Coeliac Disease: Evaluation of Diagnosis and Dietary compliance in the Iranian Children

Running Title: Coeliac Disease compliance in the Iranian Children

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Abstract

Introduction: Celiac disease is often poorly controlled in the majority of children. Most children have a gluten-free diet. A few children have difficulty adjusting their lifestyles, and gluten-free foods are difficult for them. The present study aimed to find effective factors in the growth disorders and non-response to the treatment diet in coeliac patients.

Methods: We performed duodenal biopsies on 382 patients with suspected coeliac disease in the gastrointestinal ward of Tabriz Paediatric Hospital and included 93 patients with positive pathology in the study regardless of the antibody and genetic titer, and we recorded and analyzed their demographic information.

Results: The mean age of individuals was 2-9, and 35 were male and 58 female. At the age of less than 5, there was more growth disorder than other age groups. The percentage of recovery in short stature was significantly better in children with higher marches, and they responded better to the treatment regimen. Individuals with comorbidities had higher Anti-tTG and lower Hb levels, higher incidence of growth disorder, didn't response to the treatment regimen. Those with a first-degree relative with coeliac disease had a lower growth disorder than others.

Conclusion: Identifying and correcting nutritional disorders in patients with coeliac disease needs to evaluate persistent symptoms and identify their causes to plan appropriate treatment and follow-up of patients with coeliac disease step by step and continuously.

Keywords: Coeliac disease; Gluten; Evaluation; Child

Introduction

Coeliac disease is a common cause of intolerance in the world. Data of screening studies indicate that about 1% of the world's population is affected by this disease. The prevalence of coeliac disease in the Middle East is almost the same as in the West (1). Coeliac disease, or

gluten-sensitive enteropathy is an immune-related enteropathy seen in genetically predisposed individuals as persistently sensitive to wheat gliadin or other barley prolamins in barley. The roles of both genetic and environmental factors have been investigated in the pathophysiology of Coeliac disease. The disease is significantly associated with HLAll antigens, especially DQ2 and DQ8. Coeliac enteropathy is caused by immune damage to small intestinal mucosal cells. Gliadin peptides, which are resistant to enzymes in the stomach and pancreas, reached the lamina propria of the small intestine by altering the intestinal wall's permeability and triggering immune and inflammatory reactions (2, 3). Infant nutrition, gastrointestinal infections, and intestinal bacteria may play roles in developing coeliac disease (2, 4).

Symptoms of coeliac disease can manifest as intestinal problems or as a result of malnutrition. According to the studies and based on research, there are few studies on the response rate of gluten-free diet (5). Due to the high prevalence of coeliac disease in the Iranian population and since there was not any study on the identification of various factors affecting the response to treatment and complications in patients with Coeliac disease, the present study aimed to evaluate complications and response to treatment in children with Coeliac disease in northwestern Iran in a 5-year follow-up to reduce complications and non-response to treatment and increase the quality of treatment in patients.

Materials and methods

The present study was a retrospective cohort study from 2007 to 2017 in northwestern Iran that examined 382 children suspected of having coeliac disease. Among them, 93 children had biopsy-proven coeliac disease.

The ethics committee of Tabriz University of Medical Sciences approved the study protocol with an ethical code of IR.TBZMED.REC.1398.272.

After making the necessary coordination with the management of hospitals and medical records, we gave a list of all children with coeliac disease to the project manager and included the eligible patients by reviewing files and according to the inclusion and exclusion criteria and extracted additional information from their files. The weight to age ratio and height to age ratio are calculated based on patients' visits to the clinic to the month and entered in the WHO Z-Score chart. Z-scores between -2 and -3 were considered to be of medium stunting, and Z-scores of less than -3 were considered weightless and severely stunting.

