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Research paper

Peculiarities of presentation and evolution over time of Hashimoto's thyroiditis in children and adolescents with Down's syndrome

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ABSTRACT

BACKGROUND: Studies concerning presentation and evolution over time of Hashimoto's thyroiditis (HT) in children with Down's syndrome (DS) are few, are based on limited study populations and do not include control HT groups without DS. The aim of this multicenter study was to shed further light on the relationships between DS and HT in childhood. DESIGN: In this retrospective study we compared thyroid function patterns at HT presentation in 2 groups of children with (group A) or without DS (group B), including 146 and 553 cases, respectively. All group A patients were subsequently re-examined after a median interval of 5.1 years in order to prospectively re-evaluate the evolution over time of thyroid function patterns in DS. RESULTS: In group A, female predominance, age at HT diagnosis and rates of familiarity for thyroid diseases were significantly lower than in group B, whilst the association with non-thyroidal autoimmune diseases was more frequent. The hormonal patterns that were most frequently found in the 2 groups were, respectively, subclinical hypothyroidism (in group A) and euthyroidism (in group B). Thyroid dysfunctions were, overall, more frequent in group A (86.3 vs 45.7%, $p<0.001$). At re-evaluation, DS children exhibited further deterioration of thyroid function with some cases switching towards Graves' disease (GD). CONCLUSIONS HT in DS children: a) presents earlier, is not associated with female predominance and is more frequently associated with other autoimmune diseases; b) presents only very infrequently with a euthyroid hormonal profile; c) in a limited rate of cases switches with time to GD.

Key words: Chromosomopathies, Euthyroidism, Graves' disease, Subclinical hypothyroidism, Thyroid dysfunctions

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INTRODUCTION

Down's syndrome (DS) is one of the most common chromosomal disorders and the most common cause of mental retardation. DS is frequently associated with other medical problems,[1] which may have negative repercussions on the quality of life and longevity of these patients. Among these clinical problems, thyroid pathology is a primary area of concern,[2] this being testified to the American Academy of Pediatrics recommendation that thyroid function should be evaluated at 6 and 12 months and annually thereafter in all children with DS.[3] In fact, although thyroid dysgenesis is not more frequent in DS than in the general neonatal population,[4] DS infants are more exposed to the risk of early onset hypothyroidism,[5,6] probably due to a congenital alteration in the thyroid gland itself, which would be in direct relation to the trisomy condition of chromosome 21.[7] Moreover, it must be borne in mind that DS children are also exposed to an increased risk of autoimmune disorders affecting both endocrine and non-endocrine organs.[8,9]

Hashimoto's thyroiditis (HT) is by far the most common autoimmune disorder in DS children,[2,10] although Graves' disease (GD) prevalence has also been reported to be significantly higher in DS than in the general pediatric population.[10] The available literature reports concerning presentation and evolution over time of HT in DS children are scant, based on limited study populations ranging from 2 to 85 cases and do not include control groups,[2,10,12,13] with only one exception.[14] In that report, however, the control group included only healthy non-DS subjects, but no patients with HT.[14]

In the present multicenter study, we have retrospectively investigated the clinical and biochemical patterns of HT presentation in a series of 146 children with DS and compared our results with those recorded in a control population of 553 children and adolescents with HT but without DS.[15] Furthermore, we have evaluated the evolution over time of thyroid tests in DS series in order to identify possible factors affecting the biochemical course of DS-related HT. The aim of this study was to ascertain whether presentation and long-term evolution of HT in DS may be characterized by an atypical pattern.

PATIENTS AND METHODS

Study populations

Our selected study population consisted, overall, of 699 children and adolescents with HT, diagnosed and followed up in 6 pediatric endocrinology centers of Northern and Southern Italy, who were admitted to this study according to the following recruitment criteria: 1) age ≤18 years; 2) positive thyroglobulin autoantibodies (TGAbs) and/or thyroid peroxidase autoantibodies (TPOAbs); 3) thyroid enlargement, as evaluated by ultrasonography (US); 4) hypoechogenic thyroid pattern at US consistent with autoimmune thyroid disease; 5) preliminary exclusion of Turner syndrome, GD and other causes of thyromegaly or thyroid dysfunction.

The main clinical reasons for the recruited patients having been initially referred to the pediatric endocrinology centers of our Hospitals during the period 2000-2010 were: 1) clinical evidence of thyroid enlargement and/or other signs of gland dysfunction; 2) association with autoimmune extra-thyroidal diseases; 3) family history of thyroid diseases in first-degree relatives. In none of the recruited patients was a diagnosis of HT established in the context of a screening program.

