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The association with Down's syndrome can affect phenotypic expression of Hashimoto's thyroiditis in childhood

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Summary. *Background:* It is not well known whether the association with Down's syndrome (DS) may be able to affect the phenotypic expression of Hashimoto's thyroiditis (HT). *Objectives:* To review the most recent literature data about the specific peculiarities of HT in DS children. *Design:* The main epidemiological features of DS-related HT were compared with those generally reported in HT children without DS. The prevalence rates of the different thyroid function patterns detected at the time of HT diagnosis and five years later were summarized in Tables 1 and 2. *Conclusions:* 1) the association with DS can condition a peculiar phenotypic expression of HT in pediatric age, as confirmed by the analysis of both epidemiological and biochemical features; 2) in DS children thyroid function status may be severely impaired both at HT presentation and some years later. (www.actabiomedica.it)

Key words: autoimmune thyroid diseases, chromosomopathies, epidemiological features, thyroid function presenting pattern, thyroid function prognosis

List of abbreviations

AITD: autoimmune thyroid disease; DS: Down's syndrome; GD: Graves' disease; HT: Hashimoto's thyroiditis; SH: subclinical hypothyroidism.

Background

Hashimoto's thyroiditis (HT) is by far the most common inflammatory thyroid disease in childhood (1), the most frequent pediatric thyroid disorder and also the commonest cause of goiter in children from iodine replete-areas (2).

Its prevalence is known to be distinctly preponderant in girls (3), to achieve its peak during adolescence (4) and to be significantly conditioned by alterations of environmental iodine status (5).

Other epidemiological features of HT are the relatively frequent association with other autoimmune extra-thyroidal diseases (6) and the significant clustering within the same families, with a 31.6% of children exhibiting a history of autoimmune thyroid diseases (AITDs) in first-degree relatives (6).

Another relevant risk factor for HT in pediatric age is the association with Down's syndrome (DS), a chromosomopathy that is known to be associated with an increased prevalence of AITDs (7-11).

Although there are in the pediatric literature many reports on the relationships between DS and HT (10), only few of them have specifically addressed an intriguing issue, i.e. whether the association with DS may be able to affect per se phenotypic expression of HT in children and adolescents (11-15).

Aim of the present commentary is to review the most recent literature data concerning the specific peculiarities of HT phenotypic expression in children and adolescents with DS.

Epidemiological peculiarities of DS-related HT

The prevalence rate of HT in DS children has been reported to fluctuate between 13 and 34% (16,17), which is distinctly higher than that reported in the pediatric general population, i.e. around 1.2% (18,19). Such an increased prevalence of HT in DS children might be ascribed to a dysregulation of immune system (20), with secondary impairment of inhibitory activity. These alterations may favor the development of both HT and other autoimmune diseases (21).

HT presentation in DS children occurs at a younger age with respect to that recorded in children without DS (13). Furthermore, in DS children HT does not show any gender predominance (13), as against as generally observed in the pediatric general population (3). These two epidemiological features of DS-related HT had already been described even in DS children with another AITD, i.e. Graves' disease (GD) (7, 22). Such findings as a whole reinforce the view that AITDs in DS may be characterized by an atypical phenotypic expression.

Another epidemiological peculiarity of DS-related HT is that family antecedents of AITDs are not very frequent (13), which confirms that DS children are per se more incline to the risk of developing HT, irrespective of age, gender and family predisposition, as already suggested by Rubello et al (23).

The younger age at HT diagnosis might be explained, at least partially, by the fact that many pediatricians are aware that DS children are more exposed to the risk of an association with AITDs. Consequently, the finding of a thyromegaly in a DS child is probably evaluated by pediatricians with more vigilance, which can per se justify the earlier diagnosis (13). By contrast, the lack of a female preponderance in DS patients with HT is more difficult to be explained (16,17,24).

Finally, another epidemiological feature of HT in DS children is the very frequent link with other extra-thyroidal autoimmune disorders (17,25,26), that may be detected in around 6% of these patients (13). Among these illnesses, the one that is most typically associated with DS is alopecia, which may be observed in around 10% of DS patients vs 1.7% in the general population (27).

