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Prevalence of celiac disease in patients with type 1 diabetes mellitus in the south of Iran

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Background/aims: *Celiac disease is a chronic enteropathy caused by hypersensitivity to gluten. An increased prevalence of celiac disease has been found in children with diabetes mellitus type 1. The large differences in the frequency of celiac disease in different countries show a great regional variability. Our aim was to detect the prevalence of celiac disease in diabetes mellitus type 1 children among southern Iranians.* ***Materials and Methods:*** *A prospective study was conducted on 83 diabetes mellitus type 1 children from the south of Iran. They were tested for the presence of anti-tissue transglutaminase immunoglobulin A antibody and total immunoglobulin A level. The patients testing immunoglobulin A anti-tissue transglutaminase-positive were offered small bowel biopsy.* ***Results:*** *Eighty-three children with diabetes mellitus type 1 (49 females, 34 males) aged 10.38±4.7 years were enrolled. None of the patients was immunoglobulin A deficient. Twelve diabetic children had a high titer of anti-tissue transglutaminase immunoglobulin A (14.4%). In four patients, biopsy was in favor of celiac disease (4.8%).* ***Conclusions:*** *Our study showed that the prevalence of celiac disease in diabetes mellitus type 1 children in Iran is more than in America and Europe but similar to that observed in Turkey. The age of the patient and duration of disease had an effect on this prevalence, and more studies should be done to determine the effects of ethnic, genetic and environmental factors such as diet to identify the reasons for these differences.*

Key words: Celiac disease, type 1 diabetes mellitus, Iran

Güney İran'da tip 1 diyabet hastalarında çölyak hastalığı prevalansı

Amaç: *Çölyak hastalığı, glutene karşı gelişen aşırı duyarlılığa bağlı ortaya çıkan kronik bir enteropatidir. Tip 1 diyabetli çocuklarda çölyak hastalığının prevalansının yüksek olduğu tespit edilmiştir. Çölyak hastalığı sıklığında bölgesel olarak büyük değişkenlikler görülmektedir. Bu çalışmanın amacı, güney İranlı Tip 1 diyabetli çocuklarda çölyak hastalığı sıklığının tespit edilmedir.* ***Gereç ve Yöntem:*** *Tip 1 diyabet tanısı olan güney İran'lı 83 çocuğu kapsayan prospektif bir çalışma düzenlendi. Hastalarda anti-doku transglutaminaz immunglobulin A antikorları ve immunglobulin A düzeyleri araştırıldı. İmmunglobulin A anti-doku transglutaminaz pozitif olanlara ince barsak biyopsisi yapılması önerildi.* ***Bulgular:*** *Çalışmaya 83 Tip 1 diyabetli çocuk (49 kız, ortalama yaş: 10,38±4,7) dahil edildi. Hiçbir çocukta immunglobulin A eksikliği tespit edilmedi. Çocuklardan 12'sinde (%14,4) anti-doku transglutaminaz titresi yüksek bulundu. Bu çocuklardan 4'ünde (%4,8) biyopsi çölyak hastalığını destekler özellikteydi.* ***Sonuç:*** *Çalışmamıza göre Tip 1 diyabet olan çocuklarda çölyak hastalığı sıklığı Amerika veya Avrupa'dakinden yüksek; Türkiye'dekine benzerdir. Hasta yaşı ve hastalık süresi ile prevalans arasında ilişki tespit edildi ve etnik, genetik ve diyet gibi çevresel faktörlerin etkisini araştıran çalışmalara ihtiyaç vardır.*

Anahtar kelimeler: Çölyak hastalığı, tip 1 diyabet, İran

INTRODUCTION

Celiac disease (CD) is a chronic enteropathy caused by hypersensitivity to gluten. An increased prevalence of CD has been found through screening programs in children with type 1 diabetes mellitus (DM1) compared with non-diabetic children. Prevalence of CD in populations with DM1 from different geographical areas varies widely, ranging from 0.97-16.4% (1-20). Recently, studies in North America have shown a high prevalence of CD similar to that seen in Western Europe (9-11),

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Africa (18) and Asia (16). The co-occurrence of both diseases may be explained by a similar genetic background and similar mechanisms for the autoimmune process. More than 90% of the patients with CD and approximately 60-70% of type 1 diabetics carry the human leukocyte antigen (HLA) heterodimer DQA1* 0501, DQB1*0201 (21-23). The large differences in the frequency of CD in DM1 children (0.97-16.4%) in different countries show a great regional variability. This may also be due to the differences in the type of antibody used for screening, size of the cohort, and duration of DM1.

