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The prevalence of manifest and latent celiac disease in type 1 diabetes mellitus

Tip 1 "diabetes mellituslu" hastalarda gizli ve açık çölyak hastalığının sıklığı

Serkan GÜVENÇ[1], Sabahattin KAYMAKOĞLU[1], Nuray GÜREL[2], Kubilay KARŞIDAĞ[3], Kadir DEMİR[1], Dinç DİNÇER[1], Çiğdem KEKİK[4], Serpil SALMAN[3], Temel YILMAZ[3], Fatih BEŞIŞIK[1], Yılmaz ÇAKALOĞLU[1]

Istanbul University, Istanbul Medical Faculty, Departmens of Gastroenterohepatology[1], Microbiology[2], Diabetes[3] and Medical Biology[4], Istanbul

Background/aims: *Celiac disease and type 1 diabetes mellitus are both autoimmune diseases which have a common genetic predisposition. The aim of this study was to determine the prevalence of manifest and latent celiac disease in type 1 diabetic patients.* ***Methods:*** *Anti-endomysium IgA was tested by indirect immunofluorescence using sections of human umbilical cord for screening in 100 adult patients with type 1 diabetes mellitus and in 80 age and sex matched controls with no known disease. Distal duodenal biopsy, human leukocyte antigen typing, urinary D-xylose excretion test, stool analysis, biochemistry profile, blood counts, serum ferritin level and small intestinal radiography were performed in anti-endomysium IgA positive cases. Small bowel biopsy specimens consistent with celiac disease were defined as manifest celiac disease, while positive anti-endomysium IgA and normal intestinal histology with the presence of human leukocyte antigen class II antigens consistent with the disease were defined as latent celiac disease.* ***Results:*** *Anti-endomysium IgA was positive in eight diabetic patients, while it was negative in all controls. Celiac disease was found in a total of six (6%) patients, four with manifest and two with latent disease. Only one patient had symptoms.* ***Conclusions:*** *The prevalence of celiac disease is increased in patients with type 1 diabetes mellitus. Since many patients may be asymptomatic, it is suggested that all diabetic patients should be screened for this disease.*

Key words: Celiac disease, anti-endomysium IgA, type I diabetes mellitus.

Amaç: *Çölyak hastalığı ve tip 1 diabetes mellitus, ortak genetik predispozisyona sahip otoimmun hastalıklardır. Bu çalışma ile, tip 1 diabetik hastalarda açık ve gizli çölyak hastalığı prevalansının belirlenmesi amaçlanmıştır.* ***Yöntem:*** *Erişkin tip 1 diabetik 100 olgu ile yaş ve cins uyumlu sağlıklı 80 kontrol grubunda, indirekt immunofloresan yöntemi ile anti-endomysium IgA tarama testi olarak kullanılmıştır. Anti-endomysium IgA pozitif bulunan olgularda distal duodenal biopsi, doku grubu, D-ksiloz testi, dışkı analizi, biokimyasal tetkikler, kan sayımı, serum ferritin düzeyi ve ince bağırsak pasaj grafisi çalışılmıştır. Distal duodenal biopsi örneklerinde çölyak hastalığı ile uyumlu bulguların saptandığı olgular açık çölyak hastalığı olarak kabul edilmiştir. Anti-endomysium IgApozitif bulunan normal intestinal histolojiye sahip olgularda Çölyak hastalığı ile uyumlu doku gruplarının varlığında ise latent Çölyak hastalığından söz edilmiştir.* ***Bulgular:*** *Anti-endomysium IgAA sekiz diabetik olguda pozitif bulunurken, kontrol grubunun tümünde negatif bulunmuştur. Çölyak hastalığı tanısı, dört olguda açık, iki olguda gizli olmak üzere toplam altı olguda (%6) konmuştur. Bu olguların sadece birinde hastalığın semptomları tespit edilmiştir.* ***Sonuç:*** *Tip 1 diabetik hastalarda çölyak hastalığı prevalansı artmıştır. Çölyak hastalığı, olguların büyük kısmında semptomsuz seyrettiği için diabetik bütün olguların çölyak hastalığı yönünden taranması uygun görünmektedir.*

Anahtar kelimeler: Çölyak hastalığı, anti-endomysium IgA, tip 1 diabetes mellitus.

