CLINICAL STUDY

Peculiarities of Graves' disease in children and adolescents with Down's syndrome

Filippo De Luca, Andrea Corrias 1, Mariacarolina Salerno 2, Malgorzata Wasniewska, Roberto Gastaldi 3, Alessandra Cassio 4, Alessandro Mussa 1, Tommaso Aversa, Giorgio Radetti 5 and Teresa Arrigo

Department of Pediatrics, University of Messina, 98124 Messina, Italy, 1 Department of Pediatrics, University of Turin, 10126 Turin, Italy, 2 Department of Pediatrics, University 'Federico II', 80131 Naples, Italy, 3 Department of Pediatrics, IRCCS G. Gaslini Institute, University of Genoa, 16147 Genoa, Italy, 4 Department of Pediatrics, University of Bologna, 40138 Bologna, Italy and 5 Department of Pediatrics, Regional Hospital, 39100 Bolzano, Italy

(Correspondence should be addressed to F De Luca who is now at Dipartimento di Scienze Pediatriche Mediche e Chirurgiche, Policlinico Universitario di Messina, Via Consolare Valeria, 98123 Messina, Italy; Email: wasniewska@yahoo.it)

Abstract

Objective: To compare the presentation and clinical course of Graves' disease (GD) in two pediatric populations consisting of 28 patients with Down's syndrome (DS) and 109 controls without DS respectively.

Design and methods: The evolution over time of GD was determined in both groups according to the clinical changes and the variations in TSH, free thyroxine, and TSH receptor autoantibodies serum levels during the entire follow-up.

Results: Female prevalence (50 vs 81.6%; $\chi^2 = 12.0, P < 0.0005$) and average age at GD presentation (9.9 ± 4.4 vs 11.5 ± 3.5 years, $P < 0.05$) were significantly lower in DS group than in controls. Clinical responsiveness to methimazole therapy was significantly better in DS patients, as demonstrated by both the lower relapse rates after the first cycle withdrawal (7.1 vs 31.2%; $\chi^2 = 7.4, P < 0.005$) and the higher persistent remission rates after definitive therapy withdrawal (46.4 vs 26.7%; $\chi^2 = 4.1, P < 0.05$). Moreover, in DS group, no patients needed surgery or radioiodine ablation, whereas non-pharmacological treatment was necessary in 11% of controls ($\chi^2 = 3.8, P < 0.05$). Antecedents of Hashimoto's thyroiditis (HT) were documented in 21.4% of DS patients and in 3.7% of controls ($\chi^2 = 10.4, P < 0.005$). Association with other autoimmune diseases was detected in 32.1% of DS cases and in 12.8% of controls ($\chi^2 = 5.94, P < 0.025$).

Conclusions: GD in DS children and adolescents is characterized by several peculiarities: i) earlier presentation; ii) no gender predominance; iii) less severe clinical course; iv) higher frequency of documented HT antecedents; v) more frequent association with other autoimmune diseases.

European Journal of Endocrinology

Introduction

Individuals suffering from Down’s syndrome (DS) are known to have an increased prevalence of autoimmune disorders affecting both endocrine and non-endocrine organs (1, 2). In childhood and adolescence, Hashimoto’s thyroiditis (HT) is by far the most common autoimmune disease in DS (2–4). The prevalence of Graves’ disease (GD) has also been recently reported to be clearly higher in DS children and adolescents (6.5%) than in the general population (5).

According to that very recent report, clinical features of GD in DS patients are similar to those found in the general population, with the exception of young age at diagnosis and no female predominance (5). Other salient features of GD in DS are the low prevalence of ophthalmopathy and the very short duration of clinical remission under carbimazole treatment (5).

The aim of the present multicenter study was to describe the presentation and clinical course of GD in a large series of children and adolescents with DS followed up for at least 1 year. The data recorded in this selected series of patients were compared with the ones collected in a control population consisting of peer individuals with GD but without DS.

Materials and methods

Study populations and design

For the present study, we took into consideration all the children and adolescents with DS who were referred to six Pediatric Endocrinology Centers during the period 1995–2005 owing to a clinical picture of hyperthyroidism. Among them, only the patients who fulfilled...
all the following criteria for diagnosis of juvenile GD were selected: i) age \( \leq 20 \) years at the time of hyperthyroidism clinical presentation; ii) positive TSH receptor autoantibodies (TRABs); iii) elevated free thyroid hormones and suppressed TSH serum levels; iv) no tendency to spontaneous normalization of hyperthyroidism picture before methimazole therapy onset; v) sustained follow-up (at least 1 year).