Ninety-three consecutive children following inclusion criteria were enrolled in the study according to celiac disease as per Revised ESPGHAN criteria (6). Exclusion criteria were (1) any child less than 2 years,(2) those who did not have a documented positive serology and/or biopsy suggestive of celiac disease as per revised ESPGAN criteria, (3) those on a gluten-free diet for less than 6 months, and (4) those children whose parents did not consent to be included in the study, parental dissatisfaction with telephone calls, insufficient information in pathology and clinic records, and children's non-visit for follow-up. All children enrolled in the study after signing the written informed consent form were evaluated for dietary compliance. A child who had taken even one food article containing gluten in the last 5 days was considered non-compliant and those who had strictly taken no gluten in their diet in that period were considered compliant. Diet recall was done by parents for children in preschool age up to 5 years since parents were the only ones giving the eatables to these children. Children, above 5 years of age, going to school and interacting with peers, were actively involved in the dietary recall along with the parents. After the dietary assessment, children and their parents were subjected to an interview by the investigator.

Coeliac types were divided into five groups based on the following cases: **Typical Coeliac disease**: The patient shows classic malabsorption symptoms such as diarrhea, fatty stools,

severe weight loss, and abdominal distension (7). **Atypical Coeliac disease**: The patient shows unusual manifestations such as short stature, anemia, infertility, neurological symptoms, metabolic bone disease, and liver involvement(8). **Silent Coeliac disease**: The patient has morphological changes in small bowel biopsy in the absence of clinical signs of the disease. In most cases, the patient has a relative with coeliac disease or high-risk relatives (9). **Latent Coeliac disease**: The patient has a normal bowel biopsy in a period with a gluten-free regimen, but a small intestine biopsy shows atrophy of the intestinal villi another time. Children with diagnosed coeliac disease by biopsy and on a gluten-free regimen for some time, their disease relapsed with gluten restart even though it was not recommended (10). **Potential Coeliac disease**: This group showed no histology according to coeliac disease in the small intestine biopsy, but they have immunological features such as anti-endomysial antibodies and tissue transglutaminase increased intestinal intraepithelial lymphocytes in the biopsy. These patients are often genetically predisposed to coeliac disease (10).

Furthermore, the modified pathological Marsh classification was included in the questionnaire based on the pathology report. It should be noted that patients' personal information was only available to the project manager, and we made a great effort to protect the information throughout the study.

Statistical analysis

The statistical analyses was conducted using SPSS V22. The continuous variable were reported as mean and standard deviation (SD) and the categorical variables were reported as frequency and percentages. In the analytical section, we utilized proper parametric and nonparametric tests according to statistical assumptions. The Chi-square test and independent t-test were used for between-group analysis of categorical and continuous variables respectively. The significance level was set at $P< 0.05$.

Results

In the study, we included 93 patients with coeliac disease. The patients' mean age was 9.48±3.88 years (2 to 19 years), and 35 (37.6%) of them were male. Eleven patients (11.8%) had a positive family history. Abdominal pain (40%) and diarrhea (28%) were the most common complaints of coeliac patients, and only 6.5% of coeliac patients had non-digestive symptoms.

As shown in table 1, the incidence of underweight was 20.8% in individuals with gastrointestinal symptoms and 0% in individuals with non-gastrointestinal symptoms, and the incidence of stunting was 13% in individuals with gastrointestinal symptoms and 25% in individuals with non-gastrointestinal symptoms. There was no significant association between the incidence of underweight and demographic and disease-related factors ($P>0.05$).

Individuals with hemoglobin less than 12 had more severe growth disorders, and the incidence of low weight was 18.8 in anemic individuals, and the incidence of short stature was 16.3 versus the incidence of low weight and short stature, 7.7. Individuals with higher Anti-tTG antibody titer had more severe growth disturbance, and the incidence of low weight and short stature was 16.7% vs. 11.1%.

Among the three age groups, individuals under five years of age had more growth disorders and no response to treatment. The incidence of low weight was 35.7%, and the incidence of short stature was 21.4%. Individuals with a higher Marsh biopsy were more likely to have growth disorder and failure to respond to treatment, and their incidence of low weight in the marsh was 42.93, and their short stature was 14.3. Changes in the percentages of moderate and severe underweight people did not significantly differ based on age, sex, family history, tTg, MARSH, type of Coeliac disease, comorbid disease, hemoglobin level, and symptoms before and after the regimen (Table 1).

