Short report

Coeliac disease in Williams syndrome

Aldo Giannotti, Giovanni Tiberio, Massimo Castro, Fabio Virgilii, Franco Colistro, Francesca Ferretti, Maria Cristina Digilio, Manuela Gambarara, Bruno Dallapiccola

Abstract

***Background*—Coeliac disease (CD) has been reported in several patients affected by chromosomal disorders, including Down syndrome (DS) and Turner syndrome (TS). CD has also been found in sporadic Williams syndrome (WS) patients. In this study, CD was evaluated in a consecutive series of patients with WS, in order to estimate if the prevalence of CD in WS patients is higher than in the general population.**

***Methods and results*—A consecutive series of 63 Italian patients with WS was studied by analysing the dosage of antigliadin antibodies (AGA) IgA and antiendomisium antibodies (AEA). In patients with positive AGA and AEA, small bowel biopsy was performed. The prevalence of CD in our WS population was compared with that estimated in a published series of 17 201 Italian students. Seven WS patients were found to be positive for AGA IgA and AEA. Six of them underwent small bowel biopsy, which invariably disclosed villous atrophy consistent with CD. The prevalence of CD in the present series of WS patients was 9.5% (6/63), compared to 0.54% (1/184) in the Italian students (p<0.001).**

***Conclusion*—The present results suggest that the prevalence of CD in WS is higher than in the general population and is comparable to that reported in DS and TS. AGA and AEA screening is recommended in patients with WS.**

(*J Med Genet* 2001;**38**:767–768)

Keywords: Williams syndrome; coeliac disease

Servizio di Genetica Medica, Ospedale Bambino Gesù, IRCCS, Piazza S Onofrio 4, 00165, Roma, Italy
A Giannotti
G Tiberio
F Virgilii
M C Digilio

Unità Operativa di Gastroenterologia, Ospedale Bambino Gesù, IRCCS, Roma, Italy
M Castro
F Ferretti
M Gambarara

Laboratorio di Analisi, Ospedale Bambino Gesù, IRCCS, Roma, Italy
F Colistro

Dipartimento di Medicina Sperimentale e Patologia, Università La Sapienza e Istituto CSS-Mendel, Roma, Italy
B Dallapiccola

Correspondence to:
Dr Giannotti,
giannott@opbg.net

Revised version received
24 July 2001
Accepted for publication
31 July 2001

Williams syndrome (WS) is a genetic disorder resulting from the deletion of a segment of about 2 Mb on chromosome 7q11.23, including the elastin gene (*ELN*).[1 2] The population prevalence has been estimated to be between 1 in 10 000 and 1 in 20 000.[3] Clinical features include distinctive facial anomalies, congenital heart defect, in particular supravalvular aortic stenosis, slight to severe mental retardation, herniae, and hypertension.[4–6] A diagnostic index for the diagnosis of WS has been proposed.[4] However, the diagnosis is often delayed, because the typical facial features may be not obvious at birth, the mean age at diagnosis being 6.4 years.[5]

Quite common gastrointestinal symptoms include feeding problems, colic, vomiting, constipation, and recurrent abdominal pain in the first years of life. Colon diverticula are found in adults.[5]

While coeliac disease (CD) has been reported in patients affected by different chromosomal disorders, including Down syndrome (DS) and Turner syndrome (TS),[7–10] association with WS has been reported only in sporadic subjects.[11–14] We are aware of only one study in which the prevalence of CD was assessed in a representative series of WS patients.[15]

We report the results of CD screening in 63 consecutive patients with WS undergoing a follow up evaluation, which provides new insight into the association between CD and this disorder.

Patients and methods

Sixty three WS patients, with a mean age of 11.1 years (SD 7.8), underwent screening for CD. The diagnosis of WS was confirmed in all cases by FISH analysis using the WSCR probe,[1] which discloses hemizygosity of the 7q11.23 region. Information about gastrointestinal symptoms, including diarrhoea, constipation, gastro-oesophageal reflux, anorexia, abdominal pain, and failure to thrive, were obtained from medical records or by interview. IgA and IgG antigliadin antibodies (AGA) and antiendomisium antibodies (AEA) were analysed in all patients. AGA IgA and IgG levels were studied by enzyme immunoassay (ELISA), while AEA IgA levels were determined by indirect immunofluorescence on a section of the lower third of monkey oesophagus, using a serum dilution of 1:5. Serum IgA values were also determined in all patients. Subjects with positive AGA IgA and AEA results in two consecutive assays underwent small bowel biopsy, and the diagnosis of CD was established in the presence of distinct villous atrophy,[16] which corresponded to the destructive lesions (type III) according to the classification reported by Marsh.[17]

The frequency of CD in this WS population was compared by chi-square test with that found in a published series of 17 201 Italian students aged 6-15 years,[18] subjected to AGA dosage analysis and intestinal biopsy.