There is a paucity of data on the prevalence of CD in DM1 children among southern Iranians. Therefore, the aim of the present study was to determine whether Iranian children and adolescents with DM1 have a similar or different risk of having CD than that described in other regions. For this purpose, we screened the diabetic patients with anti-tissue transglutaminase (tTG) antibody.

MATERIALS AND METHODS

A prospective study was conducted on 83 DM1 children from the south of Iran referred to diabetic clinics of Shiraz University of Medical Sciences, subspecialty of pediatric endocrinology. They were tested for the presence of anti-tTG immunoglobulin (Ig)A antibody and total IgA level. For this purpose, 3 ml of peripheral venous blood was collected from each subject. Serum was obtained, aliquoted, and immediately stored at -80°C, until assay. Serum total IgA was measured by nephelometry in all patients, and anti-tTG antibody was checked with ELISA method (BioRad, Marnes-la-Coqette, France). A positive result of tTG was recorded if tTG was >18 u/ml. To detect possible serum IgA deficiency, a condition occurring with a frequency of approximately 3% in both diabetic and the CD population (24), the total serum IgA levels were measured nephelometrically in all patients. In patients with IgA deficiency and normal anti-tTG IgA level, anti-tTG IgG was measured. The patients testing IgA-tTG-positive were offered small bowel biopsy. Three endoscopic mucosal biopsies were obtained from the distal duodenum, and the mucosa was morphologically graded according to well-established criteria (25). Intraepithelial lymphocytes (IEL) per 500 enterocytes were counted in five distinct villous microscopic areas after immunohistochemical staining for the pan-T-cell marker CD4SRO, using the streptavidin-biotin method. An elevated IEL count was defined as >40 IEL per 100 enterocytes (26). Biopsy specimens were analyzed according to a modified Marsh classification (27). The diagnosis of CD was made by the following criteria: villous atrophy, elevated IEL count, and hyperplasia of the crypts. The patients with biopsies consistent with CD were then referred for dietetic advice about a gluten-free diet.

Statistics

The Statistical Package for the Social Sciences (SPSS) program was used to determine the median age, sex, weight, height, body mass index (BMI), and family history of DM1 and DM2. The comparison of median age and BMI with tTG IgA and biopsy was done using independent T-test and the comparison of sex with tTG IgA and biopsy was done by chi-square test. Data was mentioned as median±SD.

Ethics

The Ethics Committee of Shiraz University of Medical Sciences approved the study, and written consent was obtained from the children's parents or guardians after describing the study in detail.

RESULTS

Eighty-three children and adolescents with DM1 were enrolled in this study; 49 (59%) were female and 34 (41%) were male. The mean age of the children was 10.38±4.7 years (min=1 year, max=24 years), mean height was 137±24.8 cm (min=115 cm, max=179 cm), mean weight was 34.5±14.7 kg (min=6.3 kg, max=73 kg), and mean BMI was 22.34±5.4 kg/m^2 (min=10.77 kg/m^2, max=57.5 kg/m^2). One of the patients had a family history of DM1, and 37 patients had a family history of DM2. None of the patients was IgA-deficient. Twelve diabetic children had a high titer of tTG IgA (14.4%), and none of them was IgA-deficient. Biopsy was done in these 12 patients, and in 4 patients it was in favor of CD (4.8%).

The BMI of children with positive tTG result was 17.6±5.7 and of children with negative tTG result was 17.7±3.05. There was no correlation between BMI and the tTG test result ($p>0.05$). Among 49 girls included in this study, 8 had positive tTG result, and among 34 boys enrolled in this study, 4 had positive tTG result. There was no correlation between sex and CD ($p>0.05$). Children with negative tTG result were aged 9.9±4.5 years, while those with positive tTG result were aged 13.2±4.8 ye-

ars, and there was a significant correlation between the age of diabetic children and positive tTG result (p=0.022). Duration of the disease in negative tTG results was 1.1±0.4 years and in positive tTG results was 3.4±0.8 years, and there was a significant correlation between the duration of disease and positive tTG results (p=0.04).