Case records of the 28 DS patients who fulfilled the inclusion criteria (group A) were retrospectively reviewed, and the following data at the time of GD diagnosis were collected: age; presence of exophthalmos and other clinical manifestations of hyperthyroidism; thyroid function tests free thyroxine (FT4 and TSH) and TRABs; antecedents of HT.

The evolution over time of GD was determined according to the clinical changes and the variations in TSH, FT4, and TRAB serum levels during the entire follow-up duration (average 4.0 ± 2.8 years, range 1–9.6).

All the data of group A patients were compared with those collected in a control population consisting of 109 children and adolescents with GD but without DS (group B), who were referred to our endocrine units during the same period and were followed up for 4.4 ± 3.8 years (range 3.4–7.9).

At the time of their referral to our units, treatment with methimazole was started in the patients of both groups, after having excluded other causes of hyperthyroidism and confirmed diagnosis of GD. In both groups, the initial dose of methimazole was periodically adjusted on the basis of clinical and thyroid function assessments. The first cycle of methimazole treatment was continued for an average period of 2.8 ± 1.6 years (range 1.3–7.0) in group A patients and for 3.1 ± 2.4 years (range 1.0–9.0) in group B patients.

Remission rates during the first or the next pharmacological therapy cycles and after its definitive withdrawal were evaluated.

Non-pharmacological therapies (either surgery or radioiodine ablation) were taken into consideration only in the cases with no remission under prolonged methimazole treatment or too frequent relapses.

From the time of GD diagnosis onwards, all the patients of both groups were periodically investigated in order to either confirm or exclude the association with other autoimmune diseases.

**Methods**

At the time of GD diagnosis, all the patients of both groups were retrospectively investigated in order to either confirm or exclude clinical antecedents of HT. These investigations were based on the clinical records of our centers both in the patients of group A and in the ones of group B with other pre-existing autoimmune endocrine disorders. In the subjects of group B who were not being followed in our centers at the time of GD presentation, retrospective investigations were based on questionnaires addressed to family pediatricians.

In all the cases of both groups with well-documented antecedents of HT, clinical data and laboratory investigations from the time of HT diagnosis onwards were either taken from our clinical records or reconstructed with the help of family pediatricians. Retrospective diagnosis of HT was based on the association of all the following findings: i) thyroid enlargement; ii) high titers of circulating antibodies to thyroid peroxidase and/or thyroglobulin antibodies; and iii) hypechogenic thyroid pattern.

Subclinical hypothyroidism (SH) was defined by elevated TSH concentrations (> 5 mIU/l) in the presence of normal FT4 serum levels (10.3–24.4 pmol/l) (6).

Remission of hyperthyroidism was considered definitive when it persisted for at least 2 years after withdrawal of the last methimazole cycle and in the cases who underwent thyroidectomy or radioiodine ablation.

**Statistical analysis**

Results are expressed as mean ± s.d. or median and range values as appropriate. Comparisons between groups were performed by the Student’s t-test (normally distributed data) or the Mann–Whitney U test (non-parametric data) as appropriate. Frequency rates were compared by \( \chi^2 \)-test. In both study populations, times from the discontinuation of the first methimazole cycle to relapse were analyzed for up to 2 years by plotting Kaplan–Meier curves and compared by log rank test.

The level of significance was set at 0.05.

This study design was approved by the ethical committees of our hospitals.

**Results**

**Data at GD diagnosis**

Of the 28 DS patients, 14 were females with a female:male ratio (1:1) that was distinctly lower with respect to the one recorded in group B (4.5:1; female prevalence 50 vs 81.6%; \( \chi^2 = 12.0, P < 0.0005 \)).

Age at the time of GD diagnosis was significantly lower (\( P < 0.05 \)) in group A patients (mean 9.9 ± 4.4:

**Table 1** Average (± s.d.) age and free thyroxine (FT4) and median (and range) TSH receptor autoantibodies (TRAB) serum levels at the time of Graves’ disease diagnosis in the patients with Down’s syndrome (group A) and in those without Down’s syndrome (group B).

