

Different Manifestations of Coeliac Disease (CD)

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Abstract: *Coeliac disease is an autoimmune mediated enteropathy. It develops in genetically susceptible individuals upon ingestion of proline and glutamine proteins, commonly found in wheat, barley and ray. The disease has heterogeneous clinical manifestations ranging from the classic form of CD, to asymptomatic, atypic, latent and potential form. We will present a small series of classic and atypical cases of CD, diagnosed and treated in our department, with the attempt to emphasize the atypical manifestations of the disease.*

Keywords: gluten; enteropathy, gluten-free diet

1. Introduction

Celiac disease is an immune mediated enteropathy in individuals with genetic susceptibility towards gluten and other proteins related to it. Once believed to be a rare disease, CD is a common genetic disorder in the western countries, with a prevalence of 1 – 2%.

Regarding our area, the real prevalence of CD is underestimated, mainly because of poor knowledge of atypical manifestations of the disease.

The classic manifestations of CD develop within weeks or months after exposure to dietary gluten and include malabsorption and the symptoms related to it (diarrhea, abdominal distension, reduced muscular mass, nutrient deficiency).

Atypical CD refers to patients with extraintestinal signs and symptoms, positive antibody tests and characteristic changes in intestinal biopsy.

There are no accurate studies for CD in children in Albania. With this small series of case reports we aim to raise knowledge of clinical and symptomatic variability of CD amongst health care professionals and help provide a better understanding and recognition of this disorder.

2. Case report

Case Nr. 1

A fifteen months old girl presents with prolonged diarrhea of over three weeks. Parents refer abundant watery discharge associated with vomiting with food content and no temperature. Diarrhea appears unaffected by antibiotics, probiotics or medicaments for slowing intestinal transit. In clinical examination the patient shows signs of general weakness, pallor, increased intestinal movements, but no signs of peripheral edemas.

Laboratory results show Hemoglobin = 9.9 g/dL; Iron = 11 mcg/dL (ref. Range 60 - 180); low level of Potassium; Hypoproteinemia = 5.5 g/dL (ref. Range 6.0 - 8.3); Albimune = 3.3 g/dL (ref. Range 3.5 - 5.2); Coproculture results were negative; Hemoglobin electrophoresis detects normal Hgb; Abdominal x-Ray (radiograph) shows multiple

small hydroaeric levels. Serologic tests – anti TGA IgA = 397,2 U/ml (ref. Range positive > 25 U/ml).

Case Nr. 2

A two year old girl presents with difficulty in feeding, abdominal distension and constipation. Clinical examination shows delay of growth, weight 8 kg and height 74.5 cm, and signs of malnutrition. The abdomen was distended over the chest level. We also found reduced muscular mass, dry skin, reduction of subcutaneous tissue. No signs of edemas.

Laboratory results show severe iron deficiency anemia; drop of INR to 44.2% (International Normalisation Ratio) and prolonged partial thromboplastin interval PTT = 29 sec. Metabolic acidosis (pH = 7.29); Levels of albumine and total protein below range values; Changes in electrolytes such as low potassium, low magnesium, iron deficiency. Hemoglobine electrophoresis detected normal Hgb, thus excluding Hemoglobinopathies. The first diagnostic approach was Hirschsprung disease, considering the main symptoms were abdominal distension and constipation. An irrigography was performed with normal results. The next diagnostic step was serologic testing. We found anti TgA-IgA = 216 U/L (ref. Range positive > 20 U/L); anti EMA – IgA = 1:60; anti EMA IgG = 1:40

Case Nr. 3

A three year old boy presents with signs of intestinal subocclusion – vomiting, abdominal distension, abdominal pain, constipation for three – four days. Clinical examination shows abdominal distension, pallor, abdominal discomfort. Abdominal x – Ray shows presence of hydroaeric levels. Laboratory results show iron deficiency anemia. Serologic testing results anti TgA – IgA = 104,1 U/L (ref. Range positive > 20 U/L); anti EMA – IgA = 1:40; anti EMA IgG = 1:10. Treatment consisted in bowel stimulation applying micro-enemas, which improved the symptoms.

