

ORIGINAL RESEARCH



The seroprevalence of celiac disease in Syrian refugee children with malnutrition

Yasin Sahin^{1,2}

1. Clinics of Pediatric Gastroenterology, Gaziantep Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Turkey

2. Division of Pediatric Gastroenterology, Medical Faculty, Gaziantep Islam Science and Technology University, Gaziantep, Turkey

* Corresponding Author: Yasin Sahin; E-mail: ysahin977@gmail.com

Abstract

Backgrounds

Malnutrition in children is a significant public health issue. Various factors that can cause malnutrition include inadequate intake, inadequate digestion, inadequate absorption, increased demand, and increased catabolism. Celiac disease (CD) also causes malnutrition as a result of inadequate digestion. The number of studies investigating seroprevalence of CD in children with malnutrition is limited. Therefore, we aimed to evaluate the seroprevalence of CD among Syrian refugee children with malnutrition.

Methods

The current study was conducted between January and December 2023. All children with malnutrition, who receiving enteral nutrition were included. The children's age and sex, body weight, height upon admission were recorded. Tissue transglutaminase antibody IgA test (tTG IgA) and total IgA test were used to diagnose CD in all patients. Gastroduodenoscopy was planned to be performed in all seropositive children to diagnose CD.

Results

Of the 329 patients, 179 (54.4%) were female. The mean age of patients was 5.82 ± 4.17 years. The median tTG IgA value was 2 IU/L (0.4-200.0). The seroprevalence of CD was found to be 3.34% (11/329), 9 of them had been receiving enteral feeding for at least 6 months. Gastroduodenoscopy was not performed on most of the patients because they could not be reached due to communication problems (the phone number was wrong or not in the system, etc.). But 2 of them was diagnosed without biopsy according to the ESPGHAN 2020 guidelines for diagnosing CD.

Conclusions

We detected higher seroprevalence of CD in children with malnutrition compared to general population. Because celiac disease is a chronic multi-systemic illness, early detection of CD is critical to avoiding long-term consequences. Therefore, screening for CD should be an essential part of work-up in all Syrian refugee children with malnutrition. We hereby recommend verifying the contact information of refugee patients at the time of application.

Keywords: celiac disease, malnutrition, no-biopsy approach, Syrian refugee children

Introduction

Citizens and long-term inhabitants of Syria have become refugees as a result of the civil conflict there; other wars have led to an increase in similar situations in other areas of the world. 13.5 million displaced people were designated by the United Nations (UN) as in need of humanitarian aid. Frequently considered to as one of the most serious refugee crises in history, escalating political instability and rising levels of violence in the area have prompted Syrian nationals to seek refuge by migrating to neighboring countries since the beginning of 2011^{1,2}. Approximately six million Syrian refugees are currently living abroad, mostly in Turkey, Lebanon, Jordan, Iraq, and Egypt, according to the United Nations High Commissioner for Refugees³.

The American Society for Parenteral and Enteral Nutrition (ASPEN) workgroup defined pediatric malnutrition (undernutrition) as "an imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes"⁴.

Malnutrition in children is a major public health concern,

especially in low- and middle-income nations. Various factors that can cause malnutrition include inadequate intake, inadequate digestion, inadequate absorption, increased demand, and increased catabolism⁵. Celiac disease (CD) is a multisystem disease that occurs as a result of ingestion of gluten-containing foods, which causes malnutrition as a result of inadequate digestion⁶.

The previous literature shows that malnutrition is commonly present among Syrian refugees⁷⁻⁹. Celiac disease is a immune-mediated systemic disease defined by small intestinal damage caused by gluten consumption in genetically susceptible individuals, the existence of antibodies specific to celiac disease and many gluten-dependent clinical findings⁶.

In studies conducted in Turkey, the frequency of malnutrition in celiac patients was found to be between 24.3-54.1%¹⁰⁻¹³. Studies show that malnutrition rates in children with CD range from 20.2% to 67.3%¹⁴⁻¹⁶. Malnutrition is common in celiac patients, and the risk of CD in malnourished patients is higher than healthy children. However, the number of studies investigating celiac disease in children presenting with malnutrition is limited.

