Triiodothyronine-predominant Graves’ disease in childhood: detection and therapeutic implications

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Abstract

Objective: To assess in a pediatric population, the clinical characteristics and management of triiodothyronine-predominant Graves’ disease (T3-P-GD), a rare condition well known in adults, but not previously described in children.

Design: We conducted a university hospital-based observational study.

Methods: All patients with GD followed for more than 1 year between 2003 and 2013 (n = 60) were included. T3-P-GD (group I) was defined as high free T3 (fT3) concentration (> 8.0 pmol/l) associated with a normal free thyroxine (fT4) concentration and undetectable TSH more than 1 month after the initiation of antithyroid drug (ATD) treatment. Group II contained patients with classical GD without T3-P-GD.

Results: Eight (13%) of the patients were found to have T3-P-GD, a median of 6.3 (3.0–10.5) months after initial diagnosis (n = 4) or 2.8 (2.0–11.9) months after the first relapse after treatment discontinuation (n = 4). At GD diagnosis, group I patients were more likely to be younger (6.8 (4.3–11.0) vs 10.7 (7.2–13.7) years) and had more severe disease than group II patients, with higher serum TSH receptor autoantibodies (TRAb) levels: 40 (31–69) vs 17 (8–25) IU/l, P < 0.04, and with slightly higher serum fT4 (92 (64–99) vs 63 (44–83) pmol/l) and fT3 (31 (30–46) vs 25 (17–31) pmol/l) concentrations. During the 3 years following T3-P-GD diagnosis, a double dose of ATD was required and median serum fT4:fT3 ratio remained lower in group I than in group II.

Conclusion: Severe hyperthyroidism, with particularly high TRAb concentrations at diagnosis, may facilitate the identification of patients requiring regular serum fT3 determinations and potentially needing higher doses of ATD dosage during follow-up.

Introduction

Graves’ disease (GD) is an autoimmune disorder resulting from stimulation of thyrotropin (TSH) receptor by autoantibodies. It is uncommon in children, who account for only 1–5% of all patients with GD (1). The disease may occur at different ages, but its frequency increases with age, peaking during adolescence (2). Antithyroid drug
(ATD) treatment is usually recommended as the first-line treatment and is generally well tolerated. The disease seems to be more severe in children than in adults, with a higher overall frequency of relapse, and remission achieved in only 30% of children, vs 40–60% of adults, following a first course of treatment lasting about 2 years (3, 4, 5, 6, 7, 8, 9, 10, 11). We have recently shown that more prolonged medical treatment may increase remission rates to 50% in children (12).

The clinical diagnosis of GD is generally straightforward and hyperthyroidism is confirmed by high serum free thyroxine (fT4) and free triiodothyronine (fT3) levels, with TSH undetectable in the serum (<0.05 mIU/l). However, some patients may have high serum fT3 levels with paradoxically normal or even low fT4 levels during the course of the disease. This condition, known as T3-predominant GD (T3-P-GD) or T3-toxicosis, is well known in adults and may be observed after diagnosis of relapse (10, 13). T3-P-GD has been shown to be associated with very high titers of serum TSH receptor autoantibodies (TRAb) and large goiters in adults, but its pathogenesis remains unclear (14). Little is known about T3-P-GD in children, but clinical experience suggests that some children with GD can present this form of the disease, making management and treatment difficult. Better characterization of this disorder is required for the improvement of patient management.

The aim of this study was to describe the clinical characteristics and management of T3-P-GD in a pediatric population.

Patients and methods

Patients

This observational cohort study included all consecutive patients aged up to 18 years with GD diagnosed and followed for more than 1 year at our department between 2003 and 2013 (n = 60). GD diagnosis was based on clinical signs of hyperthyroidism, combined with TSH concentrations below the detection threshold (TSH <0.05 mIU/l) and high serum fT4 concentration (fT4 > 21 pmol/l, normal range 8–21 pmol/l) and/or high serum fT3 concentration (fT3 > 8.0 pmol/l, normal range 4.4–8.0 pmol/l), together with the presence of significant titers of serum TRAb. Neonatal hyperthyroidism was excluded.

T3-P-GD (group I) was defined as high fT3 concentration (> 8.0 pmol/l) associated with normal fT4 concentration and undetectable TSH during follow-up, more than 1 month after the initiation of ATD treatment (15, 16). All patients without T3-P-GD were assigned to group II. Carbimazole (CMZ) was the ATD used to treat all patients.