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>FT4 (pmol/l)</th>
<th>TRABs (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>9.9 ± 4.4</td>
<td>43.3 ± 17.3</td>
<td>28 (9–205)</td>
</tr>
<tr>
<td>(n=28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>11.5 ± 3.5</td>
<td>41.2 ± 15.1</td>
<td>20 (2–389)</td>
</tr>
<tr>
<td>(n=109)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P &lt; 0.05 )</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
median 10.3; range 3.2–20.0 years) than in those of group B (mean 11.5; median 11.3; range 3.4–17.9 years; Table 1).

At the time of GD diagnosis, the prevalence of exophthalmos (group A 21.5 versus group B 20.2%) and even the frequency of the other clinical manifestations were very similar in the patients of both groups.

Also average FT4 and median TRAB serum levels did not significantly differ in the patients of group A with respect to those of group B (Table 1).

The initial methimazole dosage in group A patients (0.38 ± 0.08 mg/kg per day, range 0.25–0.53) was not significantly different from the one employed in group B patients (0.46 ± 0.1 mg/kg per day, range 0.31–0.66).

**Subsequent clinical evolution**

The main data concerning clinical evolution are summarized in Table 2.

Remission rates during the first cycle of methimazole therapy were comparable in the two groups (Table 2). The average methimazole dosage needed to maintain biochemical euthyroidism during the first cycle of therapy was slightly lower (P < 0.05) in group A patients (0.12 ± 0.03 mg/kg per day) than in controls (0.15 ± 0.03 mg/kg per day).

Relapse rates after the first cycle withdrawal (Table 2) and cumulative incidence of relapse (Fig. 1) were significantly lower in group A than in the other one. Median time for relapse was 6 months (range 4–9) in group A and 7 months (range 1–19) in group B.

Persistent remission rates after definitive methimazole withdrawal were significantly higher in group A than in group B (Table 2).

Twelve patients of group B and none of group A underwent non-pharmacological therapies, such as surgery or radioiodine ablation (Table 2).

At the time of the last evaluation at the end of the overall follow-up period, the percentage of patients showing a definitive remission was not significantly different in the two groups of patients, including those who underwent either surgery or radioiodine ablation (Table 2).

During the entire treatment period, 2/28 patients of group A and 2/105 cases of group B exhibited macular rash that resolved under short antihistamine treatment. Two other patients from group B exhibited prolonged, asymptomatic transaminase increase with complete recovery after methimazole discontinuation. In those two cases, an alternative drug (propylthiouracil) was used. Overall, the prevalence of side effects under methimazole therapy was not significantly different in group A patients than group B patients (7.1 vs 3.8%; χ² = 0.57, P = NS).

**Antecedents of HT and association with other autoimmune diseases**

Antecedents of HT were documented in 6/28 patients of group A (21.4%) and in 4/109 patients of group B (3.7%) (χ² = 10.4, P < 0.005). In all these cases, retrospective diagnosis of HT was substantiated by the above-described clinical, immunological, and

![Figure 1 Cumulative relapse rates (%) estimated by Kaplan–Meier curves in patients with Down's syndrome (group A) and in those without Down's syndrome (group B). Data are plotted from the end of the methimazole cycle and are limited to a 24-month period; P = 0.014 (log rank test).](www.eje-online.org)
Table 3 Age, serum levels of TSH, free thyroxine (FT₄), thyroid peroxidase antibodies (TPOA), thyroglobulin antibodies (TGA) and TSH receptor autoantibodies (TRAB) at the time of either Hashimoto’s thyroiditis (HT) or Graves’ disease (GD) diagnosis and pharmacological therapy duration in the six Down’s syndrome patients with GD following HT.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>TSH (mIU/l)</th>
<th>FT₄ (pmol/l)</th>
<th>TPOA (IU/l)</th>
<th>TGA (IU/l)</th>
<th>TRAB (IU/l)</th>
<th>Treatment Methimazole (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>7.1</td>
<td>12.6</td>
<td>95.0</td>
<td>–</td>
<td>5.5</td>
<td>20.0</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>5.3</td>
<td>12.1</td>
<td>26.0</td>
<td>28.0</td>
<td>8.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>3</td>
<td>4.0</td>
<td>8.8</td>
<td>16.8</td>
<td>180.0</td>
<td>120.0</td>
<td>9.9</td>
<td>0.05</td>
</tr>
<tr>
<td>4</td>
<td>5.9</td>
<td>5.1</td>
<td>17.4</td>
<td>75.0</td>
<td>302.0</td>
<td>11.1</td>
<td>0.01</td>
</tr>
<tr>
<td>5</td>
<td>10.0</td>
<td>5.1</td>
<td>10.5</td>
<td>20.0</td>
<td>119.7</td>
<td>15.0</td>
<td>0.001</td>
</tr>
<tr>
<td>6</td>
<td>13.5</td>
<td>4.7</td>
<td>18.0</td>
<td>23.0</td>
<td>109.0</td>
<td>20.0</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Normal values < 20 IU/l.
**Normal values < 20 IU/l.
***Normal values < 1.8 IU/l.

