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Case Report

Celiac Disease and GH Deficiency in Children: A Case Report

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Abstract

Growth is a complex and multifactorial process influenced by a combination of genetic, environmental, and hormonal factors. The regulation of growth involves a delicate balance of these factors, with hormones, such as growth hormone (GH), playing a pivotal role in the development of linear growth. Growth disorders, such as stunted growth, are common reasons for consultation in pediatric practices. However, diagnosing the cause of stunted growth can be a challenging task, as there are numerous potential contributing factors. These factors are often intertwined, with patients frequently presenting with two or more abnormalities simultaneously, such as growth hormone deficiency (GHD) and celiac disease. This overlapping of conditions can complicate diagnosis, as the symptoms of one condition may mask those of another, leading to a delay in identifying the true underlying cause. In our observation, we report two cases of patients who presented with growth disorders, each demonstrating how one condition can obscure another. The first patient was initially diagnosed with celiac disease, and while a gluten-free diet was implemented, there was little improvement in growth. Further investigations revealed an additional diagnosis of growth hormone deficiency, highlighting the importance of considering multiple diagnoses in cases of stunted growth. The second patient was first diagnosed with growth hormone deficiency, but after further evaluation, a diagnosis of celiac disease was made, which helped explain the persistence of the growth issues. In conclusion, stunted growth can result from various factors, and the presence of one disease can mask another. Thus, it is crucial to conduct thorough investigations and reconsider initial diagnoses to ensure that all potential causes are explored and appropriately addressed.

Keywords

Growth, Regulation, Growth Hormone, Celiac Disease, Autoimmune Diseases

1. Introduction

Stunted growth represents a dilemma for pediatricians due to its psychological impact on the child and the family [1], highlighting the importance of early etiological diagnosis to initiate treatment as soon as possible. Two of the most common etiologies are Growth Hormone deficiency (GHD) and celiac disease, which rarely can be intertwined and coexist in children, sometimes masking each other's manifestations due to the similarity of symptoms [2].

Although they are both autoimmune diseases, their physiopathologies are different. Celiac disease is an inappropriate

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response to gliadin [3], while. GHD is the result of a deficiency in anterior pituitary secretion [4], their manifestations are similar. A no-response to the treatment should suspect the presence of another etiology [5].

