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Clinical Picture of Classical, Atypical and Silent Celiac Disease in Children and Adolescents

Obraz kliniczny choroby trzewnej klasycznej, atypowej i utajonej u dzieci i młodzieży

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Celiac disease is a frequent disease of the alimentary tract in children. Clinical presentation of the disease is variable and depends on type of the disease.
Objectives. The aim of the study was an analysis of clinical findings, selected laboratory features and coexisting diseases in children and adolescents with celiac disease.
Material and Methods. Material of the study comprised a series of 78 children aged 8 months – 13 years. Celiac disease was diagnosed basing on clinical symptoms, histological studies of intestinal specimens and positive serologic tests (EmA, TG2).
Results. Classical celiac disease was diagnosed in 40 children (51.3%), atypical celiac disease in 26 children (33.3%) and silent celiac disease in 12 children (15.4%). The most frequent clinical symptoms of classical form of celiac disease were chronic diarrhea (90.0%), recurrent abdominal pain (70.0%), development retardation (65%), hypocholesterolemia (35.0%) and IgA deficiency (22.5%). In atypical form of the disease dominated the following symptoms: recurrent abdominal pain (76.9%), failure to thrive (38.4%), short stature (42.3%), anemia (15.3%), hypertransaminasemia (11.5%), food allergy (19.2%) and thyroid diseases (11.5%). In silent celiac disease hypercholesterolemia was present in 33.3%, hypertriglycerydemia in 16.6%, type 1 diabetes in 50%, and celiac disease in parents or siblings in 33.3%.
Conclusions. Classical celiac disease is the most frequently diagnosed clinical form of the disease. Silent celiac disease occurs frequently in children with type 1 diabetes mellitus whose parents or siblings have celiac disease. Frequent diagnosis of atypical and silent forms of celiac disease is an indication to serological examination in children with unclear clinical picture and genetic predisposition (**Adv Clin Exp Med 2013, 22, 5, 667–673)**.

Key words: celiac disease: classical, atypical, silent, children.

Streszczenie

Wprowadzenie. Choroba trzewna jest częstą chorobą przewodu pokarmowego u dzieci. Obraz kliniczny choroby jest zróżnicowany i zależny od postaci klinicznej.
Cel pracy. Ocena objawów klinicznych, wybranych parametrów biochemicznych oraz chorób współistniejących.
Materiał i metody. Badaniem objęto 78 dzieci w wieku od 8 miesięcy do 13 lat. Choroba trzewna była rozpoznana na podstawie objawów klinicznych, oceny histopatologicznej kosmków jelitowych i obecności przeciwciał w surowicy (EmA, tTG).
Wyniki. Klasyczną chorobę trzewną rozpoznano u 40 dzieci (51,3%), atypową u 26 (33,3%), a postać utajoną u 12 (15,4%). Choroba trzewna klasyczna charakteryzowała się przede wszystkim: przewlekłą biegunką (90,0%), nawracającym bólem brzucha (75%), upośledzonym rozwojem fizycznym (65,0%), powiększonym obwodem brzucha (42,5%), hipertransaminazemią (40,0%), hipocholesterolemią (35,0%) oraz niedoborem IgA (22,5%). W chorobie trzewnej atypowej dominowały bóle: brzucha (76,9%), upośledzenie rozwoju fizycznego (38,4%), niski wzrost

(42,3%) oraz u części dzieci niedokrwistość (15,3%), hipertransaminazemia (11,5%), alergia pokarmowa (19,2%), choroby tarczycy (11,5%). W chorobie trzewnej utajonej stwierdzono: hipercholesterolemię (33,3%), hipertrójglicerydemię (16,6%), cukrzycę typu 1 (50%) i chorobę trzewną u rodziców lub rodzeństwa (33,3%).
Wnioski. Choroba trzewna klasyczna jest najczęściej rozpoznawaną postacią. Choroba trzewna utajona występuje często u dzieci chorych na cukrzycę typu 1 oraz u dzieci rodziców lub rodzeństwa chorującego na celiakię. Częste rozpoznawanie postaci atypowej i utajonej przemawia za prowadzeniem badań serologicznych w kierunku choroby trzewnej u dzieci z niejasnym obrazem choroby oraz u dzieci predysponowanych genetycznie (**Adv Clin Exp Med 2013, 22, 5, 667–673**).

Słowa kluczowe: choroba trzewna klasyczna, atypowa, utajona, dzieci.

