

## Extra-intestinal manifestations of celiac disease in children

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### Abstract

Celiac disease, also known as gluten-sensitive enteropathy, is a chronic disorder of digestive tract mediated by immune mechanisms, resulting in an inability to tolerate gluten and its related proteins in genetically predisposed individuals. Gluten is one protein commonly found in wheat, rye and barley. This disease has a wide spectrum clinical presentations and affects a wide age range on which it has a significant impact in terms of development and morbidity. Therefore, we found it important to study investigation of the variety of extraintestinal manifestations in pediatric celiac patients and identification of possible strategies that can be adapted to diagnose and treat them as soon as possible.

**Key words:** Celiac Disease; Extraintestinal Manifestations; Pediatrics; Gluten Free Diet.

### 1 Introduction

Celiac disease is a immune-mediated chronic disorder of the digestive tract that results in the inability to tolerate gluten and its related proteins in genetically predisposed individuals. The majority of pediatric celiac patients are diagnosed at an older age without typical gastrointestinal symptoms.

### 2 Method

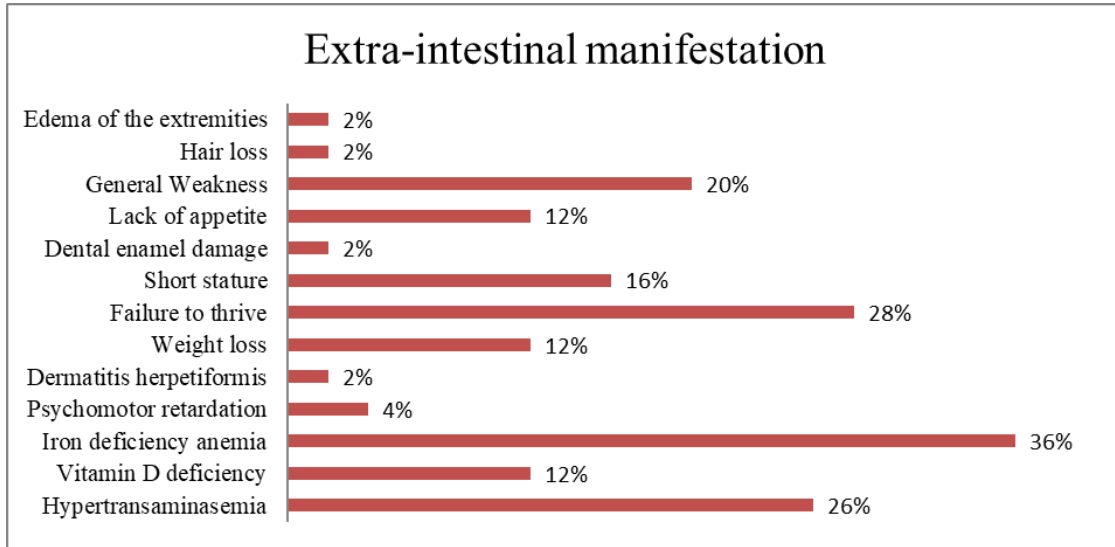
This is a retrospective study conducted among 50 pediatric patients diagnosed with Celiac Disease according to the revised ESPGHAN diagnostic criteria (European Association of Pediatric Gastroenterology, Hepatology and Nutrition) and followed at the Pediatric Service of Specialties no. 2, University Hospital Center “Mother Theresa” Albania, during the period from January 2015-December 2020. Demographics, serologic testing, intestinal biopsies, laboratory examinations such as hemogram, ferritinemia, sideremia, total serum calcium, vitamin D level, albumin and extraintestinal symptoms at presentation, 12, 24 months were recorded.

### 3 Results

In this retrospective study, 50 pediatric patients diagnosed with Celiac disease. In the subjects included in the study, it is observed that there is a predominance of gender female with 28 cases or 56% of the total compared to male patients with 22 cases or 44% of the total. The current mean age of the patients in the study is 9.18±3.58 years, with age range 2.83-17.8 years. The average age of all patients at the time of diagnosis is 5.39±3.15 years, with age range 11 months-13.25 years. 50% of patients in the study at the time of diagnosis turned out to be less than 5 years old and 75% less than 8 years old. No statistical changes are observed significant in terms of the average age by gender of the population under study (t test student t= -0.43, p= 0.668). 16% of the patients in the study belong to groups at high risk for Celiac disease, namely 8% (4) Primary hypothyroidism, 4% (2) Down syndrome, 4% (2) Diabetes mellitus type 1 and 4% (2)

