Acta Biomed 2018; Vol. 89, Supplement 9: 11-16 DOI: 10.23750/abm.v89i9-S.7872

Review

Thyroid and celiac disease in pediatric age: a literature review

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Summary. Chronic autoimmune thyroid disease or Hashimoto thyroiditis (HT) and Graves-Basedow disease (GD) are the main autoimmune thyroid diseases in pediatric age. Both are characterized by the production of anti-thyroid antibodies, by an infiltration of autoreactive B and T lymphocytes into the thyroid parenchyma and by alterations in thyroid function (hyperthyroidism in GD, normal function or subclinical hypothyroidism in HT with possible evolution towards manifest hypothyroidism). Celiac disease (CD) is a systemic autoimmune disease caused by gluten ingestion in genetically predisposed subjects, its prevalence is around 1% in Western Countries. It presents with a pathognomonic enteropathy, a variety of clinical manifestations, positivity for specific antibodies, positivity for typical haplotypes HLA DQ2/DQ8. The clinical manifestations may vary among four types: typical, atypical, silent and latent. Diagnosis can be made in presence of specific histopathologic findings in duodenal biopsies and antibodies positivity. Celiac disease is associated to various endocrine autoimmunities such as thyropathies, diabetes mellitus type 1, Addison disease, multiendocrine syndromes. The most frequent associated thyropaties are HT and GD. The present review aims to explore the associations between thyropathies and celiac disease in pediatric age. (www.actabiomedica.it)

Key words: autoimmunity, autoimmune thyropathies, celiac disease

Background

The global prevalence of autoimmune diseases in pediatric age is about 5%. Among them, the most frequent autoimmunities are represented by autoimmune thyroid diseases (AITD). Hashimoto Thyroiditis (HT) can be considered the prototype of organ-specific autoimmunity and represents the most common cause of acquired hypothyroidism in geographic areas with lack of iodine. Its prevalence is about 3% in pediatric age. Graves Disease (GD) represents the most common cause of hyperthyroidism in pediatric age, with a prevalence of about 1:5000 children; the incidence increases progressively with age, reaching a peak in adolescence up to 3:100.000 adolescents/year. All the scientific advances in the last 10 years have allowed at least partially the comprehension of the marked preponderance of AITD in females (Females: Males ratio 5:1) with the phenomena of fetal microchimerism (1) and X chromosome inactivation. Autoimmune thyropathies can be associated with other autoimmunities such as celiac disease (CD), diabetes mellitus type 1 (T1DM), Addison disease, multiendocrine syndromes, alopecia, idiopathic juvenile arthritis. While AITD in adults are strongly associated with rheumatoid arthritis, psoriatic arthritis and connective tissue diseases, they are more frequently associated to T1DM and CD in pediatric age (3, 4).

Autoimmune thyropathies

In AITD the morpho-functional damage represents the direct consequence of the interaction be-

tween environmental and genetic factors. Linkage studies have allowed the identification of two groups of susceptibility genes: haplotypes of Human Leucocyte Antigen (HLA) DQA1, DQ2and DRB1-1401. The T cells regulating gene (CTLA-4) is a transmembrane protein belonging to the superfamily of immunoglobulins and acts by reducing T lymphocytes activation; CD40, one of the receptors of Tumor Necrosis Factor (TNF) plays a critical role in adaptative immunity and is also located on antigen presenting cells (APC) and on epithelial thyroid cells; the gene encoding for thyrosin-phosphatase protein 22 (PTPN22) is one of the inhibitors of the signal pathway of T cells receptor; finally, FCRL3, IL2RA and FOXP3 are also crucial genes in the pathogenesis of autoimmune thyropathies. Thyroid-specific genes are thyroglobulin gene (TG) and thyrotropin (TSH). The recently discovered thyrotropin receptor (TSHR) Single Nucleotide Polymorphisms (SNPs) seem to be associated specifically to GD but not to HT, although the functional consequence of these intronic polymorphisms is still not clear. Anyway it is believed that they could generate RNA variants with an increase of TSHR α subunits, which could represent potential autoantigens (5). Another hypothesis suggests that SNPs could lead to a lower amount of TSHR thymic transcripts, with a consequent decrease in central immune tolerance for TSHR (6). Considering that these polymorphisms are located on intronic regions, therefore not coding, it is reasonable to assume that genetic mechanisms are much more complex (7). Studies conducted on twins demonstrate that genetic factors contribution in the determination of AITD accounts for about 70%. Moreover, homozygous twins present more pathologic similarities than heterozygous twins. Nevertheless, the rate of pathologic concordance is of about 50%, even between homozygous twins, showing once again how other environmental factors are determining in the onset of autoimmunity. Among the considered environmental factors of AITD, particular attention should be paid to obesity, according to the "accelerator hypothesis". Starting from the assumption that obese children are hyperleptinemic, it is well known that leptin promotes cells-mediated immune responses among its function, being therefore capable of promoting the onset of autoimmune response in AITD. Besides obesity, other potential "accelerators" are represented by high alimentary iodine intake as it increases antigenic sites in TG, smoke, stress, drugs including amiodarone, lithium, α-interferon, interleukin 2, antiretrovirals, vitamin D gene polymorphisms and low serum doses of selenium. With regards to selenium, literature shows controversial results: after supplementation with selenium, the reduction of anti-thyroperoxydase (TPO) was not uniform; this phenomenon was only observed in geographic areas lacking selenium (8). Finally, some authors have demonstrated the seasonal and the geographic influences in the onset of AITD, especially for GD, and the role of infectious agents (*Yersinia enterocolitica*, Coxsackie B virus, Retrovirus, Helicobacter pylori). Recently, a high prevalence of AITD has been demonstrated among patients affected by Hepatitis C Virus (HCV). Actually, HCV can infect thyrocytes, causing an increase in the production of pro-inflammatory cytokines, which could be responsible for the autoimmune aggression of the thyroid (9). In pediatric age, HT most frequently presents during puberty, while it is rare in children younger than 3 years. Graves Disease is responsible for about 95% of cases of hyperthyroidism in pediatrics, with an annual incidence of 8 patients per 1.000.000 children younger than 4 years (10).