Celiac disease is an immune-mediated enteropathy caused by permanent sensitivity to gluten and related prolamines, affecting genetically susceptible individuals. Genetic, environmental and immunological factors play a role in pathogenesis, damage of small intestinal mucosa and development of enteropathy [1, 2]. The prevalence of celiac disease in children aged 2.5 to 15 years is 3 to 13 per 1000 [2–4]. Celiac disease presents variable clinical picture. Typical classical presentation occurs mainly in the first two years of life. After the introduction of gluten into the child's diet, a set of clinical symptoms of malabsorption appears, such as chronic diarrhea, failure to thrive, abdominal distension and pain, growth delay and iron deficiency anemia. Atypical presentation is characterized by scarce clinical symptoms. Frequently, only a single symptom is observed, such as lack of body mass increase and growth retardation, anemia, dental enamel hypoplasia, osteoporosis, or pubertal delay. Silent presentation of celiac disease is diagnosed in asymptomatic patients with increased risk of the disease. Among diseases and conditions predisposing someone to celiac disease are: type 1 diabetes mellitus (6%), first-degree relatives (10%). Down syndrome (5.5%), Turner syndrome (6%), Williams syndrome (9.5%), autoimmune diseases of the liver (13.5%) and of the thyroid gland (3%), juvenile arthritis (1.5%), and selective IgA deficiency (3%) [1–3]. Frequencies of celiac disease in those conditions are given in brackets. The aim of the study was an analysis of clinical and laboratory features in children and adolescents with diagnosed classical, atypical and silent celiac disease.

Material and Methods

Material of the study comprised a series of 78 patients aged 8 months to 13 years, hospitalized in The Department of Children Gastroenterology of Wroclaw Medial University from January 2003 to December 2010. In all cases, celiac disease was diagnosed based on European and North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition criteria [2, 5]. In all children, celiac disease was diagnosed based on a histological study of intestinal specimens obtained during endoscopic examination and assessed according to the Marsh scale (grades II and III a, b, c) and on elevated titers of antibodies against endomysium of smooth muscles and/or tissue transglutaminase type 2 [2, 3, 6–9]. According to clinical symptoms, the children were classified into three groups. The first group consisted of 40 children with gastrointestinal symptoms such as chronic diarrhea and malabsorption, which was regarded as classical celiac disease. The second group included 26 children with recurrent abdominal pain, short stature and anemia. These children were classified as having atypical celiac disease. Silent celiac disease was diagnosed in 12 children and adolescents with type 1 diabetes mellitus and first degree relatives of celiac patients (Table 1). For the assessment of physical development (body mass and stature) percentile scale was used according to Palczewska and Niedźwiedzka [10]. The data was statistically analyzed by chi-square test of proportions using MedCacl Software v.12.6.1, Ostend, Belgium. Values of $p < 0.05$ were regarded as statistically significant. Bioethical Committee agreement for the study had been obtained.

Results

Number, age and sex of the studied children are presented in Table 1. Classical celiac disease was diagnosed in 40 children (51.3%) at the age of 8 months to 6 years (average age 17.5 months). In 80% of children classical celiac disease was diagnosed when they were under two years of age and in the remaining 20% at the age between three and six years. Girls outnumbered boys (75% vs. 25%, $p < 0.05$). In these children gluten was introduced into the diet between 3rd and 18th month of life (average 7.5 months). Atypical celiac disease was diagnosed in 26 children (33.3%) at the age from 2.5 to 12 years and in about 80% of them aged between 5th and 13th year of life. Also in this group there were more girls than boys (61.5% vs. 38.4%); however, the difference was not statistically significant. In the group with this clinical picture of the disease, gluten was introduced to the diet between

Table 1. Clinical types of celiac disease in children

Tabela 1. Postacie kliniczne choroby trzewnej u dzieci

Groupe (Grupa)	Celiac disease (Choroba trzewna)	Numer of children (Liczba dzieci) n = 78		Age of diagnosis – years (Wiek rozpoznania – lata)		Sex (Płeć)		Statistical significance (Istotność statystyczna) (p)	Gluten introduction into the diet – months (Wprowadzenie glutenu do diety – miesiące)	
						female	male			
		n	%	x	from–to	n %	n %		x	from–to
I	Classical celiac disease	40	51.3	1.75	8 months –6 years	30 75.0	10 25.0	0.0001	7.5	3–18
II	Atypical celiac disease	26	33.3	7.1	2.5–13	16 61.5	10 38.4	ns.	9.2	8–12
III	Silent celiac disease	12	15.4	8.75	4–13	5 41.6	7 58.3	ns.	11.3	8–14

x – mean (średnia arytmetyczna).
ns. – not significant (nieistotne statystycznie).

