Determination of celiac disease frequency in type 1 diabetes mellitus children in the Pediatric Endocrinology Clinic of Sari, Mazandaran

Original Article

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Abstract:

Background: Diabetes mellitus, type 1 (T1DM) and celiac disease (CD) are both immune-mediated. The mean rate of clinical overlap is 8%. The aim of this study was to discover the frequency of CD in children with type 1 diabetes in Mazandaran province.

Methods: This retrospective descriptive study was performed in the pediatric endocrinology referral center, in Sari from 2012 to 2014. We screened all individuals aged between six months and 18 years with diabetes diagnosis after ketoacidosis, positive anti-GAD 65 antibodies, and insulin therapy. Patients with a positive tissue Transglutaminase Immunoglobulin A (tTG-IgA) antibodies test underwent endoscopic biopsy. Categorical data were tested using chi-square and quantitative data with independent sample T-test in SPSS. Date reported with 95% confidence interval. $P<0.05$ was considered statically significant.

Results: Of the 119 children enrolled, six cases (5%) were positive for tTG-IgA antibodies and all of them were boys (P=0.013). Histopathologically, CD was confirmed in 5 persons (4.2%). The mean age of seropositive patients was 10.3±3.3 years. History of DKA was mostly negative (83.3%) in them. The mean breastfeeding duration was 21±3.2 months, and only one had started formula after 12 months of birth.

Conclusions: The results of the current study showed that the frequency of CD in T1DM children in north of Iran was similar to that other countries but lower than that in previous reports of Iran. The periodic screening test for CD in this high-risk group is necessary to diagnose the asymptomatic disease and prevent its complications.

Keywords: Diabetes Mellitus Type 1, Celiac Disease, Pediatrics, Mazandaran

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Introduction:

Diabetes mellitus, type 1 (T1DM) and celiac disease (CD) are both immune-mediated diseases. Human leukocyte antigen (HLA) as a genetic factor plays a significant role in their etiology. In addition, environmental factors interfere with their pathogenesis. The incidence of both diseases is growing worldwide. The rate of a clinical overlap of T1DM and CD was well studied in a review article and reported between 3.3% - 16.4% (with the mean of 8%), varying among countries [1]. The prevalence of CD increased significantly after 1994 (from 3.3 to 10.6%); this rapid change could be related to environmental factors, eating habits and viral infections [2, 3]. One third of HLA DQ2 homozygous patients with T1DM express celiac disease-associated transglutaminase autoantibodies. Auto-immunity to transglutaminase is remarkably prevalent amongst patients with T1DM, expressing specific class II HLA alleles [4].

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HLA-DQ 1*0501, 1*0201 heterodimer presents gluten-derived gliadin peptides on its antigen-presenting groove to stimulate intestinal mucosal T-cells [2].

CD defines as a systemic immune-mediated enteropathy, which flares when specific serum antibodies respond to the dietary gluten. Classic presentations are gastrointestinal signs and symptoms, including diarrhea, bloating, weight loss and growth failure due to the malabsorption. Most patients with underlying T1DM do not experience the typical signs and symptoms of CD, which makes the diagnosis difficult [1]. Celiac disease is found more in patients with insulin-dependent diabetes mellitus or autoimmune thyroid disease [5]. If CD is left untreated, the absorption of dietary antigens will increase through impaired intestinal permeability and induce the autoimmune reaction in individuals who are genetically susceptible to the autoimmune diseases [3].

The gold standard diagnostic test for CD is the small intestinal biopsy, but there are also serologic tests like the anti-endomysial antibody (anti-EMA) and tissue transglutaminase immunoglobulin A (tTG-IgA) antibody which are highly specific and sensitive as well as useful for screening [6]. Using HLA type DQ2 and DQ8 as the initial screening test for CD is only recommended for Down syndrome because this is an expensive test [7].

TTG-IgA antibodies testing should be performed with a diet consisting of at least 3g of gluten per day for at least six weeks; otherwise, serology may become negative within weeks of a gluten-free diet [7].

Children with suggestive symptoms of CD or in high-risk groups regardless of having symptoms should undergo screening tests. Children with T1DM are one of these high-risk groups [7]. Guidelines encourage testing celiac in individuals who have first-degree relatives with celiac disease, autoimmune thyroiditis, and T1DM [8]. Complications of untreated CD in T1DM children could be the reduced Body Mass Index standard deviation score (BMI SDS) and lowered Hemoglobin A1c (HbA1c); a gluten-free diet helps to improve the BMI SDS and HbA1c without glycemic control, worsening during puberty [9]. The approach to high-risk children for CD who are asymptomatic differs depending on the tTG-IgA antibodies results. If the test is strongly positive (>3 times the upper limit of normal), an endoscopic biopsy is recommended. If tTG-IgA antibodies are mildly elevated (positive but <3 times the upper limit of normal), subsequent testing with anti-EMA is suggested. If tTG-IgA antibodies are negative, patients should be under observation and if the symptoms develop, repeat the tests [7].

