Review Article

Growth Hormone Deficiency and Related Endocrine Disorders in Children with Celiac Disease

Mauro Bozzola[1*], Chiara Montalbano[2], Elena Bozzola[3], Nicola Lazzaro[4], Filomena A Stamati[5], Pietro Ferrara[6] and Alberto Villani[3]

[1]Department of Internal Medicine and Therapeutics, University of Pavia and Onlus "The Child and his pediatrician", Italy
[2]IRCCS San Matteo Foundation, Italy
[3]Department of Pediatrics, Child Jesus Children Hospital, Italy
[4]Pediatric Unit, St. John of God Hospital, Italy
[5]Unit of Pediatrics and Neonatology, Ferrari Hospital, Italy
[6]Institute of Pediatrics, Catholic University, Italy

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Corresponding author: Mauro Bozzola, Department of Internal Medicine and Therapeutics, University of Pavia, Italy, Email: mauro.bozzola@unipv.it

ABSTRACT

This review focuses on the management of short stature associated with celiac disease, which is a possible expression of GH deficiency; we want also to underline the importance of diagnosis and treatment of other endocrine disorders in celiac patients.

Growth failure can be a common clinical manifestation of celiac disease in children. In fact, catch-up growth is generally observed in children with Celiac Disease (CD) after the start of a strict Gluten-Free Diet (GFD). If no return to their normal growth curve for weight and height is observed within 1–2 years, an endocrinological investigation including an evaluation of GH secretion should be performed in cases of seronegativity for anti-tissue transglutaminase and/or anti-endomysial antibodies. In the event of a documented GH Deficiency (GHD) and in the presence of seronegativity, treatment should promptly be initiated with the same GH doses as for patients with idiopathic GHD.

As regards treatment, in cases of associated hormonal deficiencies, the dose of the missing hormones is the same as that used in patients without CD. In celiac patients with GHD who are following a strict GFD, the response to replacement therapy is similar to that of subjects with idiopathic GHD. Moreover, the long-term effects of GH therapy in children who follow a strict GFD are similar to those observed in children with idiopathic GHD. Compliance is very important in order to obtain a good response to GH therapy. In celiac children and adolescents, growth failure and other endocrine-related disorders must be carefully investigated to avoid permanent short stature and long-term complications in adulthood.

Introduction

Celiac Disease (CD) is a systemic immune-mediated disorder triggered by dietary gluten that primarily affects the small intestine in genetically predisposed subjects. In North America and Europe, the prevalence of CD is estimated to be approximately 0.5%-1% [1-4]. According to the report to parliament from the Italian Ministry of Health (March 2017), 182, 858 Italians have been diagnosed with CD, although it is believed that there are at least another 500,000 undiagnosed cases due to prevalent

forms of the disease with nonspecific symptoms. In fact, CD patients present with a broad spectrum of signs and symptoms depending on age, individual sensitivity to gluten and on the amount of toxic proteins ingested with the diet. Particularly in infants, classic characteristics that have identified this disease are malabsorption/ malnutrition, chronic diarrhea, abdominal distension, muscle wasting and failure to thrive. It is not unusual for pediatricians to experience the problem of short stature or stunted growth in CD subjects. In fact, the prevalence of CD in patients evaluated for short stature is reported to be between 2% and 10% [5-8]. Therefore, growth failure and other endocrine-related disorders must be carefully investigated in celiac children and adolescents, to avoid permanent short stature and long-term complications in adulthood.

The prevalence of CD seems to have increased in recent years, as witnessed also in patients with extra-intestinal manifestations including disorders of the endocrine system, mainly in older subjects. In that sense, the epidemiology of CD has been depicted as an iceberg whose visible tip represents patients with various clinical manifestations, but whose hidden mass represents those with minimal or no symptoms. Interestingly, the presence of CD is frequently observed in conditions such as Down (5-12%), Turner (4-8%) and Williams syndromes (8%), selective IgA deficiency (2%) and in 4%-5% of first-degree relatives of celiac patients [1,2].

In both adults and children with celiac disease, two endocrine diseases are frequently observed, i.e. Insulin-Dependent Diabetes (IDDM) and Autoimmune Thyroiditis (ATD). The prevalence of IDDM in celiac patients is 20 times higher than in the general population, while the risk of thyroid disease is estimated to be 3-fold compared to age-matched subjects [9,10].

It must be highlighted that celiac patients are at great risk of developing endocrine disorders because of a common genetic predisposition that may explain the association between CD and autoimmune diseases [11].

In particular, the main genetic contribution arises from the major his to compatibility complex, especially by variants of the class II HLA gene. Specifically, the HLA-DQ2 haplotype is expressed in the majority of CD patients (90%), whereas the HLA-DQ8 haplotype is expressed only in 5% of CD patients. The remaining 5% of patients have at least one of the two genes encoding DQ2 (DQB1*0201 or DQA1*0501). Nevertheless, not all patients develop multiple autoimmune diseases, suggesting the presence of other disease-specific genes besides the HLA pleiotropic ones and the influence of environmental factors.

