Management of thyrotoxicosis in children and adolescents: 35 years’ experience in 304 patients

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Abstract

Background: Diffuse toxic goiter accounts for about 15% of all childhood thyroid diseases. There is great controversy over the management of Graves’ disease in children and adolescents. This article reports our experience in 304 children and juvenile patients with Graves’ disease.

Methods: Between 1981 and 2015, 304 patients aged 5–19 years with diffuse toxic goiter were studied, of whom 296 patients were treated with antithyroid drugs (ATD) for 18 months. Patients with persistent or relapsed hyperthyroidism who refused ablative therapy with surgery or radioiodine were managed with continuous methimazole (MMI) treatment.

Results: In 304 patients (245 females and 59 males), the mean age was 15.6 ± 2.6 years. After 18 months of ATD therapy, 37 remained in remission and of the 128 who relapsed, two, 29 and 97 patients chose surgery, continuous ATD and radioiodine therapy, respectively. Of the 136 patients who received radioiodine, 66.2% became hypothyroid. Twenty-nine patients received continuous ATD therapy for 5.7 ± 2.4 years. The mean MMI dose was 4.6 ± 12 mg daily, no serious complications occurred and all of them remained euthyroid during the follow-up. Less abnormal thyroid-stimulating hormone (TSH) values were observed in these patients, as compared to patients who were on a maintenance dose of levothyroxine after radioiodine induced hypothyroidism.

Conclusions: Original treatment with ATD and subsequent radioiodine therapy remain the mainstay of treatment for juvenile hyperthyroidism. Continuous ATD administration may be considered as another treatment modality for hyperthyroidism.

Introduction

The vast majority of cases of thyrotoxicosis in children and adolescents are caused by diffuse toxic goiters which account for 10%–15% of all childhood thyroid diseases [1]. However, hyperthyroidism is rare in childhood and adolescence and only 1%–5% of all cases of Graves’ disease occur during this period of life [2]. In addition, there have been few reports indicating an increased incidence rate of juvenile hyperthyroidism over the last decades [3, 4]. Few topics have raised greater controversy than the management of Graves’ disease in children and adolescents, and only a few institutions have been able to gather enough experience to adequately provide supported guidelines for treatment [5–7]. There is no specific cure for the illness, and potential complications are associated with one of the three therapeutic options: antithyroid drugs (ATD), radioiodine and surgery [1–7]. Medical therapy, frequently chosen as the initial treatment, is associated with side effects and a high relapse rate even after prolonged therapy [6, 8]. Although radioiodine therapy achieves high rates of remission [7–11], concerns linger about the safety of radioiodine [12] in children and adolescents and the oncogenic and genetic damage potentials after such therapy [13, 14]. Subtotal thyroidectomy is a complex surgical procedure that can result in recurrent laryngeal nerve damage and hypoparathyroidism, although it may achieve high rates of remission [15]. The optimal treatment of hyperthyroidism in children and adolescents remains a matter of debate [16–18]. Most patients are initially treated with ATD. However, the remission rate in children is lower than in adults and is achieved in <30% of children after a first course of antithyroid therapy achieved for 2 years [19–21]. Therefore, many patients who are initially treated medically eventually receive ablative treatment, most often radioiodine [22, 23]. On the other hand, many patients continue ATD, after relapse, fearing occurrence of complications of radioiodine treatment and thyroidectomy. Little is known about the long-term treatment with ATD, as only a few studies have been reported regarding the outcome.
of continuous ATD and of the relationship between ATD treatment duration and remission or relapse in children and adolescents with hyperthyroidism [19, 20, 24].

In this report, we document our experience in 304 children and juvenile patients with Graves’ disease. An analysis of the long follow-up of these patients is presented as a basis for discussion of the outcomes of antithyroid and radioiodine management of thyrotoxicosis in children and adolescents.

Materials and methods

Between 1981 and 2015, 304 patients, between the ages of 5 and 19 years, with diffuse toxic goiter were included. Of the 304 patients (265 females and 59 males), 56% were referred by pediatricians and internists and 44% came directly to the clinic (Table 1). All patients had diffuse enlargement of the thyroid gland without nodularity on palpation and diffuse uptake of radioisotope in their thyroid scan. The diagnosis of hyperthyroidism was established by clinical evaluation, and confirmed by laboratory data, including serum concentrations of thyroxine (T4) >12.5 μg/dL, triiodothyronine (T3) >210 ng/dL and thyroid-stimulating hormone (TSH) <0.1 mU/L. For each patient, a detailed history and anthropometric data were documented and a physical examination was performed. All patients and their parents, following a detailed discussion of advantages and disadvantages, were given the option of selecting one of the three principal modalities of therapy.

