

Influence of specific dietary interventions on clinical manifestation of coeliac disease

Wpływ określonych interwencji klinicznych na manifestację kliniczną celiakii

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Słowa kluczowe: celiakia, obraz kliniczny, karmienie naturalne, wprowadzenie glutenu do diety.

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Abstract

Introduction: Breast-feeding duration and time of gluten introduction into infants' diet are mentioned among the most important dietary factors that influence the development of coeliac disease (CD).

Aim: To evaluate the influence of time of gluten introduction into infants' diet and/or breast-feeding duration on clinical manifestation of CD.

Material and methods: The retrospective analysis comprised 130 randomly chosen children, including 87 girls and 43 boys with CD diagnosed according to currently applied ESPGHAN criteria.

Results: Time of the first clinical symptoms and diagnosis of CD was statistically significantly later in case of gluten introduction into the infant's diet after 6 months of life in comparison to children in whom gluten was introduced into the diet before 4 months of life. Time of gluten introduction had no influence on degree of damage of the small bowel mucosa. Significantly more often classic form of CD was diagnosed in children in whom gluten was introduced into the diet before 4 months of life, but atypical form of CD occurred more often in children in whom gluten was introduced into the diet after 6 months of life ($p < 0.05$). Statistical analysis revealed a statistically significant linear relation between breast-feeding duration and time of occurrence of the first clinical symptoms ($p < 0.01$) and diagnosis ($p < 0.01$) of CD. More advanced lesions in the small bowel mucosa were observed at the moment of diagnosis of CD in children who were fed artificially from birth in comparison with breast-fed children ($p < 0.05$). Classic form of CD was diagnosed significantly more often ($p < 0.05$) in children fed artificially from birth and in children who were breast-fed for less than 6 months than in children who were breast-fed longer than 6 months. The first clinical symptoms occurred significantly later in children

Streszczenie

Wstęp: Czas trwania karmienia naturalnego oraz wprowadzania glutenu do diety niemowląt są wymieniane wśród najważniejszych czynników dietetycznych wpływających na rozwój celiakii (CD).

Cel: Ocena wpływu czasu wprowadzenia glutenu do diety niemowląt i/lub czasu trwania karmienia naturalnego na przebieg kliniczny celiakii.

Materiał i metody: Retrospektywną analizą objęto 130 losowo wybranych dzieci, w tym 87 dziewczynek i 43 chłopców, z celiakią rozpoznaną zgodnie z obecnie obowiązującymi kryteriami rozpoznania.

Wyniki: Czas pojawienia się pierwszych objawów klinicznych oraz rozpoznania celiakii był istotnie statystycznie późniejszy w przypadku wprowadzenia glutenu do diety niemowląt po ukończeniu 6. mies. życia w porównaniu z wprowadzaniem glutenu do diety niemowląt przed ukończeniem 4. mies. życia. Czas wprowadzenia glutenu do diety niemowląt nie miał wpływu na stopień uszkodzenia błony śluzowej jelita cienkiego. Klasyczną postać celiakii rozpoznawano istotnie statystycznie częściej u dzieci, u których gluten do diety wprowadzono przed 4. mies. życia, a nietypową postać celiakii – istotnie statystycznie częściej u dzieci, u których gluten wprowadzono do diety po 6. mies. życia ($p < 0,05$). Analiza statystyczna wykazała istotną statystycznie liniową zależność między czasem trwania karmienia naturalnego a czasem pojawienia się pierwszych objawów klinicznych ($p < 0,01$) i czasem rozpoznania choroby ($p < 0,01$). Bardziej zaawansowane zmiany w błonie śluzowej jelita cienkiego obserwowano w momencie rozpoznania celiakii u dzieci, które były karmione sztucznie od urodzenia w porównaniu z dziećmi karmionymi naturalnie ($p < 0,05$). Klasyczna postać celiakii była rozpoznawana istotnie statystycznie częściej ($p < 0,05$) u dzieci karmionych sztucznie od urodzenia i u dzieci karmio-

in whom gluten was introduced into the diet during breast-feeding ($p < 0.01$), CD was diagnosed later ($p < 0.01$) and atypical form of the disease was diagnosed more often ($p < 0.01$). More advanced histopathological lesions in the small bowel mucosa were observed in children who were artificially fed during gluten introduction into the diet ($p < 0.01$).