2. Observation

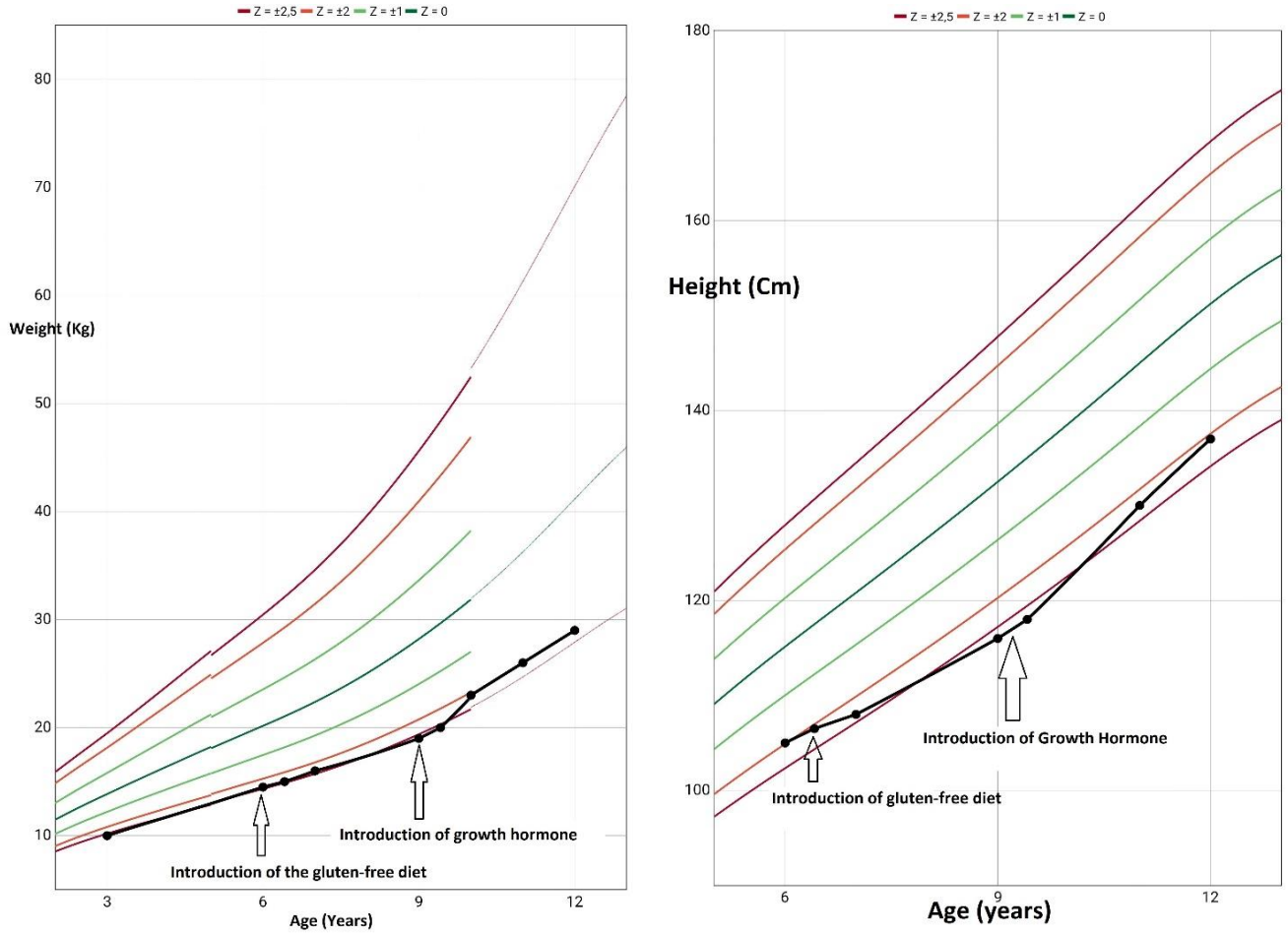

Figure 1. *Weight (Kg) and Height (Cm) versus Age (Years) curve for case A.*

The observation involves two female cases with good psychomotor development.

The first case (A) was 6 years old, with a history of asthma treated with inhaled corticosteroids and short-acting beta 2 agonists. Her asthma was well-controlled with an ACT score of 22, not requiring repeated use of oral corticosteroids. She presented with chronic diarrhea. On initial examination, case (A) had stunted growth, with weight at -2 standard deviations (SD) (Figure 1), height at -3 SD (Figure 1) without signs of hypercorticism. Blood tests showed hypochromic microcytic anemia, normal liver function, and a sweat test at 15 mmol/l (<60 mmom/l). Serology for celiac disease was made and came positive, with anti-transglutaminase antibodies at 22.6 IU/ml (<12 IU/ml), anti-gliadin IgA antibodies at 164 IU/ml (<12 IU/ml), and anti-endomysium antibodies at 329 IU/ml, with total IgA levels at 1.186 g/l (0.28-2.22 g/l). Celiac disease was confirmed by esophagogastroduodenoscopy and biopsies showing total villous atrophy with intraepithelial lymphocytosis and crypt hypoplasia. She received educational therapy with the nutritionist regarding the gluten-free diet. Despite good compliance with the diet, as confirmed by negative antibody levels (anti-transglutaminase antibodies at 6.1 IU/ml (<12 IU/ml)) after one year, there was persistent stunted growth, with a weight gain of 1.3 kg per year (2-3 kg per year) and a height gain of 2.2 cm/year (5 cm per year) (Figure 1). Since this progression cannot be justified by her illness or corticosteroid intake related to her asthma, another underlying cause has been suspected, and further complementary tests have been requested. Bone age was obtained, showing a 2-year delay compared to chronological age. A karyotype was performed, resulting in 46, XX. Endocrine causes have been suspected based on the bone age. Thyroid and liver function tests were normal, so as IGF1 levels (130.82 ng/ml -normal according to the levels of transami-