Study protocol

Clinical data of the patients were obtained from their medical records. The following were recorded at GD diagnosis, before the initiation of treatment: age, sex, ethnicity, weight and initial weight loss if any, height, pubertal status, goiter size, presence of tachycardia (pulse rate > 100/min), hypertension, presence of ophthalmic abnormalities (exophthalmos and/or upper lid retraction), serum thyroid hormone, TRAb, and thyroid peroxidase autoantibodies (TPOAb) levels. The presence of associated autoimmune disease and a family history of hyperthyroidism (first- and second-degree relatives), if any, were recorded at diagnosis and during follow-up. We then recorded the initial dose and management of ATD treatment during follow-up, total ATD treatment duration, clinical and laboratory tests results, and outcome.

There is currently no evidence that any additional benefit in terms of higher remission rates accrues from the maintenance of high doses of ATD combined with replacement doses of levothyroxine (T4) (13). All decisions concerning the management of T4 treatment were therefore made on an individual basis.

Relapse was defined as suppressed TSH levels (<0.05 mIU/l) combined with serum fT4 concentrations > 21 pmol/l or fT3 concentrations > 8 pmol/l, after the discontinuation of ATD treatment.

The study protocol was reviewed and approved by the Institutional Review Board of Robert Debre Hospital, Paris 7 University, Assistance Publique–Hôpitaux de Paris. It was explained to all subjects and their parents, who signed a written consent form for participation.

Method

Height, weight, and BMI (weight/(height)^2 in kg/m^2) were expressed as SDS, to normalize for age and sex (17, 18). Pubertal development was assessed by determining Tanner stage. Children were classified as Caucasian or non-Caucasian (African, Asian, and Caribbean) based on the geographic origin of their parents. The size of the thyroid gland was estimated on clinical examination at diagnosis and measured on an ultrasound scan. We corrected for age-related differences in the volume of the normal thyroid gland by classifying into four categories: no goiter, small (<1.5 times normal size), moderate...
(1.5–2.5 times normal size), or large (>2.5 times normal size) goiter (8).

Serum TSH, fT₄, and fT₃ concentrations were determined by competitive immunoassay, using either direct chemiluminescence technology or fluorescence depolarization. TPOAb levels were determined by hemagglutination or RIAs (normal upper limit 10 IU/l). TRAb levels were determined with human recombinant TSH receptors (DYNOtest-Trak human; BRAHMS Diagnostica (Berlin, Germany); normal upper limit 1.5 IU/l).

Reference values for serum fT₄:fT₃ ratio were obtained for 125 healthy children without thyroid disease and with a median age of 3.2 (1.2–6.1) years.

For T₃-P-GD, the baseline period corresponded to the start of ATD treatment following either the initial diagnosis of GD or the resumption of ATD treatment following disease relapse after the discontinuation of treatment for GD. For presentation of the results, given the nonstandardized timing of follow-up visits, ATD dosages and fT₄:fT₃ ratios were grouped by time period as follows: baseline, 1–6, 7–12, 13–24, and 25–36 months from baseline; and TRAb titers as baseline, 1–12 and 13–36 months from baseline.

**Statistical analyses**

Results are expressed as numerical values (percentages) for categorical variables, and as medians (25th–75th percentiles) for continuous variables.

For comparisons of the characteristics of different groups of patients, we used χ² tests for categorical variables and Wilcoxon–Mann–Whitney U tests for continuous variables. There was no adjudication for missing data. Bonferroni’s correction for multiple comparisons was applied.

To obtain normative values for children, serum fT₄:fT₃ ratio was modeled by the Royston & Wright parametric method. Z-scores were calculated by modeling the mean and S.D. for control subjects, and the 80 and 90% age-specific reference intervals were defined on the basis of the 10th/90th percentiles and 5th/95th percentiles respectively (19). All analyses were performed with SAS 9.3 Software (SAS Institute, Inc., Cary, NC, USA).

**Results**

Eight (13%) of the patients with GD went on to develop T₃-P-GD following treatment with ATD. The cumulative incidence of T₃-P-GD increased during the first 3 years of follow-up, to 5% (95% CI 2–15%) at 6 months, 7% (95% CI 3–17%) at 12 months, 8% (95% CI 4–19%) at 24 months, and 16% (95% CI 8–30%) at 36 months (Fig. 1). This condition revealed a median of 10.5 (4.6–28.6) months after diagnosis baseline (n=8), corresponding to a median of 6.3 (3.0–10.5) months after diagnosis (n=4) or 2.8 (2.0–11.9) months after the first relapse of the disease (n=4).