Conclusions: Longer breast-feeding and later gluten introduction into the diet, particularly during breast-feeding, significantly delays the time when the first clinical symptoms of coeliac disease occur, delays the time of disease diagnosis and increases the probability of atypical coeliac disease being diagnosed. Artificial feeding from birth can increase the risk that more advanced histopathological lesions will occur in the small bowel mucosa.

Introduction

Coeliac disease is a permanent gluten intolerance causing small bowel enteropathy of autoimmune origin in persons who are genetically predisposed [1]. It has been observed during recent years that the clinical picture of coeliac disease has changed. The number of newly diagnosed cases of classic coeliac disease revealed during the first years of the child's life is decreasing. Frequency of diagnosis of atypical forms manifesting in older children and in adults is increasing [2].

Pathogenesis of coeliac disease is multifactorial. First of all dietary factors are mentioned among the most important environmental factors that influence coeliac disease development, particularly breast-feeding duration, time of gluten introduction into infants' diet and especially gluten introduction into the diet during breast-feeding. The influence of the above-mentioned nutritional factors on the time when coeliac disease appears and on the clinical picture of the disease is also discussed [2].

Aim

The aim of the study was to evaluate the influence of time of gluten introduction into infants' diet and/or breast-feeding duration on clinical manifestation of coeliac disease.

Material and methods

The retrospective analysis comprised 130 randomly chosen patients of the Department of Paediatrics, Allergy and Gastroenterology or the Outpatient Clinic of the department, including 87 girls (66.9%) and 43 boys (33.1%) in whom coeliac disease was diagnosed during

naturalnie krócej niż 6 mies. niż u dzieci karmionych naturalnie dłużej niż 6 mies. U dzieci, u których gluten był wprowadzany do diety jeszcze w trakcie karmienia naturalnego, istotnie statystycznie później pojawiały się pierwsze objawy kliniczne ($p < 0,01$), celiakia była rozpoznawana później ($p < 0,01$) i częściej była diagnozowana nietypowa postać choroby ($p < 0,01$). Bardziej zaawansowane zmiany histopatologiczne w błonie śluzowej jelita cienkiego obserwowano u dzieci, które były karmione sztucznie w trakcie wprowadzania glutenu do diety ($p < 0,01$).

Wnioski: Dłuższy czas karmienia naturalnego oraz późniejsze wprowadzanie glutenu do diety niemowląt, zwłaszcza w czasie karmienia naturalnego, znacząco opóźnia czas pojawiania się pierwszych objawów klinicznych, rozpoznania choroby oraz zwiększa prawdopodobieństwo rozpoznania nietypowej postaci celiakii. Karmienie sztuczne od urodzenia zwiększa ryzyko wystąpienia bardziej zaawansowanych zmian histopatologicznych w błonie śluzowej jelita cienkiego.

the period from 1995 up to now on the basis of clinical picture, result of histopathological examination of the small bowel biopsy specimens and serological test for the presence of antiendomysial antibodies. Tests for serum IgA antiendomysial antibodies (IgAEmA), but in patients with decreased IgA level IgG antiendomysial antibodies (IgGEmA), were performed applying indirect immunofluorescence with the use of monkey oesophagus as antigen. The small bowel biopsy was performed endoscopically, taking two to three mucosal biopsy specimens at different levels of the descending part of the duodenum. Histopathological evaluation of biopsy specimens was performed on the basis of modified Marsh's classification. The following factors were analysed to assess the influence of specific dietary interventions on clinical manifestation of coeliac disease: time of occurrence of first clinical symptoms, time of coeliac disease diagnosis, clinical form of coeliac disease, degree of atrophic lesions of mucosal villi of the small bowel mucosa depending on time of gluten introduction into infant's diet, breast-feeding duration and also breast-feeding or artificial feeding at the moment of gluten introduction into the diet.