Case Nr. 4

A boy with Down syndrome was referred to our department by the hematologist because of severe refractory anemia. Clinical examination shows pallor, chronic fatigue. Constipation is also a frequent complaint, according to the parents.

Laboratory results reveal severe anemia Hgb = 6.3 g/dl; serum iron level and serum ferritin level below reference range. Other laboratory tests resulted within normal range: hemoglobin electrophoresis, Coombs test direct and indirect, G6PDH (glucose 6 phosphate dehydrogenase). Antibody serologic testing shows anti TgA – IgA = 271 U/L. Irigography findings were normal. We decided for a thyroid investigation and found an altered function: FT3 = 1.23 pg/ml; FT4 = 56 ng/ml; anti TPO = 30.7 (ref. Range positive >25). In this circumstances we performed an EGDS of upper GI tract with duodenal biopsies. Histopathology report was compatible with Marsh 3c lesions. The patient began treatment with gluten free diet.

Case Nr. 5

A nine year old girl was diagnosed with Type1 Diabetes on April 2014. The patient was asymptomatic. There was no evidence of gastro intestinal symptoms. Thyroid function was unaltered. Antibody serologic testing was found abnormal: anti TgA – IgA = 200 U/L; anti TgA – IgG = 22,2 U/l.

Case Nr.6

This is the case of a male patinet, referred to us because of recurrent abdominal pains, sometimes asocciated with pains in the lower extremities. According to the parents, the

patient has a poor performance in school, inability to concentrate, irritability, anxiety and dificulty in reading. Clinical examination was within normal range, without any particular symptom. After exluding surgical issues we performed serologic testings and found anti TgA – IgA = 220 U/l, anti EMA – IgA = 1: 10. Regarding the pain in lower extremities we didn't find movement restriction.

Total calcium and ionized calcium in blood were found at minimum range level, and vitamin D3 in insuficient level. To provide an accurate diganosis we performed an endoscopy with duodenal biopsy. Histopathology report was compatible with Marsh 2 lesions. The patient started treatment with gluten free diet. In addition, it was suggested for the patient to consult a child pshyciatrist to adress the persisting mood changes and irritability.

Case Nr. 7

The patient is a young girl of fifteen year old. The main concern of her parents was the low body hight 136 cm, low weight for age 30 kg and absent menstrual cycle, amenorrhea. Serologic tests showed anti TgA – IgA > 278 U/L. Endoscopy was performed with biopsies from second and third duodenal segments. Histopathology report was compatible with Marsh 3a lesions.

Table 1: Patients. Demographics. Clinical presentation. Examinations

Case No.	Age at diagnosis (year)	Sex	Clinical Presentation	Serology		Biopsy (Marsh classification)
				aTGA-IgA	aEMA	
1	1,3	F	Chronic diarrhea	378		Not done
2	2,5	F	Anemia ,Malnutrition, failure to thrive	216	1:160	
3	3	M	Abdominal distension,Anemia, Intstinal Suboclusion	>104,1	1:40 1:10	
4	11	M	Down Syndrome, Anemia, Chronic fatigue, Low stature	271		Marsh 3c
5	9	F	Type1 Diabetes, Asymptomatic	220		Marsh 3a
6	6,5	M	Abdominal pain, Apathy, Irritability, Low concetration, Dificulties in reading	>200	1:10	Marsh 2
7	13	F	Slow stature (low hight)	278		Marsh 3c

aTGA-IgA –tissue antitransglutaminaze IgA (>20 U/ml), aEMA-antiendomisiium antibodies IgA (>1:10); F-female; M-male

3. Discussion

Coeliac disease, otherwise known as the glutensensitive enteropathy, is an immuno – inflammatory disease of the small intestine caused by the hipersensibility towards gluten and the relatd proteins, in individuals with genetic susceptibility. It is a common disorder with a prevalence of 0.5 to 1 % of the general population[1].

Grains containing the triggering gluten proteins are wheat, ray and barley. Whether oats trigger or not the disease is as ongoing debate. The mucosa of the small intstinum improves morphologically when patients are in a gluten free diet and the lesions reappear with introducing gluten to the diet again.

