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Celiac Disease among Adolescents. Poor Growth and Delayed Puberty

Rodica Elena Cornean[1,4,*], Dan Gheban[2], Bianca Simionescu[3,4], Mircea Margescu[3,4]

[1]Department of Molecular Sciences-Medical Genetics
[2]Department of Morphological Sciences-Pathological Anatomy
[3]Department Mother and Child-Pediatrics
[4]Emergency Hospital for Children, University of Medicine and Pharmacy "Iuliu Haţieganu" Cluj-Napoca, Romania
*Corresponding author: recornean@yahoo.com

Abstract Growth is a very reliable index of health assessment, both in children and teenagers. Growth is often affected (slowed or arrested) in children who suffer from chronic diseases, including the gastrointestinal disorders. Since the use of the serologic markers and small intestinal biopsy as diagnostic tools, it has become evident that the clinical presentation is highly variable in patients with celiac disease. Some patients present the classic symptoms of the celiac disease (diarrhea, malnutrition and growth failure), while others, unveil their disorder at puberty when growth failure and delayed puberty seem to be the only symptoms of the disease. We present the clinical case of a 16 years old girl, referred to our endocrine unit for short stature, failure to thrive and lack of menarche.

Keywords: *celiac disease, late-onset, growth failure, delayed puberty*

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1. Introduction

Growth is a dynamic process that begins at conception and ends in adulthood. Growth rate and final height, although genetically conditioned, are subject to the modifying action of a large number of factors (e.g. hormons, nutrition, etc.) and, last but not least, the individual's health status. In fact, at present, growth is considered to be one of the best indicators of the state of health in a population [1].

In clinical practice, growth failure needs to be distinguished from short stature.While the growth failure may reflect an underlying pathologic process, short stature is not necessarily a sign of disease. This aspect has special connotations in medical practice: growth failure needs additional investigations without delay, while short stature does not justify further evaluation [1].

Growth failure in celiac disease is related to the malabsorption syndrome [2]. In the presence of an insufficient energy substrate (to ensure the normal linear growth), "energy compensation" is attempted, with the use of adipose and muscle tissue. The patient will experience stagnation and even weight loss. If the morbid process lasts for 3-4 months, the weight loss is followed by the growth stunting. This cascade of deleterious events is evident both in infants and small children with celiac disease (CD). Over the age of 7, we may witness the preferential slowdown in the rate of the linear growth versus weight, with the former being affected before the weight loss [3,4].

When the diagnosis is suspected, there is a two-step screening process to establish the diagnosis: 1. blood test for anti-tissue transglutaminase antibody (IgA tTG). Testing for antiendomysial antibody may also be considered; 2. if the screening blood test is positive, then upper GI endoscopy with duodenum biopsy (Marsh scale stage 1-3) is recommended [5,6].

The use of this integrated test (transglutaminase antibodies and duodenum biopsy with Marsh scale classification in assessment of villous atrophy) was able not only to confirm the diagnosis in patients with classic gastrointestinal symptoms but has also allowed delineation of new forms of celiac disease (e.g. atypical, latent and silent) [7,8].

Thus, the clinical symptoms in so called *atypical* forms of disease (iron deficiency anaemia, abnormal linear growth, delayed puberty, infertility, constipation, arthritis, etc.) [7,9] are identified to be satellite to celiac disease exclusively on positive antibody blood test and small intestine biopsy.

Individuals with *silent* and *latent* forms of celiac disease are on the other hand, clinically asymptomatic patients with a positive serology but with a positive small intestine biopsy present only in the former type of silent celiac disease [10,11]. Patients with *silent* celiac disease need further testing looking for malabsorption complications (such as anemia, osteoporosis, etc.). A gluten free diet may be implemented if these tests are positive. This is no longer the case in people with *latent or potential* celiac disease, whose duodenum biopsy is normal and theoretically, there is no justification to begin treatment with a gluten free diet. However, repeated biopsy might be considered if

signs and symptoms develop or if symptoms of malabsorption are present.

Regardless of the way in which the disease manifests itself, late-diagnosed celiac patients or failure to maintain the strict gluten-free diet regardless of the age at diagnosis is reflected by wasting, short stature, lack of progression into puberty, amenorrhea and infertility [12].