In our country, we came across one study conducted on this

subject in malnourished Turkish children¹⁷.

Table 1. The demographic and laboratory characteristics of patients

	<u>Patients (n=329)</u>
Sex (f/m)	179/150
Age (yrs)*	5.82 ± 4.17
Height (cm)*	104.45 ± 23.90
Weight (kg)**	14.00 (IQR 9.8)
BMI (kg/m ²) *	14.42 ± 1.87
tTG IgA (U/ml)**	2.00 (IQR 0.0)
Total IgA (mg/dl)**	82.80 (IQR 71)
Duration of enteral nutrition (months)**	6.00 (IQR 9.0)

tTG=tissue transglutaminase, IQR= interquartile range

*Data are presented as median ± standard deviation.

**Data are presented as median (min-max).

Table 2. The demographic characteristics and anthropometric parameters of groups according to the duration of enteral nutrition

	<u>Group 1 (n=221)</u>	<u>Group 2 (n=108)</u>	<u>p</u>
Sex (f/m)	120/101	59/49	
	0.955		
Age (yrs)*	5.35 ± 3.79	6.79 ± 4.74	
	0.003		
Height (cm)*	101.77 ± 22.06	109.94 ± 26.57	0.003
Weight (kg)**	13.30 (IQR 7.9)	15.35 (IQR 14.8)	<0.001
BMI (kg/m ²) *	14.27 ± 1.70	14.73 ± 2.17	
	0.028		
tTG IgA (U/ml)**	2.00 (IQR 0.0)	2.00 (IQR 0.0)	
	0.173		
Total IgA (mg/dl)**	75.00 (IQR 73.5)	89.00 (IQR 78.8)	0.167
Duration of enteral nutrition (months)*	13.26 ± 8.65	1.99 ± 1.08	
	<0.001		

tTG=tissue transglutaminase, IQR= interquartile range

*Data are presented as median ± standard deviation.

**Data are presented as median (min-max).

Table 3. The laboratory data of patients with tTG IgA positivity

Patient no	Age (year)/sex	Duration of enteral nutrition (months)	tTG (U/ml)	Total IgA (mg/dL)
1	14.6/m	6	200.0	185
2	4.3/f	24	82.6	152
3	6.3/f	1	35.8	163
4	3.9f	12	200.0	55
5	14.0/f	12	20.3	140
6	7.3/m	12	200.0	178
7	5.1/f	12	83.5	75
8	7.5/m	24	21.8	83
9	5.3/f	1	200.0	125
10	7.0/m	7	111.0	95
11	1.2/f	6	200.0	188

In this study, the seroprevalence of CD in children with malnutrition was found to be 1.99%, and it was determined that the seroprevalence of CD in malnourished children was higher than in healthy children. In this study, it is recommended to perform CD serological screening, especially in children with malnutrition, in regions such as our country, where the prevalence of malnutrition and celiac disease is high.

According to our knowledge, there is no study investigating the seroprevalence of CD in malnourished Syrian refugee children in our country. Therefore, we aimed to evaluate the seroprevalence of CD among Syrian refugee children with malnutrition.

Methods

The current study was conducted in Gaziantep (Turkey) between January 2023 and December 2023. All children aged between 1 and 18 years admitted to the Pediatric Gastroenterology Outpatient Clinic due to malnutrition

were included in the study. The children's age and sex, body weight, height as well as their underlying disease upon admission were recorded. Children with chronic diseases such as cystic fibrosis, renal diseases, cerebral palsy, type 1 DM, liver diseases, and malignancy were excluded from the study. Malnourished patients who were previously diagnosed with CD were excluded from the study. Additionally, patients with missing serological test results for CD were also excluded from the study. All patients were receiving enteral nutrition at the time of admission.

