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Prevalence and Clinical Picture of Celiac Disease in Turner Syndrome

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A multicenter study of Turner syndrome (TS) patients was carried out to estimate the prevalence of celiac disease (CD) and to detect clinical characteristics and laboratory data of affected patients. Three hundred eighty-nine girls with TS were screened by IgA antigliadin antibodies and/or antiendomysial antibodies. Intestinal biopsy was offered to positive cases. CD was diagnosed in 25 patients. In celiac subjects, anemia, anorexia, and delayed growth (with respect to Italian TS curves) were frequently present; whereas distended abdomen, chronic diarrhea, constipation, and vomiting occurred more rarely. In addition, low serum iron levels, hemoglobinemia, and high values of aminotransferases were observed. Ten patients showed classic CD, 8 showed atypical symptoms, and 7 showed a silent CD. In 11 symptomatic patients, the diagnosis of CD was made at the onset of symptoms, whereas 7 of them showed a median delay of 79 months in diagnosis. Other autoimmune disorders were observed in 40% of the patients. Our study confirms the high prevalence (6.4%) of CD in a large series of TS patients. Moreover, the subclinical picture in 60% of the cases, the diagnostic delay, and the incidence of other autoimmune disorders suggest that routine screening of CD in TS is indicated. (*J Clin Endocrinol Metab* 87: 5495–5498, 2002)

IN TURNER SYNDROME (TS), autoimmune pathologies (such as thyroiditis and diabetes mellitus) are frequently observed (1–3). Celiac disease (CD) is a gluten-sensitive enteropathy of autoimmune nature, which is associated with Down syndrome, another chromosomal disease (4). After some case reports of girls affected by TS and CD (5, 6), the screening for CD in some series of TS girls led to the conclusion that CD is significantly more frequent in these patients than in the general population (7–11). The prevalence of CD in TS had not been studied extensively, however (12, 13).

A multicenter survey, based on the largest series of TS patients reported up to now, was carried out to evaluate the prevalence of CD in TS subjects and to define the clinical characteristics of CD in these patients.

Subjects and Methods

Three hundred eighty-nine TS subjects (age range, 7–38 yr) were retrospectively studied. These patients were collected under the auspices of the Italian Society of Pediatric Gastroenterology and Hepatology (SIGEP) and the TS Italian Study Group from various centers of the northern, central, southern, and insular Italian regions, thus making the sample fairly representative of the whole population.

The diagnosis of TS was confirmed by karyotype in all cases. The patients underwent several routine laboratory tests: hemoglobin, serum iron, calcium, protein, albumin, aminotransferases, and IgA.

CD was diagnosed according to the revised criteria of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (14). Patients were selected for intestinal biopsy on the basis of antigliadin antibodies (AGA) IgA and/or antiendomysial antibodies (EMA) positivity. IgA AGA were assayed by ELISA by the Alfa-gliatest (Eurospital, Trieste, Italy) (15). IgA EMA were evaluated by an indirect immunofluorescence method (Eurospital). Sections from the distal portion of monkey's esophagus were used as substrate, and fluorescein-labeled goat antihuman IgA antibody was used as the second antibody. The patients' serum was diluted 1:5 in phosphate buffer at pH 7.2. The presence of a brilliant green network pattern, under a fluorescence microscope, was taken as positive (16). Patients with IgA deficiency (<33 mg/dl in patients younger than 10 yr, and under 70 mg/dl in older girls) were not included in the study. In all AGA IgA- and/or EMA IgA-positive girls, a biopsy of the small intestine was proposed. Intestinal biopsies were performed by pediatric or adult endoscopes at the level of the second/third portion of the duodenum or by Watson capsule near the Treiz ligament.

A detailed questionnaire was compiled to obtain information about CD patients, as well as their family gastroenterological history and feeding habits (breast milk or formula, age of introduction of gluten-containing foods). As to the gastrointestinal function, particular attention was paid to the features of CD, such as chronic diarrhea, vomiting, delayed growth, and anorexia. Autoimmune or neoplastic conditions were also assessed. At diagnosis, all subjects were on a gluten-containing diet. Weight and height were evaluated using TS percentile charts (17) at the time of diagnosis.