The characteristics of the 60 patients at the time of GD diagnosis are given in Table 1, according to the presence (group I) or absence (group II) of T₃-P-GD during the course of the disease. Disease severity was higher in group I than in group II, as demonstrated by the higher serum TRAb levels recorded (P<0.04). The patients in group I tended to be younger and to have higher median serum fT₄ and fT₃ levels and lower median serum fT₄:fT₃ ratios than those in group II, although these differences were not significant. All the patients in group I had medium-sized to large goiters, whereas 21% of those in group II had only a small goiter or no goiter at all. The two groups of patients were similar in terms of sex ratio, ethnicity, personal history of autoimmunity, and familial history of hyperthyroidism. All patients were initially treated with similar doses of CMZ.

The characteristics of the eight patients (seven girls and one boy) with T₃-P-GD are given in Table 2. The time from GD diagnosis to T₃-P-GD detection ranged from 2.2 to 33.2 months and the median total duration of follow-up until the last evaluation was 4.3 (1.7–6.7) years. All patients with T₃-P-GD required an increase in CMZ dose.
at the time of detection of this condition, to a median of 0.77 (0.71–1.10) mg/kg per day. Thyroid function was well controlled for all but one patient (patient 5) at the last evaluation, a median of 3.3 (1.3–4.3) years after the onset of T3-P-GD. Despite the similar proportion of patients for whom L-T4 was added to the treatment regimen for various period of time in the two groups (30% for both groups), the CMZ dose required remained higher in group I than in group II (P < 0.01) (Fig. 2). CMZ dose in group I was about twice than that in group II, at 0.62 (0.61–0.85) vs 0.28 (0.23–0.40) mg/kg per day for M7–M12 and 0.46 (0.42–0.75) vs 0.25 (0.17–0.37) mg/kg per day for M13–M24, following the occurrence of a hyperthyroid state after the diagnosis of GD or a relapse due to treatment discontinuation, for groups I and II respectively. The dose continued to be higher in group I than that in group II in the third year after diagnosis, at 0.43 (0.35–0.59) vs 0.21 (0.13–0.41) mg/kg per day. Adverse events were minor and transitory and similar numbers of such events occurred in the two groups (n = 1 (relative neutropenia) vs n = 3 (n = 2 relative neutropenia and n = 1 cutaneous rash) for groups I and II respectively).

The patients of group II had serum fT4:fT3 ratios similar to those of the control group. However, median serum fT4:fT3 ratios were slightly lower at diagnosis and remained lower in group I than in group II patients, throughout the course of the disease (P < 0.01; Fig. 3).

Median serum TRAb levels were not determined at all evaluations, but were higher in the patients of group I than in those of group II during the first year following T3-P-GD diagnosis (P < 0.04), and similar afterwards (Fig. 4).

**Discussion**

The results of this study extend our knowledge about the prevalence and characteristics of T3-P-GD among children with GD. T3-P-GD affected about 10% of the patients in this cohort of children with GD. As in adults (15),
### Table 2  Characteristics and evolution of the eight patients with T\(_3\)-predominant Graves’s disease. Secondary effects are reported only for patient 8, with transitory neutropenia (952 neutrophils/mm\(^3\)) in a context of sore throat and fever. Reference values for serum fT\(_4\) concentration (8.0–21.0 pmol/l), fT\(_3\) (4.4–8.0 pmol/l), fT\(_4\):fT\(_3\) ratio (2.38–2.75), and TSH levels (0.5–5.0 IU/l).