The 699 selected patients were divided into 2 groups according to whether they were also affected by DS (group A) or not (group B). Group A included 146 patients (66 girls) aged between 1 and 18 years, while group B included 553 patients (449 girls) aged between 2.5 and 18 years, a control population which has previously been reported elsewhere.[15]

Study design

In all the patients of both groups, gender, family history of thyroid diseases, concomitant autoimmune extra-thyroidal diseases and data at HT diagnosis (age, pubertal stages, TGAb and TPOAb serum levels and thyroid function patterns) were retrospectively reconstructed from clinical records.

Following the initial HT diagnosis, all the patients of group A were re-examined in order to prospectively re-evaluate FT4 and TSH serum levels and thyroid function patterns after a median time interval of 5.1 years (range 3.5-6.4). The patients who were under L-T4 treatment at the time of re-evaluation were

analyzed 6 weeks after therapy withdrawal. The patients who were under methimazole therapy at the time of re-assessment were included in the subgroup of children who switched over time from HT to GD, provided that TSH receptor autoantibodies (TRABs) were positive.

Methods

Serum concentrations of TSH and FT4 were measured by radioimmunoassay methods. TPOAbs and TGAbs were measured by chemiluminescent immunometric assays. In accordance with the abovementioned methods, values above 20 or 30 IU/ml, respectively, were defined as positive. TRAB serum levels were measured by a second generation radioreceptor assay using the human recombinant TSH receptor only in the patients of both groups who presented with a hyperthyroid hormonal profile and in the sub-cohort of group A patients who, at the time of re-evaluation, were under methimazole therapy. In accordance with the abovementioned method, values above 1.5 IU/ml were defined as positive.

Thyroid US examinations for the assessment of echogenicity were at all times performed by experienced ultrasonographers with high-resolution US machines.

With regard to thyroid function at HT diagnosis, patients of both groups were evaluated according to FT4 (normal range 10.3-24.4 pmol/l) and TSH (normal range 0.3-4.5 mU/l) serum levels and classified into the following groups: 1) euthyroid (both FT4 and TSH levels within normal limits), 2) overt hypothyroid (low FT4 together with elevated TSH), 3) subclinical hypothyroidism SH (normal FT4, as opposed to elevated TSH), 4) hyperthyroid (suppressed TSH, as opposed to either normal or elevated FT4).

The thyroid status of group A patients at the time of re-evaluation was defined according to the same classification that had been initially used. All the 12 patients who were classified as hyperthyroid at re-assessment were considered to be affected by GD on the basis of their history, methimazole treatment and TRAB positivity.

Statistical analysis

Results are expressed as means ± SD and range values. For comparisons between groups, we used the Student's t test for both paired and unpaired data (normally distributed data) and either the Mann-Whitney U test or the Wilcoxon test (non-normally distributed data), as appropriate. Frequency rates were compared by the chi-square ($\chi 2$) test. Correlations between quantitative variables were assessed using Pearson's correlation analysis. The level of significance was set at 0.05. The statistical analysis was performed using SPSS 16.0 version (SPSS, Inc., Chicago, IL, USA). The study design was approved by the ethical committees of the Hospitals participating in our study. Appropriate consents were preliminarily obtained also from the Study Group for Thyroid Diseases of the Italian Society for Pediatric Endocrinology and Diabetology.

RESULTS

The main anamnestic and clinical data of both groups of patients at the time of HT diagnosis are summarized in Table 1 and statistically compared.

Table 1. Female predominance, average initial age (±SD), number and rates of children with either prepubertal onset of Hashimoto's thyroiditis (HT), or family history of thyroid diseases or associated extra-thyroidal autoimmune diseases in the 2 groups of HT children, with (group A) or without Down's syndrome (group B)

	Female predominance n (%)	Age yrs	Age <10 yrs n (%)	Prepubertal onset n (%)	Family history of thyroid disease n (%)	Associated autoimmune diseases n (%)
Group A (146 patients)	66 (45.2)	6.5 ± 4.8	107 (73.3)	91 (62.3)	10 (6.9)	85 (58.2)
Group B (553 patients)	449 (81.2)	11.1 ± 3.0	180 (32.5)	190 (34.4)	174 (31.5)	104 (18.8)
p-value	<0.001*	<0.001§	<0.001*	<0.001*	<0.001*	<0.001*

*Chi-square test; §Unpaired Student's t test.