Analysing the influence of time of gluten introduction into the diet, the analysed population was divided into 3 groups: group I – children in whom gluten was introduced early into the diet, meaning before 4 months of life, group II – children in whom gluten was introduced into the diet between 4 and 6 months of life, and group III – children in whom gluten was introduced into the diet after 6 months of life.

Analysing the influence of breast-feeding duration on clinical course of coeliac disease, the analysed population was divided into 4 groups: group 1 – children arti-

ficially fed from birth, group 2 – children who were breast-fed no longer than for 1 month, group 3 – children who were breast-fed longer than 1 month, but less than 6 months, and group 4 – children who were breast-fed longer than 6 months.

Analysing the influence of breast-feeding during gluten introduction into infants' diet on clinical manifestation of coeliac disease, the analysed population was divided into group A – children who were breast-fed during gluten introduction, and group B – children who were artificially fed during gluten introduction.

Statistical calculations were made using the statistical package SPSS 14.0 PL. Results with $p < 0.05$ were acknowledged as statistically significant values.

Results

Coeliac disease was diagnosed between 7 months of life and 14 years of life, on average at 48 months of life in the analysed group of patients. In 70 patients (53.8%) coeliac disease was diagnosed before 24 months of life.

The first clinical symptoms of coeliac disease were observed between 3 months of life and 13 years of life. Coeliac disease occurred in first degree relatives in 12 patients (9.2%).

Marsh IIIC histopathological lesions within the small bowel mucosa occurred in 94 patients (72.3%), IIIA in 2 patients (1.5%), and IIIB in 34 patients (26.2%). All patients revealed the presence of serum antiendomysial antibody, including 123 patients with IgA antiendomysial antibody and 19 patients with IgG antiendomysial antibody.

Classic coeliac disease was diagnosed in 69 children (53.1%), and atypical coeliac disease in 61 patients (46.9%). The following clinical symptoms were observed most often: failure to thrive (in 78.5% of patients),

loss of appetite (in 46.2%), loss of weight (in 25.4%), psychophysical retardation (in 18.2%), height deficiency (in 13.1%), periodic diarrhoea (in 78.5%), presence of fetid stools (in 23.8%), fatty stools with undigested food debris (in 12.3%), constipation (in 6.2%), abdominal pain (in 33.1%), abdominal flatulence (in 53.8%), nausea or vomiting (in 31.5%), personality disorders (in 17.7%), concentration disorders (in 13.8%), aphthous stomatitis (in 6.9%), dermatitis herpetiformis (in 13.1%). Iron deficiency anaemia was noted in 38.5% of patients.

Gluten was introduced into the infants' diet in the analysed group of patients between 1 and 13 months of life, on average at 6 months of life. Gluten was introduced before 4 months of life in 50 patients (38.5%), between 4 and 6 months of life in 50 patients (38.5%) and after 6 months of life in 30 patients (23%).

The first clinical symptoms of coeliac disease occurred before 12 months of life in 66% of children in whom gluten was introduced before 4 months of life, in 56% of children in whom gluten was introduced between 4 and 6 months of life and in 23% of children in whom gluten was introduced after 6 months of life (Table I). The differences between groups I and III were statistically significant. Diagnosis of coeliac disease in children from group I was made on average after 35.1 months of life, from group II after 46.7 months of life, from group III after 73.1 months of life, and these differences were statistically significant between all groups.