For ordinal parameters, means and SD were computed; for categorical parameters, frequency distribution was obtained. A χ^2 test was used for independence between categorical variables, when possible.

Results

The screening of 389 TS patients, performed using IgA AGA and/or EMA antibody determinations, followed by small intestine biopsy in positive cases, led to the diagnosis of CD in 25 girls (6.4%), whose ages ranged from 8 yr and 4 months to 36 yr and 3 months (median, 17 yr and 4 months). Parents of 1 EMA-positive patient did not give permission for intestinal biopsy, and this patient was not included among celiac patients.

Abbreviations: AGA, Antigliadin antibodies; CD, celiac disease; EMA, antiendomysial antibodies; SIGEP, Italian Society of Pediatric Gastroenterology and Hepatology; TS, Turner syndrome.

As shown in Table 1, 69.6% of CD patients were IgA AGA-positive, and 95.5% were EMA-positive. In 5 cases, intestinal biopsy was performed by peroral capsule; in 20 cases, by endoscopy. Endoscopic examination revealed the presence of teleangectasias in 7 out of 20 patients (35%). Histological data are shown in Table 1.

For the 25 patients with CD, cytogenetical analysis showed 45,XO karyotype in 14 subjects (56%), mosaics [45,X/46Xi (Xq)] in 7 (28%), and other chromosomal abnormalities [46,Xi (Xq)] in the remaining 4 girls.

Short stature was present in all the patients. Phenotypical features (webbing of the neck, low posterior hairline, small mandible, epicanthal folds, high arched palate, broad chest, cubitus valgus, hyperthelorism, and multiple nevi), visceral malformations, such as cardiac anomalies (bicuspid aortic valves, aortic coarctation, ventricular septal defect), and kidney abnormalities (absence of one kidney, horseshoe kidney) were detected in 10 patients. Four girls showed just phenotypic characteristics, 4 showed only visceral malformations, the others slight phenotypical signs, not easily detectable.

As to family gastroenterological history, the grandmother of one CD girl was affected by CD, one grandfather was affected by gastric carcinoma, and another by intestinal carcinoma. One cousin of a patient was also affected by CD, and the father and grandfather of another girl complained about recurrent abdominal pains.

Seven out of 21 girls (33.3%) were breast fed (3 for 1 month or less, 3 for 3 months, and 1 for 11 months). Seven out of 20 CD patients (35%) received gluten-containing foods before the age of 5 months. Height and weight distribution of CD patients, compared with the TS population, at the time of the intestinal biopsy, is shown in Fig. 1. Height was higher than the 25th percentile in 20 patients and lower than the 3rd percentile in just 1 girl. Weight was in the normal range in 21 patients, higher than the 97th percentile in 3 girls, and lower than the 3rd percentile in 1 girl. In 9 patients, older than 15 yr, mean height was 141.4 cm, corresponding to the 50th percentile of TS Italian curves.

As shown in Table 2, delayed growth and anorexia were each observed in 28% of cases; whereas distended abdomen, chronic diarrhea, constipation, and vomiting occurred more rarely. In addition, in celiac TS patients, low hemoglobinemia and serum iron levels were frequently found, as well as high levels of aminotransferases and normal levels of calcium, protein, and albumin.

Among CD girls, 10 (40%) showed a classic form of the disease, whereas 8 (32%) showed atypical symptoms and 7 (28%) showed a silent form. Out of the 18 symptomatic patients, the diagnosis of CD in 11 patients was made at the onset of symptoms; whereas in the remaining 7 girls, it was done after a period ranging from 9–240 months (median, 79 months).