Antithyroid drug treatment

Methimazole (MMI) was the principal medication prescribed. However, if minor reactions to MMI occurred, it was replaced by propylthiouracil (PTU). The usual dose of MMI was 0.5 mg/kg/day in two divided doses. Larger doses up to 40 mg daily were seldom given to those with large goiters or severe hyperthyroidism. During MMI therapy, patients were examined after the first month and then at 3 monthly intervals until 18 months. All patients and their parents were instructed to stop MMI and to visit physician if the child developed a sore throat, fever or diffuse rash. Such patients would have had a complete blood count and assessment of percent neutrophils. The dosage of MMI was gradually reduced to a maintenance dose of 2.5–10 mg daily, depending on physical findings and thyroid function tests. When dose reduction was followed by recurrent hyperthyroidism, the previously successful dose was resumed for 3–6 months before attempts were made at dose reduction. After 24 ± 3 months of MMI therapy, the drug was discontinued and patients were re-examined after 1, 3, 6 and 12 months and then annually, both to rule out a relapse of thyrotoxicosis and to detect possible hypothyroidism. For those with persistent hyperthyroidism, ablation therapy with radioiodine was proposed and if the patient refused, surgical treatment was advised and if rejected, continuous MMI therapy was chosen.

Radioiodine treatment

When relapse of hyperthyroidism occurred following MMI withdrawal, radioiodine therapy was employed, unless patients and/or their family preferred thyroidecтомy or continuous antithyroid therapy. The radioiodine dosimeter was adjusted on the basis of thyroid size and 200 μCi (5.5 MBq) of 131I per gram of thyroid tissue was administered. In those patients taking MMI, the drug was discontinued 5–7 days before radioiodine therapy. Patients were seen at 1, 3, 6 and 12 months after radioiodine therapy. If symptoms of hypothyroidism occurred and/or if serum TSH increased to above 10 mU/L, levothyroxine treatment was given and the dose was adjusted to achieve serum TSH between 0.4 and 3.0 mU/L.

Assessments

At each visit, weight and height were measured and cigarette smoking status was assessed. Thorough physical examinations were performed and goiter was graded according to the World Health Organization (WHO) classification [21]. For every patient, a blood sample was obtained for measurement of thyroid and liver functions and routine laboratory tests.

Measurements

Serum alanine transaminase (ALT), aspartate transaminase (AST) and bilirubin concentrations were determined by routine methods. Serum T4 and T3 were measured by radioimmunnoassay, and serum TSH by immunoradiometric assay and T3 uptake by kits from Orion Diagnostica (Espoo, Finland). Antithyroperoxidase antibody (TPOAb) was measured using an immunoenzymometric assay (Radim, Italy).

The reference ranges of serum parameters for euthyroid subjects are: T4, 5.0–12.5 g/dL; T3, 80–210 μg/dL; TSH, 0.4–3.0 mU/L; resin T3 uptake 25%–35% and TPOAb <100 IU/mL. To convert values to SI units, for T4 and T3 multiply by 12.87 and 0.01536, respectively. Interassay and intra-assay variations for all tests were <8% and 10%, respectively.

Table 1: Age and sex of 304 children and juvenile hyperthyroid patients.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11</td>
<td>14 (100) [5.7]*</td>
<td>14 (4.6)</td>
<td>14 (4.6)</td>
</tr>
<tr>
<td>11–14</td>
<td>11 (19.3) [18.6]</td>
<td>46 (80.7) [18.8]</td>
<td>57 (18.8)</td>
</tr>
<tr>
<td>15–19</td>
<td>48 (20.6) [81.4]</td>
<td>185 (79.4) [75.5]</td>
<td>233 (76.6)</td>
</tr>
<tr>
<td>All</td>
<td>59 (19.4)</td>
<td>245 (80.6)</td>
<td>304 (100)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses denote the percentage of patients in each age group and numbers in brackets represent the percentage in each gender.

Statistical analysis

Results are expressed as numerical values (%) and mean ± standard deviation (SD). Baseline and outcome variables were compared using Student’s t-test, Mann-Whitney and χ²-tests, with p-values <0.05 being considered significant.
Ethical statement

The Ethical Committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences approved the protocol of this study. Informed written consent was obtained from all subjects and their parents and guardians.

Results

The mean age of patients (81% females) was 15.6 ± 2.6 years. Of the 304 patients who entered this study, 76.6%, 18.8% and 4.6% were 15–19, 11–14 and <11 years of age, respectively (Table 1). Five and three patients chose radioiodine and surgery, respectively, as the initial treatment, respectively. The remaining 296 patients were treated with antithyroid medications (Figure 1).