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder that can be defined as a state of increased immunological responsiveness to ingested gluten in genetically susceptible individuals. The typical form of the disease characterised by malabsorption is seen in only 30-40% of patients (1). It is now generally believed that asymptomatic and latent forms of the disease are more common and can sometimes present with only by iron deficiency anemia, infertility, malignancy, osteoporosis or neurological disorders (2). In the atypical forms of the disease, the diagnosis is often delayed and some complications that could have been prevented by gluten restriction may develop. Some authors therefore suggest that CD should be investigated in patients with diseases frequently

Address for correspondence: Dr. Serkan GÜVENÇ
İstanbul Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı
Çapa, 34390, İstanbul
Tel: 212 534 00 50/2245 - 2435 E-mail: sguvenc@yahoo.com

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associated with the disorder (3). One of the many diseases associated with CD is type 1 diabetes mellitus. It has been recognised that both diseases have a common genetic predisposition and the association with HLA class II antigens such as DR3-DQ2 haplotype is more common in patients with CD and type 1 diabetes mellitus (2,5).

The first stage of screening for CD is to determine the serological markers. The anti-endomysial IgA antibody (IgA-EMA) test is the most sensitive and specific in the diagnosis of CD and it has a sensitivity of more than 90% and a specificity approaching 100% (4). It is therefore useful as a screening method in patients at high risk for CD.

In this report, the prevalence and clinical features of CD in adults with type 1 diabetes mellitus is evaluated.

MATERIALS AND METHODS

A random sample of type 1 diabetic patients attending the Diabetes Department of Istanbul Medical Faculty and an age and sex matched control group (medical students and health workers) with no known disease were included in the study. Inclusion criteria for the diabetic group were as follows: 1) age between 15 and 60 yrs.,2) onset of diabetes mellitus before the age of 30 yrs., 3) history of diabetic ketosis, and 4) unbroken record of insulin treatment from the initial diagnosis. Serum samples were obtained from 100 diabetic patients (51 female, 49 male, mean age 25.6 ±8.8 yrs.) and 80 control subjects (40 female, 40 male, mean age 27.4 ± 8.3 yrs.), and stored at –20°C. IgA-EMA was tested in all sera using sections of human umbilical cord by immunofluorescence (Binding site, Birmingham, England). Those with titers of 1:10 or greater were considered as positive. All patients with positive IgA-EMA results underwent upper endoscopy with biopsy to evaluate for histologic evidence of CD, with biopsy specimens obtained from at least five different sites of the distal duodenum. Patients with positive IgA-EMA were typed for HLA class II antigens by polymerase chain reaction using sequence-specific primers. Biochemistry profile, complete blood counts, serum ferritin level and small bowel radiography were also performed on these patients. The five hour urinary excretion of D-xylose was determined by calorimetry, after oral administration of 25 g of D-xylose. Qualitative analysis of stool fat was performed by microscopical examination in the fecal samples using the Sudan III stain and steatorrhea was defined as a finding of more than eight fat globules in each field. Celiac disease was diagnosed according the following criteria: 1) positive IgA-EMA test result 2) histologic evidence of CD (subtotal/total villous atrophy, crypt hyperplasia and increased number of intraepithelial lymphocytes) (6) and 3) the presence of HLA class II antigens [DR3, DR4, DQ2 (DQA1*0501 and DQB1*0201 alleles) and DQ8 (DQA1*0301 and DQB1*0302 alleles)] that are responsible for gluten sensitivity (2,5). IgA-EMA positive patients with histologic evidence of CD were accepted as having manifest CD while those with negative intestinal histology but positive IgA-EMA test result and the appropriate HLA class II antigens were considered as latent CD (13, 14). Age of onset, complications and regulation of the diabetes were recorded in diabetic patients. Evaluation of the control of diabetes was made by serum glycosylated hemoglobin (HbA1c) level. Informed consent was obtained from all patients.