TABLE 1. Number and percentages of TS patients diagnosed with CD positive for AGA IgA and/or EMA and number and percentages of patients with partial or total villous atrophy

	Turner girls
	n (%)
AGA IgA positive	16/23 (69.6)
EMA positive	21/22 (95.5)
Partial villous atrophy	10/25 (40)
Total villous atrophy	15/25 (60)

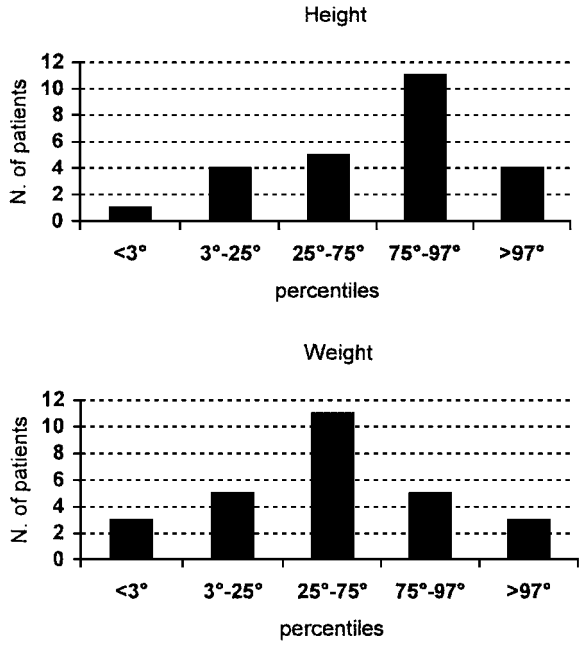

FIG. 1. A, Distribution of height percentiles of TS patients affected by CD (relative to TS charts). B, Distribution of weight percentiles of TS patients affected by CD (relative to TS charts). N, Number.

TABLE 2. Clinical characteristics and laboratory data of TS patients with CD

	n = 15 (%)
Signs/symptoms	
Delayed growth	28
Chronic diarrhea	8
Vomiting	4
Anorexia	28
Constipation	8
Distended abdomen	12
Laboratory findings	
Low hemoglobinemia	28
Low serum iron	33
Increase levels of AST	33
Increase levels of ALT	27

AST, Aspartate aminotransferase; ALT, alanine aminotransferase.

As to the autoimmune disorders, Hashimoto thyroiditis in 7 CD girls, Hashimoto thyroiditis plus type I diabetes in 2, autoimmune hepatitis in 1, and thrombocytopenia in another patient were observed. In addition, 1 case of cerebral neoplasm also occurred.

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

Statistical tests used to verify in CD patients a possible association of latency period before the diagnosis of CD and age at the introduction of gluten in the diet, clinical forms and autoimmune pathologies did not show significant results.

Discussion

The results of our multicenter study confirm the high prevalence of CD in TS patients [among 389 TS children and adults,

it was possible to diagnose 25 with biopsy-proven CD (6.4%)]. The prevalence of CD in our TS girls is lower than we previously reported (8.1% in 37 girls) (7) and higher than in other smaller series (2.2–5.0%) (8–11). These differences possibly relate both to the number of patients who underwent screening and to the different prevalence of the disease in various populations. The prevalence in TS far exceeds the prevalence of CD in the general populations (in Italy, 0.55%) (18). Therefore, we can assume that this association is not attributable to chance.

The screening for CD in TS patients is based on the determination of CD-associated antibodies, followed by intestinal biopsy in positive patients (7–11). The higher sensitivity of EMA (in respect to IgA AGA) already observed (16), emerges also in the present study, which confirms that EMA represent the more reliable marker of CD. Nevertheless, possible EMA-negative, IgA AGA-positive CD patients can be found, particularly in children younger than 2 yr (16). In prospective studies, a screening based on antitissue transglutaminase autoantibodies, using human antigen and possibly a radioimmunological method, could be considered as a low-cost alternative to EMA determination, less time consuming, and not operator-dependent (19).

Intestinal biopsy currently remains mandatory for the diagnosis of CD and could be performed either with capsule or by endoscopy; a debate is ongoing among pediatric gastroenterologists about the method of choice (20). Vascular alterations in the intestinal mucosa, such as teleangectasias, have been reported in TS (7). The detection of these lesions in a third of our CD patients lends us to recommend endoscopic biopsies.