A calibrated digital scale was used to measure weight and a portable stadiometer for children was used to measure height to the nearest 0.1 cm and 0.05 kg, respectively. Children that are underweight have a weight-for-age that is less than the median of the reference population by two standard deviations (-2 SD). Also, a child is deemed seriously underweight if their weight-for-age Z-score is less than -3 SD. The WHO standard growth charts were used to classify BMI and height Z scores for age and sex

(18). If a child's height-for-age Z score was less than -2 SD, they were considered stunted. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2)¹⁹. The population's nutritional situation was classified using the BMI-for-age Z-score (BAZ) into three categories: extreme thinness, moderate thinness (with cut-points of <-3 SD), and from -3 SD to -2 SD, respectively²⁰. In addition to that, BAZ between -1 SD and -1.99 SD was considered mild malnutrition, BAZ between -2 SD and -2.99 SD was considered moderate malnutrition, and BAZ between -3 SD or greater was considered severe malnutrition²¹.

Tissue transglutaminase antibody IgA test (tTG IgA) and total IgA test were used to diagnose CD in all patients. Tissue transglutaminase antibody IgG and anti-endomysium antibody (EMA) IgG tests were examined in patients with IgA deficiency. Gastroduodenoscopy was planned to be performed in all seropositive children to diagnose CD.

However, according to the 2020 guideline of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), if tTG IgA test result is 10 times upper limit of normal and positive EMA in a second blood sample, CD is diagnosed without an endoscopic biopsy²². According to this guideline, we also had patients who were diagnosed with no-biopsy approach in the current study.

Local Ethics Committee approval was obtained (21.02.2024/04-Gaziantep City Hospital Non-Interventional Clinical Research Ethics Committee).

Statistical analysis

"Descriptive statistics" method was used for the descriptive parameters of frequency, percentage and mean $\pm$ standard deviation in the evaluation of the data. The "Independent-Samples t test" was used to compare numerical variables, and the "chi square test" was used to compare the relationship between categorical variables. $p < 0.05$ was considered statistically significant.

Results

Between January 2023 and December 2023, 329 children and adolescents aged between 1 and 18 years were examined. Of the 329 patients, 179 (54.4%) were female. The mean age of patients was 5.82 ± 4.17 years. The mean height of patients was 104.45 ± 23.90 cm and the median weight of patients was 14.00 kg (5.7-53.5). The median IgA value was 82.80 mg/dL (1.0-315.0). The median TGA value was 2 IU/L (0.4-200.0) (Table 1).

The patients were divided into two groups according to the duration of enteral feeding; group 1 (enteral feeding duration ≥ 6 months) and group 2 (enteral feeding duration < 6 months). There were 221 patients in group 1 and 108 patients in group 2 (Table 2).

The mean enteral feeding time of patients in group 1 and group 2 was 13.26 ± 8.65 months, and was 1.99 ± 1.08 months, respectively. When both groups were compared in terms of age, height, weight and BMI, there was a significant difference between them ($p < 0.05$). When both groups were compared in terms of tTG IgA levels, no statistical difference was found between them, but 9 of the 11 seropositive patients were in group 1, meaning of that the enteral feeding duration in those patients was ≥ 6 months.

The seroprevalence of CD was found to be 3.34% (11/329) in children with malnutrition (Table 3). Nine of them did not attend their endoscopy appointment. Most of the patients

could not be reached due to communication problems (the phone number was wrong or not in the system, etc.), so we still could not reach the majority of the patients. Therefore, we could not make a definitive diagnosis of CD in those patients. However, two patients were diagnosed definitively without biopsy according to the ESPGHAN 2020 guidelines for diagnosing CD and the patients were followed up.

Discussion

Clinical features of CD such as diarrhea, abdominal distension, anemia, weight loss, growth retardation, and vomiting can also be seen in children with malnutrition^{6,23}. Thus, a CD screening should be performed on those patients.