Table 1 Coeliac disease and Williams syndrome: clinical features

Sex	F	F*	M	M	F	M
Age (at diagnosis)	1½ y	4 y	10 y	1½ y	4 y	2½ y
Diarrhoea	—	+	++	++	—	—
Constipation	+	—	—	—	—	+
Anorexia	+	+	+	++	—	—
Failure to thrive	+	+	+	+	+	+
Hypoalbuminaemia	—	—	—	+	—	—
Anaemia	—	—	—	—	++	—
Enamel defects	—	—	—	—	+	—

F = female; M = male; y = years.
*A sib with coeliac disease.

Results

Thirty of 63 WS patients had suffered from feeding difficulties, including vomiting or gastro-oesophageal reflux, in the first year of life. In two patients, symptoms were recorded during the first three years. Seven patients had diarrhoea, seven failure to thrive, five constipation, and four anorexia. Pyloric stenosis, colon diverticula perforation, and gallstones were diagnosed in one patient each. Seven subjects were positive for both AGA and AEA, while two were positive for AGA IgA and negative for AEA. Fifty four patients were negative both for AGA IgA and AEA. The six patients with isolated positive AGA IgG did not undergo biopsy in the absence of serum IgA defects. Hypoalbuminaemia and anaemia were diagnosed in one patient each. One patient had dental enamel defect. Jejunal biopsy was performed in six of the seven patients with positive AGA IgA and AEA IgA results. The parents of one patient refused biopsy. Villous atrophy consistent with CD was found in the six cases. Their clinical features are summarised in table 1. The prevalence of CD in the present sample of WS patients was 9.5%. This figure is highly significant compared to the frequency of CD calculated in a representative sample of age matched Italians ($p<0.001$). An improvement of clinical symptoms and normalisation of AGA and AEA dosage were noted in all CD patients treated with a gluten free diet.

Discussion

A previous study disclosed only one WS patient affected by CD in a series of 71 children undergoing specific screening.[15] This suggested that the association of WS and CD was rare and did not explain the gastrointestinal symptoms in these patients. However, the prevalence of CD in other types of chromosomal disorders, including DS and TS,[7–10 19–21] is high, being recently estimated at between 4% and 15%.

We have also previously reported CD in a WS subject.[14] This observation prompted a systematic screening of CD in a personal series of 63 patients. We found six cases of CD (9.5%), a figure significantly greater than the 0.54% (1 in 184 children) in the Italian paediatric population.[18] Failure to thrive was a constant feature in our CD patients, while anorexia and diarrhoea occurred in half of them. A less severe form of CD is found in some patients with WS and CD, as in some subjects with distinct chromosome disorders.[7–10 19 20] Previous studies have shown that positive AGA levels are quite common in DS and TS patients without histological features of CD. These observations have argued for the existence of a concomitant immune disorder,[7 10 20 21] while positive AGA and AEA results in our WS patients with CD could be explained by lack of susceptibility to autoimmune disorders.

In conclusion, the present results indicate the benefit of serological screening of CD by AGA and AEA analysis in patients with WS. In agreement with published guidelines supporting high specificity of AEA determinations in CD, jejunal biopsy should be indicated only in patients with positive AEA.