The high levels of aminotransferases observed in our CD patients may be related both to TS [as reported by Larizza *et al.* (21)] and to CD (4, 22, 23).

The occurrence of signs and symptoms typical of gluten intolerance in 40% of our celiac girls suggests that more attention should be paid to clinical signs during the monitoring of these patients. It is likely that some complaints are underestimated and ascribed to the main pathology. Instead, a high grade of suspicion for CD must be kept in mind in the presence of atypical symptoms, like isolated hyposideremic anemia or short stature, in respect to TS charts, as in the case reported by Arslan *et al.* (24). Short stature, a virtually universal phenotypic feature of TS, has been partly ascribed to skeletal resistance attributable to SHOX/PHOG haploinsufficiency (12, 25). Many trials of GH treatment have been performed (26–30), but the results on final height are variable, and the rationale of this approach has been debated (31); positive results are seen if GH treatment is given at an earlier age and the dose is optimized (32). Furthermore, a reasonable delay in introducing estrogen treatment, to induce puberty, seems to increase significantly the gain in final height *vs.* the projected height (33).

Short stature can be the primary manifestation of monosymptomatic CD (34, 35); though we found, in our series, only a celiac girl (4%) showing a stature less than the 3rd percentile for TS Italian curves. Of course, when we find a TS girl whose growth velocity is slower than expected for TS curves, first we have to screen for CD. To improve growth and optimize bone mineral density, we always suggest the screening for CD before beginning GH therapy.

The importance of CD screening in all TS girls is demonstrated by the fact that more than a quarter of CD in our series was completely asymptomatic. It is worth noting that in our girls, the ratio of symptomatic-to-silent forms of CD (2.7:1) was reversed, in comparison with the general population (1:8) (18). A recent report described a similar pattern in celiac patients affected by Down syndrome (4). It could be suggested that in various chromosomal disorders, the normal compensatory mechanism necessary to overcome the overt clinical manifestation of CD is less efficient.

It is well known that both TS and CD are associated with various autoimmune disorders (1–3, 36–40); moreover, the detection of antibodies against antigens related to endocrine glands is commonly observed in CD patients and could be responsible for subclinical organic damage (40, 41). In the present study, autoimmune disorders, like Hashimoto thyroiditis, type 1 diabetes, autoimmune hepatitis, and trombocytopenia, were detected in about half of the CD patients. This percentage is higher than previously reported in subjects affected by CD: an Italian multicenter study (39) showed that out of 909 celiac children and adolescents, 129 subjects were affected by autoimmune disorders (14%); and in another study on 44 celiac adolescents, a low rate of overt disease was found (4.5%), although in 34% of them, at least 1 antibody against endocrine glands was detected (40). The high prevalence of antithyroid antibodies in TS is well documented: in a Swedish study of TS girls (42), it was reported as 52%; and in an Italian multicenter study (1), 22%. Overt clinical thyroiditis prevalence has been shown to be higher in TS patients than in healthy populations. Radetti *et al.* (1) reported 49 out of 478 TS girls (10.2%) positive for antithyroid antibodies and with typical ultrasound findings of thyroiditis. Chiovato *et al.* (2) reported a thyroiditis prevalence of 13.3% in 75 TS patients.

Therefore, although the coexistence of CD and TS may increase the prevalence of autoimmune disorders, the significance of this association on the induction of other autoimmune pathologies at the moment cannot be exactly quantified. Though the relevance of age, reflecting the duration of gluten assumption, has been emphasized by some authors (38, 40, 41), only longitudinal studies involving a greater number of TS patients affected by CD can provide more significant results.

In conclusion, our study, based on large series of TS patients screened for CD, confirms the association of these pathologies and highlights the relevance of screening for CD in all TS girls. This screening could be proposed as soon as possible after the diagnosis of TS and repeated periodically. It could be advantageous to treat, with GH, subjects already screened for CD, to avoid a bad response to treatment.

A follow-up study is in progress to evaluate the effect of a gluten-free diet on final height of TS patients and to better define the immunological consequences of the association of CD and TS.

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