2. Case Report

We present the case of a 16-year-old teenage girl, referred to our endocrine unit for significant weight loss, linear growth impairment and lack of menarche.

Birth and neonatal history were not significant. The same was valid for the family history with the exception of the father who is suffering from type II diabetes.

According to the parents, the onset of the disease was insidious, with slow linear growth and marked weight loss, delayed puberty, lack of menarche, knee arthralgia, anemia not responding to oral tratment, fatigue and refractary constipation to GP's prescribed therapy.

No abnormality was noted on physical examination except for the anemia, short stature, weight loss and delayed puberty.

Auxologic data confirmed short stature, weight loss, delayed bone age versus chronological age with subsequent delayed progression into puberty and amenorrhea: Decimal chronological age (DCA): 16.099 years; height (HT): 147 cm, -2.66 SDS, p 0.39; weight (WT): 40kg, -2.46 SDS, p. 0.69); Bone age (BA/20TW2: 12.5 years; pubertal Tanner stage B2, P2, M0. Mid-parental height (MPHT: 154,2 cm, 95% CI: 145,2 cm). (Figure 1).

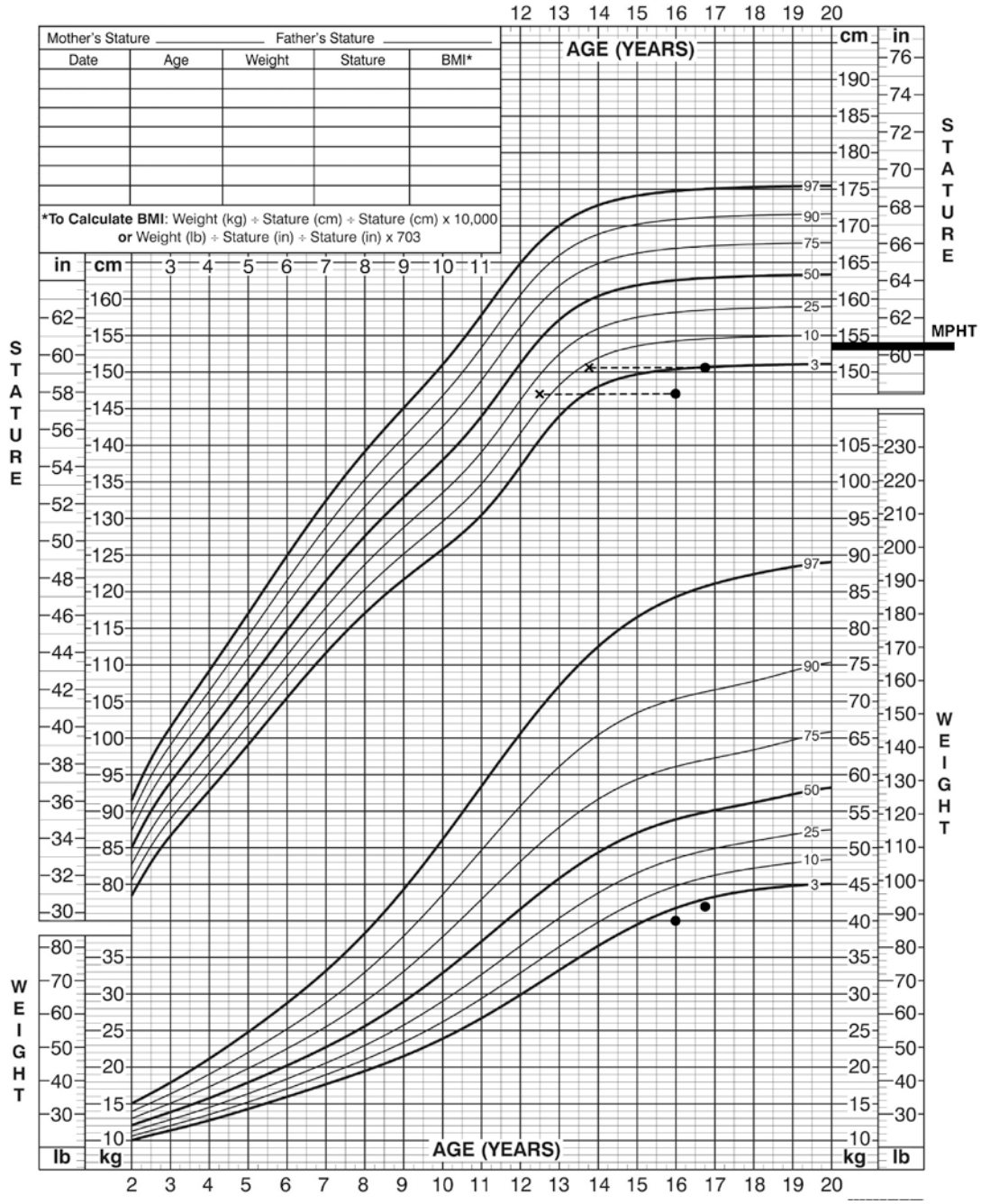

Figure 1. Patient's growth chart before and after gluten-free diet intake

Although both the HT and WT values were under the 3rd percentile in the general population, the fact that even weight gain was affected, excluded any potential hormonal disorders and directed the diagnosis towards a more “pediatric” medical condition.

In this context, the reassessment of clinical symptomatology (poor nutritional status, low growth rate, delayed puberty associated to arthralgia, constipation, anemia, fatigue) required additional investigations towards a possible malabsorption syndrome.

The flat lactose tolerance test and positive antitransglutaminase antibodies (IgA TTG: 45U/ml vs. NR<15U/ml) have "pledged" for a possible late-onset celiac disease with atypical clinical picture [13].

Upper gastrointestinal (GI) endoscopy with duodenum biopsy, revealed partial villous atrophy (a reduction in intestinal villous size by 1/3 of normal aspect), crypt hyperplasia, increased intraepithelial lymphocytes per 100 enterocytes (IEL>30) - a histopathologic result corresponding to a Marsh 3a score for celiac disease [6,14]. (Figure 2a).