1 Ewart AK, Morris CA, Atkinson D, Jin W, Sternes K, Spallone P, Stock AD, Leppert M, Keating MT. Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nat Genet* 1993;**5**:11-16.
2 Curran ME, Atkinson DI, Ewart AK, Morris CA, Leppert M F, Keating MT. The elastin gene is disrupted by a translocation associated with supravalvular aortic stenosis. *Cell* 1993;**73**:159-68.
3 Burn J. Williams syndrome. *J Med Genet* 1986;**23**:389-95.
4 Preus M. The Williams syndrome: objective definition and diagnosis. *Clin Genet* 1984;**25**:422-8.
5 Morris CA, Demsey SA, Leonard CO, Dilts C, Blackburn BL. Natural history of Williams syndrome: physical characteristics. *J Pediatr* 1988;**113**:318-26.
6 Greenberg F. Williams syndrome professional symposium. *Am J Med Genet Suppl* 1990;**6**:85-8.
7 Castro M, Crinò A, Papadatou B, Purpura M, Giannotti A, Ferretti F, Colistro F, Mottola M, Digilio MC, Lucidi V, Borrelli P. Down's syndrome and celiac disease: the prevalence of high IgA-antigliadin antibodies and HLA-DR and DQ antigens in trisomy 21. *J Pediatr Gastroenterol Nutr* 1993;**16**:265-8.
8 Pueschel SM, Romano C, Failla P, Barone C, Pettinato R, Castellano Chiodo A, Plumari DL. A prevalence study of celiac disease in persons with Down syndrome residing in the United States of America. *Acta Paediatr* 1999;**88**:953-6.
9 Bonamico M, Bottaro G, Pasquino AM, Caruso-Nicoletti M, Mariani P, Gemme G, Paradiso E, Ragusa MC, Spina M. Celiac disease and Turner syndrome. *J Pediatr Gastroenterol Nutr* 1998;**26**:496-9.
10 Ivarsson SA, Carlsson A, Bredberg A, Alm J, Aronsson S, Gustafsson J, Hagenäs L, Häger A, Kriström B, Marcus C, Moëll C, Nilsson KO, Tuvemo T, Westphal O, Albertsson-Wikland K, Aman J. Prevalence of coeliac disease in Turner syndrome. *Acta Paediatr* 1999;**88**:933-6.
11 Chiaravallotti G, Rossomando V, Quinti S, Assanta N, Ughi C, Ceccarelli M. Sindrome di Williams-Beuren associata a malattia celiaca. *Minerva Pediatr* 1995;**47**:43-7.
12 Pankau R, Partsch CJ, Gosch A, Santer R. Williams-Beuren syndrome in kombination mit einer Zoliakie. *Monatsschr Kinderheilkd* 1993;**141**:577-80.
13 Pittsschieler K, Morini G, Crepaz R. Williams syndrome and coeliac disease. *Acta Paediatr* 1993;**82**:4.
14 Castro M, Ferretti F, Lucidi V, Papadatou B, Nicolosi L, Colozzo E, Gambarara M. Sindrome di Williams associata a celiachia: descrizione di un caso. *Riv Ital Ped* 1986;**12**: 751-2.
15 Santer R, Pankau R, Schaub J, Burgin-Wolff A. Williams-Beuren syndrome and celiac disease. *J Pediatr Gastroenterol Nutr* 1996;**3**:339-40.
16 Walker-Smith JA, Guandalini S, Schmitz J, Shmerling DH, Visakorpi JK. Revised criteria for diagnosis of coeliac disease. *Arch Dis Child* 1990;**65**:909-11.
17 Marsh MN. Gluten, major histocompatibility complex, and the small intestine. *Gatroenterology* 1992;**102**:330-54.
18 Catassi C, Fabiani E, Rätsch IM, Coppa GV, Giorgi PL, Pierdomenico R,. Alessandrini S, Iwanejko G, Domenici R, Mei E, Miano A, Marani M, Bottaro G, Spina M, Montanelli A, Barbato M, Viola F, Lazzari R, Vallini M, Guariso G, Plebani M, Cataldo F, Traverso G, Ughi C, Chiaravellotti G, Baldassarre M, Scarcella P, Bascietto F, Ceglie L, Valenti A, Paolucci P, Caradonna M, Bravi E, Ventura A. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatr* 1996;**412**:29-35.
19 George EK, Mearin ML, Bouquet J, von Blomberg BME, Stapel SO, van Elburg RM. High frequency of celiac disease in Down syndrome. *J Pediatr* 1996;**128**:555-7.
20 Hansson T, Annerén G, Sjöberg O, Klareskog L, Dannaeus A. Celiac disease in relation to immunologic serum markers trace elements, and HLA-DR and DQ antigens in Swedish children with Down syndrome. *J Pediatr Gastroenterol Nutr* 1999;**29**:286-92.
21 Hilhorst MI, Brink M, Wauters EAK, Houwen RHJ. Down's syndrome and coeliac disease: five new cases with a review of the literature. *Eur J Pediatr* 1993;**152**:884-7.