It has been reported that malnutrition rates in children with CD range from 10.8% to 67.3% (14-16,24-25). In a systematic review and meta-analysis, it has been shown that the prevalence of malnutrition (stunting) under 5 years in refugee children was 26%²⁶. The prevalence of chronic malnutrition among Syrian refugees was 10.5% in Jordan²⁷.

In a multi-center study conducted in Turkey, the seroprevalence of CD was determined as 1.77% in healthy school children²⁸. There is a limited study investigating the seroprevalence of CD in children with malnutrition^{17,29}. In a study conducted in Turkey, seroprevalence of CD was determined to be 1.99% in children with malnutrition and it was determined that seroprevalence of CD was higher in malnourished children than in healthy children¹⁷.

In a study by Beniwal et al., the seroprevalence of CD was found to be 15.38% and the prevalence of biopsy-proven CD was 14.42% in children with severe acute malnutrition. In this study, it was emphasized that children with severe acute malnutrition who have abdominal pain and abdominal distension should be evaluated for CD²⁹.

In the current study, the seroprevalence of CD in Syrian refugees living in Turkey was found to be 3.34% (11/329) in children with malnutrition. 9 of the 11 seropositive patients were in group 1, meaning of that the enteral feeding duration in those patients was ≥ 6 months. Nine of them did not attend their endoscopy appointment. Most of the patients could not be reached due to communication problems (the phone number was wrong or not in the system, etc.), so we still could not reach the majority of the patients. Therefore, we could not make a definitive diagnosis of CD in those patients. However, according to the ESPGHAN 2020 guidelines for diagnosing CD, 2 of the patients were diagnosed with CD without a biopsy²². Screening for CD should be an essential part of work-up in all Syrian refugee children with malnutrition, especially who have ≥ 6 months enteral feeding.

As a result, we detected higher seroprevalence of CD in children with malnutrition compared to general population. Because CD is a chronic multi-systemic disease, early detection of CD is critical to avoiding long-term consequences such as failure to thrive, osteopenia, infertility, and malignancy. Therefore, screening for CD should be an essential part of work-up in all Syrian refugee children with malnutrition. We hereby recommend verifying the contact information of refugee patients at the time of application.

References

1. El-Khatib, Z, Scales, D, Vearey, J, Forsberg BC. Syrian refugees, between rocky crisis in Syria and hard inaccessibility to healthcare services in Lebanon and Jordan. *Confl. Health* 2013;7:18.

