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RESEARCH ARTICLE

CLINICAL ASPECTS OF CELIAC DISEASE IN CHILDREN IN ALBANIA

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ABSTRACT

Introduction: Coeliac disease is an autoimmune mediated enteropathy. It initiatesin genetically susceptible individuals upon ingestion of proline and glutamine proteins, commonly found in wheat, barley and ray. CD is perhaps the only multifactorial autoimmune disease where the antigenic trigger is well known and studied. In our study we have evaluated the clinical, laboratory, histopathology data as well as anthropometric measurements of 112 children diagnosed with CD. **Material and Methods:** The study included 112 children diagnosed with CD in the department of pediatrics, in "Mother Teresa" University Hospital Center, from 2010 to 2016. Thedata were collected during the first consultation with the patients and from the patient clinical records. The collected data are as follows: dermographic and anthropometric data, main complains of the patients, associated diseases, family history for CD etc. Besides these, data were collected from laboratory testing, hystopathology reports and duodenal biopsies. **Results:**The study included 112 children diagnosed with coeliac disease, out of which55.4%,(62 children), were females. The median age of disease outbreak was 7.16 ± 4.22 years. In 48.2% of the patients, the disease started at age 0 – 5 years. In 22.3% the disease started at age 6 – 10 years. Approximately ¼ of children diagnosed with coeliac live in the district of Tirana (25.7%), due to the high concentration of the population in this district. The main symptoms manifested by the patients are displayed in Table 7.From all cases we found only one asymptomatic patient. The most common complaints were weight loos/ short stature/ dystrophy, found in 26.8% of children; followed by chronic diarrhea in 13.4% of children. Abdominal pain was a complaint in 9.8%. We found anemia in 6.3 % of patients, vomiting in 5.4% and abdominal distension in 4.5%. 27.7 % of patients manifested a number of atypical, uncommon, symptoms of coeliac disease.51.8% or 58 children, about ¾ of them, had no associated diseases. Among all patients, 23.2% (26 children) had Type 1 Diabetes, 6.3% (7 children) had thyroiditis. Amongst patients with thyroiditis, 5 of them had also Type 1 Diabetes. In 26 children with coeliac disease we found other associated conditions such as epilepsy, autism. In 5.4% (6 children) a delay of expressive language was discovered. Some other uncommon conditions we encountered were gastropathy in 3.6% (4 children), various syndromes in 3.6%, ocular disorders in 1.8%, cardiac disorders in 1.8%, The duodenal biopsy was performed in 60% of the children. According to the histopathology reports in 13.2% of cases the intestinal mucosa resulted normal. 13.2 % resulted with stage M1 of coeliac disease. 20.8% resulted with stage M2, 28.3% resulted with stage M3a, 17% resulted with stage M3b and 7.4% with stage M3c.It is obvious that, in children affected by CD, the indicators of growth are delayed, according to the guidelines of World Health Organization (WHO). Children with CD are -0.8683 standard deviations under the optimal weight for age. They are – 1.3642 standard deviations under the optimal height for age and their BMI is – 0.3475 standard deviations under the optimal BMI for age. With regard to laboratory testing, we found low level of Hemoglobin in 39% of cases, low red cell count in 3.7%, low level of iron in blood in 64.9%, low level of MCV in 71.2%, increased level of AST in 55.1% and increased level of ALT in 14.7% of the children. **Conclusion:** For many a year coeliac disease was considered a disorder of the pediatric age, characterized by classic clinical manifestations such as steatorrhea and malabsorption. Though it is a frequent disease, CD is often undiagnosed and underestimated because of the variability of symptoms and heterogeneous clinical manifestations. From different studies, CD results under diagnosed in 1 – 3 % of general European population, both in adults and in children.Recognizing and understanding the various clinical presentations of CD allow us to establish an early diagnose, to start a gluten free diet as soon as possible, to achieve a normal growth and developent of the affectet children and to prevent the long term complications of the disease.

INTRODUCTION

Coeliac disease is an autoimmune mediated enteropathy. It originates in genetically susceptible individuals upon ingestion of proline and glutamine proteins, commonly found in wheat, barley and ray.

CD is perhaps the only multifactorial autoimmune disease where the antigenic trigger is well known and studied. In our study we have evaluated the clinical, laboratory, histopathology data as well as anthropometric measurements of 112 children diagnosed with CD.