Classic form of coeliac disease was diagnosed in 64% of children in whom gluten was introduced before 4 months of life (group I), in 52% of children in whom gluten was introduced between 4 and 6 months of life (group II) and in 37% of children in whom gluten was introduced after 6 months of life (group III). Atypical coeliac disease was recognized in 36, 48 and 63%,

Table I. Analysis of influence of time of introduction of gluten into the infant's diet on time of occurrence of first clinical symptoms

Tabela I. Wpływ czasu wprowadzenia glutenu do diety niemowlęcia na czas wystąpienia pierwszych objawów klinicznych

Group of patients	Total N (% of column)	Age of occurrence of first clinical symptoms of coeliac disease [months]			
		till 8 months of life n (% of line)	9-12 months of life n (% of line)	13-54 months of life n (% of line)	after 54 months of life n (% of line)
I	50 (38%)	21 (42%)	12 (24%)	10 (20%)	7 (14%)
II	50 (38%)	13 (26%)	15 (30%)	10 (20%)	12 (24%)
III	30 (24%)	1 (3%)	6 (20%)	11 (37%)	12 (40%)
Total	130	35	33	31	31

group I – children in whom gluten was introduced into the diet before 4 months of life

group II – children in whom gluten was introduced into the diet between 4 and 6 months of life

group III – children in whom gluten was introduced into the diet after 6 months of life

respectively. The differences between groups I and III were statistically significant (Table II).

There were no statistically significant differences between groups I, II and III concerning influence of gluten introduction time on the degree of the small bowel mucosa lesions. In 76% of children from group I, 72% of children from group II and 67% of children from group III there occurred IIC lesions according to Marsh's classification.

Time of breast-feeding in the analysed group of children varied from 0 to 26 months of life and was 4.2 months on average. 36 children (27.7%) were artificially fed from birth and 31 children (23.8%) were breast-fed only for the first month of life.

Pearson's correlation analysis revealed a statistically significant linear relation ($p < 0.01$) between breast-feeding duration and time of first clinical symptoms of coeliac disease. The longer the breast-feeding period maintained, the later was the time of disease occurrence. The first clinical symptoms occurred in the first year of life in 64% of children artificially fed from birth (group 1), in 74% of children breast-fed only for the first month of life (group 2), in 50% of children breast-fed longer than 1 month but less than 6 months (group 3), and in 15% of children breast-fed longer than 6 months (group 4).

Analysis using Pearson's correlation coefficient also revealed a statistically significant linear relation ($p < 0.01$) between breast-feeding duration and age at which coeliac disease was diagnosed. The longer the duration of breast-feeding maintained, the later was the time of disease diagnosis. Coeliac disease was diagnosed before 14 months of life in 30% of children from group 1, 29% of children from group 2, 36% of children from group 3 and 7% of children from group 4. Late diagnosed coeliac disease (after 70 months of life) occurred in 14% of children from group 1, 10% of children

from group 2, 14% of children from group 3 and 71% of children from group 4 (Table III).

Analysis using Pearson's correlation coefficient also showed the presence of a statistically significant linear relation ($p < 0.05$) between breast-feeding duration and degree of the small bowel mucosa lesions. More advanced changes in small bowel mucosa (Marsh IIIC) were observed in children who were fed artificially from birth (81% of children from group 1) in comparison with children breast-fed longer than 6 months (59% of children from group 4).

Analysis of Student's *t*-test showed the presence of statistically significant differences ($p < 0.05$) concerning incidence of different forms of coeliac disease depending on breast-feeding duration (Table IV). Classic coeliac disease was diagnosed in 30% of children who were breast-fed longer than 6 months and in 59.2% of those who were fed artificially from birth and who were breast-fed for less than 6 months. Atypical coeliac disease was recognized in 70 and 40.8%, respectively.

Table II. Influence of time of gluten introduction into infant's diet on clinical type of coeliac disease

Tabela II. Wpływ czasu wprowadzenia glutenu do diety niemowlęcia na kliniczną postać celiakii

Group of patients	Total N (% of column)	Form of coeliac disease	
		classic n (% of line)	atypical n (% of line)
I	50 (38%)	32 (64%)	18 (36%)
II	50 (38%)	26 (52%)	24 (48%)
III	30 (24%)	11 (37%)	19 (63%)
Total	130	69	61

group I – children in whom gluten was introduced into the diet before 4 months of life

group II – children in whom gluten was introduced into the diet between 4 and 6 months of life

group III – children in whom gluten was introduced into the diet after 6 months of life