nases- (>79 ng/ml and <499 ng/ml). A growth hormone stimulation test by insulin showed a complete deficiency in growth hormone with a growth hormone response at 8 (< 10 mIU/L (3.3 µg/L)) and cortisol level at 40 µg/dL (20 µg/dL (550 nmol/L)). The study of the pituitary axis came back normal with a cortisol level of 196 ng/mL (> 140 ng/mL), FSH at 5 IU/L (0.2-11 IU/L), and LH at 0.98 (0,1 -1,5 UI/L). For the etiological assessment, an MRI of the pituitary gland showed no abnormalities and anti-NMDA receptor antibodies came negative ruling out lymphocytic hypophysitis. She was started on recombinant growth hormone, and there was catch-up growth, with weight gain of 3.3 kg per year and height gain of 6 cmper year.

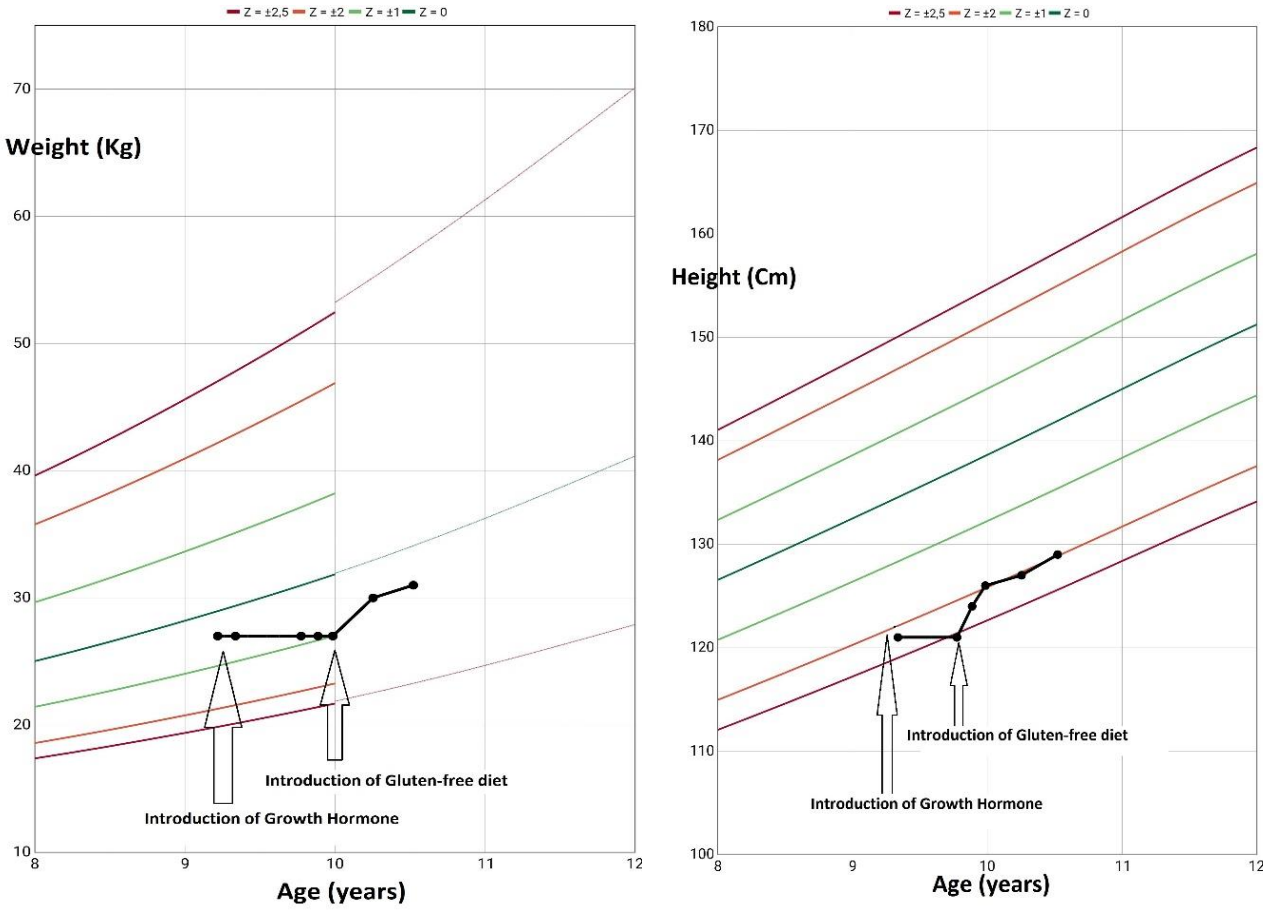

Figure 2. *Weight (Kg) and Height (Cm) versus Age (Years) curve for case B.*

The second case (B) was 9 years old with fourth-degree consanguinity. She had a history of epilepsy with confirmed absence seizures on EEG, treated with lamotrigine. She presented with pallor associated with confirmed dermatological alopecia areata through biopsy. Initial examination showed weight at -0.6DS (Figure 2), height between -2.3 DS (Figure 2). Blood tests showed a hypochromic microcytic anemia, normal liver function and malabsorption tests were normal. Bone age showed a 5-year delay compared to chronological age. A karyotype was performed, resulting in 46, XX. Endocrines causes have been suspected, and a thyroid panel came within the normal range, with TSH at 5.6 UI/ml (<4 UI/ml). IGF1 levels were decreased compared to liver function at 132.31 ng/ml (>247 ng/ml and <396 ng/ml). In view of these results, insulin stimulation test was made and confirmed a complete deficiency in growth hormone response at 7.1 mUI/L (< 10 mIU/L (3.3 µg/L)) and cortisol level at 45 µg/dL (>20 µg/dL (550 nmol/L)), eliminating an associated corticotrope insufficiency. For the etiological assessment, an MRI of the pituitary gland showed no abnormalities. She was started on hormone replacement therapy. The evolution was marked by growth stagnation, with weight gain at 0 kg per year (Figure 2) and height 0 cm per year (Figure 2). On questioning, there was poor therapeutic compliance due to lack of means and anorexia. Another underlying cause has been suspected and blood tests were required showing persistent anemia despite iron supplementation, along with hypocalcemia and 25-OH vitamin D deficiency <8.1 ng/ml (>20 ng/ml) with a PTH level ranging from 6 to 50 pg/ml. Thyroid function was rechecked and was within the normal range, with negative anti-TPO antibodies., and a corticotrope axis evaluation (cortisol and ACTH levels)

