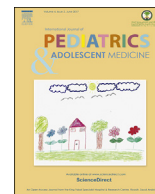


HOSTED BY



Contents lists available at ScienceDirect

International Journal of Pediatrics and Adolescent Medicine

journal homepage: <http://www.elsevier.com/locate/ijpam>

Review article

Prevalence of celiac disease in Saudi children with Down syndrome: A retrospective study



Fawzah AlRuwaily^a, Hoda A. Kattan^{a,*}, Ali M. AlMehaidib^b, Wajeeh AlDekhail^b

^a Section of General Pediatrics, Pediatrics Department, MBC58, Saudi Arabia

^b Section of Gastroenterology, Pediatrics Department, King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia

ARTICLE INFO

Article history:

Received 2 June 2016

Received in revised form

26 December 2016

Accepted 27 December 2016

Available online 9 February 2017

Keywords:

Celiac disease

CD

Down syndrome

DS

Saudi

Children

ABSTRACT

Celiac disease (CD) is an immune-mediated disease affecting the small intestine secondary to gluten exposure. The currently available treatment is lifelong adherence to a gluten-free diet (GFD). Several disorders are known to be associated with celiac disease, including Down syndrome (DS). In several studies, the prevalence of CD in DS ranged between 4 and 17%.

CD is prevalent in Arabs; however, few studies have been performed to determine the prevalence of CD in DS patients. Our study aimed to determine the prevalence of CD in Saudi Down syndrome patients using serological markers and small bowel biopsy.

This is a retrospective study in which files relating to Down syndrome patients who were followed up in a general pediatric clinic at King Faisal Specialist Hospital and Research Center were reviewed regarding demographic data, serological markers and biopsy results.

Of the total number of patients reviewed (91), 7 were excluded because data were missing; the remaining 84 patients included 35 females and 49 males. The age range of the patients at the time of screening was from 1 to 18 years. Patient demographic data are shown in Table 1. Among the studied patients, anti-gliadin antibody (AGA) IgA was high in 27 patients (32.14%), and AGA IgG was high in 44 patients (52.38%). Twelve patients (14.28%) tested positive and 58 (69.04%) tested negative for anti-endomysial antibodies. Anti-tissue glutaminase antibody IgA was found to be high in 13 patients (15.5%) and normal in 54 patients (64.28%). Serum IgA levels were normal in 36 patients (43%) and low in 1 patient (1.2%). Biopsy was performed in 22 patients who tested positive for anti-endomysial or anti-tissue transglutaminase antibodies. The biopsies provided positive results in 9 patients (10.7%).

Our study showed a confirmed prevalence of 10.7% for celiac disease in Saudi patients with Down syndrome based on serology and biopsy; together with previous cases reported in the literature, this result indicates a need to screen these patients for celiac disease.

© 2017 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Celiac disease (CD) is an autoimmune-mediated disease affecting the small intestine secondary to gluten exposure in genetically susceptible individuals. The currently available treatment is life-long adherence to a gluten-free diet (GFD).

The globally accepted diagnostic criteria were promulgated by

the European Society of Pediatric Gastroenterology Hepatology and Nutrition in 1990 [1]. Celiac disease can present with a variety of gastrointestinal and non-gastrointestinal symptoms, although some patients are asymptomatic [2]. The diagnosis can be based on serological markers, genetic studies and confirmed by small intestine biopsy. The serological markers include anti-gliadin antibodies (AGA) IgA and IgG which are sensitive but less specific and can be elevated in other conditions [3]. Tests based on anti-endomysial antibodies (EMA-IgA) have high sensitivity and specificity (95% and 100%, respectively), and the current practice is to conduct an intestinal biopsy when a patient tests positive [4]. Anti-tissue transglutaminase IgA antibodies (TTG) are similar to EMA-IgA in terms of sensitivity and specificity. Although these tests are good, they exhibit some limitations [5]. Intestinal biopsy is the gold

* Head Section of General Pediatric, Pediatrics Department, MBC58, Riyadh 11211, Saudi Arabia.

E-mail address: hoda@kfsshr.edu.sa (H.A. Kattan).

Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

standard procedure for diagnosing CD [6–8]. Histological changes can range from increased intraepithelial lymphocytes and crypt hyperplasia to total villous atrophy. Those changes have been graded by March from 0 to 4, where grade one is considered non-specific and grades 3 and above are considered diagnostic for celiac disease [8,9].