Table III. Influence of breast-feeding duration on time at which coeliac disease was diagnosed

Tabela III. Wpływ długości karmienia naturalnego na czas wystąpienia pierwszych objawów klinicznych celiakii

Group of patients	Total N (% of column)	Time of coeliac disease diagnosis [months]			
		0-13 n (% of line)	14-24 n (% of line)	25-70 n (% of line)	over 70 n (% of line)
1	36 (28%)	11 (30%)	15 (42%)	5 (14%)	5 (14%)
2	31 (24%)	9 (29%)	12 (39%)	7 (22%)	3 (10%)
3	36 (28%)	13 (36%)	6 (17%)	12 (33%)	5 (14%)
4	27 (20%)	2 (7%)	2 (7%)	4 (15%)	19 (71%)
Total	130	35	35	28	32

group 1 – children artificially fed from birth

group 2 – children who were breast-fed no longer than for 1 month

group 3 – children who were breast-fed longer than 1 month, but less than 6 months

group 4 – children who were breast-fed longer than 6 months

Table IV. Influence of breast-feeding duration on clinical form of coeliac disease

Tabela IV. Wpływ długości karmienia naturalnego na kliniczną postać celiakii

Group of patients	Total N (% of column)	Form of coeliac disease	
		classic n (% of line)	atypical n (% of line)
1	36 (28%)	19 (53%)	17 (47%)
2	31 (24%)	23 (74%)	8 (26%)
3	36 (28%)	19 (53%)	17 (47%)
4	27 (20%)	8 (30%)	19 (70%)
Total	130	69	61

group 1 – children artificially fed from birth

group 2 – children who were breast-fed no longer than for 1 month

group 3 – children who were breast-fed longer than 1 month, but less than 6 months

group 4 – children who were breast-fed longer than 6 months

The majority of children (78%) during gluten introduction into the diet were fed artificially (group B). Only 22% of children were breast-fed at the moment of gluten introduction into infants' diet (group A).

Analysis with χ^2 test showed the presence of a statistically significant difference ($p < 0.01$) in time of occurrence of the first symptoms of coeliac disease between groups of children who were breast-fed and artificially fed during gluten introduction into the diet. In 71% of children from group A and only 11% of children from group B the first clinical symptoms of coeliac disease occurred after 54 months of life.

A statistically significant difference ($p < 0.01$) was also proved concerning the time of diagnosis of coeliac disease between groups of children who were breast-fed and artificially fed during gluten introduction into the diet (Table V). Coeliac disease was diagnosed late (after 70 months of life) in the majority of children (75%) in whom gluten was introduced during breast-feeding.

Table V. Influence of feeding type during gluten introduction into infant's diet on time of coeliac disease diagnosis

Tabela V. Wpływ rodzaju karmienia w trakcie wprowadzania glutenu do diety niemowlęcia na czas rozpoznania celiakii

Group of patients	Total N (% of column)	Age of coeliac disease diagnosis [months]			
		0-13 n (% of line)	14-24 n (% of line)	25-70 n (% of line)	> 70 n (% of line)
A	28 (22%)	1 (4%)	2 (7%)	4 (14%)	21 (75%)
B	102 (78%)	34 (34%)	33 (33%)	24 (23%)	11 (10%)
Total	130	35	35	28	32

group A – children who were breast-fed during gluten introduction

group B – children who were artificially fed during gluten introduction

More advanced changes in small bowel mucosa (Marsh IIIC) were observed in children who were fed artificially during gluten introduction (78% of children from group B) in comparison to those breast-fed during gluten introduction (54% of children from group A) and the difference was statistically significant ($p < 0.01$).

It was also noted that statistically significantly more often atypical form of coeliac disease ($p < 0.01$) was diagnosed in breast-fed children (71% of children from group A) than artificially fed (40% of children from group B) during gluten introduction into the diet (Table VI).