For many years CD was defined simply as a group of clinical manifestations. The combination of serologic, genetic and histopathological data brought a better understandig of the highly variability of clinical

manifestations of the disease and provided new definitions and clasification of CD.

In the past decades CD usualy manifested in children of young age, mainly with malabsorbption and failure to thrive. In present days, CD has a tendency to develop sometime in a latter age and manifest with gastrointestinal and extraintestinal symptoms. Clinical presentation of the disorder varies by age groups.

Typicaly CD developes between the age of 6 – 24 months, after introducing gluten to the diet[1]. Children experience chronic diarrhea, anorexia, abdominal pain and distension, failure to thrive, vomiting and low weight. If diagnosis delays, patients present with symptoms of svere malnutrition.

In our series (case 1 and 2), chronic abundant diarrhea over three weeks, abdominal distension and fluctuation may lead to intestinal suboclusion(case 3).

When malnutrition is present, some important alterations become evident, such as changes in blood electrolytes, hypomagnesemia, metabolic acidosis, impaired glucose metabolism. Malabsorption causes multiple nutritional deficiencies of liposoluble vitamins (A,D,E dhe K), of Vitamine B12 and iron (7). Vitamins level in blood is an expensive test, but with great diagnostic benefits. In our cases (case 2) we found a drop in INR and prolouget PTT time; vitamin D insufficiency (case 3 and case 6). The small intestinal mucosa is the target area of inflammation. Iron is absorbed in the proximal portion of the small intestine. In our series (case 4, 2, 3, 1) we came across moderate and severe anemia, in some of the children. Case four had the most severe form of anemia with Hgb 6 g/dl. Adjustment of Hgb level requires iron supplement intake. However it will take some more time to refill the depleted iron storages of the body(9). Iron deficiency is a frequent symptom in children with CD. According to ESPGHAN iron deficiency is one of the indications of screening for CD, especially refractory iron deficiency anemia, with unexplained cause and non responsive to iron supplements.

Non typical symptoms of CD include unusual gastrointestinal signs, recurrent abdominal pain, nausea, vomiting, constipation (case 6), and extra intestinal manifestations. There are a number of well known extraintestinal manifestation of CD (Table 2). In some cases extraintestinal manifestations are the first introducing symptoms of CD. The presence of these symptoms requires serologic testing.

Table 2

Growth and Development
Short stature Delayed puberty
Neurologic and behavioural disorders
Hypotonia Failure to thrive Learning disorders Headache Cerebelary ataxia Epilepsia
Hepatic involment
Iron deficiency
Skin
Dermatitis herpetiformis Others (cutan amyloid ,vaskulitis, iktiosis,)
Damage of the dental enamel
Metabolic bone disease
Arthritis

In our series the patient in case 7 is referred because of short stature and absence of the secondary sexual signs.

Children with clinical disease expres delay in growth. 8 – 10 % of children with idiopathic short stature have positive serologic tests for CD [1]. The growth delay occurs even when the weight/height ratio is normal and there is no evidence of significant gastrointestinal signs[85,86]. Probably growth delay is not entirely attributed to malnutrition. In young adolescent girls the symptoms of CD include altrations in the menstrual cycle, dalayed menarche and in adult age infrtility and early menopause [93-97].

The most common neurological and psychiatric symptoms related to CD are depression, anxiey, irritability, mood changes, hypotonia, developemental delay, cefalea, ataxia, dificulty in concetration, ADHD (Attention- Deficit / Hyperactivity Disorder) [101,104], epilepsy, peripheral neuropathies. In our series, in case six, we found psychiatric symptoms, apathy, irritability, mood changes, dificulty in reading. To adress the psychiatric symptoms the patient consulted with a child psychiatrist.

The pathogenesis of the neurological symptoms is still unclear. Some of the disorders, hypotonia and developemental delay, may be caused by malnutrition or by the deficit in specific microelements. All symptoms tend to regress once the patients begin the gluten free diet. Recent data suggest that the neurological disorders may have an underlying autoimmune mechanism.