Discussion

As far as we know, this is the first study aiming to compare the presentation and clinical course of GD in DS children and adolescents and in peer patients without DS. Moreover, to the best of our knowledge, this is the largest series of DS patients with GD that has been hitherto reported in the literature.

Hyperthyroidism was not caused by an overtreated pre-existing hypothyroidism in any of our patients. Furthermore, due to the very selective inclusion criteria that we have adopted, the remaining causes of hyperthyroidism were previously excluded. In accordance with the recent report by Goday-Amo et al. (5) also in the present study, the diagnosis of GD was suggested by clinical picture and confirmed biochemically, rather than based on the specific thyroid function screening programs for DS. GD presentation was not substantially different in the patients with DS and in those without DS, as suggested by the similar frequencies of both ophthalmopathy and other clinical manifestations in the two groups of patients. Moreover, even FT₄ and TRAB serum levels at GD diagnosis were very similar in DS cases and in the other ones. Nevertheless, GD presentation in our DS patients occurred at a younger age and did not demonstrate any gender predominance, against that observed in the control group. These two peculiarities of GD in DS had already been described by Goday-Amo et al., although that DS population was not compared with a control study population (5).

In our study, the most striking differences between DS patients and controls concern GD clinical course, which was significantly less severe in DS, as showed by both the lower relapse rates during the first methimazole therapy cycle and the higher persistent remission rates after definitive methimazole withdrawal. Moreover, the methimazole dosages requested to maintain biochemical euthyroidism during the first methimazole cycle were slightly lower in DS patients than in controls. Consequently, the use of alternative non-pharmacological therapies was not necessary in our DS patients. With regard to this point, our results disagree with those by Goday-Amo et al. In that study population, in fact, no patients achieved remission longer than 6 months under pharmacological treatment and almost all of them underwent radiiodine therapy (5).

Another relevant peculiarity of our DS study population concerns the high prevalence of documented HT antecedents, a finding that would not be surprising considering that HT is the most common autoimmune disease in DS (2) and that HT is more frequently screened for in patients with DS than in subjects without DS. Nevertheless, the development of GD from HT has been only sporadically described until now in DS patients (7) and has been infrequently reported even in individuals without DS (8, 9). An immunological mechanism that may be hypothesized to account for a change from HT to GD is alteration in the biological activity of TRABs from predominantly thyroid-blocking antibodies during the hypothyroid phase to thyroid-stimulating antibodies when GD manifests itself (10). However, blocking antibodies as a cause of HT are very rare and therefore this remains a controversial point, with no good evidence that the change from one disorder to the other one really reflects changes in the biological activity of TRABs. Moreover, unfortunately in none of our patients had we measured serum TRABs prior to GD presentation.
Finally, another feature of GD in our DS study population is the more frequent association with other autoimmune diseases, which confirms that DS patients are at higher risk for developing autoimmune diseases than those of the general population (1, 6, 11–13).

To summarise, the aim of the present study was to compare the presentation and clinical course of GD in two different study populations consisting of either patients with DS or patients without DS. On the basis of our results, we can infer that GD in DS children and adolescents is characterized by several peculiarities: i) earlier presentation; ii) no gender predominance; iii) less severe clinical course; iv) higher frequency of documented HT antecedents; v) more frequent association with other autoimmune diseases.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References
10 Ludgate M & Emerson CH. Metamorphic thyroid autoimmunity. Thyroid 2008 18 1035–1037.

Received 19 November 2009
Accepted 1 December 2009