The aim of this study was to determine the frequency of celiac disease in the pediatrics with T1DM in Mazandaran province, and evaluate the possible risk factors.

Methods:

The present study retrospectively reviewed all children who were diagnosed with T1DM from six months to 18 years old, referred to Baghban Clinic in Sari, Mazandaran from 2012 to 2014. This clinic is one of the pediatric endocrinology referral centers in Mazandaran province.

Screening contained all individuals a) whose first presentation of diabetes was with diabetic ketoacidosis (DKA), b) had a history of DKA and positive anti GAD65 antibody, and c) needed insulin therapy. Children aged less than six months were excluded from the current study because the introduction of a gluten-containing diet usually happens after six months of birth. To evaluate the presence of CD, all patients underwent tTG-IgA antibodies test at the time of diabetes diagnosis. All of the tTG-IgA antibodies tests were performed on a volume of 2-3 milliliter of whole blood using the enzyme-linked immunosorbent assay (ELISA) method with a standard kit (Euroimmun, Germany) in the same laboratory at Baghban Clinic. We selected the patients with positive tTG-IgA antibodies test (>50 Ru/ml) for endoscopic biopsy. Considering the high prevalence of IgA deficiency in CD, the total IgA was measured in all patients.

Patients' demographics, history of birth (term or preterm, cesarean or vaginal delivery), fetal growth, DKA, and the age of diabetes diagnosis, breastfeeding duration, use of formula and cow's milk, history of using supplements (vitamin D), and a family history of diabetes and CD were extracted from files or verbally recorded in the questionnaire.

Data analysis was performed using SPSS 16 and categorical data were tested using chi-square and quantitative data with T independent simple test. Data was reported with 95% confidence interval. $P<0.05$ was statistically considered significant.

The study was approved by the Ethics Committee of the Mazandaran University of Medical Sciences. All data were collected anonymously. All the principles outlined in the Helinski Declaration have been followed during the current study.

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Results:

Of the 119 children enrolled in the study, the proportion of girls to boys was similar (50.4% girls, 49.6% boys) and the mean age was 10.7±4.4 years. Table 1 illustrates the patients' demographics.

In six cases (5%), who were all boys (P=0.013), tTG-IgA antibodies tests were positive. Their mean age was 10.3±3.3 years, and the mean age of diabetes diagnosis was 6±3.5 years. All were term babies. History of DKA was mostly negative (83.3%) in cases. All were breastfed for a mean duration of 21±3.2 months. Only one case started formula after 12 months of birth. Five cases began feeding with cow's milk from the age of 6 months, and one after 18 months. All 6 cases underwent endoscopic biopsy. The histopathological results confirmed CD in 5 persons (4.2%).

Only one of 119 cases had a positive family history of CD, whose anti-tTG test was negative. A family history of diabetes was positive in 50.4% of the patients. Between positive and negative tTG-IgA antibodies tests groups, except for gender, there was no statically significant difference in factors such as type of delivery, birth weight, family history of CD, formula feeding or the use of vitamins and supplements during infancy. Table 2 shows all the aspects considered for CD in our type 1 diabetes population.

For one of the seropositive cases with no evidence of CD in his biopsy, an anti-tTG test was repeated after nine months and he underwent the endoscopic biopsy. There was no sign of pathologic changes, too.

Table 1: Patients with type 1 diabetes characteristics

Characteristics		n (%)
Sex	Male	59 (49.6)
	Female	60 (50.4)
Type of delivery	Vaginal	81 (68)
	Cesarean	38 (32)
Preterm		7 (5.9)
Term		112 (94.1)
Relative parents		21 (17.6)
History of hospitalization		27 (22.6)
Family history of diabetes		56 (47.0)
GDM history in mother		6 (5.0)
DKA history		23 (19.3)
Fed by breast		118 (99.1)
Vitamin D use in infancy		113 (95)
Fed by formula		17 (14.2)
Caw milk use		118 (99.1)
Anti tTG positive		6 (5.0)

GDM: gestational diabetes mellitus,
DKA: diabetes ketoacidosis,
tTG IgA: tissue transglutaminase immunoglobulin

Table 2: Comparing factors for CD in T1DM children

Factors		Anti tTG (mean±SD) / n (%)		P value
		Positive (n=6)	Negative (n=113)	
Birth weight (gr)		3150±367.4	3157.8± 678.3	0.978
Age (years)		10.3±3.3	10.7±4.4	0.840
Age at diabetes diagnosis (years)		6±3.5	6.8±3.4	>0.05
Age at formula start (month)		6.0±0.0	5.98±0.3	>0.05
Duration of breastfeeding (month)		21.0±3.2	22.0±4.0	>0.05
Sex	Male	6 (100)	53(46.9)	0.013
	Female	0 (0)	50 (44.2)	
Gestational age	Preterm	0 (0)	7 (6.2)	>0.05
	Term	6 (100)	106 (93.8)	>0.05
Cesarean delivery		2 (33.3)	36 (31.8)	>0.05
Relative parents		2 (33.3)	19 (16.8)	0.286
Family history of diabetes		2 (33.3)	52 (46)	0.683
GDM history in mothers		0 (0)	6 (5.3)	0.1
DKA history		1 (16.6)	22 (19.4)	>0.05
Breastfed		6 (100)	112 (99.1)	>0.05
Vitamin D use in infancy		5 (83.3)	108 (95.5)	>0.05
Fed by formula		1 (16.6)	16 (14.1)	>0.05
Cow's milk use		6 (100)	113 (100)	>0.05