MATERIALS AND MATERIALS

The study included 112 children diagnosed with CD in the department of pediatrics, in "Mother Teresa" University Hospital Center, from 2010 to 2016.

Data collection

The data were collected during the first consultation with the patients and from the patient clinical records. The collected data are as follows: dermographic and anthropometric data, main complains of the patients, associated diseases, family history for CD etc.. Besides these, data were collected from laboratory testing, hystopathology reports and duodenal biopsies. Based on hospitalization medical records and ambulatory medical records of the children included in this study, we collected the following data: birthday, date of hospitalization, age of presentation of CD (based upon birthday and hospitalization date), gender, residence, duration of breastfeeding (months), time of introduction of gluten containing foodsin the diet (patterns of infant feeding), detailed medical history (associated diseases etc.).

In all children we measuredthe anthropometric parameters, height and weight, to calculate the body mass index (BMI) of each patient included in the study. For each patient included in the study a complete clinical evaluation was required. The complete clinical evaluation included detection, description and documentation of typical and atypical signs and symptoms of the disease. With regard to laboratory tests in all patients the following were performed: hematological tests, biochemical tests, endocrinology tests, serological tests, histological reports, genetic testing / HLA typing (when possible, because the testing is too expensive in our country).The statistic analysis of all data was calculated using the SPSS statistic softwear (Statistical Package for Social Sciences), version 20.

RESULTS

The study included 112 children diagnosed with coeliac disease, out of which 55.4%, (62 children), were females. The median age of disease outbreak was 7.16 ± 4.22 years. In 48.2% of the patients, the disease started at age 0 – 5 years. In 22.3% the disease started at age 6 – 10 years. Approximately ¼ of children diagnosed with coeliac live in the district of Tirana

Table 1. Main complaints according to age – groups

Variable	Age Group			Value of P
	0-5 yrs	6-10 yrs	>10 yrs	
Main complaints				0.641*
Chronic diarrhea, intestinal disorder	10 (16.9)	3 (11.5)	2 (7.4)	
Weight loss, Failure to thrive	16 (27.1)	6 (23.1)	8 (29.6)	
Short stature, dystrophy				
Anorexia, loss of apetite	1 (1.7)	0 (0.0)	1 (3.7)	
Vomiting	6 (10.2)	0 (0.0)	0 (0.0)	
Abdominal distension	2 (3.4)	2 (7.7)	1 (3.7)	
Abdominal pain	5 (8.5)	4 (15.4)	2 (7.4)	
Anemia	1 (1.7)	3 (11.5)	3 (11.1)	
Constipacion	1 (1.7)	0 (0.0)	1 (3.7)	
Asthenia, irritability, convulsions	1 (1.7)	0 (0.0)	1 (3.7)	
Other symptoms	15 (25.4)	8 (30.8)	8 (29.6)	
Asymptomatic	1 (1.7)	0 (0.0)	0 (0.0)	

* Value of P according to chi-square test

Table 2.

Variable	Absolut Number	Percentage
Age of T1DM outbreak(mean value ± Standard Deviation)	6.27 ± 3.76	
Age of T1DM outbreak		
0-5 years	15	57.7
6-10 years	7	26.9
>10 years	4	15.4
Age of outbreak of Thyroiditis(mean value ± standard deviation)	10.82 ± 2.54	
Thyroiditis outbreak		
0-5 years	-	-
6-10 years	2	28.6
>10 years	5	71.4

Table 3. Distribution of CD children according to other accompanying diseases

Variable	Absolute number	Percentage
Associated diseases		
Dermatitis herpetiformis +dermatitis	2	1.8
Epilepsy, autism, delay of expressive language	6	5.4
Articular disorders	1	0.9
Growth Hormone deficiency GH-IgF1	2	1.8
Gastropathy	4	3.6
Hepatitis B	1	0.9
Cardio -vascular	2	1.8
ORL	2	1.8
Respiratory	1	0.9
Turner syndrome, Other syndromes	4	3.6
Urinary	1	0.9
T1DM (5 of this children have thyroiditis)	26	23.2
Thyroiditis	2	1.8
Wihout associated diseases	58	51.8
Total number	112	100.0