Table 2. Symptoms in patients with celiac disease according to type of the disease

Tabela 2. Ocena objawów choroby trzewnej w zależności od postaci choroby

No (Lp.)	Symptoms (Objawy)	Classic celiac disease – I (n = 40) (Choroba trzewna klasyczna – I (n = 40))		Atypical celiac disease – II (n = 26) (Choroba trzewna nietypowa – II (n = 26))		Silent celiac disease – III (n = 12) (Choroba trzewna utajona – III (n = 12))		Statistical significance (p) (Istotność statystyczna (p))		
		n	%	n	%	n	%	I/II	I/III	II/III
1.	Chronic diarrhea	36	90.0	0	0	0	0	< 0.0001	< 0.0001	ns.
2.	Abdominal pain	30	75.0	20	76.9	2	16.6	ns.	0.0009	0.0017
3.	Failure to thrive	26	65.0	10	38.4	0	0	ns.	0.0003	0.0354
4.	Abdominal distension	16	40.0	4	15.3	0	0	ns.	0.02	ns.
5.	Constipation	0	0	1	3.8	2	16.6	ns.	ns.	ns.
6.	Vomiting	4	10.0	1	3.8	0	0	ns.	ns.	ns.
7.	Short stature	5	12.5	11	42.3	1	8.3	0.01	ns.	ns.
8.	Peripheral odema	4	10.0	0	0	0	0	ns.	ns.	ns.

n – numer (liczba).
ns. – not significant (nieistotne statystycznie).

8th and 12th month of life, average 9.2 months. Silent celiac disease was diagnosed in 12 children (15.4%) at the age between 7 and 13 years. There were more boys than girls (58.1% vs. 41.6%) but the difference was not statistically significant. In this group gluten was introduced to the diet between 8th an 14th month of life, average 11.3 months.

The most frequent clinical symptoms of classical form of celiac disease were: chronic diarrhea (90.0%), frequently greasy, recurrent abdominal pain (70.0%), abdomen distention (40%) and development retardation (65%) (Table 2). In children with atypical form of the disease recurrent abdominal pain (76.9%), failure to thrive 38.4%), short stature (42.3%) and abdominal distention (15.3%) were most frequent. In children with silent celiac disease there were no characteristic symptoms. Only in single cases, abdominal pain, delayed increase of stature and constipation were observed.

There was a statistically significant difference in diarrhea frequency between the group with classical celiac disease and the groups with atypical or

silent forms of the disease ($p < 0.0001$). Moreover, in the group with classical picture of the disease, the occurrence of recurrent abdominal pain, disturbed development and abdominal distention were more frequent than in children with silent form of the disease. In children with atypical celiac disease, growth retardation was observed more often than in the group with classic picture of the disease ($p < 0.01$) and in comparison with silent disease, abdominal pain and development retardation were more frequent ($p < 0.001$ and $p < 0.03$, respectively).

The most frequent diseases coexisting with celiac disease depending of the clinical picture of the disease are presented in Table 3. In children with classical celiac disease iron deficiency anemia (42.5%), increased activity of transaminases (40%) and decreased serum cholesterol (35%) were frequently observed. In 22.5% of the children selective IgA deficiency was observed. In single cases, Dühring disease, atopic dermatitis, food allergy and thyroid diseases were present.

In children with diagnosed atypical celiac disease with untypical disease, the following problems occurred the most often: iron deficiency anemia (15%), increased activity of transaminases (11.5%), food allergy (19.2%), thyroid gland diseases and pollinosis in 11.5%. In children with silent picture of celiac disease, hypercholesterolemia was present in 33.3% and hypertriglicerydemia in 16.6%. Type 1 diabetes was diagnosed in 50% of these children and celiac disease in parents or siblings in 33.3%. Statistical significance of the difference between frequencies of clinical symptoms in various types of celiac disease is presented in Table 3.