CD: celiac disease, T1D: type 1 diabetes mellitus, GDM: gestational diabetes mellitus, DKA: diabetes ketoacidosis, tTG IgA: tissue transglutaminase immunoglobulin

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Discussion:

Based on the results of this study, the frequency of CD in the T1DM children population was 5%. According to a review article published by Chon et al.'s this rate is higher in some countries like France and Estonia (3.4% and 3.3% respectively), but less than the mean prevalence of 8%, reported from different countries and a study in Iran [1]. However, Zamanfar et al.'s reviewed three articles in which the prevalence of CD was from 4.3 to 6.8% in T1DM Iranian patients [10]. They have found a mean prevalence of 5.6% which is similar to our finding.

A systematic review investigated the overall prevalence of CD in different cities in Iran and various health conditions and it was concluded that 3% of patients had positive serologic tests and CD was confirmed in 2% of them via biopsy [8]. The asymptomatic CD is typical in the Middle East as in Europe. It could be because the Iranian diet is mostly based on wheat, and high exposure to wheat proteins develops immune tolerance [11]. Our seropositive cases were asymptomatic, too.

More than ten years ago, Shahbazkhani and et al.'s reported a different prevalence of CD among subgroups, in which 2.4% of CD cases had T1DM [12]. One of the possible reasons for that low rate of CD is the development of highly specific and sensitive screening tests in previous decades.

The occurrence of CD is geographically variable. In our country, the prevalence of CD is reported 3% in central, 1% in northern, 2% in southern, 5% in western and 4% in eastern areas [13]. CD rate is growing in developing regions such as the Middle-East where diets are high in grains, especially wheat [14]. The first report of CD prevalence in Sari was 0.8% in the adult population in 2004. At that time this rate was similar to western countries [15].

A newer study, Fallahi et al.'s found CD in 6.25% of children with T1DM using tTG antibody. Histopathological changes were compatible with CD in intestinal biopsies in all cases [16]. Results of the present study were between those of Shahbazkhani and Fallahi studies, but the prevalence of CD in Iranian patients with T1DM seems relatively high which makes it more important to screen CD in these children regardless of the presence or absence of symptoms.

Wheat content has been high in the Iranian diet for thousands of years, alongside the presence of about 57.6% frequency of HLA DQ2 and DQ8 in the general population suggests that a high percentage of our community can be susceptible to different presentations of CD [17].

Prolonged breastfeeding in developing countries as an environmental factor might be responsible for the milder symptoms and a higher age of CD diagnosis [18]. The mean duration of breastfeeding in the CD positive cases was 21 months. A delayed gluten introduction or a gradual introduction of gluten-containing food to breastfeed the infants can be related to a later onset of the disease, which can protect against the development of CD during early childhood [19].

Prevalence of CD is not different between male and female in the general Iranian population [17]. The causes of gender differences in CD are supposed to be physiological and men have evidence of greater malabsorption than females [20]. A cohort study represented that girls were significantly more predisposed to have T1DM and CD [21]. All the CD positive patients in this study were boys; however, the proportion of both genders was equal in our T1DM patients.

The results of a cohort study showed that there was a statistically significant increased risk of ketoacidosis in females with CD before the age of 20 [22]. Only one of six CD cases had a history of DKA.

Cesarean section was not related to develop the CD in this study. The potential influence of alteration of microbial exposures and the bacterial colonization in neonates born with cesaeian delivery on pathogenesis intestinal inflamatoary diseases like CD have been discussed by Decker et al.'s but there is need for more investigation in this area [23].

An American study on presentation of celiac in pediatrics found that prenatal factors including fetal growth, birth weight, mode of delivery, parental smoking, and maternal education did not associate with developing CD [24]. Our findings were in accordance with these results.

Vitamin D supplementation during infancy is proven to reduce the risk of T1DM [25]. By consideration of common genetic basis for T1DM and CD, we would have found no reduction in the incidence of CD if patients had taken vitamin D supplements during infancy.

In this retrospective study, the frequency of CD in type 1 diabetic children (5%) was similar to that of other countries but lower than that in previous reports of Iran. The only significant difference between CD positive and negative patients was gender. The periodic screening test for CD in type 1 diabetic patients is necessary to diagnose the asymptomatic, milder

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symptomatic and silent CD and prevent its complications.

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