(25.7%), due to the high concentration of the population in this district. The main symptoms manifested by the patients are displayed in Table 7. From all cases we found only one asymptomatic patient. The most common complaints were weight loos/ short stature/ dystrophy, found in 26.8% of children; followed by chronic diarrhea in 13.4% of children. Abdominal pain was a complaint in 9.8%. We found anemia in 6.3 % of patients, vomiting in 5.4% and abdominal distension in 4.5%. 27.7 % of patients manifested a number of a typical, Uncommon, symptoms of coeliac disease. 51.8% or 58 children, about ¾ of them, had no associated diseases. Among all patients, 23.2% (26 children) had Type 1 Diabetes, 6.3% (7 children) had thyroiditis. Amongst patients with thyroiditis, 5 of them had also Type 1 Diabetes.

disease. 20.8% resulted with stage T2, 28.3% resulted with stage T3a, 17% resulted with stage T3b and 7.4% with stage T3c. It is obvious that, in children affected by CD, the indicators of growth are delayed, according to the guidelines of World Health Organization (WHO). Children with CD are -0.8683 standard deviations under the optimal weight for age. They are – 1.3642 standard deviations under the optimal height for age and their BMI is – 0.3475 standard deviations under the optimal BMI for age. With regard to laboratory testing, we found low level of Hemoglobin in 39% of cases, low red cell count in 3.7%, low level of iron in blood in 64.9%, low level of MCV in 71.2%, increased level of AST in 55.1% and increased level of ALT in 14.7% of the children.

Table 4. Laboratory findings in patients with CD

Lab . Parameter	Absolute Number	Percentage
Hemoglobine(g/dl) *		
Low	32	39.0
Normal	50	61.0
RBC (10^6) *		
Low (<3.7x$10^{6)}$	3	3.7
Normal (3.7-5.1x$10^{6)}$	78	96.3
Sideremia (µg/dl) *		
Low (<60 µg/dl)	24	64.9
Normal (60-80 µg/dl)	13	35.1
MCV (μm^3) *		
Low (<80 μm^3)	42	71.2
Normal (80-100 μm^3)	17	28.8
AST (U/l) *		
Normal (0-35 U/l)	31	44.9
High (>35 U/l)	38	55.1
ALT (U/l) *		
Normal (0-45 U/l)	58	85.3
High (>45 U/l)	10	14.7

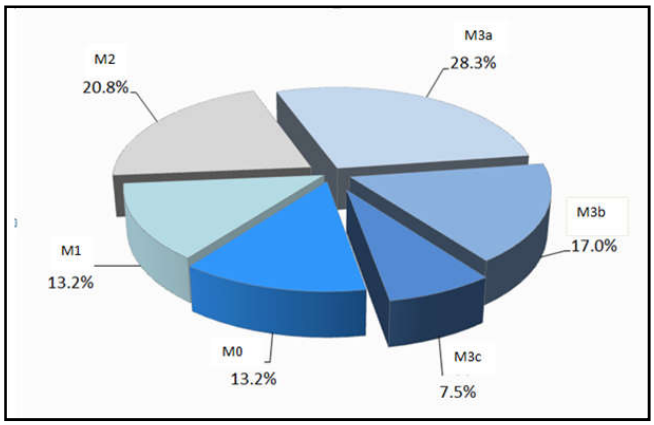

Table 5. Median values of TGA-IgG, TGA-IgA, AGA-IgG, AGA-IgA according to biopsy stage

Variabli	Stadi i sëmundjes sipas biopsisë						Value of P
	M0	M1	M2	M3a	M3b	M3c	
TGA-IgG	-	11.0	17.3	11.8	17.0	-	0.662 *
TGA-IgA	44.3	46.4	89.1	82.7	220.0	313.4	0.001
AGA-IgG	-	-	-	-	6.0	2.0	-
AGA-IgA	-	-	65.9	-	76.1	278.7	0.230

In 26 children with coeliac disease we found other associated conditions such as epilepsy, autism. In 5.4% (6 children) a delay of expressive language was discovered. Some other uncommon conditions we encountered were gastropathy in 3.6% (4 children), various syndromes in 3.6%, ocular disorders in 1.8%, cardiac disorders in 1.8%, The duodenal biopsy was performed in 60% of the children. According to the histopathology reports in 13.2% of cases the intestinal mucosa resulted normal. 13.2 % resulted with stage T1 of coeliac

