

Prevalence of celiac disease in children with Down syndrome screened by anti-tissue transglutaminase antibodies

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Down syndrome (DS) is the most common chromosomal disorder in newborns. The basic chromosomal abnormality in DS is the presence of trisomy of human chromosome 21. This defect results from a maternal meiotic non-disjunction of the chromosome 21 pair, or less commonly from other genetic aberrations, including translocation and mosaicism. Down syndrome is associated with mild-to-moderate learning disability, craniofacial abnormalities and hypotonia in early infancy. The association of immune-related disorders including celiac disease (CD) with DS is well-recognized.¹ Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. Typically, CD presents with chronic diarrhea, abdominal distention, and growth failure. In most cases, it is asymptomatic. Early diagnosis and treatment with a gluten free diet (GFD) may prevent various complications, including malignancy. The gold standard for the diagnosis of CD is small bowel biopsy and clinical improvement on GFD. Anti-endomysial (EMA) and anti-tissue transglutaminase (anti-tTG) antibodies are considered the most specific and sensitive tests among various available serological tests for CD screening. The objective of the present study is to investigate the prevalence of CD in children and adolescents with DS.

A retrospective study of all children and adolescents with DS attending Down Syndrome Clinic at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia, between January 2007 and August 2011 was conducted. Out of 130 patients identified, only 51 patients who had celiac screen performed were included in the analysis. Inclusion criteria were

confirmed trisomy 21 in children below the age of 18 years. Patients older than 18 years were excluded. The study was approved by the Biomedical Ethics Research Committee at King Abdulaziz University and the study was conducted according to the principles of Helsinki Declaration.

Demographic data, clinical symptoms, growth parameters, and laboratory investigations were retrieved and recorded. The specific DS growth charts were used to calculate the percentile for weight and height. The z scores for weight and height were calculated by using anthropometric software (Epi-Info, Centres for Disease Control and Prevention, Atlanta, GA, USA). Enzyme linked immunosorbent assay (ELISA) based anti-tTG (IgA) was carried out by Quanta Lit tTG ELISA kit (Inova, California CA, USA). Blood samples were separated and serum was pre-diluted with HRP washing buffer. Then HRP-IgA conjugate was added to each well of the ELISA wells and after incubation and washing TMB chromogen substrate was added to stop the reaction. Results were read at 450 nm within one hour of stopping the reaction. Final results were calculated and interpreted according to the high positive cutoff. The cutoff was 20 unit/ml. Total serum IgA was measured for all patients using the nephelometry system (Semen, Germany). Patients who had an elevated level of anti-tTG underwent upper endoscopy. Multiple small bowel biopsy specimens were obtained by an upper gastrointestinal endoscopy from the distal duodenum and sent for histopathological examination. The severity of small bowel mucosal damage was graded according to the Marsh classification from I to III. The diagnosis of CD was based on compatible serologic tests, small bowel biopsy, and response to a GFD.

Statistical analyses were performed using SPSS 19 software (SPSS, Inc, Chicago, III). Data were expressed as percentage of the total for categorical variables, as mean with standard deviation (SD) for normally distributed continuous variables, or as median with interquartile range for skewed distributed variables. When comparing groups, the p value of less than 0.05 was considered significant.

Fifty-one patients with DS were identified and screened for CD. The baseline characteristics are shown in Table 1. The median age was 3.58 years (range, 0.57-16.64 years). Thirty-eight (74.5%) were males. Twenty-six (51%) were Saudis. All patients had confirmed diagnosis by chromosomal analysis. Gastrointestinal symptoms recorded in 17 (33.3%) patients including constipation (n=12), vomiting (n=2), chronic diarrhea (n=1), and recurrent abdominal pain (n=1). Twelve

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Table 1 - Baseline characteristics of Down syndrome patients screened for celiac disease.

Baseline characteristics	n	(%)
Age (years)		
Mean±SD	4.69 ± 16.6	
Range	0.57 - 16.64	
Male to female ratio	2.9:1	
Nationality, Saudis	26	(51.0)
Associated autoimmune disorders		
Autoimmune thyroid disease	16	(31.4)
Type-1 diabetes mellitus	1	(2.0)
Growth parameters (n=44)		
Weight percentile		
<5 th	23	(52.3)
5 th to <50 th	1	(2.2)
50 th	10	(22.7)
50 th to <95 th	3	(6.8)
≥95 th		
Height percentile		
<5 th	6	(13.6)
5 th to <50 th	22	(50.0)
50 th	6	(13.6)
>50 th to <95 th	7	(16.0)
≥95 th	3	(6.8)
Body mass index (n=20)		
Mean±SD	18 ± 5.3	
Range	11.2 - 37	
Weight for age z-score		
Mean±SD	-1.98 ± 1.7	
Range	-5.6 - 2.44	
Height for age z-score		
Mean±SD	-2.44 ± 1.46	
Range	-6.0 - 0.88	

(25.5%) patients were anemic, 5 (14.3%) had elevated aspartate aminotransferase (ALT) level and 11 (28.9%) had low serum albumin level at the time of screening. Anti-tTG antibody was positive in 2 (4%) patients. None of the patients had IgA deficiency. All anti-tTG positive patients subsequently had upper gastrointestinal endoscopy with multiple small bowel biopsies. Only one patient had total villous atrophy compatible with Marsh grade III C giving a prevalence rate of 2% for confirmed CD. This patient was a 2.5-year-old male with associated hypothyroidism who had symptoms of diarrhea and poor weight gain.