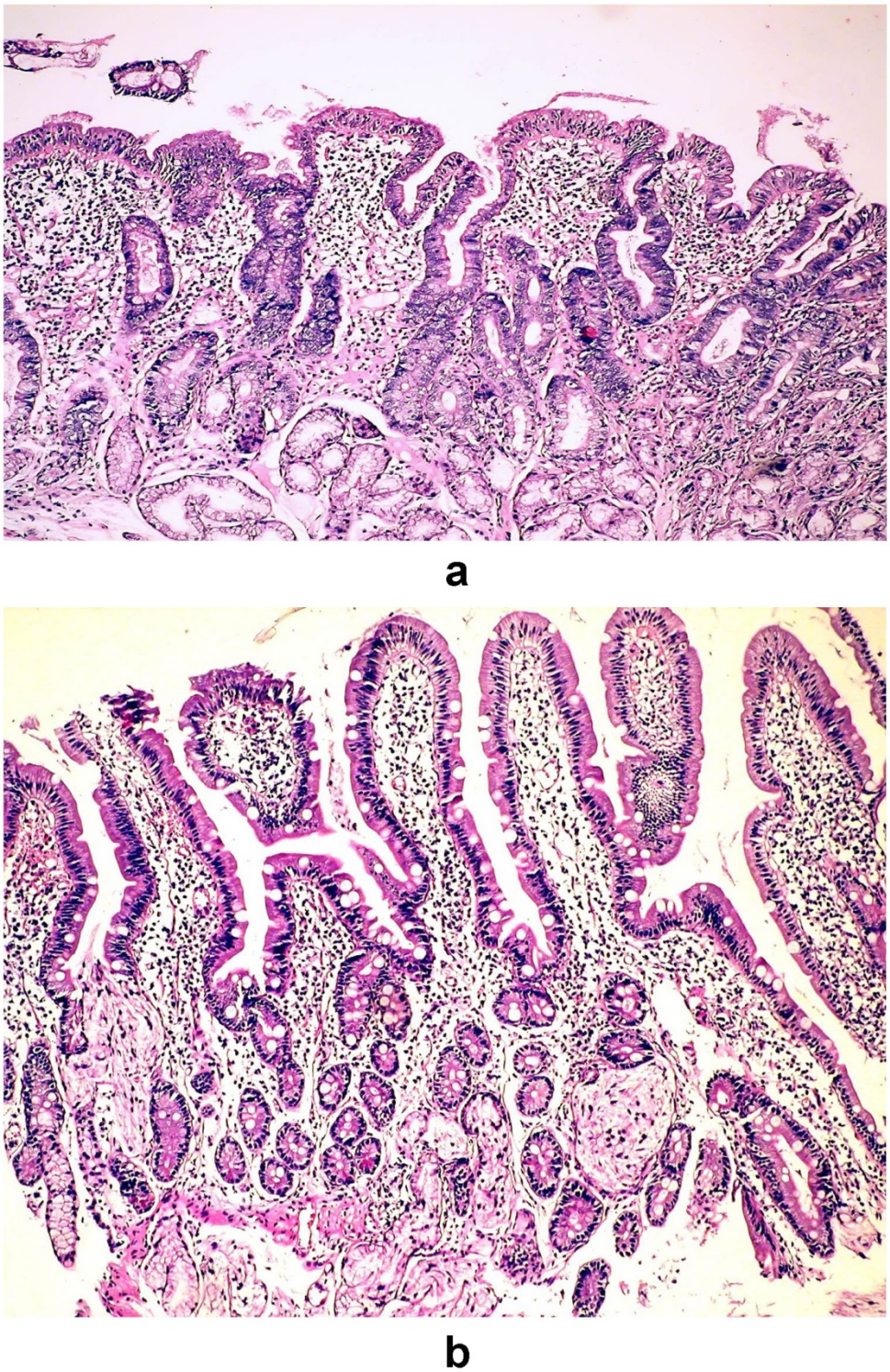

Figure 2. The results of the duodenal biopsy (HEx200): a. before treatment- Marsh3a score (villous atrophy, pathologic exocytosis and inflammation); b. after gluten-free diet- Marsh1 score (pathologic exocytosis and inflammation)

Although the pubertal delay is important compared to the chronological age of the patient (CA:16 years), pelvic ultrasound revealed consonance between the ovarian activation the size and shape of the uterus, the stage of pubertal progression for breast volume (Tanner B2) and the delayed bone age (BA/20TW2:12.5 years).

Today, the direct relationship between the level of estradiol and all its pubertal effects (the breast enlargement, growth spurt, the increasing size and the "pear-shape" change of the uterus and finally the endometrium thickness) is unanimously recognized. The same is valid under normal circumstances, between the bone age (BA) and the progression in puberty. In our patient, due to the consonant findings in terms of delayed BA, ovarian activation, breast volume, size of the uterus and no endometrium echo on ultrasound, estrogen supply is undoubtedly lower than her chronological age, so, dosing gonadotropins and estradiol is completely useless. Furthermore, her delayed BA (BO: 12.5years vs. decimal chronologic age DCA: 16.099 years) correlates not only with the pubertal delay but also with her short stature. At the same time, delayed bone age improves the patient's final height prediction.

Our final diagnosis was late-diagnosed, atypical celiac disease, the impairment of weight, low growth rate, delayed puberty, constipation, arthritis, etc. being interpreted in the context of the underlying disease [4,9,13,15,16]. Gluten-free diet was recommended.

Ten months later, the auxologic reassessment revealed improvement in bone age and height. In the presence of a bone age (BA/20Tanner Whitehouse Mark 2 method) of 13.8 years, the actual height of 151 cm (-2.06 SDS) was plotted on the 3rd percentile, while the weight (G: 42kg, -2.27SDS) continues to be under the same percentile in the general population (Figure 1). A favorable trend was also followed by the pubertal progression, Tanner stage B3 for breast enlargement being recorded after 10 months of restrictive diet for gluten.

We would like to note, that despite the fact that the current height of our patient is at the lower limit of the normal variation range in general population, this is not the case any more when compared to her average parental height (adjusted to the child's gender) which is 154.2 cm (p3-10, 95% CI: 145.2 cm). As a result, the recorded short stature in this child is not exclusively a consequence of the underlying disease (e.g. celiac disease) but also has a main genetic component in the context of her short parents [12].