Several disorders are known to be associated with celiac disease, including Down syndrome and Turner syndrome [10,11]. Additionally, the disease can be found with other autoimmune disorders; e.g., type 1 diabetes mellitus, Addison's disease, and autoimmune thyroiditis [12].

Down syndrome (DS) is chromosomal anomaly that can lead to multiple systemic involvements, such as those with the cardiac, gastrointestinal and central nervous systems. In addition, DS can be associated with autoimmune diseases, such as celiac disease. The prevalence of celiac disease in DS ranges between 4 and 17%.

In a small-population study by Saadah et al examining 51 Saudi children with Down syndrome, 4% had positive serological markers, and 2% had proven biopsy of celiac disease [13].

The aim of our study was to determine the prevalence of biopsy proven celiac disease in Saudi children with Down syndrome and to describe the serological characteristics, presence of symptoms and other disorders associated with this disease.

2. Patients and methods:

This is retrospective chart review study of Saudi children with Down syndrome visiting King Faisal Specialist Hospital and Research Center, Riyadh between 2003 and 2013 who were screened for celiac disease. Our inclusion criteria were as follows: children less than 18 years of age and confirmed Down syndrome by chromosomal analysis; both males and females were included.

The collected data included age, gender, serological test and biopsy results.

Children with positive biopsy results were further reviewed regarding the presence of symptoms, growth patterns (plotted against a specific Down syndrome growth chart) and hemoglobin level.

Total IgA levels were determined by turbidimetry and were considered normal when <70 ng/dl. Anti-tissue glutaminase antibodies were determined by enzyme-linked immunosorbent assay (ELISA) with human recombinant TTGA as antigen using a commercially available kit (Eu-tTGA, Eurospital, Trieste, Italy), and the test was considered positive at levels >20 units. Anti-gliadin IgA and IgG were determined using a modified enzyme-linked immunosorbent assay (ELISA) method named the fluoroenzyme immune assay (FEIA) using a Pharmacia UniCAP-100 system; children were considered IgA-positive if levels were >3 mg/l and IgG-positive if levels were >18 mg/l.

Anti-EMA and ARA were determined using indirect immunofluorescence methods involving rat kidney and monkey esophagus tissue substrates, respectively (INOVA CAT#508170 and 5083300), and the results are reported as positive, weakly positive or negative [15]. Biopsy was considered positive at March grade 3 and above [8,9].

Statistical analysis was performed using SPSS software; the Chi square test was used for categorical variables, and Fisher's exact test was used for continuous variables. *P* values < 0.05 were considered significant.

3. Results

The total number of patients reviewed was 91; of these, 7 were excluded because data were missing, and the remaining 84 patients included 35 females and 49 males. The age range of the patients at

the time of screening was 1–18 years. Patient demographic data are reported in AGA Table 1. Among all patients, AGA IgA was high in 27 (32.14%) and IgG was high in 44 (52.38%). Twelve patients (14.28%) tested positive and 58 (69.04%) tested negative for anti-endomysial antibodies. Anti-tissue glutaminase antibody IgA was found to be high in 13 patients (15.5%) and normal in 54 patients (64.28%). Serum IgA levels were normal in 36 patients (43%) and low in 1 patient (1.2%) and were not measured in the remaining patient (1.2%) Table 2.

Biopsy was performed in 22 patients who tested positive for anti-endomysial or anti-tissue transglutaminase antibodies. The biopsies were positive in 9 of these patients (10.7%).

Patients with positive biopsy were reviewed; 6 patients had symptoms including poor weight gain in 2, vomiting in 2, diarrhea in 1 and constipation in 2. Three of these patients were asymptomatic Table 3.

4. Discussion

Several disorders are known to be associated with celiac disease; these diseases include Down syndrome (in 4–14% of patients), type I diabetes mellitus (in 3–8% of patients), Turner's syndrome (in 4.1–8.1% of patients), William's syndrome (in 8.2% of patients) and IgA deficiency (in 2% of patients) [7]. Strong evidence also exists that first-degree relatives of celiac patients are at increased risk of developing CD, with a prevalence of 4–5% [10].

Down syndrome (DS, also known as trisomy 21) is a major cause of mental retardation, affecting 1 of 800 newborns. Approximately 95% of DS cases are caused by the presence of 3 copies of chromosome 21 (complete T21). DS can lead to multiple system involvement, including the cardiac, gastrointestinal, and central nervous systems, among others. In addition, DS can also be associated with autoimmune diseases such as celiac disease, autoimmune thyroiditis, and type I DM [11,16,18–22].