<table>
<thead>
<tr>
<th>Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
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<td>4.1</td>
<td>4.4</td>
<td>5.5</td>
<td>8.1</td>
<td>10.5</td>
<td>11.4</td>
<td>13.2</td>
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<td>Age at T(_3)-P-GD detection (years)</td>
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<td>6.3</td>
<td>5.4</td>
<td>5.9</td>
<td>8.3</td>
<td>11.4</td>
<td>13.9</td>
<td>13.7</td>
</tr>
<tr>
<td>Timing of T(_3)-P-GD onset</td>
<td>20.3 months after relapse(^{a})</td>
<td>3.5 months after relapse(^{a})</td>
<td>12.1 months after diagnosis</td>
<td>3.7 months after diagnosis</td>
<td>2.2 months after diagnosis</td>
<td>8.8 months after diagnosis</td>
<td>2.0 months after relapse(^{a})</td>
<td>2.0 months after relapse</td>
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<tr>
<td>fT(_4) (pmol/l)</td>
<td>20.1</td>
<td>15.9</td>
<td>19.5</td>
<td>13.4</td>
<td>18.0</td>
<td>20.8</td>
<td>15.0</td>
<td>19.9</td>
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<td>fT(_3) (pmol/l)</td>
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<td>8.3</td>
<td>10.2</td>
<td>9.0</td>
<td>11.1</td>
<td>8.7</td>
<td>9.8</td>
<td>15.1</td>
</tr>
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<td>fT(_4):fT(_3) ratio</td>
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<td>1.9</td>
<td>1.9</td>
<td>1.5</td>
<td>1.6</td>
<td>2.4</td>
<td>1.5</td>
<td>1.3</td>
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<tr>
<td>Age (years)</td>
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<td>9.9</td>
<td>8.2</td>
<td>7.6</td>
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<td>20.8</td>
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<td>fT(_4) (pmol/l)</td>
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<td>17.7</td>
<td>14.9</td>
<td>18.1</td>
<td>13.8</td>
<td>17.4</td>
<td>9.7</td>
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<td>fT(_3) (pmol/l)</td>
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<td>6.9</td>
<td>6.6</td>
<td>4.5</td>
<td>9.9</td>
<td>5.1</td>
<td>6.6</td>
<td>4.9</td>
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<tr>
<td>TSH (pmol/l)</td>
<td>0.3</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.04</td>
<td>1.1</td>
<td>0.2</td>
<td>0.08</td>
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<tr>
<td>NMZ dose (mg/kg per day)</td>
<td>0.19</td>
<td>0.25</td>
<td>0.26</td>
<td>0.37</td>
<td>0.46</td>
<td>0.16</td>
<td>0.13</td>
<td>0.08</td>
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<tr>
<td>fT(_4):fT(_3) ratio</td>
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<td>2.2</td>
<td>2.7</td>
<td>3.3</td>
<td>1.8</td>
<td>2.7</td>
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<tr>
<td>Total duration of follow-up (years)</td>
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<td>5.8</td>
<td>3.9</td>
<td>2.1</td>
<td>1.1</td>
<td>4.8</td>
<td>9.4</td>
<td>1.4</td>
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<tr>
<td>Maximum dose of CMZ during follow-up after the diagnosis of T(_3)-P-GD (mg/kg per day)</td>
<td>0.78</td>
<td>0.96</td>
<td>1.23</td>
<td>1.28</td>
<td>0.61</td>
<td>0.76</td>
<td>0.71</td>
<td>0.70</td>
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<tr>
<td>Duration of CMZ treatment at doses &gt;0.4 mg/kg per day (years)</td>
<td>1.5</td>
<td>4</td>
<td>3.2</td>
<td>1.2</td>
<td>1</td>
<td>1.2</td>
<td>0.6</td>
<td>0.5</td>
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<td>No</td>
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<td>First-degree relatives</td>
<td>First-degree relatives</td>
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<td>No</td>
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<tr>
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<td>Type 1 diabetes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</table>

\(^{a}\)Patients 1, 2, and 7 showed first relapse at the age of 5.2, 6.0, and 13.7 years respectively.
T3-P-GD was observed either a few weeks after diagnosis or after a relapse following the discontinuation of ATD treatment. The timing of T3-P-GD onset was thus highly variable, with this condition occurring 2.2–33.2 months after the diagnosis of GD. As also demonstrated in adults (16, 20), T3-P-GD was more frequently observed in individuals with larger thyroid glands and higher serum TRAb levels. The slightly higher serum fT4 and fT3 concentrations and lower fT4:fT3 ratio at GD diagnosis also demonstrate higher initial disease severity in these patients. Patients with T3-P-GD had median serum fT4:fT3 ratios that were lower than those of patients with the common form of GD, throughout the course of the disease. These ratios were also significantly lower than those in the control population, for which fT4:fT3 ratio remained similar throughout childhood. The main consequence for the management of our patients with T3-P-GD was the requirement for higher doses of ATD treatment to maintain satisfactory control over TH levels in affected patients, to keep these levels in the normal range, both during the first few weeks after the onset of T3-P-GD and during the first 2–3 years of treatment, during which the dose required was about twice that for patients with the common form of GD without T3-P-GD. By contrast, in a study of adult patients (15), a doubling of the dose of ATD for 1–3 months was not always followed by a normalization of serum T3 levels, such normalization being observed in only two of the six adult patients tested. Furthermore, the normalization of serum T3 levels 2 months after subtotal thyroidectomy in all patients suggested that a radical therapeutic option should be offered rapidly to all patients with T3-P-GD (15). ATD drugs inhibit thyroid hormone synthesis by interfering with the thyroid peroxidase-mediated iodination of the tyrosine residues in thyroglobulin. CMZ and its active metabolite, methimazole, are the recommended pharmacological treatments for hyperthyroidism in children. However, propylthiouracil (PTU) may be of greater benefit in T3-P-GD, as it can also block the conversion of T4 to T3. A switch from methimazole to PTU treatment was tested in a study of adult patients with T3-P-GD, with a positive effect on serum T3 levels after 1 month in only one of the six patients studied (15). However, the use of PTU in children is no longer recommended because of the high risk of PTU-induced severe hepatitis (21, 22), therefore none of our patients received PTU as ATD treatment. The frequency of adverse effects has been reported to be dose-related and our patients with T3-P-GD required high doses for a long period of time, but only minor and transitory reactions were observed in few patients, and no severe adverse effects occurred in our

