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Autoimmune diseases in Turner syndrome

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Abstract. It has been known that females with Turner syndrome (TS) have an increased prevalence of autoantibodies and are at increased risk of developing autoimmune diseases. Immunological disturbances have been described in TS: a slight decrease in immunoglobulin serum levels and in circulating T and B cells percentages. This data is not entirely in concordance with some more recent studies. The effects of the immune derangement, found only by some studies, may account for the association of TS with autoimmune disease. In TS there is an increased risk of celiac disease (CD), though the risk is considerably smaller than that for thyroiditis. Some multicenter studies have been performed (Sweden, Canada, Poland, Italy and Germany) and the reported prevalence of CD is 4.2–6.4% in TS versus 0.35–0.5% in the general population (GP). Apparently the risk is very low before school age. TS subjects with CD do not show particular dysmorphic signs. Only half of the CD subjects had a typical clinical picture and this finding speaks in favour of screening rather than just investigating TS patients with symptoms. In 44% of patients with CD and TS various autoimmune disorders were found vs. the 4.5–14% of CD subjects of the GP. In the subjects whose CD diagnosis was made before 15 years of age the autoimmune pathologies were found in 32% and in 55% in the subjects diagnosed afterward. *Conclusions* – As a high risk population TS girls and women should be screened for CD – if positive have diagnosis confirmed – according to North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines, which represent the most up-to-date guidelines. Measurement of tissue transglutaminase IgA antibodies should begin at age 6 and repeated every 2–5 years. In TS subjects, positive to antibody determination, intestinal endoscopic biopsy was recommended, because in a third of CD subjects vascular alterations in the intestinal mucosa were detected. The screening for CD could be proposed as soon as possible after the diagnosis of TS. CD screening should be performed before the beginning of GH-therapy: to avoid a bad response to treatment, to improve growth and optimize bone mineral density.

Keywords: Celiac disease; Autoimmune disease; Antitransglutaminase antibodies; Turner stigmata

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It has been known that females with TS have an increased prevalence of autoantibodies and are at increased risk of developing autoimmune diseases such as: Hashimoto thyroiditis, pernicious anemia, Addison disease, celiac disease, inflammatory bowel disease, diabetes, autoimmune hepatitis, autoimmune colitis, thrombocytopenia, and juvenile rheumatoid arthritis [1–9].

1. Immunity and Turner syndrome

Immunological disturbances have been described in TS [1,10–12]. Cacciari et al. [12] reported abnormalities of immunoglobulin serum levels: IgG serum level significantly reduced in comparison with age-matched controls males and females and IgM level intermediate between female and male values. 45,X subjects had IgM serum concentration very close to male values. Decreased IgM levels were found also by Jansen et al. [10] and Adinolfi et al. [11] and it has been ascribed to the lack of X-chromosome. A slight but significant decreased percentage of circulating T and B cells and a decreased responsiveness of lymphocytes to mitogens were also found [12,13]. This data is not entirely in concordance with some more recent studies [14,15]. Also Stenberg et al. [16], that investigated immunoglobulin and lymphocyte subpopulations in TS to explain the increased incidence of otitis media of these individuals, did not find any major immunological deficiency.

The effects of the immune derangement, found only by some studies, do not seem to be severe, but they could assume clinical relevance with advancing age and may account for the association of TS with autoimmune disease.

2. Celiac disease

2.1. Introduction

CD is a gluten-sensitive enteropathy of autoimmune nature characterized by villous damage of small intestinal mucosa. It is a life-long affliction. CD is a multifactorial disease. *Gluten* is the critical environmental component. Gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamines) of barley and rye in genetically susceptible subjects cause the damage. These peptide sequences trigger a sequence of immune reactions leading to a damage of intestine and malabsorption symptoms. A g*enetic* component is involved in the development of the disease. CD is an HLA-associated disease. The large majority of CD patients express HLA-DQ2 and the remainders are usually HLA-DQ8 positive. HLA-DQ2 and DQ8 are class II molecules that bind and present peptides to $CD4^{+}$T cells. DQ2 modified gut receptor causing altered presentation of gliadin proteins and activation of the T-cell responses in the small intestine. In CD patients there is an abnormal T-cell response to gluten (*immunological* mechanism). In patients HLA-DQ2 and DQ8 the transglutaminase (TG enzyme) modifies gluten peptides and the new complexes trigger inflammatory T-cell in the small intestine [17,18].

CD occurs in symptomatic individuals with gastrointestinal and non-gastrointestinal symptoms (classic and atypical form) and in some asymptomatic individuals who have conditions that are associated with CD: autoimmune diseases (insulin-dependent diabetes

mellitus, thyroiditis) and some chromosomal diseases (Down syndrome, Turner syndrome, Williams syndrome) [19]. Chromosomal anomalies predispose to immunological disturbances.

2.2. Epidemiology

Population-based studies in Europe and the United States have shown a prevalence of CD from 1:150 to 1:250; the ratio of symptomatic to asymptomatic cases diagnosed was 1:2 [20–23].

2.3. Diagnosis

The diagnosis of CD is based on: clinical history, physical examination, measurement of quantitative serum IgA, specific serologic tests: IgA antibodies to human recombinant tissue transglutaminase (tTG) – now recommended as initial test – and anti-endomysium antibodies (EMA). Antigliadin antibody tests (AGA IgA and IgG) were used in the past, but because of their inferior accuracy, they are no longer recommended for detecting CD. The confirmation of the diagnosis require an intestine biopsy. In circumstances where diagnosis is uncertain, additional tests can be considered as well as determination of HLA genotyping [23–26].

2.4. Therapy

The cornerstone therapy is a life-long gluten-free diet.