DISCUSSION

At present days, coeliac disease is considered a common disease with an increase in the global prevalence (Kang *et al*., 2013). Growth delay, abdominal distension, chronic diarrhea, vomiting and a general discomfort are the classic signs of CD. Short stature, iron deficiency anemia, osteoporosis, delayed puberty, dental damages, arthritis, chronic abdominal pain and neurologic disorders are the some of the other complaints

described by the patients (Rashid, 2016). In our study, the majority of patients complained about abdominal distension, chronic diarrhea, vomiting, short stature and anemia. None of the patients had dental damages of rheumatic disorders. The study collected interesting information regarding the coeliac disease, the common conditions associated with it and the characteristics in our country. The study included 112 children diagnosed with CD from 2010 to 2016, in the Department of Pediatrics, the Clinic of Specialties, in "Mother Teresa" University Hospital Center. The median age range was from 6 months (1infant) to 15.6 years (1 child). The average age of disease outburst was 7.16 ±4.22 years. In most of the cases, 48.2%, the disease was first discovered at 0 – 5 years of age. In 22.3 % of cases the disease was discovered at 6 – 10 years of age and in 29.5% of cases in children older than 10 years. In the district of Tirana live about 25.7% of all children affected by CD, due to the high concentration of the general population in this area.

In addition, from the data collected, 9.5% of children live in the district of Elbasan, 7.6% live in the district of Lezha, 6.7% in Dibra, 6.7% in Vlora. 10.5% of children with coeliac disease live in Kosovo. The data from the patient medical records show that the main diagnose at hospitalization was "diabetes mellitus" in 27% of cases. In 10.8% of cases the admission diagnose was "coeliac disease - diagnosed elsewhere". We found the patients diagnosed with "failure to thrive" in 10.8% of cases. 9% of patients were hospitalized because of the "abdominal pain". "Anemia" was the admission diagnose in 6.3% of cases, "constipation" in 4.5% of cases. In 4.5% of the cases, the hospitalization was due to "chronic diarrhea" and in 3.6% was the rheumatic pain. Regarding the main complaints presented by the patients with CD in our department, we had the following results: the major complaint was "weight loss/short stature/ dystrophia in 26.8% of cases; followed by chronic diarrhea in 13.4% of children. Abdominal pain was a complaint in 9.8%. We found anemia in 6.3 % of patients, vomiting in 5.4% and abdominal distension in 4.5%. 27.7 % of patients manifested a number of atypical, uncommon, symptoms of coeliac disease at the time of hospitalization in the department of pediatrics.According to our data, the prevalence of the main symptoms had no significant statistical changes referring to age- groups of children with CD. However, the clinical significance suggests that gastrointestinal symptoms prevail in early age. This is supported by the presence of chronic diarrhea in 16.9% of children with CD in the age group of 0 – 5 years old, 11.5% in age group 6-10 years old and in 7.4% in age > 10 years old. Vomiting is present in only 10.2% in children 0-5 years old and is almost absent in elder age groups. In 40% of cases the patients had no secondary complaints. In those who had other complaints, in 13.5% the associated symptom was "weight loss/short stature/dystrophia", in 10.8% was "abdominal distension" and in 8.1% of cases was "chronic diarrhea".

Thus the prevalence of the secondary complaints had significant statistical changes based on the age groups of children with CD. Chronic diarrhea was present in 10.3% of children 0-5 years old and in 11.1% of children older than 10 years old. Also the weight loss was most common in patients 0 – 5 years old and in patients older than 10 years old. However, we have to be careful in analyzing the data collected, because all information is based in a limited number of patients, expressing various signs and symptoms, creating this way a probability of misinterpretation and bias.The majority of patients, (70%), had no tertiary complaints, apart from the main complaint. The most common tertiary complaint was "abdominal distension" in 6.3% of children, "weight loss/short stature/dystrophia" in 4.5 % of children, "anemia" in 3.6% of children and "chronic diarrhea" in 2.7% of children. The coeliac disease may manifest with the classic, typical symptoms as well as with atypical ones. The typical, classic CD has a frequency of 1/ 1000 (Laass *et al*., 2015). The typical symptoms of the classic form of CD are chronic diarrhea, abdominal distension and weight loss. Symptoms arise about 6 -24 months after introducing gluten containing foods in the diet. However, almost 50 % of patients are firstly diagnosed with extra intestinal symptoms. The clinical manifestations of CD depend on the age of the patient, duration and extension of disease and with the presence of extra intestinal complications (Fasano *et al*., 2005). According to population based studies and from reviewing the literature we can conclude that coeliac disease is a systemic disease which is a result of cooperation of genetic, immune and environmental factors (Guandalini, 2004). The importance and duration of breast feeding are well known, positive factors, particularly in the first 6 months of the infant life. In our study, we could determine the duration of breast feeding in only 52.6% of the children (59 children). In the cases where information was available, the mean duration of breast feeding was 357 days, with a median value of 360 days and a mode value of 720 days; variance between 30 days to 72 days. While analyzing the data, we found a positive association between the age of disease outbreak and the duration of breast feeding, although this association shows no statistical significance.