Female predominance and age of diagnosis were significantly lower in group A, whilst the rate of children below 10 years of age at diagnosis was significantly lower in group B (Table 1). Whereas the prevalence of patients with a family history of thyroid diseases was significantly higher in group B, the rates of patients with either prepubertal onset of HT or associated extra-thyroidal autoimmune diseases were significantly higher in group A (Table 1). In particular, alopecia was relatively frequent in group A patients, whereas it was very uncommon in those of group B (11.4 vs 0.9%; p<0.001). In both groups, other frequent autoimmune diseases included diabetes mellitus and celiac disease, with comparable prevalence, which was, respectively, 3.4 vs 6.9 % (p = 0.123) and 11.0 vs 7.2% (p = 0.140).

Thyroid function test results showed that the most frequent hormonal patterns at HT presentation were, respectively, SH in group A and euthyroidism in group B (Table 2). Overall, the prevalence rates of thyroid dysfunctions were distinctly higher in group A than in group B: 86.3% vs 45.7% (p <0.001).

At HT diagnosis, both TPOAb and TGAb serum levels were, on average, significantly lower in group A patients than in those belonging to group B (Table 2).

When the thyroid function patterns found in group A patients at HT presentation were compared with those detected in the same patients approximately 5 years later, a further significant decrease in the prevalence rate of euthyroidism was recorded (Table 3). As an obvious consequence of this decrease, almost the totality of group A patients at the time of re-evaluation exhibited a hormonal pattern compatible with thyroid dysfunction: either SH or overt hypothyroidism or hyperthyroidism (Table 3).

In particular, all the 12 patients who, at re-evaluation, were included in the hyperthyroid subgroup had developed from HT presentation onwards a classical picture of GD and needed methimazole therapy. The switch from HT to GD in these 12 patients was confirmed by the finding of positive TRABs at the time of re-assessment. In 3 out of these 12 patients who switched over time from HT to GD, TRAB serum levels had been measured previously at the time of

Table 2. Prevalence rates of the different thyroid hormonal patterns and median (range) serum levels of thyroid peroxidase (TPOAbs) and thyroglobulin autoantibodies (TGAbs) at diagnosis of Hashimoto's thyroiditis (HT) in the 2 groups of HT children, with (group A) or without Down's syndrome (group B)

	Euthyroidism n (%)	Subclinical Hypothyroidism n (%)	Overt Hypothyroidism n (%)	Hyperthyroidism n (%)	TPOAbs IU/ml	TGAbs IU/ml
Group A (146 patients)	20 (13.7)	92 (63.0)	28 (19.2)	6 (4.1)	83 (0.2–4045)	100 (0–3673)
Group B (553 patients)	300 (54.3)	95 (17.2)	122 (22.1)	36 (6.5)	554 (22–4600)	237 (0–3536)
p-value	<0.001*	<0.001*	0.450*	0.278*	<0.001§	<0.001§

*Chi-square test; §Mann Whitney U test.

Table 3. Prevalence rates of the different thyroid hormonal patterns in the group of 146 patients with Down syndrome, both at the time of Hashimoto's thyroiditis diagnosis and at re-evaluation, after a median time interval of 5.1 years (range 3.5 – 6.4)

	Euthyroidism n (%)	Subclinical Hypothyroidism n (%)	Overt Hypothyroidism n (%)	Hyperthyroidism n (%)	Overall dysfunctions n (%)
At diagnosis	20 (13.7)	92 (63.0)	28 (19.2)	6 (4.1)	126 (86.3)
At re-evaluation	5 (3.4)	92 (63.0)	37 (25.4)	12 (8.2)	141 (96.6)
p-value*	0.002	1.000	0.205	0.144	0.002

*Chi-square test

HT diagnosis due to the initial finding of a transient hyperthyroid biochemical picture, but at that time they had been negative. Another 6 GD cases had initially exhibited a biochemical picture of SH, whilst 2 other cases had been found to be overtly hypothyroid and the remaining 1 case was initially euthyroid.

At the time of re-evaluation, 87 DS patients (59.5%) were under L-T4 therapy aiming to treat either overt hypothyroidism (in 28 cases) or SH (in 59 cases), but treatment was withdrawn 6 weeks before blood sampling.

