Acta Biomed 2016; Vol. 87, N. 2: 136-140

Phenotypic expression of Hashimoto's thyroiditis is absolutely atypical in girls with Turner syndrome

Giuseppina Salzano, Mariarosa Calafiore, Cristina Mignosa, Stefano Passanisi, Jessica Trombatore, Giuseppina Zirilli

Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy

Summary. *Background:* It is unknown whether phenotypic expression of Hashimoto's thyroiditis (HT) might be conditioned by the association with Turner syndrome (TS). *Objectives:* To focus on the most recent pediatric studies concerning epidemiology and biochemical course of HT in TS girls. *Design:* The epidemiological peculiarities of TS-related HT in pediatric age were compared with those usually observed in non-TS girls with HT and results are summarized in Tables 1 and 2. *Conclusions:* 1) phenotypical expression of HT in TS girls is significantly different from that observed in girls without TS; 2) such differences concern the epidemiological picture, the biochemical presentation modes and also the natural history from HT diagnosis onwards; 3) these peculiarities of TS-related HT are not necessarily linked with a specific karyotype. (www.actabiomedica.it)

Key words: autoimmune thyroid disorders, chromosomopathies, epidemiological peculiarities, thyroid function presenting pattern, thyroid function evolution pattern

List of abbreviations

AITD: autoimmune thyroid disorder; GD: Graves' disease; HT: Hashimoto's thyroiditis; SH: subclinical hypothyroidism, TS: Turner syndrome.

Background

Turner syndrome (TS) is one of the commonest chromosomopathies, with an estimated incidence of around 1:1900 female live births (1). From a clinical point of view it is characterized by growth and puberty delay, gonadal dysgenesis, heart and kidney congenital defects and several dysmorphic features: nail dysplasia, high arched palate, low-set ears, retrognathia, neonatal lymphedema, low posterior hairline, cubitus valgus, multiple nevi, webbed neck, pectus excavatum and short fourth metacarpal.

Another relevant clinical feature of TS women is the elevated susceptibility towards autoimmune-mediated disorders, which is already evident in childhood and progressively increases with age. The autoimmune disease that is most frequently associated with TS is by far Hashimoto's thyroiditis (HT) (2-5), followed by celiac disease, type 1 diabetes mellitus, juvenile idiopathic arthritis, inflammatory bowel diseases and uveitis.

In TS girls HT is characterized by many epidemiological and clinical peculiarities, which have raised, in the last years, an intriguing issue, i.e. whether the association with TS may be able to affect per se phenotypic epression of autoimmune thyroid disorders (AITDs) in children and adolescents (4,6-8).

Aim of the present paper is to focus on the most recent data of pediatric literature about the specific

features of HT phenotypic expression in young patients with TS.

Epidemiological peculiarities of TS-related HT

The prevalence rate of HT in TS girls has been reported to fluctuate from 10 to 21% (9-11). Such a prevalence is distinctly higher than that generally reported in the pediatric general population, i.e. 1,2% (12). In TS girls even the prevalence rate of another autoimmune thyroid disease, that is Graves' disease (GD), has been reported to be significantly higher than in children without TS: 1.7-3.0% (7,9,11,13) vs 6.5‰ (14). Therefore, on the basis of the most recent epidemiological reports, it can be argued that the association with TS may be responsible for an enhanced children' susceptibility to AITDs, although the pathophysiological bases of such a predisposition have not been clearly elucidated to now.

There are at least ten genes located on X-chromosome, that are known to be possibly involved in immunoregulation process (15). The most relevant one is FOXP3, which encodes a transcription factor for the function of regulatory T-cells (16). Polymorphisms of this gene are linked with AITDs in Caucasian people (17), thus suggesting that FOXP3 haploinsufficiency might be involved in the pathogenesis of the increased susceptibility to AITDs, which is detectable in TS girls (16). Another possibility is that the increased risk of AITDs in TS girls might be associated with haploinsufficiency of the genes in the pseudoautosomal region of X-chromosome (3,10,16).

According to other studies, the risk of AITDs is especially elevated in TS girls with X-isochromosome (6,11), thus suggesting that a gene on the long arm of X-chromosome might be responsible for the predisposition to AITDs of TS patients (6). Nevertheless, it has to be considered that other authors have described no significant relationships between AITDs and a specific karyotype (4,7,9,18).