Table 1

Baseline demographic data of patients with Down syndrome who were screened for celiac disease.

Baseline characteristics	Mean ± SD	range
Age (y)	6.1 ± 3.1	1–18 y
Female (n)	35	
Male (n)	49	
Height (cm)	101 ± 22.2	(53–154)
Weight (kg)	20.5 ± 14.3	(3.2–77.5)
Hgb (mg/dl)	128.5 ± 17.1	(77–170)
TSH (μmol/l)	6.1 ± 2.8	(1.4–14.4)

Table 2

Serological marker and biopsy results.

Serological markers	Frequency (%)
Antigliadin antibody	
IgG	
High	45 (57.7%)
Normal	33 (42.3%)
IgA	
High	27 (32.14%)
Normal	50 (52.38%)
EMS	
Positive	12 (14.3%)
Negative	58 (69.04%)
tTG	
High	13 (15.47%)
Normal	54 (64.28%)
Biopsy	
Positive	9 (41%)
Negative	13 (60%)

Table 3

Characteristics of down syndrome patients with positive biopsy.

Patient	Sex	IgA	AGA IgA	AGA IgG	EMS	TTG	WT (percentile)	Hgb mg/dl	symptoms	Thyroid status
1	M	ND	H	H	POS	H	75	11	Gastritis	Hypo
2	F	N	H	H	POS	H	50	14	No	Hypo
3	F	N	H	H	NEG	N	25	14	FTT	Hypo
4	F	N	H	H	POS	H	5	9.9	Vomiting/FTT	Hypo
5	F	N	N	H	NEG	H	95	14	NO	Hypo
6	F	H	H	H	POS	H	50	12	NO	N
7	F	H	H	N	NEG	N	95	13.5	Constipation	Hypo
8	F	H	N	N	NEG	ND	5	9.9	Diarrhea	N
9	F	ND	N	H	POS	ND	50	9	constipation	Hypo

(M = male; F = female; N = normal; ND = not done; H = high; POS = positive; NEG = negative; FTT = failure to thrive; Hypo = hypothyroidism). (WT based on a standard Down syndrome growth chart).

CD is also prevalent in other Arab populations and is underdiagnosed in high-risk groups; however, limited studies have been conducted in Arabic countries to determine the prevalence of CD in DS patients. In a study performed in Tunisia, in which 27 patients with DS were studied prospectively, more than 10% of the patients were confirmed to have CD by intestinal biopsy [16]. In other studies, the prevalence was found to range between 2 and 3.8% [13,17].

In a study of 123 Saudi children with type I diabetes mellitus, six (4.9%) had histological evidence of CD, and all were asymptomatic [14].

Another cross-sectional study was conducted in 42 Saudi children with idiopathic juvenile rheumatoid arthritis (JRA) (2.38%) with positive AEA and showed histological evidence of intestinal villous atrophy [15].

The prevalence of CD in patients with DS is high based on biopsy results; these results are similar to those found in the previous studies mentioned. Most patients with positive biopsies are symptomatic; however, some had no symptoms despite showing features of CD in their biopsy; this might have occurred because detection was early and occurred before the patients became symptomatic. The patients also had other associated autoimmune disorders, such as hypothyroidism, which is quite common in patients with Down syndrome. The prevalence found in our study might have been greater if we consider that some patients were not measured for total IGA level and normal serological markers. In addition, not all patients were measured for TTG IgA levels because this test was unavailable at the time of screening.

The study was performed at a tertiary hospital with certain acceptance criteria, and this might have affected our result.

5. Conclusion

Our study showed a high prevalence of celiac disease in patients with Down syndrome based on positive serology and biopsy results, and these patients included both symptomatic and asymptomatic individuals. The prevalence might be higher when we consider that patients with minimal histological changes might have celiac disease. This high prevalence indicates the need to screen such patients, even if they are asymptomatic.

Conflict of interest

We confirm that none of the authors have any conflicts of interest associated this manuscript.

