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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Prevalence and clinical forms of celiac disease in siblings of children with verified disease

Zoran Leković[1,2], Vladimir Radlović[1,2], Marija Mladenović[3], Siniša Dučić[1,2], Goran Đuričić[1,2], Jelica Predojević-Samardžić[4,5], Biljana Vuletić[6,7], Petar Rosić[2], Srđa Janković[1], Nedeljko Radlović[8]

[1]University Children's Hospital, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Singidunum University, Faculty of Health, Legal and Business Studies, Valjevo, Serbia;
[4]University Clinical Center of the Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[5]University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[6]Kragujevac University Clinical Center, Pediatric Clinic, Kragujevac, Serbia;
[7]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia;
[8]Serbian Medical Society, Academy of Medical Sciences, Belgrade, Serbia

SUMMARY

Introduction/Objective Celiac disease (CD) is the result of a polygenic predisposition and gluten-containing diet. The aim of this study was to determine the prevalence and clinical forms of CD in siblings of children with verified disease.

Methods The study included 83 siblings, aged 1.5–27 (11.77 ± 6.2) years, of 64 children with CD diagnosed according to ESPGHAN criteria (1990/2012). In addition to a detailed history and clinical examination, serum levels of IgA and antibodies to tissue transglutaminase (AtTG) IgA and IgG classes were determined in all subjects. All with elevated AtTG levels underwent multiple duodenal enterobiopsy. The diagnosis of CD was confirmed by the finding of characteristic histological changes.

Results The diagnosis of CB was made in 13 of 83 subjects (15.67%). Nine of them had an asymptomatic form of the disease, while in the others the disease was clinically manifested – in three the form was classical, in one it was accompanied by severe malnutrition (-26.80%), and in one the manifestation was nonclassical (only short stature). Except for sideropenia and hypoferritinemia in four patients, of which two with hemoglobin below the reference value, standard laboratory findings were within normal limits.

Conclusion Our research shows that the prevalence of CD in siblings of children with verified disease is 15.67%. It is mostly detected in its asymptomatic form. In accordance with this, routine application of serological screening for CD in this population group is necessary for its timely diagnosis and treatment.

Keywords: celiac disease; children; siblings; prevalence

INTRODUCTION

Celiac disease (CD) is a multisystem autoimmune disease that occurs in genetically predisposed individuals on a gluten-containing diet [1]. It occurs in all population groups, and most often in members of the white race (~1%) [2, 3, 4]. In relatives of the first and second order, as well as in patients with other autoimmune diseases, selective IgA deficiency and some of the chromosome abnormalities (Down, Turner, and Williams–Beuren syndromes), the incidence of the disease is many times higher [1, 2, 4–8]. The basis of the disease and the key finding in its diagnostics is nonspecific inflammation of the small intestinal mucosa that is resolved by gluten-free diet [1].

The pillar of hereditary predisposition to CD is the presence of genes encoding HLA DQ2 and HLA DQ8, which are registered in over 99% of patients [2]. DQ2 is registered in 85–95% of subjects, and HLA DQ2 in 5–15% [2, 9]. However, in addition to having HLA DQ2 or HLA DQ8 and exposure to gluten, the presence of non-HLA genes is necessary for the disease to occur [2, 5, 10]. In addition, non-gluten external factors have a, to date, unclear role in the appearance of the disease [5, 10, 11].

The aim of this study was to determine the prevalence and clinical form of CD in siblings of children with verified disease.

METHODS

The study included 83 siblings, 46 male and 37 female, aged 1.5–27 (11.77 ± 6.2) years, of 64 children (18 boys and 46 girls) with CD diagnosed according to the criteria created by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 1990 and 2012 [12, 13]. All patients with verified CD and their siblings subjected to the examination originated from the same parents. One of the study participants, a 14-year-old girl, had verified type 2 diabetes mellitus. The research was performed in accordance with the current ESPGHAN recommendations [1]. The study protocol was approved by the local ethics committee.

In addition to a detailed history and clinical examination, serum levels of IgA and antibodies

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Correspondence to:
Zoran LEKOVIĆ
University Children's Hospital
Tiršova 10
11000 Belgrade, Serbia
zlekovic2000@yahoo.com

to tissue transglutaminase (AtTG) IgA and IgG classes were determined in all siblings. Also, blood tests and standard biochemical analyses (serum iron and ferritin concentrations, total proteins, albumin, urea, total cholesterol, 3-glyceride, calcium, phosphorus, alkaline phosphatase, and the liver function test) were performed in all of them. The obtained findings were compared with reference values [14, 15]. The diagnostic criterion for anemia was the level of hemoglobin (Hb) for children up to 5 years old below 110 g/l, for those 5–11 years old below 115 g/l, and for those older than 11 years the diagnostic criterion was below 120 g/l [15].