Discussion

This study made an attempt to analyse the clinical picture of coeliac disease depending on time of gluten introduction into the diet, breast-feeding duration and feeding type (breast-feeding, artificial feeding) at the moment of gluten introduction. The retrospective analysis comprised 130 randomly chosen children with coeliac disease diagnosed according to ESPGHAN criteria. Medical documentation of children comprised information about breast-feeding duration and time of gluten introduction into the diet. The authors are aware of the imperfection of the analysis that results from the retrospective character of the study. This fact means that there is a high risk of systematic error connected with inclusion in the study (selection bias) and recalling facts (recall bias).

Our studies proved that later (i.e. after the first 6 months of life) gluten introduction into the infants' diet reschedules the occurrence time concerning the first symptoms of coeliac disease and also the time of coeliac disease diagnosis for later periods of the child's life. This fact also increases the frequency of diagnosis concerning atypical form of coeliac disease, but it has no influence on lesion degree of the small bowel mucosa. Division of children included in the analysis into three groups depending on time of gluten introduction

into the infants' diet reproduced the division proposed by Norris *et al.* [3]. The study published in 2005 stated that children from the group with high risk of coeliac disease development, to whom gluten was served before 3 months of life or after 6 months of life, carry a high risk of coeliac disease in comparison with children to whom gluten was served between 4 and 6 months of life. Results of the study of Norris *et al.* suggest that the optimal period to introduce gluten into the diet may be 4-6 months of life, but earlier (< 4 months of life) similarly as later (≥ 7 months of life) gluten introduction into the diet may not be advantageous. It is still not clear whether such management really decreases the risk of coeliac disease occurrence or only delays the time of appearance of clinical symptoms of coeliac disease until a later period.

Currently the multicentre study financed by the European Union PREVENTCD is being performed and its aim is to explain whether gluten introduction in small amounts even during breast-feeding really decreases the risk of coeliac disease occurrence. The results of the study may become a rational reason to change previous dietary recommendations for infants [4].

It has been a common opinion so far that extending the time of breast-feeding and later introduction of gluten into infants' diet are responsible for the tendency for a changing clinical picture of coeliac disease that has been observed for several dozen years. This change of clinical picture of coeliac disease consists of decreased incidence of classic form in favour of atypical forms [5, 6]. Our studies really proved that later gluten introduction into the diet (< 4 months of life vs. ≥ 7 months of life) significantly decreased the frequency of diagnosis of classic coeliac disease and increased the incidence of atypical coeliac disease. A similar tendency was also observed by Mowszet *et al.* [2], who noted later occurrence of the first clinical symptoms of coeliac disease (> 2 years of life) statistically more often in children for whom gluten was introduced into the diet later (after 9 months of life). Classic symptoms of coeliac disease (diarrhoea, failure to thrive, abdominal flatulence) were observed more rarely in this group of children, but abdominal pain and short stature occurred more often. Similarly, Peters *et al.* [7] confirmed later occurrence of first symptoms of coeliac disease in children in whom gluten was introduced later into the diet. Simultaneously they observed no effectiveness of this management in protecting against coeliac disease development.

Similar dependences as in the case of later gluten introduction into the diet on clinical manifestation of coeliac disease were also observed in our studies in the case of longer breast-feeding and gluten introduction

Table VI. Influence of feeding type during gluten introduction into the diet on clinical type of coeliac disease

Tabela VI. Wpływ rodzaju karmienia w czasie wprowadzania glutenu do diety na postać kliniczną celiakii

Group of patients	Total N (% of column)	Form of coeliac disease	
		classic n (% of line)	atypical n (% of line)
A	28 (22%)	8 (29%)	20 (71%)
B	102 (78%)	61 (60%)	41 (40%)
Total	130	69	61

group A – children who were breast-fed during gluten introduction
group B – children who were artificially fed during gluten introduction