Patient characteristics

Table 2 shows the summary of the clinical characteristics of 304 patients with thyrotoxicosis. Goiter and exophthalmses were present at admission in 99% and 43% of subjects, respectively. The mean serum T4, T3, and resin T3 uptake was 19.7 ± 3.8 μg/dL, 482 ± 161 ng/dL and 40.3%, respectively, clearly within the hyperthyroid range. Only 4% received PTU and 96% were treated with MMI.

Table 2: Summary of clinical characteristics of 304 patients with juvenile hyperthyroidism.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic information</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>15.6 (2.6)*</td>
</tr>
<tr>
<td>Female, %</td>
<td>80.6%</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
</tr>
<tr>
<td>Pulse rate</td>
<td>112 (21)</td>
</tr>
<tr>
<td>Goiter</td>
<td>99%</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>43%</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
</tr>
<tr>
<td>T4, μg/dL</td>
<td>19.7 (3.8)</td>
</tr>
<tr>
<td>T3, ng/dL</td>
<td>482 (161)</td>
</tr>
<tr>
<td>Resin T3 uptake, %</td>
<td>40.3 (3.2)</td>
</tr>
</tbody>
</table>

*Mean (SD).

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Antithyroid drug treatment

Of the 296 patients treated with ATD, 284 (96%) and 12 (4%) patients were given MMI and PTU, respectively. The initial dose of MMI was $0.5 \pm 0.2 \text{ mg/kg/day}$ and that of PTU was $6.2 \pm 2.9 \text{ mg/kg/day}$.

During 2 years of treatment with ATD, 33 patients were lost to follow-up and eight developed drug reactions. There was no case with hepatic or bone marrow complication. In 33 patients, there was persistence of hyperthyroidism; seven chose surgery and 26 patients underwent radioiodine treatment. Therefore, 214 patients completed 20 ± 3 months of treatment with ATD, and were followed 6.4 ± 4.7 months after discontinuation of ATD. Ten were lost to follow-up. Of the remaining 204 patients, 76 (37%) remained in remission and of 128 (63%) who relapsed, two, 29 and 97 patients chose surgery, ATD and radioiodine therapy, respectively.

Radioiodine therapy

Altogether 136 patients received radioiodine; 20 had persistence of thyrotoxicosis and required a second dose of radioiodine.

Table 3 compares the characteristics of patients treated with ATD and radioiodine before treatment, showing no difference in age, sex distribution and thyroid function tests between the two groups. Those who became hypothyroid following radioiodine therapy were older than those who remained euthyroid ($16.1 \pm 2.2$ vs. $14.5 \pm 3.3$ years, $p < 0.001$), respectively. We did not observe important complications following radioiodine treatment, e.g. exacerbation of ophthalmopathy, thyroid storm, local cord paralysis, parathyroid dysfunction or any malignancy.

Outcomes

The final results of the three treatment modalities are shown in Table 4. Almost 54.4% of those treated with ATD had either persistence or recurrence of hyperthyroidism, and only 25.7% achieved long-term remission. Of those treated with radioiodine, 66.2 and 33.8 were hypothyroid and euthyroid, respectively. Following thyroidectomy, nine became hypothyroid and three achieved euthyroidism. Hypothyroidism and recurrent nerve palsy were not observed in these patients.

Continuous ATD treatment

Twenty-nine patients chose continuous ATD therapy and received ATD for 5.7 ± 2.4 years. Except for minor allergic symptoms, no serious complications occurred. The

Table 4: Final results of 3 years of three types of treatment in 304 patients with juvenile hyperthyroidism.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithyroid (n = 296)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>76</td>
<td>25.7</td>
</tr>
<tr>
<td>Relapse</td>
<td>128</td>
<td>43.2</td>
</tr>
<tr>
<td>Persistent hyperthyroidism</td>
<td>33</td>
<td>11.2</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>43</td>
<td>14.5</td>
</tr>
<tr>
<td>Drug reaction</td>
<td>8</td>
<td>2.7</td>
</tr>
<tr>
<td>Spontaneous hypothyroid</td>
<td>8</td>
<td>2.7</td>
</tr>
<tr>
<td>Radioiodine (n = 136)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>90</td>
<td>66.2</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>46</td>
<td>33.8</td>
</tr>
<tr>
<td>Surgery (n = 12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euthyroid</td>
<td>3</td>
<td>NA*</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>9</td>
<td>NA</td>
</tr>
</tbody>
</table>

*NA, not applicable because of inadequate number of patients.
mean MMI daily dose was 4.6 ± 1.2 (range 2.5–10 mg). All 29 patients were euthyroid after an average of 5.7 years of follow-up.