The biopsy result was positive in 4 patients (3 female, 1 male). The mean age in positive biopsy results was 18.7±3.77 years and in negative biopsy results was 9.96±4.3 years. Mean BMI in positive biopsy result was 20.63±3.5 and in negative biopsy result was 17.5±5.4. There was no correlation between the result of biopsy and sex (p>0.05) or BMI (p>0.05). However, there was a significant correlation between age or duration of disease and positive biopsy results (p=0.000, p=0.015).

Family history of DM1 or DM2 had no correlation with CD (either tTG or biopsy result) (p>0.05).

One of 4 patients with positive biopsy results had an increased IEL count (47/400 enterocytes) and partial villous atrophy (Marsh grade 3a). Three patients had partial villous atrophy with IEL counts of 28.6, 30 and 37/100.

DISCUSSION

Our study showed that the prevalence of CD in DM1 children in the south of Iran was 14.4% according to tTG IgA titer and 4.8% according to the biopsy results, and there was a correlation between CD and age of the diabetic child and duration of DM1 (p<0.05).

Despite many similarities between DM1 and CD, such as underlying genetic susceptibility associated with HLA class II and autoimmune phenomena, the prevalence rate of CD in DM1 appears to differ greatly in different geographical areas (1-20). Both diseases were associated with a high frequency of HLA DQA1* 0501 and DQB1*0201 (DQ2) molecules worldwide (5). The CD prevalence that was found by serology in other studies was: Sweden, 4.6% (9); Italy, 4.5% (10); Czech Republic, 4.1% (5); United Kingdom, 4.8% (11); Austria, 5.1 (12); Canada, 5.1% (2); United States of America, 4.6% (4); Brazil, 8.7% (1); Tunisia, 8.3% (18); Spain, 13.4% (19); Turkey 20.8% (20); and the north of Iran, 14.28% (16). The prevalence detected in our diabetic population was much higher than in Europe and North America and was close to that in the north of Iran and Turkey. Thus, it may due to differences in genetics and the environment. Further studies are required to establish whether the prevalence we found reflects the ethnic diversity of other areas or may be due to differences in diet (starting gluten earlier in life or more gluten in the diet) or may be due to some HLA that makes them prone to CD. Our study also showed that screening for CD with serologic tests in diabetic patients is necessary to facilitate early diagnosis and prevent severe complications because CD was more common in our diabetic children than in many other areas.

Among 12 patients with positive tTG results in our study, 4 had positive biopsy results (4.8% of diabetic children). In all previous studies in other areas of the world (1-20), the prevalences of biopsy-positive patients are nearly the same (1-5%). It has been demonstrated recently that all patients with elevated serum tTG IgA and intact duodenal villi will develop CD (28). In another study, serology found at the diagnosis of DM1 was predictive of future development of CD (29). Therefore, a "normal biopsy" never excludes the underlying presence of latent CD (30).

Like in other studies (18,31-34), diabetics with positive tTG result were older and had longer duration of disease, but in contrast, DM1 did not occur at an earlier age in other studies. Some studies also showed the latter (23,35).

We found that there was no correlation between sex, BMI and family history of DM in developing CD in our DM1 children. However, as in other studies (18,31-34), females in our study had positive serology more frequently, whereas in serology-negative children with DM1, there was no female predominance, as is normally found in children with diabetes.

Our finding confirms that CD may be present but remain unsuspected in DM1 subjects, consistent with previous reports showing that most cases of CD in DM1 appear to be atypical or silent, detected only by a screening procedure (11,37). The consequences of long-standing unrecognized CD in diabetics are that these patients are at risk of avoidable complications, including poor growth and diabetic control (38). Further, we showed that prevalence of CD in our DM1 children was more than that in Europe and America, but close to that seen in the Middle East (1-20). Thus, many other genetic, ethnic and environmental factors such as diet could have an effect on this autoimmune disorder. Many cohort and case control studies should be done in this regard.

In conclusion, our study showed that the prevalence of CD in DM1 children in the south of Iran was 14.8% through serology and 4.8% through biopsy. It is higher than the prevalence in America and Europe but similar to that in Turkey and the north of Iran. The age of the patient and duration of disease had an effect on this prevalence, and more studies should be done to determine the effect of ethnic, genetic and environmental factors such as diet to identify the reason(s) for the differences.

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