Lab tests were negative for antiendomisium antibodies with the persistence of a mild increase of the transglutaminase antibodies (24 U/ml vs. 15 U/ml which is the normal reference value). Histological examination by repeated duodenum biopsy confirmed disease amelioration according to Marsh stage 1. (Figure 2b).

The girl admitted that despite strict adherence to the gluten and lactose-free diet, she briefly consumed bread on the occasion of the religious service. This aspect may be responsible both for the persistence of transglutaminase antibodies and the minor restant histological changes (e.g. increased intraepithelial lymphocytes but no villous atrophy).

The pelvic ultrasound showed the bilateral ovarian multicystic change (4-5 follicles, 3 to 4 mm diameter), the increase in uterine size (39.5/20.2 mm) and endometrium thickening (3 mm). Since the endometrium thickness is not more than 5 mm, it is still premature for the menarche onset regardless of the actual chronological age of the girl.

Compliance to the gluten-free regimen remains a prerequisite in favor of catch-up growh, weight gain and pubertal maturation so, the need to continue the diet has been reiterated.

3. Discussion

Celiac disease is an extremely heterogeneous autoimmune condition. Its onset is marked by a very broad spectrum of symptoms and this aspect is reflected by the the different incidence figures reported for this disorder. Figures range from 3-4% in Sweden to 0.01-0.1% in Denmark and the US. However, the use of celiac disease screening with serologic markers in populations considered to be healthy led to the prevalence of celiac disease similar to those with high incidence. In fact, the values in all studied populations were surprisingly similar. This suggests that celiac disease is in fact underdiagnosed in countries where its reporting is made only for the classical forms of disease [4,17].

Growth impairment in celiac disease usually occurs after the age of 6 months [2,12]. Classical forms of illness evolve with overt gastrointestinal (GI) symptoms like diarrhea, steatorrhea, abdominal distension, malnutrition, etc. Growth failure is due to intestinal villi atrophy and secondary malabsorption. As a consequence, in small children, the weight loss is followed by stunting growth, but the decline in weight is far more severe compared to that of the liniar growth.

In children older than 7 years and in teenagers, the patient's short stature compared to the parental height is a constant of the clinical picture in celiac disease, even in the absence of the characteristic overt gastrointestinal symptoms. Also, the genetic short stature does not exclude celiac disease [12,16,18]. Furthermore, at this age, the symptoms may be atypical, with classical diarrheic syndrome being replaced by constipation [4,19,20]. In the absence of treatment, the affected adolescents develop iron deficiency anaemia, short stature and delayed puberty [9,14,15]. Sometimes, growth and weight deficit may be the only symptom of the disease, 10% of the cases of so called "idiopatic short stature" being in fact the expression of an atypical celiac disease [4,14,21].

In fact, most of the endocrine changes observed in celiac disease seem to occur secondary to malnutrition [4,19,22]. A significant inverse correlation between IGF-1 level (insulin-like growth factor 1) and the duration of exposure to gluten has been found in celiac patients. The secretion of IGF-1 is significantly affected only in the case of long-term exposure, a situation which precedes the decrease in the growth velocity. Moreover, in the case of untreated celiac patients, the disruption of the hypothalamic control of growth hormone secretion (GH) seems to be involved as well.

In case of an active form of celiac disease (with clinically validated malnutrition), a GH-resistance status occurs, the poor nutritional status being unveiled by low serum levels of IGF-1, IGFBP3 (IGF- binding protein 3) and GHBPs ("growth hormone binding proteins"). GH is

not able to stimulate IGF-1 production until the complete nutrition recovery is achieved [3]. Under poor energy conditions, the described endocrine changes may be the expression of the physiological adaptation of the human body in favor of vital processes rather than preservation of the growth velocity [23]. A rapid increase of IGF-1 level was reported after the initiation of the gluten-free diet.

In early childhood, a significant delayed bone age compared to their low height for chronological age was reported, while in older children and adolescents the delayed bone age was found to be consonant to their growth delay for the chronological age.

In adolescent female patients, pubertal delay is consonant with their delayed bone age, primary amenorrhea and infertility being the common intrinsec expression of the untreated cases [24].