Furthermore, changes in the percentages of moderate and severe short stature individuals did not significantly differ based on age, sex, family history, tTg, type of Coeliac disease, comorbid disease, hemoglobin level, and symptoms before and after the regimen. However, in the term of stunting, it was found that the percentage of improvement in short stature was significantly better in children with a higher march score (p-value= 0.04). As presented in Table 2, the percentage of improvement in short stature was significantly better in children with higher marsh, and they responded better to the treatment regimen (Table 2).

Table 1: Percentage of moderate to severe low weight before and after diet and its relation with variables

underweight %	Before GFD		After GFD		Percentage of Changes		P value*
	Intermediate	Severe	Intermediate	Severe	Decrease	Increase	
Age							
≤5 years	21.4	35.7	7.1	14.3	35.7	0	0.69
5 -10 years	4.8	19.9	7.1	7.1	16.7	2.4	
≥10 years	10.8	10.8	18.9	14.5	8.1	21.6	
Gender							
Male	11.4	20	8.6	11.4	17.1	5.7	0.77
Female	8.6	17.2	13.8	10.3	17.2	10.3	
Family History							
NO	11.1	18.5	12.3	11.1	19.8	8.6	0.24
YES	0	9.1	9.9	9.1	0	9.1	
tTg							
Negative	0	11.1	22.2	0	11.1	11.1	0.64
Positive	11.1	11.1	16.7	5.6	16.7	11.1	
MARSH							
1	0	9.1	0	9.1	0	0	0.69
2	9.5	19	9.5	4.8	23.5	4.89	
3a	6.9	20.7	13.8	17.2	13.8	13.1	
3b	17.4	17.4	13	13	17.4	8.7	
3c	14.3	28.6	28.6	0	42.9	14.3	
Coeliac disease							
Typical	11.4	12.9	10	8.6	15.7	8.6	0.52
Atypical	6.7	40	26.7	20	26.7	13.3	
Silent	0	25	0	25	0	0	
Potential	0	0	0	0	0	0	
Accompanying disease							
NO	9.7	16.7	9.7	12.5	16.7	8.3	0.91
YES	9.5	19	19	4.8	19	9.5	
Hemoglobin							
Low level	10	17.5	10	8.8	18.8	6.3	0.34
Normal	7.7	15.4	15.4	23.1	7.7	15.4	
Signs							
Digestive	11.7	14.3	13	6.5	20.8	9.1	0.52
Non-digestive	0	50	0	50	0	0	
Both	0	20	20	20	0	0	

*p-value of chi-square test

Table 2: Percentage of moderate to severe short stature before and after GFD and its relation with variables

stunting %	Before GFD		After GFD		Percentage of Changes		P value*
	Intermediate	Severe	Intermediate	Severe	Decrease	Increase	
Age							
≤5 years	14.3	14.3	14.3	7.1	21.4	0	0.54
5 -10 years	0	9.5	9.5	7.1	10.8	18.9	
≥10 years	5.4	10.8	13.5	8.1	16.2	5.6	
Gender							
Male	2.9	14.3	14.3	11.4	14.3	2.9	0.61
Female	5.2	8.6	10.3	5.2	13.8	8.6	
Family History							
NO	3.7	12.3	13.6	8.6	14.8	7.4	0.2
YES	0	0	0	0	0	0	
tTg							
Negative	0	0	22.2	0	11.1	1.1	0.62
Positive	5.6	11.1	0	0	16.7	0	
MARSH							
1	0	0	9.1	0	0	9.1	0.04
2	4.8	19	9.5	4.8	23.8	0	
3a	3.4	10.3	10.3	17.2	6.9	13.8	
3b	8.7	8.7	17.4	4.3	21.7	4.3	
3c	0	14.3	14.3	0	14.3	0	
Coeliac disease							
Typical	4.3	8.6	11.4	5.7	11.4	4.3	0.27
Atypical	6.7	20	6.7	20	26.7	13.3	
Silent	25	0	0	25	0	25	
Potential	0	0	0	0	0	0	
Accompanying disease							
NO	4.2	11.1	8.3	8.3	12.5	5.6	0.57
YES	4.8	9.5	23.8	4.8	19	9.5	
Hemoglobin							
Low level	5	11.3	11.3	5	16.3	2.5	0.11
Normal	0	7.7	7.7	23.1	0	23.1	
Signs							
Digestive	2.6	9.1	13	5.2	13	5.2	0.58
Non-digestive	0	25	0	25	25	25	
Both	0	20	0	20	20	0	