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have first-degree relatives with Celiac disease. The incidence of celiac disease (CD) has increased in recent years due to the recognition of atypical forms. Over time, celiac disease has changed its clinical presentation. In our study 16% of patients manifested the "atypical form" and 18% were asymptomatic. Any organ from the central nervous system to joints, liver or teeth can be affected. Most frequent extraintestinal symptoms observed were: 36% with iron deficiency anaemia followed by failure to thrive 28% and 26% hypertransaminasemia. Some of these manifestations are direct consequences of autoimmunity, such as dermatitis herpetiformis, whereas others are indirectly related to inflammation and malabsorption including deficiency anaemia, vitamin D deficiency, dental enamel damage and short stature. Hypertransaminasemia was significantly associated with ages younger than 6 years, and children diagnosed at a later age were at greater risk for short stature.



**Figure 1** Extraintestinal manifestations frequency

**Table 1** Extraintestinal manifestations frequency according to patients age group

	Age Group			Total	P value
	Under 3 years old N (%)	3-6 years old N (%)	Over 6 years old N (%)		
Hypertransaminasemia	3 (6%)	6 (12%)	4 (8%)	13 (26%)	0.84
Vitamin D deficiency	2(4%)	3(6%)	1(2%)	6(12%)	0.19
Iron deficiency anemia	7(14%)	6(12%)	5(10%)	18(36%)	0.21
Psychomotor retardation	1(2%)	1(2%)	0(0%)	2(4%)	0.33
Dermatitis herpetiformis	0(0%)	1(2%)	0(0%)	1(2%)	0.24
Weight loss	3(6%)	1(2%)	2(4%)	6(12%)	0.21
Failure to thrive	6(12%)	4(8%)	4(8%)	14(28%)	0.18
Short stature	1(2%)	2(4%)	5(10%)	8(16%)	0.044
Dental enamel damage	1(2%)	0(0%)	0(0%)	1(2%)	0.24
Lack of appetite	3(6%)	1(2%)	2(4%)	6(12%)	0.21
General Weakness	3(6%)	4(8%)	3(6%)	10(20%)	0.91
Hair loss	0(0%)	1(2%)	0(0%)	1(2%)	1
Edema of the extremities	1(2%)	0(0%)	0(0%)	1(2%)	0.24