Although three subjects (two boys and one girl) had an AtTG IgA titer over 10 times the upper reference value and clinical signs of classical CD, all underwent multiple duodenal enterobiopsy for reliable disease verification [1, 5, 13]. Classification of pathohistological damage of the small intestinal mucosa was performed according to modified Marsh criteria on infiltrative (I), infiltrative-hyperplastic (II), destructive (III), and hypoplastic (IV) type [16]. According to the degree of mucosal damage, destructive enteropathy is additionally classified into partial (IIIa), subtotal (IIIb), and total (IIIc).

Oslo definitions for CD were used for differentiation of the clinical types of the disease [17]. According to these criteria, CD is classified into two basic types: symptomatic and asymptomatic (subclinical). Symptomatic disease is further differentiated into classical and nonclassical. Classical CD is characterized by poor appetite, chronic diarrhea, failure to thrive, muscle wasting, abdominal distension and irritability, while nonclassical type of the disease are dominated by atypical (nonclassical) digestive and/or various extraintestinal manifestations, either single or combined, such as constipation, recurrent abdominal pain, short stature, delayed puberty, chronic fatigue, iron deficiency anemia, isolated hypertransaminasemia and others.

RESULTS

The diagnosis of CB was found in 13 of 83 siblings (15.67%), seven females and six males, aged 2.58–20 (10.58 ± 5.49) years. The type of the disease in nine was asymptomatic and in four it was clinically manifest, in three classical and in one nonclassical. All three subjects with classical CD were younger than three years. One of them also had severe malnutrition, i.e., a body weight deficit of 26.8% compared to normal. In patients with non-classical disease, only short stature was noted. Except for sideropenia and hypoferritinemia in four patients, of which two with hemoglobin below the reference value, both with clinical classical disease, other standard laboratory findings were within normal limits. In one of them, aged 1.5 years, a selective IgA deficit (0.06 g/l) was found. Histological examination of the small intestinal mucosa in one subject revealed infiltrative-hyperplastic enteropathy, while in others it was destructive, of which in six it was partial, in five subtotal, and in one total. In two subjects with classical CD, subtotal enteropathy was found, and in one, the most severe case among them, total enteropathy. The patient with short stature, a 13-year-old boy, had subtotal enteropathy. In siblings with asymptomatic CD, enteropathy was subtotal in two cases, it was partial in six cases, and infiltrative-hyperplastic in one case. In patients with the classical type of the disease, gluten-free diet resulted in the withdrawal of symptoms within a week or two and complete recovery after 3–6 months. Also, the patient with short stature normalized his body height after two years of dietary treatment.

DISCUSSION

CD is a gluten-induced autoimmune disease of polygenically predisposed individuals [1, 5]. Accordingly, it is characterized by a high prevalence in close relatives, especially first-degree relatives, as well as in patients with other autoimmune diseases [1, 5]. Additionally, the disease is highly present in people with selective IgA deficiency and patients with Down, Turner, and Williams syndromes [1, 5]. Given this fact, as well as the much more frequent asymptomatic compared to clinically recognizable CD expression, as part of the ESPGHAN diagnostic guide published in 2020, it was recommended that these groups should be tested for its presence [1]. The basis of an active approach in the diagnosis of CD in these high-risk groups is that timely detection and adequate treatment of the disease prevents its immediate and far-reaching complications, which can sometimes be very serious [1]. As part of this diagnostic protocol, subjects should undergo total IgA and AtTG-IgA testing as an initial screen. If total IgA concentrations are low, the second step should consist of an IgG-based test (deamidated gliadin peptide, anti-endomysial, or tissue transglutaminase). In cases where AtTG-IgA serum concentration is greater than 10 times above the reference value for a diagnosis of CD, enterobiopsy is not necessary. As part of our study, all the above criteria were consistently met. Although three subjects had an AtTG IgA titer over 10 times the upper reference value, in order to reliably verify the disease, all subjects underwent multiple duodenal enterobiopsy.

According to data from the literature, the prevalence of CD among the first-degree relatives is 3–22%, on average about 10%, which fits our finding [9, 10, 18–25]. In addition, two siblings in our group of subjects also had additional disorders, one type 2 diabetes mellitus, and the other selective IgA deficiency [5, 7, 8].