Another epidemiological peculiarity of TS-related HT is that the prevalence rate of family HT antecedents is generally lower than the one usually recorded in non-TS girls with HT (Table 1). Furthermore, the association with other extra-thyroidal disorders is not more common in TS girls than in those without TS (Table 1). These epidemiological features of TS-related HT support the view that TS girls are per se more exposed to the risk of developing AITDs, irrespective of familial predisposition or association with other autoimmune disorders (19).

Table 1. Median age (and range), rates of girls with family history of thyroid diseases or associated extra-thyroidal autoimmune disorders in two cohorts of girl with or without Turner syndrome TS (from reference 19, partially modified)

	Age (yrs)	Family history of thyroid diseases (%)	Associated autoimmune diseases (%)
TS girls (Nos. 90)	13.0 (4.5-18.0)	7.0	15.5
Non-TS girls (Nos. 449)	11.0 (2.8-18.0)	31.5	17.1
p-value	n.s.*	<0.0005	n.s.*

* not significant

Peculiarities of biochemical presentation of TS-related HT

According to the results of a recent study on the presentation patterns of HT in TS children, this disorder in TS girls seems to present with a less severe biochemical picture that in the ones without TS (19).

In fact, median TSH serum levels at HT diagnosis were significantly lower in TS patients, whereas FT4 levels did not significantly differ in the two patient groups with or without TS (19). In both groups the most frequent hormonal pattern at entry was euthyroidism, but the prevalence rate of girls presenting with euthyroidism was significantly higher in TS group (Table 2). On the contrary, the prevalence rate of patients presenting with a thyroid dysfunction picture was obviously higher in non-TS group (Table 2). The thyroid dysfunction pattern that was most frequently observed in the patients with TS was subclinical hypothyroidism (SH), while the prevalence rate of cases with overt hypothyroidism was very low in TS group (Table 2). By contrast, the prevalence of cases with overt hypothyroidism was relatively elevated in non-TS group (Table 2).

Table 2. Prevalence rates of the different thyroid function patterns at diagnosis of Hashimoto's thyroiditis (HT) in two cohorts of girls without or with Turner syndrome (TS); in TS girls thyroid function patterns were also re-evaluated 5 yrs after HT diagnosis (from reference 19, partially modified)

	Euthyroidism (%)	Subclinical hypothyroidism (%)	Overt hypothyroidism (%)	Hyperthyroidism (%)
Non-TS girls (Nos. 449)	54.2	16.7	22.2	6.9
TS girls (Nos. 90)	73.3	23.4	3.3	0
p-value	<0.001	n.s.*	<0.0005	<0.025
TS girls at re-evaluation (Nos. 90)	25.6	18.9	52.2	3.3
p-value	<0.0005	n.s.*	<0.0005	n.s.*

* not significant

The less severe biochemical picture which has been observed in TS girls at HT presentation might be explained on the basis of a less aggressive autoimmune pattern of HT, as suggested by the lower serum concentrations of thyroid peroxidase autoantibodies that have been, at least initially, detected in TS population (19). Another possible explanation is that many pediatricians are aware that TS girls are more exposed to the risk of AITDs and, therefore, in a TS girl, HT diagnosis may be often suspected by pediatricians even in the presence of a minimal thyroid dysfunction picture (15,19).

Peculiar biochemical evolution of TS-related HT

Phenotypical expression of TS-related HT in terms of natural history has been only occasionally investigated (11,19).

According to the report of Livadas et al (11), the prevalence of hypothyroidism in TS girls progressively increases with age after HT presentation.

According to the results of another more recent study, thyroid status significantly deteriorates over time, both in the TS girls who were euthyroid at the time of HT diagnosis and in those who had presented with a thyroid dysfunction (Table 2). Thyroid status deterioration, throughout follow-up, seems to be especially relevant in the girls who were SH at HT diagnosis. In fact, most of them exhibited, at the end of observation period, a biochemical picture of frank hypothyroidism (Table 2). Very similar results, concerning the natural history of HT-related SH in TS patients, were just recently found in another prospective study aiming at ascertaining whether long-term thyroid function prognosis may differ in the girls with either idiopathic or HT-related mild SH and whether the association with TS can modify the outcome of HT-related SH (20).