## 4 Discussions

The variety of extraintestinal manifestations in celiac patients can make diagnosis of the disease difficult. The diagnostic facility with non-invasive examinations such as serological tests plays an important role for pediatricians or gastroenterologists to diagnose celiac children in time, leading to a better prognosis of the disease and prevention of complications. Two main mechanisms are thought to contribute to extraintestinal manifestations: malabsorption as a consequence of mucosal damage and secondary changes as a result of the response to autoimmune disease [1]. The most frequent extraintestinal manifestation observed in the celiac children we studied was iron deficiency anemia followed by failure to thrive and hypertransaminasemia. 26% of patients had hypertransaminasemia, 12% of patients had vitamin D deficiency, 36% of patients had iron deficiency anemia, 4% had psychomotor retardation, 2% had dermatitis herpetiformis, 12% had decreased in weight, 16% resulted in short stature, 2% presented damage to the dental enamel, 12% anorexia and 20% general symptoms, 2% hair loss and 2% edema of the extremities. Hypertransaminasemia is a frequent finding in children with celiac disease and there are cases where it may be the only manifestation of the disease, therefore liver tests are important to perform in children diagnosed with celiac disease. Hypotheses have been raised that the alteration of the permeability of the intestinal mucosa in celiac disease increases the portal circulation of hepatotoxins leading to hepatic damage. A role of autoimmunity in the contribution of hepatic damage in celiac disease is also thought since deposits of anti-TG2 antibodies in the liver have been found [2][3]. Hypertransaminasemia responds very well to a gluten-free dietary regimen with normalization of hepatic enzymes in 75-95% of cases within the first 12-24 months of the diet [4]. In our study, at the time of diagnosis, 26% of patients had hypertransaminasemia. The average age of celiac children with hypertransaminasemia is  $3.57 \pm 1.92$  years with a statistically significant difference with the average age of children with normal transaminases of  $5.65 \pm 3.22$  years. A significant relation was found between the young age of the patients and the presence of hypertransaminasemia. ( $p=0.039$ ; OR = 0.8; 95% CI). There was a statistically significant difference in the mean serum ALT level between patients of the 3 clinical forms. Patients with the classic form of the disease have a higher frequency of cases with hypertransaminasemia than the other two clinical forms of the disease. In a study conducted on hypertransaminasemia in celiac children at the time of diagnosis, 32% of patients had high levels of transaminases. Also, as in our study, it was found that children with hypertransaminasemia were younger than children with normal transaminase levels. In agreement with our study, children with the classic form of the disease had a higher tendency of hypertransaminasemia (73% of the classic form) than children with the atypical form of the disease (27%) [100]. 2% of the patients we studied presented dental enamel damage. Dental enamel damage is related to malnutrition and hypocalcemia in particular, but also to autoimmunity [5]. Alopecia was encountered in 2% of cases in our study, from the literature it is reported that it was observed in 1% of celiac children, ranging from Alopecia Areata to totalis. It is thought to be a consequence of autoimmune mechanisms. In 50% of cases it recovers after the first 12-24 months of the gluten-free diet [6]. Dermatitis herpetiformis is considered one of the extraintestinal manifestations of celiac disease, in our study it was observed in 2% of cases. Patients with subclinical celiac disease are thought to manifest DH. It has a rare prevalence in children. There are cases when it improves only with a gluten-free diet, but there are cases where Dapsone therapy is also needed [7][8][9]. As expected, patients affected by celiac disease before starting the gluten-free diet result in deficits such as the level of iron, folic acid, zinc, copper, calcium, vitamins B6, B12, D and all these deficits are related to malabsorption from enteropathy. In our study, due to diagnostic limitations, results were obtained on the deficit of ferritinemia, vitamin D and calcium levels. It must be said that in celiac patients micronutrient deficiencies at moderate levels exist even after starting a gluten-free diet, therefore these patients should be supported with supplements and during follow-up [10]. It should be noted that gluten-free dietary regimens contain lower levels of vitamin D, E, B12, iron, folate, magnesium, potassium, and sodium compared to gluten-containing dietary products [11]. Studies have shown that only 5% of gluten-free products are fortified with adequate levels of basic micronutrients, which can lead to deficiencies of these micronutrients in celiac patients, therefore, in most cases, compensation needs with additional supplements. Of the patients in the study, 36% were found to have anemia at the time of diagnosis. Patients manifesting the classic form of the disease had lower hemoglobin and ferritinemia levels than the other groups. More than 1 in 10 celiacs suffer from Ca, Mg and Zn mineral deficiency [12]. Iron is one of the main deficient micronutrients in celiac children and celiac patients of any age group even when gastrointestinal symptoms such as diarrhea are absent. In celiac patients we have impaired iron absorption from the duodenal mucosa as a result of the reduction of the absorptive surface of the duodenum that occurs due to damage to the intestinal mucosa from the disease [13]. The most common form of anemia in celiac subjects is iron deficiency anemia in 81.5% of cases [14], therefore it is important that celiac children consume iron-rich foods such as fruits, vegetables or red meat [15]. It is recommended that iron supplements be taken for a long time (over 6 months) after the intestinal mucosa has regenerated and continued until hemoglobin and iron stores have normalized [16][17]. Vitamin D plays an important role in development, bone health and the immune system. Low levels of bone mineral density have been found in celiac children as a result of vitamin D and calcium deficiency from malabsorption and inflammation present in these patients. It is recommended to monitor the serum level of vitamin D and calcium in celiac patients and especially in children [18]. In our study, 12% of patients from laboratory examinations were found to be vitamin D deficient (with vitamin D levels below 20 ng/mL). A study conducted in pediatric celiac

patients reported that a 2-year period of calcium (1g/day) and vitamin D (400 IU/day) supplementation positively affects mineralization and increases bone density [19]. In a study conducted on 54 celiac children with hyperparathyroidism, hypokalemia and hypovitaminosis D, it was found that 6 months after removing gluten from the diet, the resolution of hyperparathyroidism and hypocalcemia was observed in 100% of the subjects, while the level of vitamin D normalized in 65% of children [20] supporting the idea of the need for vitamin D supplement support [21][22].

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## 5 Conclusion

We report a changing pattern in the presentation of pediatric CD. CD should be considered in the presence of atypical presentations. An increased awareness among pediatricians of the variety of extraintestinal manifestations of CD is essential to improve diagnosis, better prognosis and prevention of complications of celiac disease.

### *Recommendations*

Deficiencies in micronutrients can contribute to the presence of extraintestinal manifestations in celiac children such as neurological complications (epilepsy, myelopathy), psychiatric symptoms (anxiety, depression), osteoarticular alterations (osteopenia or osteoporosis), so it is necessary to insist not only on compensating with additional supplements but also fortification of gluten-free dietary products with basic micronutrients such as calcium and iron.

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## Compliance with ethical standards

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### *Disclosure of conflict of interest*

The author and co-authors of the manuscript declare no conflict of interest.

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