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Evaluating the Timing of Gluten Introduction into Infant's Diet and Other Influential Factors in Children with Celiac Disease

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Abstract

Background: Gluten is recognized as the main causative factor of celiac disease (CD), affecting many children worldwide.

Objective: This study aimed to assess the potential relationship between the timing of gluten introduction into infants' diet and other influential factors in children diagnosed with CD.

Methods: This descriptive-analytical cross-sectional study was conducted from January 2016 to 2022 and included all patients, aged 1-18 years, who were referred to our hospital over this 6-year period. Patients had a confirmed diagnosis of CD. Patient hospital records were retrospectively reviewed, and the investigated variables included patients' age, gender, mode of delivery, infant feeding mode, and timing of introducing gluten into their diet. A P-value <0.05 was considered statistically significant.

Results: A total of 155 children, comprising 101 (65.2%) girls and 54 (34.8%) boys, met the inclusion criteria. Patient age ranged from 1 to 17 years (mean: 9.68 ± 4.03 years). The average duration of breastfeeding was 23.14 ± 2.2 months. Most patients were born through vaginal delivery (57.4%) and were exclusively breastfed without any supplementary milk (67.7%). The majority of children (59.4%) had a timely introduction of gluten into their diet. There was no statistically significant correlation between the timing of gluten introduction and the other investigated variables (P > 0.05 for all).

Conclusion: Within this cohort of children with confirmed celiac disease, the timing of gluten introduction was not associated with the measured early-life factors. Prospective studies with non-celiac controls are needed to clarify potential causal relationships.

Key Words: Breast milk, Cesarean section, Celiac, Gluten.

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1- INTRODUCTION

Celiac disease (CD) is a gastrointestinal disorder characterized by malabsorption and diarrhea (1). CD, also known as enteropathy, couses damage upon ingesting grains containing gluten in genetically predisposed individuals (2, 3). In individuals with CD, these peptides are resistant to gastric acid and pancreatic enzymes, resulting in them not being digested (4). CD is a chronic inflammatory bowel disease caused by the destruction of the epithelial cells of the small intestine, leading to malabsorption of nutrients (5-7). In this disease, the intestinal villi are lost, reducing the absorptive capacity of the bowel (8, 9). The onset of this disease most commonly occurs during infancy and is rarely seen in adults (2, 10, 11).

CD involves a wide range of clinical presentations and manifestations, that can vary significantly among patients. The primary categories of presentation are typically classified as classic, non-classic, silent, refractory and potential forms. Manifestations may include failure to thrive and malnutrition, vomiting, severe bloating and chronic diarrhea, which are a consequence of lesions in the small intestine (2). Other non-gastrointestinal symptoms of this disease include growth disturbances, delayed puberty, dermatitis herpetiformis, liver and biliary tract diseases, arthritis, osteoporosis, osteopenia, neurologic and/or psychiatric disorders, iron-deficiency anemia, hypoplasia of tooth enamel, as well as miscarriage and fertility problems in women. CD can even be life-threatening in pediatric patients by causing severe diarrhea and disturbances in water and electrolyte balances (12, 13).

The clinical spectrum of CD is broad, and some individuals may experience only a few of these symptoms or even none at all, which often leads to underdiagnosis or misdiagnosis. Despite increasing awareness and knowledge about CD, approximately 95% of patients remain undiagnosed (14-16). If CD is suspected, serological tests are generally the first step, followed by confirmation through an intestinal biopsy (17).

Gluten has been proposed to be responsible for CD. Gluten is a general term for a group of water-insoluble proteins found in various cereals, referred to by different names (18, 19).Non-adherence to a gluten-free diet (GFD) in these children can result in growth failure and malnutrition, increasing the risk of depression, osteoporosis, cancer, infertility, and malnutrition in adulthood (20, 21). One common issue is that the nutritional content of a GFD is typically lower than that of a conventional diet (22, 23). Studies have shown that not only does breastfeeding have a protective role against the development of CD, but breastfeeding during the introduction of gluten-containing products also provides protection. Furthermore, early initiation of gluten (under three months of age) can act as a risk factor in susceptible individuals (8). Currently, the only treatment for CD is adherence to a GFD (13). Delayed adherence to this diet can expose the child to complications such as intestinal lymphoma and osteoporosis (24).Breastfeeding, mode of childbirth, and the timing of the introduction of gluten in infants' diets can influence the risk of developing CD (18, 25-27).

Therefore, considering the potential early introduction of supplementary food (gluten), the absence of exclusive breastfeeding, and a history of cesarean delivery as risk factors for celiac disease, we aimed to investigate the prevalence of these factors in children with celiac disease.

2- MATERIALS AND METHODS

2-1. Study Design and Participants

The protocol of this retrospective descriptive-analytic cross-sectional study

was approved by the Research and Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1399.245).
The study was conducted from January 2016 to January 2022 and followed all relevant principles of the Declaration of Helsinki. All pediatric patients between 1 and 18 years of age, previously diagnosed with CD, who were admitted to the outpatient clinic and gastroenterology department of Akbar Children's Hospital, in Mashhad, Iran within this six-year period, were included in this study. The diagnosis of CD was established and confirmed through histopathological analysis.