The results of those recent prospective studies are especially surprising, considering that spontaneous evolution of SH in non-TS children is generally reported to be characterized by a more favorable trend, both in the cases with an idiopathic form (21-23) and in the ones with underlying HT (24-27).

In the light of the most recent data on this topic, it can be argued that the association with TS is able to significantly affect the natural course of thyroid status from HT presentation onwards. Therefore, in TS patients with HT, thyroid function evolution should be carefully followed up, in order to recognize, at the proper time, a shifting from euthyroidism or SH to either overt hypothyroidism or hyperthyroidism (19).

In the study of Aversa et al (19), a 3.3% of TS girls with HT developed, during the observation period, a picture of GD, a sequence of events that may be sporadically observed also in non-TS children (28-31).

Finally, the evolution pattern of thyroid tests in TS girls does not seem to be significantly conditioned by karyotype abnormalities (19).

Conclusions: 1) phenotypical expression of HT in TS girls is significantly different from that observed in girls without TS; 2) such differences concern the epidemiological picture, the biochemical presentation modes and also the natural history of biochemical picture from HT diagnosis onwards; 3) these peculiarities of TS-related HT are not necessarily linked with a specific karyotype.

References

1. Nielsen J, Wohlert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Hum Genet 1991; 87: 81-3.
2. Larizza D, Calcaterra V, Martinetti M. Autoimmune stigmata in Turner syndrome: when lacks an X chromosome. J Autoimmun 2009; 33: 25-30.
3. Jørgensen KT, Rostgaard K, Bache I, et al. Autoimmune diseases in women with Turner's syndrome. Arthritis Rheum 2010; 62: 658-66.
4. Gawlik A, Gawlik T, Januszek-Trzciakowska A, Patel H, Malecka-Tendera E. Incidence and dynamics of thyroid dysfunction and thyroid autoimmunity in girls with Turner's syndrome: a long-term follow-up study. Horm Res Paediatr 2011; 76: 314-20.
5. Grossi A, Crinò A, Luciano R, Lombardo A, Cappa M, Fierabracci A. Endocrine autoimmunity in Turner syndrome. Ital J Pediatr 2013; 39: 79.
6. Elsheikh M, Wass JA, Conway GS. Autoimmune thyroid syndrome in women with Turner's syndrome--the association with karyotype. Clin Endocrinol 2001; 55: 223-6.
7. Valenzise M, Aversa T, Corrias A, et al. Epidemiology, presentation and long-term evolution of Graves' disease in children, adolescents and young adults with Turner syndrome. Horm Res Paediatr 2014; 81: 245-50.
8. Aversa T, Lombardo F, Corrias A, Salerno M, De Luca F, Wasniewska M. In young patients with Turner or Down syndrome, Graves' disease presentation is often preceded by Hashimoto's thyroiditis. Thyroid 2014; 24: 744-7.
9. Radetti G, Mazzanti L, Paganini C, et al. Frequency, clinical and laboratory features of thyroiditis in girls with Turner's syndrome. The Italian Study Group for Turner's Syndrome. Acta Paediatr 1995; 84: 909-12.
10. Invernizzi P, Miozzo M, Selmi C, et al. X chromosome monosomy: a common mechanism for autoimmune diseases. J Immunol 2005; 175: 575-8.
11. Livadas S, Xekouki P, Fouka F, et al. Prevalence of thyroid dysfunction in Turner's syndrome: a long-term follow-up study and brief literature review. Thyroid 2005; 15: 1061-6.
12. Tozzoli R, Perini R. Malattie autoimmuni nei primi anni di vita: dai sintomi alla diagnosi di laboratorio. La Rivista Italiana della Medicina di Laboratorio – Italian Journal of Laboratory Medicine 2007; 3: 45-50.
13. Wasniewska M, Corrias A, Messina MF, et al. Graves' disease prevalence in a young population with Turner syndrome. J Endocrinol Invest 2010; 33: 69-70.
14. Goday-Arno A, Cerda-Esteva M, Flores-Le-Roux JA, et al. Hyperthyroidism in a population with Down syndrome (DS). Clin Endocrinol 2009; 71: 110-4.
15. Aversa T, Lombardo F, Valenzise M, et al. Peculiarities of autoimmune thyroid diseases in children with Turner or Down syndrome: an overview. Ital J Pediatr 2015; 41: 39.
16. Bakalov VK, Gutin L, Cheng CM, et al. Autoimmune disorders in women with turner syndrome and women with karyotypically normal primary ovarian insufficiency. J Autoimmun 2012; 38: 315-21.
17. Ban Y, Tozaki T, Tobe T, et al. The regulatory T cell gene FOXP3 and genetic susceptibility to thyroid autoimmunity: an association analysis in Caucasian and Japanese cohorts. J Autoimmun 2007; 28: 201-7.
18. El-Mansoury M, Bryman I, Berntorp K, Hanson C, Wilhelmsen L, Landin-Wilhelmsen K. Hypothyroidism is common in Turner syndrome: results of a five-year follow-up. J Clin Endocrinol Metab 2005; 90: 2131-5.
19. Aversa T, Messina MF, Mazzanti L, et al. The association with Turner syndrome significantly affects the course of Hashimoto's thyroiditis in children, irrespective of karyotype. Endocrine 2015; 50: 777-82.
20. Wasniewska M, Aversa T, Salerno M, et al. Five-year prospective evaluation of thyroid function in girls with subclinical mild hypothyroidism of different etiology. Eur J Endocrinol 2015; 173: 801-8.
21. De Luca F, Wasniewska M, Zirilli G, Aversa T, Arrigo T. At the end of a two-year follow-up elevated TSH levels normalize or remain unchanged in most the children with subclinical hypothyroidism. Ital J Pediatr 2010; 36: 11.
22. Cerbone M, Bravaccio C, Capalbo D, et al. Linear growth and intellectual outcome in children with long-term idiopathic subclinical hypothyroidism. Eur J Endocrinol 2011; 164: 591-97.
23. Wasniewska M, Corrias A, Aversa T, et al. Comparative evaluation of therapy with L-thyroxine versus no treatment in children with idiopathic and mild subclinical hypothyroidism. Horm Res Paediatr 2012; 77: 376-81.
24. Monzani A, Prodam F, Rapa A, et al. Endocrine disorders in childhood and adolescence. Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review. Eur J Endocrinol 2012; 168: R1-R11.
25. Radetti G, Maselli M, Buzi F, et al. The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto's thyroiditis and isolated hyperthyrotropinaemia: a 3-year follow-up. Clin Endocrinol 2012; 76: 394-8.
26. Bona G, Prodam F, Monzani A. Subclinical hypothyroidism in children: natural history and when to treat. J Clin Res Pediatr Endocrinol 2013; 5(Suppl 1): 23-8.