Discussion

Celiac disease belongs to one of the most frequently diagnosed diseases of the alimentary tract. The frequency of celiac disease in developed countries is about 1% [11]. Among predisposing factors are genetic predispositions determined by HLA markers of DQ2 and DQ8 types, which are present in more than 95% of celiacs [11]. It should be emphasized that in spite of the frequent occurrence of these markers in the general population (30–40%), only 1 to 4% of these subjects develop celiac disease [12]. It is thought that about 20 other genes are the risk factors of celiac disease. It has been observed that celiac disease is present in about 10% of children whose parents have this disease [12]. Environmental factors are also of great importance. The most distinguished factor is the timing of introduction of gluten into the diet of a child. Gluten introduced before the 3rd month of life causes more rapid development of celiac disease than when it is introduced between 4th and 6th month of life. However, the introduction of gluten later than in the 7th month of life increases the risk of the occurrence of celiac disease later in life [13]. The withdrawal of gluten from the diet does not cause the subsidence of the symptoms in all patients. Up to 30% of the patients do not respond to gluten-free diet and in about 5% refractory celiac disease develops. Among factors preventing the development of celiac disease is breast feeding longer than 2 months, which decreases the risk of the disease by 63% [14]. It has been proven that also the type of birth influences the frequency of celiac disease. Studies of Decker et al. demonstrated that children born by planned cesarean birth had more frequently celiac disease than children born naturally and unexpectedly [15, 16]. In prematurely born children the risk of the development of celiac disease at later age was greater than in children born in term (16). From many observations it can be infered that bacterial colonization of the intestine from birth and, in consequence, the function of epithelial barrier and intestinal mucosa permeability play an important role in the development of celiac disease [16]. This view is supported by the more frequent incidence of celiac disease in children who had two or more intestinal infections (with rotavirus or other infectious organisms). In our studies classical celiac disease with all clinical symptoms was most frequently diagnosed. The introduction of serological tests to the diagnostics of celiac disease such as the estimation of antibodies against endomysium of smooth muscles and antibodies against type 2 transglutaminase increased the rate of diagnosis of atypical and silent forms of celiac disease. In our study classical celiac disease was diagnosed in 51.3% of cases, atypical in 33.3% and silent in 15.4%. Classical celiac disease was most often diagnosed in the youngest children between 7th and 13th month of life and more frequently in girls. Atypical celiac disease was most frequently diagnosed between 5th and 13th year of age and silent form between 7th and 13th year of age. Also, other authors have demonstrated a greater frequency of diagnosis of classical form of celiac disease. Kuloglu et al. reported that from 106 analyzed cases of celiac disease, the classical form was diagnosed in 60.6% and the atypical form in 37.6% (19). Most cases (77.5%) of classical celiac disease were diagnosed before the end of the second year of life and in girls (75%). The shift in the time of diagnosis of celiac disease after second year of life was probably connected with the later introduction of gluten to the diet [11, 19–21]. In our study in single cases gluten was introduced into the diet even in 18th month of life. According to

Table 3. Occurrence of coexisting diseases in celiac disease

Tabela 3. Choroby współistniejące z chorobą trzewną

No (Lp.)	Name of disease (Nazwa choroby)	Classic celiac disease (n = 40) (Choroba trzewna klasyczna) (n = 40) (I)		Atypical celiac disease (n = 26) (Choroba trzewna atypowa) (n = 26) (II)		Silent celiac disease (n = 12) (Choroba trzewna utajona) (n = 12) (III)		Statistical significance (p) (Istotność różnic (p))		
		n	%	n	%	n	%	I/II	I/III	II/III
1.	Iron deficiency anemia	17	42.5	4	15.3	1	8.3	0.04	ns.	ns.
2.	Increased aminotransferase activity	16	40.0	3	11.5	0	0	0.026	0.023	ns.
3.	Hypercholesterolemia	0	0.0	1	3.8	4	33.3	ns.	0.001	0.047
4.	Hypocholesterolemia	14	35.0	0	0	0	0	0.002	0.043	ns.
5.	Hypertriglicerydemia	5	12.5	0	0	2	16.6	ns.	ns.	ns.
6.	Herpetiformis dermatitis (Dürhing's disease)	2	5.0	0	0	0	0	ns.	ns.	ns.
7.	Atopic dermatitis	2	5.0	0	0	0	0	ns.	ns.	ns.
8.	Food allergy	3	7.5	5	19.2	1	8.3	ns.	ns.	ns.
9.	Pollinosis, Bronchial asthma	1	2.5	3	11.5	0	0	ns.	ns.	ns.
10.	Diabetes mellitus type 1	0	0	0	0	6	50.0	ns.	< 0.0001	0.0006
11.	IgA deficiency	9	22.5	3	11.5	0	0	ns.	ns.	ns.
12.	Autoimmune thyroiditis	1	2.5	0	0	0	0	ns.	ns.	ns.
13.	Hypothyriod gland disorder	1	2.5	3	11.5	0	0	ns.	ns.	ns.
14.	Nephrolithiasis	0	0	0	0	1	8.3	ns.	ns.	ns.
15.	Alopecia areata	0	0	1	3.8	0	0	ns.	ns.	ns.
16.	Family members of celiac patients (parents, siblings)	0	0	0	0	4	33.3	ns.	0.001	0.01