Diagnostic criteria: Children were considered to have celiac disease if the treating pediatric gastroenterologist had documented a diagnosis and the pathology report supported celiac-type enteropathy on small-bowel biopsy. Additionally, we extracted supporting serology (e.g., tissue transglutaminase IgA and/or endomysial antibody) where available in the record. Histology interpretation at our center follows standard approaches such as the Marsh–Oberhuber framework; however, the exact Marsh grade was not consistently documented in archived files for all patients and was therefore not analyzed as a variable.

Patients' medical records were retrieved from archived hospital files and data were extracted and recorded in a corresponding checklist.

The investigated variables included demographic data such as the patient's age and gender, type of infant feeding (breast milk, formula milk, cow's milk, or pasteurized milk), duration of exclusive breastfeeding, mode of delivery (vaginal delivery or cesarean section), and timing of gluten introduction in the diet within four months or less (timely or early). In cases of incomplete information, we contacted the patients' guardians and asked for further details.

Bias and missing data: This retrospective chart review study is subject to selection bias due to the single-center, referral-based population and information bias. For some variables, missing data were fill in by contacting guardians, which could introduce recall bias, particularly for early-life feeding details. We recorded variables as documented in the chart or as reported by guardians when documentation was incomplete.

Study subjects were enrolled using a census sampling method.

Sample size consideration: This study was a retrospective census of all eligible children with confirmed celiac disease seen at our center from January 2016 to January 2022. Therefore, an a priori power calculation was not performed. The analyses should be interpreted as exploratory and hypothesis-generating.

2-2. Statistical Analysis

The data underwent subjected to statistical analysis using SPSS version 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics including mean, standard deviation, and 95% confidence intervals for all tests and groups were calculated. Normally distributed variables were compared using independent-samples T-test, while non-parametric data were evaluated using the Mann-Whitney-U test. Pearson's correlation coefficient or Spearman's test were used to analyze correlations between quantitative variables. The Chi-square test was also utilized for qualitative variables. A p-value less than 0.05 was considered statistically significant.

3-RESULT

A total of 155 patients, with a mean age of 9.6 years and an age range of 1-17 years old met the inclusion criteria and were retrospectively enrolled in this study.

Among the 155 children with confirmed celiac disease, gluten was introduced before 4 completed months of age in 63 (40.6%) and at/after 4 months in 92 (59.4%). The timing of gluten introduction was not associated with gender (P=0.745), mode of delivery (P=0.11), or infant feeding mode (P=0.416). Infant feeding mode also did not differ between early vs timely gluten introduction (Table 1; P=0.67), and age and breastfeeding duration were similar between groups (Table 2).

Gender distribution frequency consisted of 101 girls (65.2%) and 54 boys (34.8%). A total of 89 infants (57.4%) were delivered vaginally, while the remaining 66 (42.6%) were delivered by cesarean section.

The most common infant feeding modes in descending order of frequency were: exclusive breastfeeding (n=105, 67.7%), breastfeeding and formula milk (n=43, 27.7%), just formula milk (n=5, 3.2%), breastfeeding and pasteurized milk (n=1, 0.6%) or a combination of breastfeeding and cow's milk (n=1, 0.6%).

The timing of introducing gluten into the child's diet was assessed in all patients. Gluten was introduced to the infant's diet before 4 completed months of age (early introduction) in 63 cases (40.6%).

However, in 92 (59.4%) cases, gluten introduction accurred after 4 months of age, which is considered timely introduction. Breastfeeding duration ranged from 12 to 24 months, with an average of 23.14 ± 2.20 months. Using the chi-square test, no significant association was found between the timing of gluten introduction and gender, mode of delivery, or feeding mode (P=0.745, P=0.11 and P=0.416, respectively). Table 1 illustrates the relationship between the timing of gluten introduction and infant feeding mode, showing no statistically significant relationship between the two variables (P= 0.67). Table 2 summarizes the data related to subjects' age and duration of breastfeeding in infants with early and timely introduction of gluten.

Table-1. Comparison of infant feeding modes between children with early and timely gluten dietary introduction.

Timing of gluten introduction	Infant feeding mode	Number (%)	Chi-square test results
Timely introduction (N= 92)	Exclusive breastfeeding	63 (68.5%)	P-value= 0.67
	Formulated milk	2 (2.2%)	
	Combination feeding method	27 (29.3%)	
Early introduction (N=63)	Exclusive breastfeeding	42 (66.7%)	
	Formulated milk	3 (4.8%)	
	Combination feeding method	18 (28.6%)	

Table-2. Patients' age and duration of being breastfed in regards to early or timely introduction of dietary gluten.

Timing of gluten introduction	Infant feeding mode	Mean ± SD	Median	Min-Max
Timely introduction (N= 92)	Age(years)	9.16 ± 4.13	9.25	1-16
	Duration of breastfeeding (months)	23.05 ± 2.2	24	16-24
Early introduction (N=63)	Age(years)	10.45 ± 3.77	10	2-17
	Duration of breastfeeding (months)	23.27 ± 2.22	24	12-24

SD: Standard deviation

4- DISCUSSION

CD is a relatively common condition that, if left undiagnosed in childhood, can lead to irreversible complications. Finding a suitable alternative for gluten is one of the biggest challenges in producing gluten-free products, which can be attributed to the importance of this protein in creating the appropriate tissue structure and appearance of the product.