The association between autoimmune disorders and DS has been observed for decades. It is not clear whether the autoimmunity plays a role in the etiology of DS, or the susceptibility gene or genes may exist on chromosome 21. The location of the autoimmune regulator (AIRE) gene and the presence of a susceptibility gene for type-1 diabetes on chromosome 21 may suggest a role for chromosome 21 in controlling autoimmunity.² However, none of the loci that are reported to be loci possibly related to CD susceptibility have been revealed in chromosome 21.³ Therefore, the reason for the association between CD and DS remains unknown.

Screening for CD has evolved over the years from the least specific serological tests, such as anti-gliadin antibodies (IgA and IgG) and antireticulin antibody to more sensitive and specific serological tests, such as ELISA based anti-tissue transglutaminase antibody (IgA) and immunofluorescence based anti-endomysial antibody (IgA), which are now widely used for identifying patients who might require small bowel biopsy. Both have sensitivity of more than 95% and specificity of almost 100%. Because both anti-tTG and anti-EMA test for IgA antibodies, total IgA estimation is recommended to avoid false negative cases associated with IgA deficiency. Patients with DS have higher risk of developing CD compared to the general population (adjusted rate ratio 4.7 (95% confidence interval: 1.3-12.2)).¹ A prevalence rate of 4.5% was reported from a multicenter Italian study of 1,202 DS patients.⁴ No epidemiological studies, indicating the prevalence of CD in children in Saudi Arabia were published. In addition, and to the best of our knowledge, no publications exist about the local prevalence of CD in children with DS. Data from the Middle East regarding screening of DS for CD are limited. Shamaly et al⁵ found CD in 2 out of 52 Arab children from Haifa with DS screened using various serological markers giving a prevalence of 3.8%. Our study found a 4% seropositivity using anti-tTG and total immunoglobulin A and a 2% prevalence of biopsy proven CD in 51 children with DS which is considered among the lowest prevalence rates reported.

Screening of children with DS for CD has been recommended by professional organizations and in DS health care guidelines. In the general population, most of the patients with CD are asymptomatic. In contrast, DS associated CD patients tended to have more overt clinical symptoms than silent disease. Therefore, physicians are required to have a lower threshold for testing for CD in DS symptomatic patients. There has been reluctance in recommending routine screening for asymptomatic DS patients since the long term implications of screening are unknown. In addition to the doubtful cost-effectiveness of screening asymptomatic children, in order to prevent lymphoma that leads to mortality in CD patients. The study is limited by its retrospective nature and lack of control group in addition to the relatively small number of patients.

Future research should focus in finding none invasive reliable methods for diagnosing CD in DS population.

In conclusion, CD is an important comorbidity in children with DS; therefore, the authors recommend routine screening for CD in patients with DS in order to avoid associated complications.

Received 8th October 2011. Accepted 12th December 2011.

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References

1. Goldacre MJ, Wotton CJ, Seagroatt V, Yeates D. Cancers and immune related diseases associated with Down's syndrome: a record linkage study. *Arch Dis Child* 2004; 89: 1014-1017.
2. Concannon P, Onengut-Gumuscu S, Todd JA, Smyth DJ, Pociot F, Bergholdt R, et al. A human type 1 diabetes susceptibility locus maps to chromosome 21q22.3. *Diabetes* 2008; 57: 2858-2861.
3. Babron MC, Nilsson S, Adamovic S, Naluai AT, Wahlstrom J, Ascher H, et al. Meta and pooled analysis of European coeliac disease data. *Eur J Hum Genet* 2003; 11: 828-834.
4. Bonamico M, Mariani P, Danesi HM, Crisogianni M, Failla P, Gemme G, et al. Prevalence and clinical picture of celiac disease in italian down syndrome patients: a multicenter study. *J Pediatr Gastroenterol Nutr* 2001; 33: 139-143.
5. Shamaly H, Hartman C, Pollack S, Hujerat M, Katz R, Gideoni O, et al. Tissue transglutaminase antibodies are a useful serological marker for the diagnosis of celiac disease in patients with Down syndrome. *J Pediatr Gastroenterol Nutr* 2007; 44: 583-586.

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Rostami-Nejad M, Rostami K, Sanaei M, Mohebbi SR, Al-Dulaimi D, Nazemalhosseini-Mojarad E, et al. Rotavirus and coeliac autoimmunity among adults with non-specific gastrointestinal symptoms. *Saudi Med J* 2010; 30: 891-894.

Bin-Abbas BS, Faiyaz-Ul-Haque M, Al-Fares AH, Al-Gazlan SS, Bhuiyan JA, Al-Muhsen SZ. Autoimmune polyglandular syndrome type 1 in Saudi children. *Saudi Med J* 2010; 31: 788-792.

Aydog E, Yesilli O, Sever A, Usan H. Dermatitis herpetiformis and rheumatoid arthritis. *Saudi Med J* 2006; 27: 881-884.