was normal. Given the epilepsy and growth hormone deficiency with initially borderline TSH, lymphocytic hypophysitis was suspected but ruled out due to negative anti-NMDA receptor antibodies and a normal MRI. Due to persistent anemia, hypocalcemia, serology for celiac disease was requested and came positive, with anti-transglutaminase antibodies >200 mg/l (<10 mg/l). An esophagogastroduodenoscopy showed normal findings, but biopsies confirmed a celiac disease association and revealed stage 3 villous atrophy according to Marsh classification. She received educational therapy with the nutritionist for gluten-free diet. The evolution was marked by improvement in stunted growth, with height gain of 5 cm per year and improvement in rickets with correction of vitamin D deficiency and serum calcium levels.

3. Discussion

These two case reports highlight the importance of considering endocrine causes in children with stunted growth and other associated symptoms. In the first case (A), the use of corticoids may lead to stunted growth but the well-controlled asthma led to suspect other etiologies [6]. Chronic diarrhea, poor growth and malabsorption syndrome led to the diagnosis of celiac disease especially that the prevalence of Celiac disease in Tunisia is estimated to be 1/157. [7] Despite adherence to a gluten-free diet confirmed with negative antibodies, the patient continued to experience stunted growth, prompting further investigation [8]. The delayed bone age helped to suspect an underlying endocrine cause associated with other autoimmune diseases [9]. Despite a normal IGF1 level, a complete deficiency in growth hormone identified through stimulation testing suggested an endocrine cause for the persistent growth impairment. The normal pituitary axis and negative anti-NMDA receptor antibodies ruled out other potential causes, leading to the diagnosis of isolated growth hormone deficiency. Treatment with recombinant growth hormone resulted in catch-up growth.

