 17.6 mm. In a series of 87 children treated with iodine-131 for GD, Safa et al. (63) reported that eye signs improved in 90% of the children, did not change in 7.5% and worsened in 2% after treatment. Gruters (21) found among 43 child patients with hyperthyroidism that 37% had upper lid retraction, lid lag or proptosis, but only three of the group had soft tissue involvement and significant exophthalmos. None required specific treatment. In the study of Young (22), only one of 33 patients seen required a course of steroid therapy, and none were offered orbital decompression or radiotherapy. Uretsky et al. (23) noted that in 34 patients with childhood GD no instances of sight-threatening complications were noted, and only three patients showed evidence of ophthalmoplegia. Liu et al. (24) described two patients who had surgical removal of orbital fat for severe proptosis. Finally, in a recent Chinese study, Chan et al. (83) investigated 83 patients with GD aged 16 years or below. A comprehensive ophthalmic assessment, including ocular motility, exophthalmometry, intraocular pressure, slit lamp and fundus examinations, was performed. A total of 52 patients (62.7%) were identified with positive ocular changes. However, none had visually threatening complications or debilitating myopathy. In a recent study of eight children aged 4–14 years, none had deterioration of eye disease after RAI therapy (84). The expectation remains, however, that the expression of Graves’ ophthalmopathy in children is, in most instances, both mild and transient. Steroids and decompression will very rarely be needed in early childhood. It has to be kept in mind that prolonged prednisone administration, which should be used in some severe cases of TED, is associated with weight gain, immune suppression and growth failure in children (49).

Recent studies have shown successful therapy with the long-acting somatostatin analogs (SM-a), octreotide and lanreotide in adult patients with active TED (85–87). The rationale of this therapy is based on recent studies in which somatostatin receptors have been identified within the orbital tissues in TED, both in vitro and in vivo (88–90).

We recently had the opportunity to treat three adolescents (two girls and one boy) aged 14, 15 and 16 years, with moderately severe TED, with SM-a. The results of the first two have been presented previously (91). All had increased clinical activity scores (CAS) – 4, 5 and 6 respectively. All were on antithyroid therapy and euthyroid at the time of initiation of treatment. They received 20 mg octreotide (sandostatin-LAR) i.m., one injection every 30 days for 4 months. Their ophthalmopathy improved substantially, and CAS decreased in all patients. In view of the encouraging therapeutic results in these three pediatric patients, SM-a may prove to be a valuable treatment in childhood ophthalmopathy and a good alternative to corticosteroids. The results using SM-a in the treatment of TED seem promising, but it is still premature to suggest this therapeutic option, without any prospective, double-blind controlled study.

In summary, there are wide differences between individual physicians and between the physicians in different countries on the optional treatment for childhood hyperthyroidism. While ATD remains the initial treatment of choice in almost all the medical centers in Europe, surgery being used mainly to deal with antithyroid failures, there is increasing interest in the use of radioiodine especially in the USA. A European questionnaire study (92), which was conducted by the European Thyroid Association ( ETA) in 1993, and in which 99 individuals or groups from 22 countries participated, found that 22 out 99 physicians from nine countries would consider radioiodine treatment as the treatment of choice for children with recurrent thyrotoxicosis after surgery, or with recurrent thyrotoxicosis 2 years after ATD. However, radioiodine was preferred by only a small percentage of physicians for this group of patients in Europe. Hardly any of the respondents chose radioiodine for the patients with a toxic adenoma or a multinodular, toxic goiter (92). In view of the difficulties with medical therapy in children and adolescents, including poor compliance, high rate of relapse, drug toxicity, and continued thyroid enlargement, eminent US physicians emphasize the safety, simplicity and economic advantages of iodine-131 ablation, which should be considered more commonly in children (60). Although there are data showing no significant increase in thyroid neoplasia, gonadal injury or congenital abnormalities in the offspring of older children and adults receiving outpatient doses of radioiodine, endocrinologists and parents continue to shy away from this therapy in young children, especially in Europe. Given the considerable increase in the risk of thyroid cancer in young children exposed to external radiation, it has been hypothesized that there may be a small increase in the risk of thyroid cancer in young children treated with radioiodine. This theoretical risk is probably highest in children before the age of 5 years and progressively lower in those treated at 5–10 and 10–20 years (49). Until long-term data on safety are available, specifically for young children, differences between the physicians in...
different countries concerning the optimum therapy of childhood GD will remain.

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