We used chi-squared test, unpaired t test and Spearman correlation analysis for the statistics. A p value less than 0.05 was accepted as significant.

RESULTS

IgA-EMA positivity was found in eight of 100 diabetic patients with titers ranging from 1:10 to 1:40. None of the controls were IgA-EMA positive. The clinical and laboratory features of IgA-EMA positive patients are shown in Table 1. Four of the eight IgA-EMA positive patients (patients 1-4) showed histological evidence of CD, thus the diagnosis of manifest CD was confirmed. Three of them (patients 1, 2 and 4) had DR3-DQ2 (DQB1*0201) haplotype in HLA typing, while the other (patient 3) had DR4 positivity. In the remaining four patients with IgA-EMA (patients 4-8), the intestinal histology was normal. Patients 5 and 6 had DR3-DQ2 (DQB1*0201) haplotype in HLA typing. These two patients with normal intestinal morphology but appropriate HLA phenotypes were defined as latent CD. Patients 7 and 8 did not show any of the HLA class II antigens associated with CD. Thus it was found that the prevalence of CD in adult type 1 diabetes mellitus was 6% (four male, two female; age range 16-42 yrs.). Only one patient (patient 4) was symptomatic (diarrhea and weight loss). Steatorrhea was detected in two patients (patients 1 and 4), while two patients had other autoimmune diseases: bronchial asthma in patient 1 and autoimmune

Table 1. Clinical and laboratory features of the IgA-EMA positive patients.

Patient no	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Age / Sex	19/F	26/F	26/M	42/M	16/M	26/M	45/M	28/M
Age at onset of diabetes (yr.)	15	14	16	29	15	14	29	27
Diabetes duration (yr.)	4	12	10	13	1	12	16	1
Diabetic complications	None	BDR	None	PDR-HT-NP	None	None	PDR	None
Gastrointestinal symptoms	None	None	None	Diarrhea	None	None	None	None
Steatorrhea (qualitative)	Yes	None	None	Yes	None	None	None	None
Hemoglobin (NR:12-18 g/dl)	13.2	10.2	14.8	9.8	13.8	16.5	13.7	13
Ferritin (NR:9-370 ng/ml)	22.4	4.5	11.7	158	8.9	1.6	67.9	253
HbA1C (NR< %7.5)	5.9	8.3	7.6	10	9.4	9.6	11.3	6.5
D-Xylose test (NR:5-7 g/5 hours)	6.11	3.45	4.47	1.39	2.34	5.62	ND	6.72
IgA-EMA titer	1:40	1:10	1:40	1:10	1:10	1:10	1:20	1:20
HLA class-II antigens	DR3	DR3	DR4,6	DR3,4	DR3,7	DR3,4	DR2,5	DRI,6
	DQB1*0201	DQB1*0201	DQB1*0601	DQB1*0201	DQB1*0201	DQB1*0201	DQB1*0601	DQB1*0501
	DQB1*0601			DQB1*0304	DQB1*0601	DQB1*0601	DQB1*0301	
Small bowel histology	CD	CD	CD	CD	Normal	Normal	Normal	Normal
Response to gluten free diet								
- Compliance	Poor	Good	Poor	Good	Good	Poor		
- Steatorrhea (qualitative)	Yes	None	None	None	None	None		
- IgA-EMA titer	1:20	(-)	1:20	(-)	(-)	1:10		
- Histology	TVA	ND	TVA	ND	ND	ND		

BDR, background retinopathy; PDR, proliferative retinopathy; HT, hypertension; NP, nephropathy; CD, Celiac disease; HbA1c, glycosylated hemoglobin; ND, not determined; NR, normal range.

thyroiditis in patient 5. Serum ferritin levels were subnormal in three patients (patients 2, 5 and 6) and urinary D-xylose excretion test was outside of the normal range in three patients (patients 2, 4 and 5). All patients had normal small bowel radiography. There was no significant relationship between CD and age of onset, complications and control of diabetes ($p>0.05$).