European Societies for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), recommendations in breast fed infents gluten should be introduced to the diet between 4th and 6th month of life. This allows the organism to establish tolerantion against gluten and to reduce the risk of celiac disease [22].

Among clinical symptoms of classical celiac disease the following dominated: chronic diarrhea, abdominal pain, distention of abdomen and retardation of development. In atypical celiac disease – abdominal pain, short stature and retardation of development. These symptoms were not observed in silent celiac disease.

Laboratory tests and analysis of coexisting diseases demonstrated more frequent increase in aminotransferases activity, hypocholesterolemia, iron deficiency anemia and IgA deficiency in children with classical celiac disease in comparison with atypical form. Thyroid gland diseases dominated in atypical celiac disease. In silent celiac disease significantly more frequent increase of serum cholesterol and coexistence of type 1 diabetes was observed. Szaflarska-Popławska observed that in 40.85% of children with celiac disease activity of ALT or/and AST was elevated. According to this author, all patients with celiac disease should undergo assessment of liver function at the time of diagnosis of the disease and after 6–12 months of gluten-free diet. Lack of normalization after such a time may indicate lack of adherence to the diet or coexistence of autoimmune liver diseases [21]. From our studies it can be seen that the frequency of hyperatransaminasemia depends on celiac disease clinical form and on the age of patients. Other studies confirm this observation [19, 23, 25]. Iwańczak et al. in earlier studies compared the frequency of hypertansaminasemia and iron deficiency anemia in children and adults with celiac disease [23]. The age of the 59 children included in that study was 7 to 18 years (mean 12.5) and that of 52 adults from 19 to 75 years (mean (32.0). In children, the clinical picture of the disease was not analyzed. The study demonstrated significantly more frequent hypertransaminasemia in adults than in children ($p < 0.001$) as well as more frequent anemia in adults (80.7% vs. 28.8%, $p < 0.001$). Diseases of thyroid gland were also more frequent in adults than in children with celiac disease (15.4% vs. 5.1%). In our present study from among coexisting diseases, type 1 diabetes was the most frequent disease in children with silent form of celiac disease. According to numerous studies, type 1 diabetes is the most frequent disease in patients with celiac disease [19, 24, 25]. Iwanicka et al. conducted a study on frequency of celiac disease among patients with type 1 diabetes in a group of 83 children aged 3 to 18 years. Celiac disease was diagnosed based on positive antiendomysial antibodies (IgAEmA) in the serum and villi atrophy in duodenum mucosa specimens. In 6% of the studied children celiac disease was diagnosed. Titer of IgAEmA in those children was 160 to 2560. In one female patient concomitant celiac disease and Graves-Basedov disease were diagnosed. According to the authors of the cited work, the risk of autoimmune diseases is greater in patients with celiac disease than in the general population. Grzędo-Adamek et al., in a screening study conducted on a group of 109 children with autoimmune disease of the thyroid gland, found only one case of celiac disease without any symptoms [26].

In summary, it should be recapitulated that the most frequently diagnosed clinical form of celiac disease is classical celiac disease. Silent celiac disease occurred most frequently in children with type 1 diabetes whose parents or siblings had celiac disease. In classical celiac diseases dominated diarrhea, abdominal pain, disturbance of physical development, iron deficiency anemia, hypertransaminasemia, hypocholesterolemia and IgA deficiency. In silent celiac disease, hypercholesterolemia was observed the most frequently. High frequency of celiac disease in the general population and variable clinical picture is an indication of serological examination, which will allow detection and treatment of the disease, Early detection of celiac disease will enable the child to develop properly and will prevent frequent and dangerous health complications.

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