Increased prevalence of celiac disease in girls with Turner syndrome detected using antibodies to endomysium and tissue transglutaminase

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PM Gillett, HR Gillett, DM Israel, et al. Increased prevalence of celiac disease in girls with Turner syndrome detected using antibodies to endomysium and tissue transglutaminase. Can J Gastroenterol 2000;14(11):915-918.

OBJECTIVE: To establish the prevalence of celiac disease (CD) in girls with Turner syndrome (TS) in British Columbia.

METHODS: Forty-five girls with TS were prospectively screened for CD using blinded testing with the current 'gold standard' – immunoglobulin A (IgA) endomysium antibody (EmA) and the novel IgA tissue transglutaminase antibody (tTG). Those with positive results were offered small bowel biopsies, and a gluten-free diet was recommended if CD was confirmed.

RESULTS: One asymptomatic prepubertal East Indian girl was positive for EmA, had an elevated tTG concentration of 560 U/mL and histological evidence of CD. Seven girls were negative for EmA but had elevated tTG concentrations (175 to 250 U/mL); five were white, one was Asian and one was East Indian. Small bowel biopsies were performed on three girls, and the histologies were normal. The remaining four patients declined biopsy.

CONCLUSIONS: One girl with TS was identified with CD from

45 screened, giving an overall biopsy-confirmed prevalence of 2.2%. This study confirms previous observations placing girls with TS at higher risk for CD and suggests a similar high prevalence in British Columbia.

Key Words: Antiendomysium antibodies; Antitissue transglutaminase antibodies; Celiac disease; Children; Turner syndrome

Prévalence accrue de la maladie cœliaque chez des fillettes atteintes du syndrome de Turner décelée au moyen d'anticorps dirigés contre l'endomysium et la transglutaminase tissulaire

OBJECTIF : Établir la prévalence de la maladie cœliaque (MC) chez des filles atteintes d'un syndrome de Turner (ST) en Colombie-Britannique.

MÉTHODES : On a fait subir un test de dépistage de la MC à quarante-cinq fillettes atteintes du ST de façon prospective au moyen d'épreuves à l'insu par test standard : l'anticorps endomysial (EmA) dirigé contre l'im-

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munoglobuline A ou le nouvel anticorps dirigé contre la transglutaminase tissulaire (tTG). Les sujets ayant présenté des résultats positifs se sont fait offrir de subir une biopsie du grêle et on leur a recommandé une alimentation sans gluten si le diagnostic de MC était confirmé.

RÉSULTATS : Une fillette d'origine antillaise, prépubère et asymptomatique, s'est révélée positive à l'égard de l'EmA et présentait des concentrations élevées de tTG, soit 560 AU/mL et des signes histologiques de MC. Sept fillettes ont présenté des résultats négatifs à l'EmA, mais des taux élevés de tTG (175 à 250 AU/mL), cinq étaient de race blanche, l'une

asiatique et l'autre antillaise. Des biopsies du grêle ont été effectuées sur trois fillettes et les résultats de l'analyse histologique étaient normaux. Les quatre autres patientes ont refusé la biopsie.

CONCLUSION : Une fillette atteinte du ST a été identifiée comme porteuse d'une MC sur les 45 sujets sélectionnés, ce qui donne une prévalence globale confirmée par la biopsie de 2,2 %. Cette étude confirme les observations antérieures selon lesquelles les fillettes atteintes de ST sont exposées à un risque plus grand de MC et donne à penser que la prévalence est aussi élevée en Colombie-Britannique.

An association between Turner syndrome (TS) and celiac disease (CD) has been suggested in several case reports (1-4). More recently, studies from Italy and Sweden showed that the prevalence of biopsy-proven CD among girls with TS is 5% to 9% (5-7). This study aimed to ascertain the prevalence of CD in the girls with TS followed at British Columbia's Children's Hospital, University of British Columbia (UBC), Vancouver, British Columbia.