Peculiarities of biochemical presentation in DS-related HT

According to the results of a recent report on the presentation patterns of HT in DS children, this disease in DS patients presents with a more severe biochemical picture than in those without DS (13). This inference was substantiated by both the lower prevalence rate of euthyroidism and the higher prevalence rates of subclinical hypothyroidism (SH) and overall thyroid dysfunctions, which were recorded, at the time of HT diagnosis, in DS children (Table 1).

SH is a very common thyroid dysfunction manifestation in DS children (25,26), that may frequently resolve within few years (28). The high prevalence of SH in DS patients could be probably interpreted in the light of a congenital alteration in the regulation of thyroid gland (13), that seems to be peculiar of DS (28,29). On overall, the more severe presentation picture of HT in DS children cannot be interpreted on the basis of a more aggressive autoimmune pattern. In fact, thyroid autoantibody serum levels are not generally very elevated in the children with DS-related HT (13,14). Therefore, it can be argued that other factors, apart from autoimmunity, might be involved in the pathogenesis of the thyroid function alterations which are found at HT presentation in DS children (13,14).

Peculiar evolution over time of DS-related HT

Natural history of DS-related HT has been just recently investigated by other authors through a prospective 5-year study aiming at ascertaining whether the long-term thyroid status prognosis of HT may differ in children with or without DS (13).

According to the results of that study it seems that the association with DS might be able to condition a peculiar biochemical course of HT, by increasing the risk of a thyroid function deterioration over time (Table 2). In fact, when the thyroid function patterns detected in DS children at the end of follow-up period were compared with those found in the same children five years earlier, a further decrease in the prevalence of biochemical euthyroidism was recorded (Table 2).

Table 1. Prevalence rates (%) of the different thyroid function patterns detected at diagnosis of Hashimoto's thyroiditis (HT) in two cohorts of age-matched children and adolescents with (Group A) or without (Group B) Down's syndrome (from reference 13, partially modified)

	Euthyroidism	Subclinical hypothyroidism	Overt hypothyroidism	Hyperthyroidism dysfunctions	Overall
Group A (Nos. 146)	13.7	63.0	19.2	4.1	86.3
Group B (Nos. 553)	54.3	17.2	22.1	6.4	45.7
p-value	<0.001	<0.001	n.s.*	n.s.*	<0.001

* not significant

Table 2. Prevalence rates (%) of the different thyroid function patterns detected, in a cohort of 146 children and adolescents with Down's syndrome, at diagnosis of Hashimoto's thyroiditis and 5 years later (from reference 13, partially modified).

	Euthyroidism	Subclinical hypothyroidism	Overt hypothyroidism	Hyperthyroidism	Overall dysfunctions
At diagnosis	13.7	63.0	19.2	4.1	86.3
5 years later	3.4	63.0	25.4	8.2	96.6
p-value	0.002	n.s.*	n.s.*	n.s.*	0.002

* not significant

As an obvious consequence of such finding, the almost totality of DS children exhibited, at the end of follow-up, a hormonal pattern compatible with thyroid dysfunctions: either SH, or overt hypothyroidism or hyperthyroidism (Table 2).

An interesting finding which emerges from the analysis of the most recent reports on the natural history of DS-related HT is that in 8.2% of cases, HT may switch over time to GD (13). This finding might appear surprising considering that a metamorphosis from HT to GD has been reported to occur in only 3.7% of children without DS (31). However, it has been just recently demonstrated that the association with DS might play some favorable role in conditioning this shifting from HT to GD (12,15). Therefore, it may be argued that DS children might be particularly prone to develop over time a phenotypic picture of AITD, although the pathophysiological bases of this inclination have not been clarified to now (15,32).

To conclude: 1) the association with DS can condition a peculiar phenotypic expression of HT in pediatric age, as confirmed by the analysis of both epidemiological and biochemical features; 2) in DS children thyroid function status may be severely impaired both at HT presentation and some years later.

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