The second case (B) was a more complex one. The patient had absence epilepsy. She presented with pallor and dermatological alopecia areata, along with delayed growth. Initial investigations revealed hypochromic microcytic anemia, and a thyroid panel came within the normal range. An autoimmune mechanism has been suspected in front of the alopecia areata. Decreased IGF1 levels with normal liver function suspects a growth hormone deficiency but it also may be decreased in malnutrition and celiac disease. Thyroid panel levels may also be elevated in growth hormone deficiency. As for the prevalence of hormone growth deficiency isranging from 1/4000 to 1/30,000 [10, 11]. Further testing, including an insuline stimulation test, confirmed a complete deficiency in growth hormone response with absence of corticotrope insufficiency association. Even though on questioning, there was poor therapeutic compliance due to lack of means, the patient's persistent anemia, hypocalcemia, and vitamin D deficiency raised suspicion for an additional underlying condition, even though rickets can also be a cause of stunted growth. In front of the history of epilepsia growth hormone deficiency with initially borderline TSH, lymphocytic hypophysitis was suspected but ruled out due to negative anti-NMDA receptor antibodies and a normal MRI. TSH level was rechecked and returned to normal after treatment with growth hormones. Subsequent serology for celiac disease came back positive, and biopsies confirmed an association of celiac disease. Implementation of a gluten-free diet resulted in improved growth and resolution of the rickets. To conclude, in this case, many etiologies were implicated in stunted growth such as the non-compliance with treatment, rickets, growth hormone deficiency and celiac disease.

These cases highlight the importance of a comprehensive evaluation in children with stunted growth, even in the presence of other diagnosed conditions. If there is no catch-up growth, a deviation in the growth curve, or the appearance of other abnormalities in a patient with celiac disease or growth hormone deficiency, another underlying condition should be suspected [5], prompting the search for another organic etiology, such as their coexistence, as described in the literature [12]. The prevalence of the association between celiac disease and growth hormone deficiency was ranging from 0.23% to 8.3% [13-15]. Several factors can contribute to growth retardation, as seen in our second case where the outcome was not favorable. Poor treatment adherence could have been one explanation, but with the appearance of rickets, a malabsorption disorder was suspected and confirmed.

In the second case, the presence of coeliac disease was found along with growth hormone deficiency, and there was also an existing anemia from the beginning based on laboratory tests. This raises the question of which initial examinations should be requested for a child presenting with growth failure. Considering the limited resources in our country and the high cost of tests done privately or even at the hospital, it is worth considering whether an incremental approach, requesting each test step by step and treating according to the results, would minimize expenses but potentially miss an underlying diagnosis. Alternatively, performing a comprehensive range of tests may lead to a more expensive approach.

4. Conclusion

Celiac disease and growth hormone deficieny may be intertwined. The complexity of stunted growth raises the question of the most cost-effective approach to initial diagnostic testing, considering limited resources and the high cost of comprehensive evaluations. Further research and clinical guidelines may help guide clinicians in determining the most appropriate diagnostic and treatment strategies for children with growth failure.

Abbreviations

GH	Growth Hormone
GHD	Growth Hormone Deficiency
ACT	Asthma Control Test
SD	Standard Deviations
IGF1	Insulin-like Growth Factor 1
FSH	Follicle Stimulating Hormone
LH	Luteinizing Hormone
MRI	Magnetic Resonance Imaging
NMDA	N-methyl-D-aspartate
TSH	Thyroid Stimulating Hormone
Anti-TPO	Anti-Thyroid Peroxidase
ACTH	Adrenocorticotropic Hormone
Kg	Kilogramme
Cm	Centimeter

Statement on Consent for Publication

The authors certify that they have obtained the parent's consent for image and clinical information to be reported in the journal. Parent understand that the name of his baby will not be published.

Statement on Ethical Approval and Informed Consent

The authors consciously assure that for the manuscript, the following is fulfilled:

(1) This material is the authors' own original work, which has not been previously published elsewhere.
(2) The paper is not currently being considered for publication elsewhere.
(3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
(4) The paper properly credits the meaningful contributions of co-authors.
(5) The results are appropriately placed in the context of prior and existing research.

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Conflicts of Interest

The authors declare no conflicts of interest.

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