Total withdrawal of gluten is the only therapeutic method able to heal the intestinal mucosa [25]. Strict compliance with the gluten-free diet rapidly triggers the catch-up growth process. As already mentioned, in children diagnosed at an early age their weight is more severely affected than their height. As such, weight gain occurs first, normalization of weight being recorded on average 6 to 12 months after the initiation of the gluten-free therapy. In most studies, catch-up growth and improvement in bone age, occur later in comparison to weight gain and normalize only after 2 to 3 years of gluten-free diet. This model initially leads to weight above the standard weight-for-height, thus the median weight gain being a transient symptom of the recovery process [2,3,12,26].

In older children, during the first year on a gluten-free diet, the catch-up growth is reported to involve both weight and height. However, the rate of linear growth has been shown to increase much more in boys than female patients whose period of catch-up growth is considerably longer.

In late-diagnosed cases, delayed bone age should be accepted as a prognostic factor favorable to the final height, because theoretically it provides a prolonged period of growth for these patients. When the catch-up growth is not validated after the prohibition of dietary gluten, another underlying medical condition should be ruled out (e.g. familial short stature, GH deficiency, etc.).

In relation to her chronological age of 16 years, the teenager was definitely diagnosed too late, not only for the celiac disease but for her lack of progression into puberty as well. The request for medical examination was mainly motivated by the absence of her menstrual cycle and not for the recurrent gastrointestinal symptoms (refractary constipation) or short stature and inappropriate weight gain [27].

The absence of the classical defining symptoms for celiac disease (e.g. gastrointestinal symptoms: diarrheic syndrome, steatorrhea, malabsorption, etc.) may lead to the formulation of the diagnosis of atypical celiac disease, but the reevaluation and quantification of the symptoms related to her chronological age, showed that in fact, she presented 5 out of 8 characteristic symptoms of the diagnostic criteria of celiac disease in adolescence (delayed linear growth, inappropriate weight gain, delayed puberty, constipation, anemia, arthralgia) [28].

Furthermore, we would like to point out the fact that her pubertal delay is intrinsically related to the reported delayed bone age and primary amenorrhea and infertility are the late, *sine qua non* complications in any case of undiagnosed, untreated or inappropriately treated female celiac patients. In keeping with the general observation, this article draws attention to the delayed puberty as a constant finding in this category of patients [29]. As such, the particular aspect of the case is not represented by the pubertal delay, but by the association of celiac disease with a familial genetic cause of short stature [12,18].

This is, in fact, the only plausible explanation for the delay of the diagnostic approach of the current patient. Even though the family genetic component of her short stature has masked the celiac symptoms, it might be considered as a favorable prognostic factor in relation to her log-term catch-up growth, because in this case, her height deficit is not completely due to the celiac disease and so, her delayed growth which is really mediated by the celiac disease is far less important. This also explains the rapidly favorable evolution of both the linear growth and pubertal progression under the gluten-free diet.

Although serum autoimmune markers may be useful for selecting patients for duodenum biopsy, we note that none of them have a 100% sensitivity and/or specificity. Moreover, the sensitivity of anti-endomisium and transglutaminase antibodies decreases with age, which is why their absence is not a reliable sign of compliance with therapy. So, an older celiac patient who does not grow well is definitely a non-compliant patient to the gluten-prohibited diet even when the above-mentioned antibodies are negative. In keeping with the age of our female patient, even if a negative result for the celiac disease-specific antibodies remains a subject of debate, the significant catch-up growth confirmed the appropriate evolution of the case.

4. Conclusions

According to the already presented data, our patient represents a case of a late-diagnosed atypical celiac disease. Even if compared to children, the non-GI symptoms seem to be “the sneaky signs to watch for” [9], poor growth, suboptimal weight gain, delayed puberty, primary amenorrhea, joint issues and anemia are quite frequent findings among adolescent celiac patients. Thus, the routine screening of celiac disease should be recommended not only in case of pubertal delay but in any other teenager pacient with such a myriad of symptoms.

Monitoring linear growth and nutritional status is crucial not only for the diagnostic approach but for the long-term follow-up progress of these patients as well. Auxology is the most accurate method to assess compliance to gluten-free diet, especially since the method is simple, rapid and noninvasive compared to the duodenal biopsy.

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