The basis of the CD and the key finding in its diagnostics is gluten-sensitive enteropathy, i.e., a nonspecific inflammation of the small intestinal mucosa, resolved by gluten-free diet [1]. Beside enteropathy, either symptomatic or asymptomatic, the disease is also characterized by different extraintestinal manifestations, which can sometimes be the only sign of the disease [5, 26, 27, 28]. From the clinical aspect, CD is divided into two basic types: symptomatic (classical and nonclassical) and asymptomatic [17]. The classical CD form is most often seen at the age of 9–36 months, and non-classical in later childhood,

adolescence, and in adulthood [5]. Of the 13 siblings with CD detected in our study, nine had the asymptomatic type of the disease, one had an atypical manifestation (short stature as the only manifestation), and three had the classical type. All nine with asymptomatic CD and the patient with short stature were in adolescence, while all three with clinically classical CD were younger than three years. In addition, four subjects, three with classical and one with asymptomatic CD, had iron deficiency, of which two, both with classical CD, and low Hb. In the group of siblings with asymptomatic CD, infiltrative-hyperplastic enteropathy was registered in one case, partial enteropathy in six, and subtotal enteropathy was registered in two patients. Subtotal enteropathy was found in boys with short stature and in two siblings with classical CD, and total enteropathy was found in subjects with the most severe form of the disease. Although the degree of damage to the small intestinal mucosa obtained by enterobiopsy does not correlate with the clinical expression of CD, in the group of our subjects this association was quite convincing [29, 30].

All siblings with diagnosed CD are advised to follow a permanent gluten-free diet [1]. In addition, four subjects requested oral correction of iron deficiency. Respondents with classical CD also received folic acid for 2–4 months. Strict adherence to the elimination diet in patients with classical CD resulted in rapid withdrawal of symptoms and consequent complete recovery, and in boys with short stature normalization of body height after two years of treatment.

CONCLUSION

According to our findings, the prevalence of CD in siblings with verified disease is 15.67%, or more than 15 times that of the general population. It is mostly detected in its asymptomatic form. Having in mind this fact, it is clear that it is necessary to test this group of children for CD in order to achieve its timely diagnosis and treatment and thus prevent both immediate and far-reaching complications.

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Преваленција и клинички облици целијачне болести код браће и сестара деце са верификованом болешћу

Зоран Лековић[1,2], Владимир Радловић[1,2], Марија Младеновић[3], Синиша Дучић[1,2], Горан Ђуричић[1,2], Јелица Предојевић-Самарџић[4,5], Биљана Вулетић[6,7], Петар Росић[2], Срђа Јанковић[1], Недељко Радловић[8]

[1]Универзитетска дечја клиника, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитет „Сингидунум", Факултет здравствених, правних и пословних студија, Ваљево, Србија;
[4]Универзитетски клинички центар Републике Српске, Бања Лука, Република Српска, Босна и Херцеговина;
[5]Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина;
[6]Универзитетски клинички центар Крагујевац, Клиника за педијатрију, Крагујевац, Србија;
[7]Универзитет у Крагујевцу, Факултет медицинских наука, Крагујевац, Србија;
[8]Српско лекарско друштво, Академија медицинских наука, Београд, Србија

САЖЕТАК

Увод/Циљ Целијачна болест (ЦБ) резултат је полигенске предиспозиције и исхране са присуством глутена.
Циљ рада је био да се утврди преваленција ЦБ код браће и сестара деце са верификованом болешћу.

Методе Студијом је обухваћено 83 браће и сестара, старости 1,5–27 (11,77 ± 6,2) година, 64-оро деце са ЦБ дијагностикованом у складу са *ESPGHAN* критеријумима (1990/2012). Поред детаљне анамнезе и клиничког прегледа, код свих испитаника одређени су серумски нивои *IgA* и антитела на ткивну трансглутаминазу (*AtTG*) *IgA* и *IgG* класе. Сви са повишеним нивоом *AtTG* подвргнути су мултиплој дуоденалној ентеробиопсији. Дијагноза ЦБ је потврђивана налазом карактеристичних хистолошких промена.

Резултати Дијагноза ЦБ је постављена код 13 од 83 испитаника (15,67%). Девет њих су имали асимптоматски облик болести, док је код осталих болест била клинички манифестна, код три класична, код једног праћена тежом малнутрицијом (-26,8%) и код једног некласична (само низак раст). Сем сидеропеније и хипоферитинемије код четири болесника, од чега код два са хемоглобином испод референтне вредности, стандардни лабораторијски налази су били у граници нормале.

Закључак Наше истраживање показује да преваленција ЦБ код браће и сестара деце са верификованом болешћу износи 15,67%. Претежно се открива у асимптоматском облику. У складу са тим, неопходна је рутинска примена серолошког скрининга на ЦБ у овој популационој групи у циљу њене правовремене дијагностике и третмана.

Кључне речи: целијачна болест; деца; браћа и сестре; преваленција