A gluten free diet was prescribed to all patients, but three of them (patients 1, 3 and 6) did not tolerate it well and IgA-EMA was positive in these patients following three months of this dietary regimen. The patients who did tolerate the diet (patients 2, 4 and 5), showed a significantly good response: in patient 4, diarrhea and steatorrhea ceased, while in patients 2 and 5, ferritin levels returned to normal. IgA-EMA was negative in all these patients who tolerated the diet. Only two patients (patients 1 and 3) gave consent for a follow-up endoscopy with biopsy. These were the patients who did not tolerate the gluten-free diet. The was continued histologic evidence of CD in their follow-up biopsies.

DISCUSSION

In this Turkish study, the prevalence of CD in adult type 1 diabetes mellitus was 6%, which is compatible to the data previously reported from England (7), Finland (8, 9), USA (10), Italy (11, 12), Sweden (13) and Ireland (14). In these studies the prevalence ranged between 1.1% and 7.8%. The prevalence of CD in type 1 diabetes mellitus was found to be high in the studies having small sample sizes where as it was lower those with a larger sample size. The reason for the relatively higher prevalence in the present study compared with others with large sample sizes was that we diagnosed CD not only by histology but also with IgA-EMA positivity and the appropriate HLA class II antigens responsible for gluten sensitivity. Latent CD is defined as a state of gluten sensitiv-

ity with normal intestinal histology on a normal diet (15). These patients can be either symptomatic or asymptomatic and their clinical presentation can simply be due to complications of the disease. In a study performed in patients with idiopathic ataxia and CD, most of the gluten sensitive patients had normal intestinal histology. After commencment ofa gluten free diet, complete resolution of ataxia was seen in some of these patients (16). The definition of a latent or an asymptomatic patient still remains a problem. Evidence of serological markers in addition to the HLA class II antigens associated with CD are widely used to define such patients (15, 16). Other markers are the increased number of intraepithelial lymphocytes bearing the g/d receptor in intestinal biopsy, high levels of intestinal IgM antigliadin antibodies and IgA antigliadin antibodies in samples of jejunal fluid (15). More than 90% of patients with CD carry DR3-DQ2 haplotype. DQ2 is encoded by the alleles DQA1*0501 and DQB1*0201. DR4-DQ8 (DQA1*0301 and DQB1*0302) is present in a small minority of patients. However, some studies showed that other HLA class II antigens were present in patients with CD having mild enteropathy (15). Furthermore, DQ2 is present in about 20% of the general population. It is therefore possible that other genes showing gluten susceptibility inside or outside the HLA region can be present. Recently, CTLA-4 gene polymorphism, a non-HLA gene, was found to predispose to CD (18). The other problem in defining latent patients is the low sensitivity of serological markers. The most sensitive serological marker known is IgA-EMA. Rostami et al (19) showed that the sensitivity of the IgA-EMA was 100% in patients with total villous atrophy but only 31% in patients with partial villous atrophy. Thus the sensitivity of IgA-EMA in latent CD patients is unclear.

In this study, there were four patients with normal proximal mucosal biopsy and IgA-EMA positivity. Two of them did not have appropriate HLA phenotypes showing gluten sensitivity. These patients may have had non-HLA linked CD susceptibility genes and follow-up of such patients is necessary.

One or more than one HLA class II antigens associated with CD were detected in all patients who were diagnosed as CD. Interestingly, DQB1*0601 allele was found in five patients with IgA-EMA positivity, four of whom had CD. This allele may be another HLA class II antigen associated with CD in the studied population. Further studies are needed to show whether this allele is an antigen that indicates gluten sensitivity.

Some investigators have found that in diabetic patients with CD, the complications of diabetes are increased and the metabolic control of diabetes deteriorates (20). In contrast, other authors found no difference between diabetic patients with and without CD in terms of the complications and metabolic control of diabetes (5), which was also the case in this study.

In conclusion, this study shows that CD is more common in diabetics than the general population. Since only a very small group of these patients are symptomatic, the diagnosis of CD in diabetic patients can only be made by screening methods.

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