3. Celiac disease and Turner syndrome

In Turner syndrome a higher frequency of CD than in the general population (GP) has been reported [27–29]. The prevalence of CD is 4.2–6.4% in TS vs. 0.35–0.5% in GP.

3.1. Multicenter studies

In *Sweden* a multicenter study was undertaken by Ivarsson et al. [27] and 87 subjects with TS (3–16 years of age) and 199 female controls were enrolled. AGA and EMA (IgA, IgG) analysis was performed. Of the TS series 5% (4/87) were EMA+, as compared with 0.5% of the controls. In their study they evaluated the reliability of the two serologic tests AGA and EMA performing also intestinal biopsy. They found EMA to be superior to AGA for screening purpose and for the high predictive value in TS as in the GP.

A *Canadian* study was performed by Gillet et al. [28] on 45 subjects with TS. The prevalence of biopsy-confirmed CD was of 2.2%.

In *Poland* Rujner et al. [29] evaluated 48 TS subjects (2–21.64 years) with EMA and AGA and intestinal biopsy in the positive cases. In their series they found a prevalence of CD of 4.15% (2/48), confirming the association of TS and CD.

The largest multicenter survey was performed in *Italy* (Bonamico and the ISGTS) [30]. It was a retrospective study and 389 subjects with TS (7–38 years) were collected

under the auspices of the Italian Society of Pediatric Gastroenterology and Hepatology (SIGEP) and the Italian Study Group for TS (ISGTS) from various centers of the northern, central, southern and insular Italian regions. The diagnosis was made according the revised criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [24], the screening was performed using IgA AGA and/or EMA antibody determinations, followed by small intestine biopsy in positive cases.

CD was diagnosed in 25 TS girls (6.4%), whose ages ranged from 8.3 to 36.25 years (median, 17 years and 4 months). This prevalence far exceeds the prevalence of CD in the GP (in Italy, 0.55%). In TS subjects intestinal endoscopic biopsy was recommended, because in a third of CD subjects vascular alterations in the intestinal mucosa, such as teleangectasia (7 out 20 cases) were detected.

3.2. Clinical aspects

In the Italian multicenter study TS subjects were evaluated not only for CD prevalence, but also for the clinical characteristic associated with CD.

The age at diagnosis of CD had a wide range, but the median was 17.32 years.

Only for 10 of 25 CD subjects the evaluation of Turner stigmata was done. CD subjects did not show particular dysmorphic features: 4 of them had severe stigmata, 2 mild dysmorphic signs and 4 showed only visceral malformations.

Of the 25 cases (of 389) who were diagnosed with CD, only 10 had the typical clinical picture of celiac disease, while 8 showed an atypical picture (anemia, anorexia, delayed growth) and 7 had no symptoms [30]. This finding speaks in favour of screening rather than just investigating TS patients with symptoms.

It has been reported that short stature can be the primary manifestation of otherwise asymptomatic CD [31,32], but in this study only one patient showed a stature less than the 3rd percentile for Italian TS suggesting that screening for CD in TS cannot only be done in girls showing growth retardation in relation to TS curves.

Karyotype distribution of the 25 subjects with CD demonstrated a high prevalence of subjects with 45,X karyotype (14–56%) and isochromosome rearrangement (11–48%). One of these subjects had a hidden Y chromosome.

In a recent multicenter study in *Germany* reported by Bettendorf et al. [33], autoimmunity (thyroid or celiac) were associated with a less favourable outcome from growth hormone treatment. In a follow up study with 120 near-adult subjects (>16 years) the prevalence of positive tTG was of 4%; the subjects without autoantibodies gained +1.1 S.D. in final height, while those with autoantibodies only gained +0.7 S.D. ($p<0.01$). The explanation – and implications – of this finding is not clear, but adds to the evidence for frequent screening for autoimmunity in TS in order to assure early detection and appropriate treatment.

3.3. Other autoimmune disease

In the Italian study various autoimmune disorders were found in 44% (11/25) of patients with CD and TS vs. the 4.5–14% of CD subjects of the Italian GP [34,35] (Table 1). In the

Table 1
Associated autoimmune pathologies in TS subjects with CD

Autoimmune pathologies	%
Hashimoto thyroiditis (HT)	28
HT and diabetes type I	8
Autoimmune hepatitis	4
Thrombocytopenia	4

subjects whose CD diagnosis was made before 15 years of age the autoimmune pathologies were found in 32% and in 55% in the subjects diagnosed afterward.

3.4. Conclusion

In TS there is an increased risk of CD, though the risk is considerably smaller than that for thyroiditis. As a population 4–6% of individuals are affected [27–30,33]. Apparently the risk is very low before school age [30], but probably also in adulthood, even if we have no long-term follow-up for CD in these subjects.

Only half of the CD subjects had a typical clinical picture and this finding speaks in favour of screening rather than just investigate TS patients with symptoms.

TS subjects with CD do not show particular dysmorphic signs.

3.5. Recommendations

As a high risk population TS girls and women should be screened for CD – and if positive have diagnosis confirmed – according to NASPGHAN guidelines [26], which represent the most up-to-date guidelines.

- The screening for CD could be proposed as soon as possible after the diagnosis of TS.
- Measurement of tissue transglutaminase IgA antibodies should begin at age 6 and repeated every 2–5 years.
- Alternatively, HLA-typing with regard to DQ2/DQ8 status can be performed, as individuals without DQ2 or DQ8 need no further screening.
- CD screening should be performed before the beginning of GH-therapy: to avoid a bad response to treatment, to improve growth and optimize bone mineral density.

In Italy a collaborative study, proposed by SIGEP and the ISGTS, is in progress to evaluate in a long-term follow-up the effect of gluten-free diet on final height of TS subjects and to better define the immunological consequences of the association CD and TS [30].

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