During follow-up, 29 patients on continuous ATD had 445 measurements of thyroid function tests with 1.2% showing TSH levels ≤ 0.4 mU/L and 1.9% showing TSH levels > 3.0 mU/L. Those 46 patients who were treated with radioiodine and were on levothyroxine therapy for hypothyroidism had 1928 measurements of thyroid function tests: 7.2% with TSH levels ≤ 0.4 mU/L and 19.1% with TSH levels > 3.0 mU/L (p < 0.001, as compared to those treated with continuous ATD).

At the final visit, those treated with continuous ATD had 78% goiter and the mean TPOAb level was 286 ± 212 IU/mL. In those treated with radioiodine, the goiter rate was less (55%, p < 0.05) and the TPOAb level was decreased (53 ± 79 IU/mL, p < 0.001), as compared to those on continuous ATD. There were no significant differences in serum weight, blood pressure, pulse rate, percent smoking and serum concentrations of T₄ and T₃ between the two groups.

### Final thyroid status

In the final evaluation, of 304 patients, 14% were lost to follow-up, 107 (35%) were hypothyroid, 90 after radioiodine, nine following surgery and eight spontaneously while on ATD; 154 (51%) were euthyroid, 76 after ATD therapy were discontinued, 46 following radioiodine, three after thyroidectomy and 26 with continuous ATD therapy.

### Discussion

This is the largest report to date on the management of juvenile hyperthyroidism. There is some controversy on the use of MMI as a first-line treatment of pediatric hyperthyroidism and we used, similar to other studies, methimazole as the first-line therapy in all patients [19, 20, 22–25]. Remission rates after ATD withdrawal varied in different studies ranging from 33% to 64% [6, 23, 26]. In the present study, remission was achieved in 36% of patients.

For those patients who do not achieve remission after approximately 2 years’ treatment with ATD therapy, experienced side effects or had difficulties with compliance, ablative therapy with radioiodine or surgery should be offered [6–8, 11]. Some families and patients prefer radioiodine ablation over thyroid surgery due to concerns over the cosmetic appearance of a surgical scar. Others may have concerns over the potential association of radioiodine treatment with secondary malignancy [27].

Radioiodine treatment is associated with a high cure rate and is considered to be the simplest and least expensive treatment for Graves’ disease [6, 8, 11]. In the present study, no important complication was observed in 128 children and adolescents treated with radioiodine.

Most patients develop hypothyroidism following ablative therapy [7]. In the present study, 20% of patients had to use radioiodine twice and 66% of those treated with radioiodine became hypothyroid. Most clinicians believe that hypothyroidism is preferable to hyperthyroidism, because it is easier to treat and has less serious morbidity than hyperthyroidism [6]. In practice, it is not that easy to maintain normal TSH in hypothyroid patients taking levothyroxine. In the present study, of the 46 radioiodine-induced hypothyroid patients on levothyroxine, 7.2% had suppressed TSH and 19.1% had TSH above the normal range, a finding in accordance with many reports in adult patients [28–30].

Recognizing that treatment practices have evolved over the course of this study period, the doses of ATD used in the present study are greater than those used currently; in addition, 29 patients who preferred long-term MMI treatment attained euthyroidism during 5.7 ± 2.4 years of therapy. In addition, the rates of suppressed and increased TSH levels were only 1.2% and 1.9%, respectively, which is in accordance with previous studies of adult patients with hyperthyroidism [28, 29]. Interest in long-term treatment with ATD is also being considered in pediatric patients. Many retrospective studies [19, 25, 31, 32] and one prospective study have shown that the duration of medical treatment may be a predictive marker of relapse in juvenile hyperthyroidism. Another prospective study showed that relapse risk of hyperthyroidism decreased with the duration of the first course of ATD and every additional year of ATD therapy was associated with a decrease in the relapse rate [20]. Another study evaluated the effect of the duration of ATD treatment after three consecutive courses, each lasting for 2 years and found a remission rate of 50% after discontinuation of ATD treatment [24]. We did not study the relapse rate of hyperthyroidism following discontinuation of long-term ATD treatment.

The main strength of the present study was the largest number of patients with juvenile hyperthyroidism, adoption of long-term MMI treatment and comparison of abnormal serum values in two groups of patients, one on long-term MMI therapy and the other group of radioiodine-induced hypothyroid patients on levothyroxine treatment.
The major limitation of this study was its retrospective nature and the lack of thyrotropin receptor antibody (TRAb) measurement. In addition, as this clinical experience started 35 years ago, we continued with serum T₄ and resin T₃ uptake measurements for the evaluation of thyroid function to have uniform results for all patients.

In conclusion, the search for the optimal treatment of hyperthyroidism in childhood and adolescents which should convert into and maintain long-term euthyroidism should definitely be continued. Continuous ATD treatment of juvenile hyperthyroidism may be considered in future clinical trials and may prove to be a treatment modality closer to the optimal treatment for this condition.

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References