*p-value of chi-square test

Discussion

The present study was conducted to evaluate the clinical outcome of children with coeliac disease for ten years. In the study, we included 382 patients with suspected coeliac disease, among whom 93 (24.34%) had coeliac disease in the biopsy. The patients' mean age was 9.48±3.88 years (2 to 19 years).

Although a well-planned gluten-free diet may provide adequate nutrition, it may be restrictive. Strict adherence to gluten-free diet may be more challenging in children and adolescents than in adults. The heterogeneous clinical picture of celiac disease makes it difficult to recognize and predisposes to long diagnostic delay, further increasing the risk of permanent growth failure (11). In order to prevent this complication it would be important to better understand the factors associated with poor growth in celiac disease.

The present study evaluated the clinical outcome of children with coeliac disease for ten years.

In a study by Janczyk W. et al. (2015), they introduced patients who had the coeliac disease but had a high incidence of various complications and did not respond to a gluten-free regimen. The study indicated that if no latent source of gluten was detected, other causes of persistent villous atrophy, other than a coeliac disease, should be considered, including inflammatory diseases, immunity, and endocrine diseases of the gastrointestinal tract. In severe cases of childhood coeliac disease, which do not respond to a gluten-free regimen, enteropathy should be performed autoimmune, and the disease should be considered the resistant celiac disease (12). Our study found that some patients did not have any changes in weight and height, and some patients had worsened status after treatment. However, there was less worsened condition in patients with high marsh, but it did not significantly differ in other cases that require more detailed studies in subsequent studies.

In a study by Samuli Nurminen et al. (2015), who examined the effect of treatment on children's growth with coeliac disease, 530 children with biopsy-proven coeliac disease were included in the study. The researchers compared children with growth disorder and those with normal growth in terms of serological histology and clinical features. Children with growth disorder were younger and had lower hemoglobin, higher coeliac antibodies, higher alanine aminotransferase, and higher levels of thyroid-stimulating hormone. Furthermore, patients with growth disorder were at the age of under three years. Abdominal pain reduced the risk, while there was no effect of diarrhea, constipation, other chronic diseases, and lack of growth in patients with coeliac disease (13). Our study indicated that only a higher march was associated with patients recovering after the diet. The difference may be due to differences in the sample size, differences in patients' demographic indices, differences in follow-up duration, and differences in inclusion and exclusion criteria.

Radlović N et al. (2009) investigated the effect of a gluten-free treatment diet on children's growth with coeliac disease. The effect of a gluten-free treatment diet was very significant. None of the children showed a slow growth rate or weight loss above 20%, increasing height percentiles and reducing weight loss after the treatment period. In 86 patients (95.5%), Hb control values were normal in the blood, while mild anemia was recorded in 4 patients, all of whom were on a gluten-free diet. It was concluded that a gluten-free treatment diet for 1-3 years had a very significant effect on children's growth rate and nutritional status with the classic form of coeliac disease. There was no significant difference in the disease parameters between fully compatible and non-compatible types (3). Our study found that treatment diet significantly improved children's growth, and only children with higher marsh had a better recovery than those with the lower marsh. According to the present study's findings and the above studies, the treatment diet was necessary for patients with coeliac disease and improved the patients' growth. However, patients were not examined more accurately based

on compatibility and non-compatibility to the diet in the present study, so that the issue requires further study.

Conclusion

Our study indicated that the incidence of growth failure was higher in younger individuals, those with atypical coeliac disease, anemia, and higher antibody titers.

GFD in patients with coeliac disease improved their weights and heights, and it was found that patients' heights with higher marsh significantly improved after the diet. Therefore, the therapeutic focus should be on the diet during diagnosis for all patients with coeliac disease to improve their growth status.

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