In this study, the number of girls (65.2%) diagnosed with CD was greater than the number of boys. Within each group, children with early and timely introduction of gluten, most infants were delivered through cesarean section (65.1% and 52.2%, respectively). Regardless of the timing of gluten introduction, exclusive breastfeeding was the most common infant feeding mode. Furthermore, infants' mean age and average duration of being breastfed were similar in children who had both early and timely introduction of gluten into their diet. Our findings did not reveal any statistically significant correlations between any of the investigated variables and the timing of gluten introduction.

Importantly, this study describes children who already have confirmed celiac disease and does not include a non-celiac control group. Therefore, our results should not be interpreted as showing whether early gluten exposure, feeding mode, or delivery mode increase or decrease the risk of developing celiac disease. Instead, we evaluated whether the timing of gluten introduction differed across demographic and early-life factors within a cohort of children with celiac disease.

A study by Shahraki et al. (28) was conducted between 2004 and 2008 involving 43 children who sought care at Tehran Children's Medical Center. The age range of the subjects was between 6 months to 14 years (with a mean age of 8.3±4.7 years). Contrary to our study, most of the patients were boys. Assessment of patients on a gluten-free diet indicated improvement of symptoms after monthly follow-ups.

Radlovic et al. (29) conducted a study on 89 infants with celiac disease in Serbia consisting of 59 girls and 30 boys. Similar to our study, there were more girls than boys in the sample. The children's ages ranged from 7 to 24 months, with an average age of 14 months. The time to initiate a GFD in these children was also , 4 months, mirroring our study. The findings of this study suggest that a longer duration of breastfeeding in the early years of a child's life may decrease the risk of exacerbating CD.

Akobeng et al. (30) investigated the relationship between breastfeeding and celiac disease. The results of this study indicate that the longer the duration of breastfeeding during the time of gluten introduction, the lower the risk of developing CD. Prolonging the duration of breastfeeding delays the start of a gluten diet. According to the findings of this study, neither the duration of breastfeeding nor the timing of gluten diet initiation affects the severity of CD.

In 2002, Ivarsson et al. (31) conducted a study involving 627 children with CD. Similar to our study, most of the patients were girls and children were under 15 years of age. According to the findings of this study, introducing gluten-containing foods into the infants' diet while they are still being breastfed reduces the risk of developing CD in early childhood and possibly later in childhood.

A case-control study by Auricchio et al. (32) included 216 children with CD and their healthy siblings. They evaluated the frequency and duration of breastfeeding as well as the timing of gluten introduction in their diet. They study revealed that the relative risk of developing clinical celiac

symptoms was four times greater in children who breast fed or used other supplemental milk for less than 30 days compared to those who breastfed or used supplemental milk for more than 30 days. In contrast to our findings, the cited authors reported a significant correlation between these two variables. Similar to our study, there was no apparent relationship between the early introduction of gluten into the diet and the prevalence of CD.

By identifying and eliminating risk factors that influence the onset of this disease, the incidence of CD can be reduced. Early identification of children at the highest risk of CD and the initiation of a GFD, along with targeted and appropriate treatment, may enhance therapeutic outcomes. Given the positive results obtained in this research and similar studies, we can devise suitable therapeutic guidelines for the timely and rapid diagnosis of this disease, thus reducing treatment costs and preventing the consequences of late treatment for these children. Additionally, establishing appropriate guidelines for recognizing this disease helps prevent an increase in complications, mortality and morbidity due to delayed diagnosis.

Limitations: This study was a retrospective, single-center study without a non-celiac control group, so making causal inferences about risk factors for developing celiac disease is not possible. Some exposure data were missing in archived files and were completed by contacting guardians, which may introduce recall bias, especially for timing of gluten introduction and infant feeding details. Additionally, children were diagnosed across a wide age range (1–17 years). For those diagnosed later, early-life exposures may be reported less accurately, and the relevance of infancy-related factors may be diluted. Lastly, we did not consistently have access to detailed histopathology grading (e.g., Marsh stage) in all archived records, so severity by histology could not be analyzed.

Children can be examined and compared in two groups: one group consist of children who have been fed a gluten-based diet, breastfed, and born through Cesarean section, while the other group includes children who have had a gluten-free diet, were not breastfed, and were born through natural childbirth. It is further suggested that this study be conducted in a prospective manner.

5- CONCLUSION

In this cohort of children with confirmed celiac disease, the timing of gluten introduction (before vs at/after 4 months) was not associated with gender, mode of delivery, infant feeding mode, age, or breastfeeding duration. Since the study did not include a non-celiac control group, these findings should be interpreted as associations within affected children rather than evidence of causal predictors of celiac disease. Larger, prospective studies with appropriate controls are needed to clarify how early-life exposures relate to the risk and timing of celiac disease onset.

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7- CONFLICT OF INTERESTS

The authors have declared that they have no competing interests.

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