The clinical significance of this correlation suggests that increasing the duration of breast feeding in infants, postpones the age of disease outbreak. Thus, the breast feeding model is considered a protective factor against the early outbreak of coeliac disease. The age and timing of introduction of the gluten containing foods, as dietary supplements to breast milk or as the principal way of feeding, is of paramount importance for confirming the diagnose of coeliac disease in children with typical and atypical symptoms. In our study, we asked the mothers about the time of introducing the food supplements. On this argument we obtained detailed information for 48 children. In 1/3 of children, the gluten containing foods started at 6 months of age (in accordance with the recommendations of WHO). In 18.8% of cases the gluten containing food started at 4 months and in 16.7% of cases at 5 months of age. In 12.5% of cases gluten was introduced in the infant diet at the age of 7 months, in 10.4% of cases at the age of 8 months and in 6.3% of cases at the age of 9 months. In only one child, 2.1%, gluten was introduced in the diet at 3 months. As was mentioned before, there is a correlation between the timing of introducing gluten containing foods in thediet and the outbreak of the disease, though this association has no statistical significance. The clinical significance of this correlation suggests that delaying the time of introducing gluten in the diet, postpones the outbreak of the disease in these children. Hence, the prolongation of breast feeding period, as well as delaying the time of introducing gluten to the diet, have an impact and are protecting factors against the coeliac disease It is not very clear if breast feeding provides a long lasting protection or simply delays the outbreak of CD. The results from the literature review are compatible with the results of a meta-analysis presented lately by author Szajewska (Dickey, 2005). In this review, the articles were chosen based on the risk for systematic bias. Furthermore the results were discussed from

another point of view, involving the additional variables that contribute to pathogenesis of CD, such as microbiotics (the beneficial bacteria in the digestive tract) and composition of breast milk. The author Szajewska focuses exclusively in the role of introducing gluten in the diet. There are no actual recommendations regarding the time of introducing gluten containing foods in the diets; weather to start early (at 4 months) or delay (at 6 months or 12 months) the introduction of gluten containing foods in children with high risk for developing CD. As mentioned before, CD is a systemic disease. With evolving of diagnostic techniques, with a better recognition of the dynamics of the classic and atypical disease, the incidence of CD has increased significantly in the past 20 years.

The improvements and widening of knowledge on celiac disease have made possible the diagnosis at very young age and in early stages.We believe that for each child diagnosed with CD there are 5 -7 children that remain undiagnosed. Because of the atypical cases and somewhat silent symptoms, the clinic manifestations of CD are consistent with the "iceberg" model. According to this model, the top of the iceberg is made of the symptomatic patients, who consist of only 10 % of all CD patients (Rodrigues, 2006). The latest recommendations emphasize the necessity to screen the groups with high risk (individuals with type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, selective IgA deficiency and first degree relatives of patients with CD). In one study, amongst patients with type 1 diabetes mellitus, the prevalence of positive serologic tests was 9.87%. This value is compatible with the results of other studies in the literature (Cerutti, 2004), which vary from 3.9 % to 16.8% (including the longitudinal study, with an average follow up of 12 years). The results of this study also show that there is a constant appearance of coeliac antibodies for a time up to 13 years after the diagnosis of diabetes mellitus. After this period the coeliac antibodies can't be found in the serologic tests.The normalization of antibody titer was spontaneous, even in the cases with very high initial level of antibodies. This is confirmed by the authors Waisbourd – Zinman and Castellaneta, who, in their studies, followed up patients diagnosed with type 1 diabetes mellitus and positive celiac serology (Demir *et al*., 2000). Coeliac disease is usually associated with other conditions. In our study, 26 children suffered at the same time from diabetes mellitus. 7 other children were affected from thyroiditis. Amongst the patients with thyroiditis, 5 of them had also diabetes mellitus. Mean age of outbreak of diabetes mellitus in children with CD was 6.27 ±3.76 years. Among the patients with concomitant coeliac disease and diabetes mellitus, in 57.7% the outbreak of diabetes occur at age 0 – 5 years, in 26.9% at age 6 – 10 years and in 15.4% in children older than 10 years. Mean age of thyroiditis outbreak in children with CD was 10.82 ± 2.54 years. In children with coexisting coeliac disease and thyroiditis, in 28.6% of cases the outbreak of thyroiditis was at age 6-10 years and in 71.4% of cases the outbreak was in children older than 10 years.