References

- [1] Fasano A, Troncone R, Branski D. *Frontiers in celiac disease. Pediatr Adolesc* 2008;12:1–11.
- [2] Murray JA. The widening spectrum of celiac disease. *Am J Clin Nutr* 1999 Mar;69(3):354–65.
- [3] Volta U, Granito A, Fiorini E, Parisi C, Piscaglia M, Pappas G, et al. Usefulness of antibodies to deamidated gliadin peptides in celiac disease diagnosis and follow-up. *Dig Dis Sci* 2008 Jun;53(6):1582–8.
- [4] Caicedo RA, Hill I. Current guidelines for the diagnosis and treatment of celiac disease. In: Fasano A, Troncone R, Branski D, editors. *Frontiers in celiac disease. Karger*; 2008. p. 107–13.
- [5] Lagerqvist C, Dahlbom I, Hansson T, Jidell E, Juto P, Olcen P, et al. Antigliadin immunoglobulin A best in finding celiac disease in children younger than 18 months of age. *J Pediatr Gastroenterol Nutr* 2008 Oct;47(4):428–35.
- [6] Pais WP, Duerksen DR, Pettifrew NM, Bernstein CN. How many duodenal biopsy specimens are required to make a diagnosis of celiac disease? *Gastrointest Endosc* 2008 Jun;67(7):1082–7.
- [7] Gianfrani C, Troncone R, La Cava A. Autoimmunity and celiac disease. *Mini Rev Med Chem* 2008 Feb;8(2):129–34.
- [8] Bonamico M, Thanasi E, Mariani P, Nenna R, et al. Duodenal bulb biopsies in celiac disease: a multicenter study. *J Pediatr Gastroenterol Nutr* 2008 Nov;47(5):618–22.
- [9] Memeo L, Jhang J, Hibshoosh H, Green PH, Rotterdam H, Bhagat G. Duodenal intraepithelial lymphocytosis with normal villous architecture: common occurrence in *H. pylori* gastritis. *Mod Pathol* 2005 Aug;18(8):1134–44.
- [10] Mazzili MC, Ferrante P, Mariani P, Martone E, Petronzelli F, Trigloni P, et al. A study of Italian pediatric celiac disease patients confirms that the primary HLA association is to the DQ (alpha 1*0501, beta 1*0201) heterodimer. *Hum Immunol* 1992 Feb;33(2):133–9.
- [11] Wouters J, Weijerman ME, van Furth AM, et al. Prospective human leukocyte antigen, endomysium immunoglobulin A antibodies, and transglutaminase antibodies testing for celiac disease in children with Down Syndrome. *J Pediatr* 2009 Feb;154(2):239–42.
- [12] Korponay-Szabo IR, Dahlbom I, Laurila K, et al. Elevation of IgG antibodies against tissue transglutaminase as a diagnostic tool for coeliac disease in selective IgA deficiency. *Gut* 2003 Nov 52;(11):1567–71.
- [13] Saadah O, Al-Aama J, et al. Prevalence of celiac disease in children with Down syndrome screened by anti-tissue transglutaminase antibodies. *Saudi Med J* 2012;33(2):208–10.
- [14] Al-Ashwal A, Shabib S, Sakati N, et al. Prevalence and characteristics of celiac disease in type 1 diabetes mellitus in Saudi Arabia. *Saudi Med J* 2003;24(1):1113–5.
- [15] Al-Mayouf S, Al-Mehaidib A, Al-Kaff M. The significant of elevated serological markers of celiac disease in children with juvenile rheumatoid arthritis. *Saudi J Gastroenterol* 2003;9(2):75–8.
- [16] Zitouni M, Gharbi Yermi M, Laadhar Kharrat L, et al. Prevalence of serological markers in celiac disease in trisomy 21 in Tunisia. *Ann Biol Clin* 2003;61:673–7.
- [17] Rawashdeh MO, Khalil B, Raweily E. Celiac disease in Arabs. *J Pediatr Gastroenterol Nutr* 1996 Nov;23(4):415–8.
- [18] Shamaly H, Hartman C, Pollack S, Hujeat 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 May;44(5):583–6.
- [19] Zitouni M, Gharbi Y, et al. Prevalence of serologic markers in celiac disease. *Ann Biol Clin Paris* 2003 Nov-Dec;61(6):673–7.
- [20] Alanay Y, Buduro A, et al. Celiac screening in 100 down syndrome Turkish patients. *Turk J Pediatr* 2005, April– Jun;47(2):138–40.
- [21] Kurppa K, Collin P, Vilijamaa M, Haimila K, Saavalanainen P, Partanen J, et al. Diagnosing mild enteropathy celiac disease: a randomized, controlled clinical study. *Gastroenterology* 2009 Mar;136(3):816–23. Epub 2008 Nov 24.
- [22] Leeds JS, Hopper AD, Sanders DS. Coeliac disease. *Br Med Bull* 2008;88(1):157–70.