DISCUSSION

To the best of our knowledge, this is the first literature study aiming to compare the presentation patterns of HT in DS children with those observed in a population of HT children and adolescents without DS. According to our results, HT in DS presents with a significantly more severe biochemical picture, as substantiated by the lower prevalence rate of euthyroidism and the higher prevalence rate of SH. These findings are probably associated with a congenital alteration in the regulation of thyroid gland itself, which seems to be typical of DS individuals and has recently been implicated to explain the increased risk of SH in children with this syndrome.[7,16] By contrast, the more severe biochemical picture found in our DS series cannot be explained on the basis of a more aggressive autoimmune pattern of HT in these patients, in consideration of the significantly lower TPOAb and TGAb serum levels detected in DS population.

Our results confirm the non-casual association between DS and various autoimmune extra-thyroidal diseases in addition to HT, which has previously also been reported by other authors.[10,17,18] In the present DS population, the associated autoimmune disease that was found to be relatively most frequent was alopecia, a skin manifestation that was recently reported in 6-10% of DS patients vs 1.7% in the general population.[19]

HT presentation in our DS children occurred at a younger age and did not show any gender predominance, as against what was recorded in the control group. These two peculiarities have also already been described in DS children with GD,[11,20] a finding which underlines the atypical phenotype of autoimmune thyroid diseases in DS. The difference in sex ratio between HT children with DS and those without DS has also previously been reported by other authors, but the reasons for it are unclear.[2,10,13] By contrast, the younger age at HT diagnosis might be explained, at least partially, by the fact that many pediatricians are aware that DS patients are more prone to the risk of developing concomitant thyroid diseases and, therefore, the finding of a thyroid enlargement in a DS child is probably treated with more vigilance. Indeed, Shalitin and Phillip described two DS infants with HT diagnosed at 5 and 8 months of life, which are not typical ages for suspecting HT.[12]

Another interesting finding of the present study is that the frequency of family antecedents of HT in the DS series was very low, which reinforces the view that DS patients are per se more exposed to the risk of autoimmune thyroid disease irrespectively of family predisposition, as also suggested by Rubello et al.[14]

At the time of biochemical re-evaluation, the DS children exhibited a further deterioration in thyroid function tests, as shown by the negligible prevalence rate of euthyroidism found at re-assessment. SH was the most frequent hormonal pattern detected in our DS population, both at presentation and at re-evaluation. It has recently been reported that SH is a very common thyroid disorder in DS children,[17,18] which frequently (70% of cases) spontaneously resolves within a few years.[16] By contrast, in the present study the prevalence rate of SH remained unchanged during the time interval between HT diagnosis and biochemical re-evaluation, which is not surprising considering the different composition of our cohort to that of Claret at al,[16] i.e. only subjects with HT in this study and only subjects with no underlying diseases in the other report.[16] On the other hand, it is well known that SH may have a different outcome in idiopathic cases[21-25] and in those with an underlying HT.[26-29]

It has clearly been shown that in children without HT or other thyroid diseases, DS may be associated with higher TSH levels, probably due to an inherent TSH setting disorder which seems to be peculiar to DS.[30] On the basis of such findings, these authors concluded that diagnosis of SH might be overestimated in DS and that L-T4 therapy in these patients should be contemplated only when TSH values are

above their own 95th percentile.[30] However, it must also be considered that the study of Meyerovitch et al[30] included only individuals with idiopathic and mild thyroid dysfunctions.

Another finding of the present study which needs to be underlined is that in 8.2% of cases HT switched to GD from presentation to re-evaluation. This is not surprising considering that an evolution from HT to GD has occasionally been observed in the natural history of children with HT.[31] Moreover, such a conversion has just recently been demonstrated to occur even more often in patients with DS than in those without DS.[32]

To sum up, many studies on the relationships between DS and thyroid function include heterogeneous groups of patients with both autoimmune and idiopathic thyroid disorders, whereas in this study only selected groups with autoimmunity were recruited, thus making interpretation of results more transparent. A limitation of our study is that the control group was not simultaneously re-examined, as was the case of the DS group and, therefore, there are no data for the control group at re-evaluation.

We conclude that HT in DS children: a) presents earlier, is not associated with a female predominance and is frequently associated with other autoimmune diseases; b) presents only very infrequently with a biochemical euthyroid picture; c) in a limited number of cases switches over time to GD.

AUTHOR DISCLOSURE STATEMENT

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