27. Aversa T, Valenzise M, Corrias A, et al. Underlying Hashimoto's thyroiditis negatively affects the evolution of subclinical hypothyroidism in children irrespective of other concomitant risk factors. Thyroid 2015; 25: 183-7.
28. Champion B, Gopinath B, Ma G, El-Kaissi S, Wall JR. Conversion to Graves' hyperthyroidism in a patient with hypothyroidism due to Hashimoto's thyroiditis documented by real-time thyroid ultrasonography. Thyroid 2008; 18: 1135-7.
29. Ludgate M, Emerson CH. Metamorphic thyroid autoimmunity. Thyroid 2008; 18: 1035-7.
30. Kamath C, Young S, Kabelis K, et al. Thyrotrophin receptor antibody characteristics in a woman with long-standing Hashimoto's who developed Graves' disease and pretibial myxoedema. Clin Endocrinol 2012; 77: 465-70.
31. Troisi A, Novati P, Sali L, et al. Graves' thyrotoxicosis following Hashimoto's thyroiditis. Res Rep Endocr Disord 2013; 3: 13-5.

Received: 7 April 2016
Accepted: 21 May 2016
Correspondance:
Dott.ssa Giuseppina Zirilli
Dipartimento di Patologia Umana dell'Adulto e
dell'Età Evolutiva, Policlinico Universitario di Messina,
Via Consolare Valeria, 98125 Messina, Italy
Tel. +39 090 692407
Fax +39 090 2212143
E-mail: zirillig@gmail.co