Figure 2
Carbimazole dose at diagnosis and during the course of the disease, expressed for 6-month periods for the first year and then for 12-month periods for the second and third years from baseline, for patients with T3-P-GD and classic GD. Box plots show the median values and the first and third quartiles for each group. T-bars represent the rest of the data, with outliers not shown.

Figure 3
Ratio of serum fT4 and fT3 concentrations at diagnosis and during the course of the disease, for 6-month periods during the first year and 12-month periods during the second and third years after baseline, in patients with T3-P-GD and classic GD. Box plots show the median values and the first and third quartiles for each group. T-bars represent the rest of the data, with outliers not shown.
Study population, even in those given maintenance treatment consisting of a high dose of ATD together with replacement doses of L-T4, regardless of whether they had T3-P-GD or the common type of GD. Moreover, only a limited number of patients received the combination therapy with ATD and L-T4, for various periods of time and at various doses, with no difference between the two groups. We therefore did not take into account the possibly of exogenous L-T4 being responsible for the increase in T3 levels via T4 deiodination due to an increase in type 1 and type 2 iodothyronine deiodinases (DIO1 and DIO2) enzyme activities.

The pathogenesis of T3-P-GD is still not fully understood. High titers of TRAb followed by intense TSH stimulation were thought to underlie the condition and to explain the large goiter observed in affected patients. Current knowledge is not consistent with the hypothesis that high levels of T3 production result exclusively from the enhanced conversion of T4 to T3. About 80% of the circulating T3 is generated by the peripheral deiodination of T4, but the thyroid is also an important source, as 20% of T3 is secreted by the thyroid gland (23). The molecular mechanism of the disease remains unclear, although DIO1 and DIO2, which catalyze the conversion of T4 to T3 and increase intracellular levels of T3, are known to be overexpressed in the thyroid tissues of patients with T3-P-GD (24, 25), and several genes have recently been shown to be overexpressed in these tissues (26). Given the similarities between thyroid follicular tumors, which contain high levels of DIO1 and DIO2, these data suggest that T3-P-GD may be caused by an increase in the number of differentiated fetal thyroid cells, leading to high levels of proliferation and accounting for the younger age and larger goiter in T3-P-GD patients (23).

Several studies in adults have suggested that the prevalence of T3 or T4 toxicosis and iodine intake is related, with T3 toxicosis being more prevalent in areas of iodine deficiency (27, 28, 29). Another hypothesis relates to the selenium status of the patients, which is thought to affect the occurrence of thyroid disease, although this aspect has never been explored in patients with T3-P-GD (29, 30).

This is the first study to demonstrate the occurrence of T3-P-GD in children, and one of its major strengths is that all patients diagnosed with GD in a defined population from one clinical center were included. The main limitation of our study was the observational nature of retrospective data collection. Despite the inclusion of all patients with T3-P-GD, the number of subjects investigated was small, because this complex condition is very rare, and our study thus provides no further insights into the mechanism underlying severe T3-P-GD.

**Conclusion**

These results have important clinical implications. Based on our findings, we identified two groups of children with GD: one group with the classical form of GD and another with T3-P-GD. These findings highlight the need to measure serum fT3 levels and to evaluate fT4:fT3 ratio in patients with GD, particularly those displaying persistent hyperthyroid symptoms with suppressed serum TSH levels but serum fT4 levels within the normal range. We found that patients with T3-P-GD required doses of ATD twice as high as those used in patients with classic GD, over long periods of time, although it remains unclear why the maintenance of high doses is required. The efficacy of long-term ATD therapy on the occurrence of remission during childhood in affected patients has yet to be studied, but a good approach might be to treat these patients with ATD until they become euthyroid, thereby decreasing the risk of cardiovascular, growth, and skeletal complications. Careful discussion with the parents and the child is then required to determine the best choice of treatment between long-term ATD and more definitive options, such as radioiodine treatment and thyroidectomy, as large...
prospective randomized trials with long-term quality-of-life assessment have not yet been carried out to address this issue in children.

Declaration of interest
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