The majority of patients with CD, 86 children or 76.8%, had no associated diseases, except for diabetes mellitus and thyroiditis, which are discussed in the previous paragraph. On the other hand, in 6 children or 5.4% of cases, we found epilepsy, autism and a delay of expressive language. Also we diagnosed gastropathy in 4 children or 3.6% of cases, various syndromes in 3.6% of cases, ocular disorders in 1.8% of cases and cardiac disorders in 1.8% of cases (Table 3). The overall trend is a late manifestation of symptomatic CD, usually in grown children. The common complaints are atypical and most often extra intestinal, such as short stature, iron deficiency, hepatic impairment). Short stature was found in 81.4% of children included in the study. Short stature as a single, primary symptom was found in only 24 (17.1%) of patients. This result is compatible with data from other studies. The author and researcher, Demir (Demir *et al*., 2000), found short stature as a primary symptom in only 1.9 % of children with CD. Other diseases and conditions associated with CD are selective IgA deficiency, Type 1 Diabetes Mellitus, alopecia areata, vitiligo. Coeliac disease is 10 times more frequent in patients with selective IgA deficiency than in general population (Cataldo *et al*., 1998). In the study mentioned above, the IgA deficiency was present in 9 patients or 6.4%. The gluten induced hepatitis is a benign condition, characterized by a rising in the serum levels of the aminotransferases, abnormal liver architecture, usually mild and nonspecific, and periportal inflammation. All changes in gluten induced hepatitis are reversible under the GFD treatment. Treatment with GFD results in normalization of biochemical and histologic signs of hepatitis (Doganci, 2004). Anemia is a commonly found symptom in patients with CD. All CD patients should be tested for iron deficiency anemia (Ojetti *et al*., 2005). In a study from a group of authors, almost 50% of their patients had iron deficiency anemia (Ojetti *et al*., 2005). Duodenal biopsy was performed in 53 patients, whereas in 59 patients we were not able to complete the procedure. In the patients where we could complete the biopsy, the histopathology reports resulted as follows: 13.2% resulted with normal mucosa, 13.2% resulted with coeliac disease at stage M1, 20.8% resulted with stage M2, 28.3% resulted with stage M3a, 17 % resulted with stage M3band7.5% with stage M3c. Table 5 shows the average values of TGA-IgG, TGA-IgA, AGA-IgG and AGA-IgA antibodies, in accordance with the stage of the disease (biopsy staging). As you can see, there is a significant increase of TGA-IgA titer with higher biopsy stages, whereas the changes of the other parameters have no statistical significance. Considering the technique, the credibility and the cost, we can conclude that TGA-IgA is the most reliable serologic marker for diagnosis of CD. The intestinal biopsy, though, remains the golden standard in the diagnosis of CD(18). Data from a study in Iran show that tTG titer ≥200 IU/mL (10 fold the normal value), is 100% specific for Marsh 3 lesions. The published results from this study resemble those of different previous studies.

Conclusions

For many years coeliac disease was considered a disorder of the pediatric age, characterized by classic clinical manifestations such as steatorrhea and malabsorption. Though it is a frequent disease, CD is often undiagnosed and underestimated because of the variability of symptoms and heterogeneous clinical manifestations. From different studies, CD results underdiagnosed in 1 – 3 % of general European population, both in adults and in children. Recognizing and understanding the various clinical presentations of CD allow us to establish an early diagnose, to start a gluten free diet as soon as possible, to achieve a normal growth and developent of the affectet children and to prevent the long term complications of the disease.

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