Data from the screening programs suggest that the prevalence of CD is higher in certain groups compared to the general population. These groups are consiered to have higher risk for CD:

- First and second degree relatives of patients with CD
- Down syndrome (case 4)
- Type 1 Diabetes (case 5)
- Selective IgA immunodeficiency
- Autoimmune Thyroiditis (case 4)
- Turner syndrom,
- Williams syndrome

Because of the high risk, it is advisable to perform routine screening in these groups (although the approach is somewhat controversial).

The risk of developing CD in these groups is 3 – 10 fold higher compared to the general population [1,5.6.20-24]. The discussion wether to perform routine testing in the high risk groups is still open. Th guidelines are constantly changed and improved with new data regarding to risk / potential benefit ratio of the screening programs.

In our series, in case 5 the patient was asymptomatic, whereas in case 4, the patient with Down syndrome showed severe anemia associated with growth retardation (weight and hight).

The diagnosis of CD is often missed beacuse of the variability of symptoms, the intensity of clinic signs and in addition because of the asymptomatic cases [1:3 – 1:7 adult patients with CD are asymptomatic]. The avaiable serologic test, anti TG-IgA dhe anti EMA, have a great value in the every day practice, allowing an accurate diagnosis.

In our series, we measured the titer of anti TGA – IgA. In case 1 we found the titer 10 fold higher than the upper reference value. According to ESPGHAN’s guidelines, in cases where there is an increase in the titer of 10 fold higher than the reference value, associated with classic symptoms of CD, the biopsy may not be performed; the diagnosis can be confirmed with an anti EMA test and/or with HLA gene typing. In Albania, the HLA gene typing method is avaiable but unfortunately too expensive. Hence in most cases we rely on serologic results and clinical

suspicion to approach the next step of diagnosis, the endoscopic biopsy, which in our series we performed in case 4,5,6,7.

The measurement of anti TGA – IgA is the test of choice to identify the celiac patients and to monitor their compliance to the gluten free diet. It is a test of high sensibility and specificity, with reasonable cost-effectiveness compared to other serologic tests.

The anti-endomyosal EMA test is as accurate as tTG- IgA, but more expensive and prone to individual interpretation errors. EMA is used as a second line testing when the results of tTG-IgA are equivocal

In patients with positive serologic results, characteristic changes in intestinal biopsy and who respond to the gluten free diet, the provisional diagnosis of CD can be established.

The characteristic changes in intestinal biopsies compatible with CD are Marsh 2 and Marsh 3 lesions.

Performing an endoscopic biopsy of the upper GI tract will allow for a macroscopic view of the intestinal mucosa, evaluating the major features of CD such as proximal small bowel involvement, decreasing distally, patchy distribution and changes in mucosal architecture. The characteristic patchy distribution of the lesions requires procurement of 4 - 5 biopsy specimens to avoid false negative results and secure the diagnosis. The biopsies are obtained from the proximal portion of the small bowel, the duodenum. In our series all biopsies were obtained from the 2nd and 3^d segment of the duodenum.

The histopathologic changes in the intestinal mucosa will repair over time after initiating the gluten free diet.

Treating the celiac patient starts with diet counseling. The gluten free diet is the only effective treatment that can reliably and safely prevent the mucosal damage caused by exposure to gluten. It is important to address the nutritional needs and provide supplement intake (preventing osteoporosis). Response time to GFD differs from patient to patient. In 70 % of patients the clinical response to treatment is evident within two weeks [39]. Clinical signs usually improve before the repair of intestinal mucosa.

Children with CD should adhere to a strict gluten free diet for life. A GFD entails strict avoidance of all products containing proteins from wheat, rye and barley. Gluten free products are available in our country. The main concern is the affordability of these products and as we see in many cases not all families are able to procure them. Another problem is the continuous monitoring of the celiac patients, every 6 months, in particular for patients living in remote distant areas,

4. Conclusion

CD should be always considered as differential diagnosis in children with failure to thrive, persisting diarrhea, children with unusual gastrointestinal signs that persist for a long time, children with extraintestinal signs of CD, diseases that are

often associated with CD. Recognition and understanding the various clinical presentations of CD allow us to establish an early diagnosis, to start a gluten free diet as soon as possible, to achieve a normal growth and development of the affected children and to prevent the long term complications of the disease.

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