PATIENTS AND METHODS

All girls with TS followed by the Division of Endocrinology at British Columbia's Children's Hospital between December 1998 and October 1999 were invited to participate in the study. Approval was obtained from the Clinical Research Ethics Board of UBC. After obtaining written consent from the parent or guardian, the residual serum from samples drawn for annual thyroid studies was sent to the Gastroenterology Research Laboratory at UBC, where immunoglobulin A (IgA) endomysium (EmA) and IgA tissue transglutaminase (tTG) antibody concentrations were determined by a single investigator. IgA EmA was detected using indirect immunofluorescence against human umbilical cord using the method described by Ladinser et al (8), measuring the serum at an initial dilution of 1:5. All positive sera were repeated at increasing dilutions until they became negative. Titres of IgA tTG antibody were measured using an ELISA method based on that reported by Dieterich et al (9) but modified to account for local differences in scientific sup-

plies. During the initial validation of the assay, a reference range of up to 140 U/mL (3 SDs above the mean, 99% confidence limits) was calculated from titres on adult gastrointestinal disease control subjects with normal small bowel biopsies and on sera from adult patients with biopsy-proven CD (10). During validation, all IgA-deficient patients were found to have tTG titres of 5 U/mL or lower. For this study, therefore, samples with titres of 5 U/mL or lower were tested for IgA deficiency using NOR-Partigen Total IgA kit (Behring Diagnostics Inc, USA).

Patients positive for one or both antibodies were contacted by telephone by one of the authors, and the significance of the results was discussed with the family. The girls were seen at the hospital for further consultation. Upper gastrointestinal endoscopy with small bowel biopsy was offered to those positive for one or both antibodies to confirm the diagnosis, and four biopsies were taken from the distal duodenum of each consenting patient.

RESULTS

All of the families who were invited to participate gave consent. The clinic has records for 70 girls with TS, and sera were obtained from 45 girls who were seen during the study period. The median age was 12.5 years (range 4.6 to 19 years). There were 32 white, 10 Asian and 3 East Indian girls. Median tTG concentration was 33 U/mL (range 8 to 560 U/mL). One prepubertal girl (patient 1, Table 1) of East Indian descent aged 8.6 years, recently diagnosed with TS

TABLE 1
Details of patients positive for immunoglobulin A (IgA) endomysium antibody (EmA) and/or with elevated IgA tissue transglutaminase (tTG) antibody

Patient	Age (years)	Ethnic group	EmA titre*	tTG titre (AU/mL) [†]	Symptoms	Biopsy
1	8.6	East Indian	Positive 1 in 100	560	None	Partial villous atrophy
2	4.6	East Indian	Negative	250	Abdominal pain	Normal
3	12.2	White	Negative	220	Occasional diarrhea	Normal
4	18.7	White	Negative	216	None	Declined
5	19.0	White	Negative	208	None	Declined
6	17.8	White	Negative	200	None	Normal
7	17.6	Asian	Negative	183	None	Declined
8	6.5	White	Negative	175	None	Declined

*Reference range is negative; [†]Reference range is 140 arbitrary units (AU)/mL or less

(karyotype 45,X/46,X,i[X](q10)), was positive for EmA (up to a dilution of 1:100) and had an elevated tTG concentration of 560 U/mL. She also had highly positive thyroid microsomal antibodies (1:25,600), but her thyroid-stimulating hormone levels remained normal. She had no gastrointestinal symptoms. Histology of small bowel biopsies demonstrated partial villous atrophy (Marsh type 3, infiltrative hypoplastic [11]) typical of CD. Before treatment with a gluten-free diet, her height was 115.3 cm (0.44 SDs on a Turner chart) and weight was 20.3 kg (28th percentile for height). After 10 months on a gluten-free diet, her height velocity was 3.4 cm/year, and she had gained 0.9 kg in weight.