Celiac disease

Celiac disease is a chronic autoimmune disorder which manifests in genetically susceptible subjects triggered by the ingestion of gluten. At present, the only available treatment is a strict gluten-free diet. Epidemiologic studies demonstrate that CD is a common condition allover the world, with a predilection of Caucasian populations and a prevalence varying between 1:266 and 1:80 individuals. The disease is more common among females and may present at any age, although the onset seems to be more frequent in early childhood and around the fifth decade. Celiac disease presents a familiar predisposition, as it presents more frequently among first-degree relatives, reaching the highest concordance between homozygous twins up to 70% (12). This genetic predisposition is strongly dependent from the HLA setting. About 90-95% of

patients affected by CD presents the HLA haplotype DR3-DQ2, encoding for DQA1*0301/DQB1*0302 (12).

Considering auto-antibodies development, various antibodies have been tested for the serological diagnosis of CD, for the identification of subjects at risk who are candidates for undergoing esophagogastroduodenoscopy with duodenal biopsy, and for the monitoring of the gluten-free diet. Anti-reticulin antibodies and anti-gliadin antibodies were the first tests available, but nowadays anti-endomysium antibodies (EMA) and anti-transglutaminase antibodies IgA (t-TGAbs) are used for the higher sensitivity and specificity (12, 13). According to international guidelines, the diagnosis of CD is based on specific histopathologic findings in duodenal biopsies, on positive values of the specific antibodies, regardless of patients' symptoms (14, 15).

Gliadin, a type of prolamin and a component of gluten, is a class of proteins present in wheat and several other cereals within the grass genus Triticum. Gliadin is an excellent substrate for tissue transglutaminase, the enzyme identified as the principal auto-antigen in CD. This enzyme plays a crucial role in the maintenance of cellular homeostasis, by regulating the duplication cell cycle, differentiation and apoptosis. Studies have demonstrated the presence of HLA DQ2/DQ8 specific T-cells in mucosal lesions of celiac patients. Antigen presenting cells expose and present pre-digested gluten to T-lymphocytes CD4 positive, thanks to their molecules HLA DQ2. Transglutaminase then modifies gliadin peptides by deaminating glutamine residues, therefore facilitating the binding of gliadin peptides to HLA. This provokes an increase in the binding-affinity, which exacerbates T cells reactivity into the intestinal mucosa with a consequent local immune response that continues until gliadin is ingested. Stimulated T helper 1 (Th1) cells secrete cytokines such as TNFα and interferon-γ, which can further damage the intestinal mucosa. At the same time, a T helper 2 (Th2) response manifests, with the consequent production of t-TGAbs. These autoantibodies are able to inhibit *in vitro* the differentiation of cryptic epithelial cells, anyway the same effect remains to be established in vivo (13). Besides gluten, various environmental factors influence mode and type of clinical presentation of CD: viral antigens (e.g. *Rotavirus*) increasing intestinal mucosa permeability, the length of breastfeeding period, type and mode of weaning including the age of introduction of gluten in the infant diet seem to play a role.