during breast-feeding. The first clinical symptoms of coeliac disease occurred statistically significantly later in children who were breast-fed for at least 6 months and in children in whom gluten was introduced into the diet during breast-feeding. Also coeliac disease was diagnosed later and more often atypical form of coeliac disease was diagnosed in these groups of children. Damage of the small bowel mucosa at the moment of diagnosis was also less intensive in breast-fed children and also in children in whom gluten was introduced into the diet during breast-feeding in comparison with children who were artificially fed from birth. Studies of D'Amico *et al.* [8], similarly as in our studies, found that exclusively breast-feeding for the first 6 months of life significantly delayed the time of occurrence of the first symptoms of coeliac disease and the time of final diagnosis. Children who were exclusively breast-fed for the first half year of the first year of life more rarely presented clinical symptoms typical for classic coeliac disease, i.e. diarrhoea, inhibition of physical development, vomiting, abdominal pain and abdominal distension, but physician visits were performed more often and time from the moment of the first symptoms of coeliac disease to diagnosis of this disease was longer. However, Mowszet *et al.* [2] did not observe any difference in time of first clinical symptoms and time of diagnosis of coeliac disease (early childhood, later) between groups of children who were breast-fed and artificially fed. Ascher *et al.* [9] even proved a reverse tendency – children with diagnosed coeliac disease were breast-fed longer and they ate smaller amounts of gluten in comparison with the control group of healthy children. According to the results of a meta-analysis performed by Akobeng *et al.* [10], both prolonged breast-feeding and breast-feeding during gluten introduction into the diet decrease the risk of coeliac

disease. It is not clear whether this protective effect is maintained for the whole of life or rather breast-feeding only delays the time of occurrence of the first clinical symptoms of the disease. Decreased risk concerning suffering from coeliac disease was also observed by Ivarsson *et al.* [11] when gluten was introduced into the infant's diet during breast-feeding and particularly when gluten was administered in small and moderate amounts and infants were still breast-fed. Significantly lower risk of suffering from coeliac disease in studies of Peters *et al.* [7] was connected with breast-feeding or mixed feeding for at least 2 months of life.

On the basis of our studies it can be stated without doubt that time of occurrence of the first clinical symptoms of coeliac disease, time of disease diagnosis and clinical form of coeliac disease depend on applied feeding interventions (longer breast-feeding, longer time to introduce gluten into the diet, gluten introduction during breast-feeding). However, it is difficult to state which of these facts is the most important. Probably children who are breast-fed longer receive other supplementary food, including gluten, into the diet later. There have been no reliable data so far enabling it to be established that introduction of supplementary food after 4 months of life, but before 6 months of life, in comparison with their introduction after 6 months of life affects breast-feeding time [12]. Only Mowszet *et al.* [2] have explicitly determined that time of occurrence of clinical symptoms of the disease is connected with time of gluten introduction into the diet and that way of feeding (breast-feeding, artificial feeding) does not affect time of disease occurrence.

Also, the benefits resulting from the applied dietary interventions are debatable. Later occurrence of the first clinical symptoms connected with longer breast-feeding and late gluten introduction into the diet delays disease diagnosis and introduction of dietary treatments as a result. Longer lasting disease within the small bowel despite less expressed clinical expression increases the risk of severe and even life-threatening complications of untreated coeliac disease, including bone disorders, reproduction disturbances and autoimmune diseases.

Delay of coeliac disease diagnosis, similarly as non-compliance to a gluten-free diet, is also a main factor that increases the risk of neoplasia in patients with coeliac disease, but detection of this disease during early childhood and rigorous maintenance of a gluten-free diet allow the risk of neoplasia to be reduced to the average population level [1]. The risk of autoimmune complications observed in about 20% of patients with coeliac disease also increases together with time of exposure to gluten, but early introduction of a gluten-free diet prevents their occurrence [13].

Conclusions

1. Longer breast-feeding and later gluten introduction into the diet, particularly during breast-feeding, significantly delays the time when the first clinical symptoms of coeliac disease occur, delays the time of disease diagnosis and increases the risk of diagnosis of atypical coeliac disease, but decreases the risk of diagnosis of classic form of coeliac disease.
2. Artificial feeding from birth can increase the risk that more advanced histopathological lesions will occur in the small bowel mucosa.

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