Seven other girls, aged 4.6 to 19 years, were negative for EmA but had elevated tTG concentrations (175 to 250 U/mL). Five were white, one was Asian and one was East Indian (patients 2 to 8, Table 1). All were euthyroid, and none was on growth hormone treatment. Small bowel biopsies were performed on three girls (one had abdominal pain, one had occasional diarrhea and one had type I diabetes but no gastrointestinal symptoms); in all three, the histology was normal. The remaining four patients declined biopsy.

The 37 girls who were negative for EmA and had tTG concentrations ranging from 8 to 111 U/mL had no significant gastrointestinal symptoms. Two had hypothyroidism, and one had hyperthyroidism. One was currently on growth hormone, and one had completed growth hormone therapy. Within this group, a 12-year-old girl of East Indian descent had diarrhea with poor weight gain over the preceding year and elevated IgA antigliadin antibody concentration of 52 U/mL (normal 30 U/mL or lower). She was negative for EmA, her tTG concentration was normal at 9 U/mL and results of a small bowel biopsy were also normal.

DISCUSSION

Our study demonstrates a biopsy-proven prevalence of at least 2.2% for CD in our population of girls with TS, which is somewhat lower than that reported from Italy and Sweden (5-7). Our group of girls with TS has a large proportion (28%) of Asian and East Indian patients. In previous studies (5-7), the ethnic origin of patients was not outlined. If there were only a few non-white children in these studies, this might explain our lower prevalence because CD is thought to be less prevalent in Asian and East Indian populations.

The prevalence of CD in girls with TS is, therefore, significantly higher than that of the general population, where it is estimated to be one in 200 when Northern European populations are screened (12). Nevertheless, the benefits of screening and treating asymptomatic TS girls with CD remain to be seen, and long term follow-up is required. Our patient with TS and CD did not demonstrate a change in her linear growth while on a gluten-free diet for over 10 months, but her growth parameters will continue to be followed. Women with TS are considered to have a higher risk of osteoporosis than those with untreated CD (13). The combination of the two conditions may compound this problem,

and early recognition and treatment of CD in these patients may well improve bone mineral density, given that accretion of bone mineral ceases in early adulthood.

We looked for IgA deficiency in cases where the IgA tTG titres were 5 U/mL or lower. All our patients had tTG titres above 8 U/mL and, therefore, were not likely to have IgA deficiency. One case report dealt with IgA deficiency and CD in a girl with TS (1), which may have been due to shared human leukocyte antigen (HLA) types in both conditions (14) or to failure to clear food antigens, which may trigger the onset of CD (15).

Seven of our patients who were negative for EmA had tTG titres of 140 U/mL or higher – a level three SDs above the mean (99% confidence limits), which was set a priori as the cutoff to diagnose CD. Two of the seven patients who had gastrointestinal symptoms and one with diabetes had normal biopsy results. Four others declined small bowel biopsy. The significance of mildly elevated tTG concentrations in isolation is uncertain, and serology will be repeated with their annual screening to monitor the trend in both tTG and EmA. One possible explanation is that the cutoff for tTG was set too low, resulting in a higher sensitivity but lower specificity for the test. Another possible explanation is that these girls have latent CD and that they will eventually develop a positive EmA test and histological evidence of CD. Accordingly, it will be important to follow these girls over the long term.

There are no reports of an increased incidence of enteropathy-associated T-cell lymphoma in patients with TS. The majority of malignancies in this syndrome involve gonadal, endometrial and neurogenic tissues (16). Many women with TS are lost to follow-up once they leave the pediatric clinic, which may lead to relative underreporting of this association.

While suggesting an increased association between TS and CD, our study did not look at the potential causes of such an association. As suggested, studying the HLA types of these patients and any potential linkages with other loci may provide more candidate genes in the HLA and non-HLA domains that lead to the phenotypic expression of CD (as has been seen in those with type I diabetes and CD [17]).

This study has confirmed previous observations placing girls with TS at higher risk for CD. Further larger studies, perhaps on a national level, are warranted to establish this association (as is happening with type I diabetes in North America) and to monitor the benefit of the gluten-free diet on growth, puberty and the reduction of the long term complications in girls with TS found to have gluten-sensitive enteropathy.

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