With regards to clinical presentation, CD may manifest in four different forms: typical, with gastrointestinal symptoms, manifest malabsorption, weight loss and/or growth delay; atypical, with extraintestinal manifestations such ad herpetiform dermatitis or amelogenesis imperfecta; silent, with positive serum markers and positive histopathology but lack of symptoms or signs of malabsorption; latent, with positive serum markers but normal duodenal biopsies.

Prevalence of autoimmune thyropathies in CD patients

As well as for adults, an association between CD and AITD has been demonstrated also in pediatric age, in variable percentages between 2% and 7.8%, three times higher than in general population (16). A study conducted on CD children living in Sardinia, demonstrated a prevalence of AITD of 10.5%, therefore 4 times higher than in general population (17). Further studies evaluating the prevalence of AITD in CD patients have proven that a percentage variable between 2.4% and 40.4% of the patients in the cohort was affected (17-23). Details are shown in table 1. Two hypotheses have been suggested to explain this association: firstly, CD and AITD share one or more genes; secondly, a continued introduction of glu-

Tabella 1. Prevalence of AITD (clinical, subclinical, potential) in patients with CD

Country	Authors	N. patients	Pevalence AITD
Italia	Meloni (17)	34	10.5
Italia	Ventura (18)	90	14.4
Polonia	Kowalska (19)	34	41
Italia	Oderda (20)	41	2.4
Brasile	Da Silva (21)	52	40.4
Turchia	Kalyoncu (22)	67	4.5
Italia	Diamanti (23)	558	12

Tabella 2. Prevalence of CD in patients affected by AITD

Country	Authors	Type of AITD	CD prevalence %	N. patients with CD	N. patients with AITD
Italia	Larizza (31)	Hypo	8.8	6	68
Italia	Larizza (31)	Hyper	4.6	1	22
Polonia	Kaczorowska (32)	Hypo/Hyper	4.3	2	47
Turchia	Sari (33)	Hypo	5.0	5	101
Italia	De Martino (34)	Hypo/Hyper	9.9	9	91
Polonia	Grzenda-Adamek (35)	Hypo/Hyper	0.6	7	115

ten in celiac patients not on a gluten-free diet (GFD) may lead to a loss of integrity of the intestinal barrier, with a consequent alteration in the systemic immune response which may favor the onset of other autoimmune diseases (17, 24). Despite, other studies have demonstrated that the duration of the exposition to gluten in CD does not correlate with the risk of developing further autoimmune diseases, and in parallel that the cessation of gluten ingestion is not protective against autoimmunities (17, 25-27). These results are anyway controversial, as other authors suggest that a strict adhesion to the GFD is associated with a reduction of the risk of developing AITD and anti-thyroid antibodies disappear on a gluten-free diet (18, 28). Finally, GFD seems to have a favorable effect on other autoimmune comorbidities, although it is not able to stop the progression of an autoimmune process which has already started (29).

Prevalence of CD in patients with AITD

A recent meta-analysis has observed the prevalence of CD in patients affected by AITD (30). The prevalence has been demonstrated to be higher in children (6.2%) compared to adults (2.7%). Celiac disease was more prevalent in patients with hyperthyroidism (2.6%) compared to patients with hypothyroidism (1.4%) (31-35). Details are shown in table 2. Literature clearly shows a strong correlation between CD and AITD and the importance of investigating AITD in celiac children, either clinic, subclinic or potential, performing an accurate familial and personal history, a careful clinical examination, a dosage of TSH, Free T4 (FT4) and anti-thyroid antibodies, as well as a thyroid ultrasound.

Similarly, current international guidelines recommend performing the screening for CD in children affected by AITD (36). It is recommended to perform an accurate familiar and personal history of children affected by AITD, as well as an attentive research of typical and atypical signs and symptoms od CD, moreover it is recommended to dose EMA and t-TG IgA antibodies at diagnosis and every 2-3 years if negative (37).

Conclusions

A clear and strong association between CD and AITD has been demonstrated, therefore it is of paramount importance to carefully investigate both CD patients and AITD patients at diagnosis and during follow up, to precociously diagnose the simultaneous presence of these two autoimmunities. This awareness is even more essential if we think at the frequency of subclinic presentations both of CD and AITD, which could delay diagnosis. Overall, a multidisciplinary approach with the cooperation between gastroenterologists and endocrinologists should always be encouraged to optimize the management of patients affected by CD and AITD.

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