2. Mroue T, Heras B, Soriano JM, Morales-Suarez-Varela M. Prevalence of Malnutrition among Syrian Refugee Children from Lebanon. *Life* (Basel) 2023;13:453.
3. United Nations High Commissioner for Refugees (UNHCR). Situation Syria Regional Refugee Response. Available online: <https://data2.unhcr.org/en/situations/syria/location/71> (accessed 2023 Jan 20)
4. Mehta NM, Corkins MR, Lyman B, et al. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *JPEN J Parenter Enteral Nutr* 2013;37:460-481.
5. Altaş B, Kuloğlu Z. Approach to children with malnutrition. *Turkish J Pediatr Dis* 2011;5:54-64.
6. Sahin Y. Celiac disease in children. *World J Clin Pediatr* 2021; 10: 53-71
7. El Harake MD, Kharroubi S, Hamadeh SK, Jomaa L. Impact of a pilot school-based nutrition intervention on dietary knowledge, attitudes, behavior and nutritional status of Syrian refugee children in the Bekaa, Lebanon. *Nutrients* 2018;10: 913.
8. Pernitez-Agan S, Wickramage K, Yen C, Dawson-Hahn E, Mitchell T, Zenner D. Nutritional profile of Syrian refugee children before resettlement. *Confl Health* 2019;13:22.
9. Bucak IH, Almis H, Benli S, Turgut M. An overview of the health status of Syrian refugee children in a tertiary hospital in Turkey. *Avicenna J Med* 2017;7:110-114.
10. Selbuz S. Çölyak Hastalığı Olan Çocuklarda Beslenme Durumu ve Mikro Besin Yetersizliklerinin Değerlendirilmesi. *Türkiye Klinikleri J Pediatr* 2021;30:48-55.
11. Kuloğlu Z, Kirsacıoğlu CT, Kansu A, Ensari A, Girgin N. Celiac disease: presentation of 109 children. *Yonsei Med J* 2009;50:617-23.
12. Balamtekin N, Uslu N, Baysoy G, et al. The presentation of celiac disease in 220 Turkish children. *Turk J Pediatr* 2010;52:239-44.
13. Sahin Y. Clinical evaluation of children with celiac disease: A single-center experience. *Arch Clin Gastroenterol* 2020;6:26-30.
14. Wierdsma NJ, Nijeboer P, de van der Schueren MAE, Berkenpas M, van Bodegraven AA, Mulder CJJ. Refractory celiac disease and EATL patients show severe malnutrition and malabsorption at diagnosis. *Clin Nutr*. 2016;35:685-691.
15. Setavand Z, Ekramzadeh M, Honar N. Evaluation of malnutrition status and clinical indications in children with celiac disease: A crosssectional study. *BMC Pediatr*. 2021;21:147.
16. Kalleveen MVV, Meij T, Plötz FP. Clinical spectrum of paediatric coeliac disease: A 10-year single-centre experience. *Eur J Pediatr*. 2018;177:593-602.
17. Üstkoyuncu PS, Sevinç E, Eren E, Torun YA. Tek Bir Merkezde Çocuklarda Malnütrisyon Değerlendirilmesi ve Malnütre Hastalarda Çölyak Hastalığı Görülme Sıklığı. *Abant Med J* 2021;10:219-225.
18. World Health Organization (2006) WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development. Geneva: World Health Organization. (accessed 2024 Apr 10)
19. World Health Organization (2008) Training Course on Child Growth Assessment: Interpreting Growth Indicators. Geneva: World Health Organization. (accessed 2024 Apr 10)
20. WHO Child Growth Standards based on length/height, weight and age. WHO Multicentre Growth Reference Study Group. *Acta Paediatr Suppl* 2006;450:76-85.
21. Becker P, Carney LN, Corkins MR, et al. Academy of Nutrition and Dietetics; American Society for Parenteral and Enteral Nutrition. Consensus Statement of the Academy of Nutrition and Dietetics/ American Society for Parenteral and Enteral Nutrition: Indicators Recommended for the Identification and Documentation of Pediatric Malnutrition (Undernutrition). *Nutr Clin Pract* 2015;30:147-161.
22. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *J Pediatr Gastroenterol Nutr* 2020;70:141-156.
23. Kumar P, Mishra K, Singh P, Rai K. Should We Screen Children with Severe Acute Malnutrition for Celiac Disease? *Indian Pediatr* 2012;49:330-331.
24. Setavand Z, Ekramzadeh M, Honar N. Evaluation of malnutrition status and clinical indications in children with celiac disease: a cross-sectional study. *BMC Pediatrics* 2021;21:147.
25. Barone M, Della Valle N, Rosania R, et al. A comparison of the nutritional status between adult celiac patients on a long-term, strictly gluten-free diet and healthy subjects. *Eur J Clin Nutr* 2016;70:23-27.
26. Choudhary P, Padhi BK, Mital AK, et al. Prevalence of stunting among under-five children in refugee and internally displaced communities: a systematic review and meta-analysis *Front Public Health* 2023;11:1278343.
27. Hossain SM, Leidman E, Kingori J, Al Harun A, Bilukha OO. Nutritional situation among Syrian refugees hosted in Iraq, Jordan, and Lebanon: Cross sectional surveys. *Confl Health* 2016;10:26.
28. Dalgic B, Sari S, Basturk B, et al. Prevalence of celiac disease in healthy Turkish school children. *Am J Gastroenterol* 2011;106:1512-1517.
29. Beniwal N, Ameta G, Chahar CK. Celiac Disease in Children with Severe Acute Malnutrition (SAM): A Hospital Based Study. *Indian J Pediatr* 2017; 84:339-43.