The high risk for CD subjects of developing other autoimmune diseases seems to be related also to the duration of gluten exposure, although even a completely gluten-free diet cannot protect celiac subjects from developing autoimmune thyroid damage.

Diagnosis of CD is based on serological testing for specific markers, such as circulating anti-transglutaminase and anti-endomysial antibodies, and by histological analysis of duodenal biopsies.

A strict lifelong Gluten-Free Diet (GFD) is the only effective treatment for celiac disease and usually results in a resolution of symptoms, disappearance of serum antibodies and repair of intestinal damage within 24 months. Moreover, full compliance to gluten-free diet reduces the risk of malignancy including T-cell lymphoma and non-Hodgkin's lymphoma [12].

Discussion

For every Pediatric Endocrinologist, the first step in the diagnostic approach when dealing with a short child must be the exclusion of CD, which may be responsible for growth failure [8,13].

In particular, before evaluating Growth Hormone (GH) secretion in a short child in whom GH Deficiency (GHD) is suspected on the basis of auxological data, CD must be excluded since false GH responses to pharmacological stimuli have been observed, followed by their normalization after starting a GFD [14,15].

Moreover, Insulin-like growth factor I (IGF-I), which is considered to be the main peripheral GH mediator, is low in patients with insufficient GH secretion, but is not a discriminating factor in the evaluation of GH secretion, since its level is influenced also by the subject's nutritional status. Low levels of insulin-like growth factor 1 and Insulin-Like Growth Factor Binding Protein (IGFBP) have been reported in patients with CD [16].

On the other hand, once a diagnosis of celiac disease has been confirmed, careful follow-up is mandatory in order to verify

normal growth progression and negativity of the serum anti-tissue transglutaminase and/or anti-endomysial antibodies.

Catch-up growth is generally observed after starting a GFD and the CD child usually returns to their normal growth curve for weight and height within 1–2 years. An endocrinological investigation, including an evaluation of GH secretion, should be performed in CD children who show no catch-up growth after at least one year of a strict GFD, in cases of seronegativity for anti-tissue transglutaminase and/or anti-endomysial antibodies [8,15].

In clinical practice, at least two stimulation tests including different pharmacological stimuli are required to confirm the diagnosis of GHD, on account of the poor reproducibility of these tests. Provocative tests should be performed in pediatric endocrinology centers with experienced teams; particular attention is required when administering insulin and glucagon, due to the risk of symptomatic hypoglycemia. Furthermore, it is necessary to bear in mind that GH basal levels should not be taken into account in confirming GH deficiency because of the variability of spontaneous GH secretion.

Moreover, serum GH cut-off values for pharmacological stimulation tests depend on the type of stimulus and the method used for determining serum GH [17,18].

In cases of normal GH response to at least one pharmacological stimulus and IGF-I values within the normal range for sex and age, the auxological follow-up should be carried out every 6 months in order to verify growth. It is worth bearing in mind that non-GHD-dependent growth failure may also be attributable to generalized or selective malnutrition, such as zinc malabsorption [19,20].

In the event of a serum peak response of less than 8 ng/ml to at least two pharmacological stimuli, and in the presence of negative serologic tests for anti-transglutaminase antibodies, a diagnosis of GHD is confirmed.

Before starting GH treatment, it is necessary to check glucose tolerance by performing an Oral Glucose Tolerance Test (OGTT), as growth hormone may contribute to insulin resistance.

Possible deficiencies of other pituitary hormones including TSH, ACTH, ADH should be investigated, especially in cases of severe GH deficiency (GH peak <4 ng/ml). Deficiencies in pituitary gonadotropins, LH and FSH on the other hand, can be assessed only during puberty when an increase in pubertal gonadotropin occurs.

In the rare cases of GHD associated with a deficiency of one or more pituitary hormones, adequate hormonal secretion should be restored with replacement therapy before starting GH therapy. The doses of the missing hormones, such as levothyroxine, hydrocortisone, estradiol, testosterone and desmopressin, are the same as those administered to idiopathic GHD patients.

Brain magnetic resonance imaging may be required to rule out morphological abnormalities of the hypothalamus-pituitary region such as pituitary hypoplasia, ectopic posterior pituitary gland and a thin or absent pituitary stalk. These could be predictive for a subsequent occurrence of other hormone deficiencies, i.e. multiple pituitary hormone deficiency.

In a previous study, we clearly demonstrated reduced GH secretion in three pre-pubertal children with CD who showed no catch-up growth after 12 months of a strict GFD in spite of seronegativity for celiac antibodies [15].

The coexistence of other hormone deficiencies, including thyroid and adrenal function, was also reported. Therefore, GH replacement therapy was started at the recommended dosage of 0.21-0.25 mg/kg, subdivided into 6 doses per week, as in patients with isolated idiopathic GHD, while hydrocortisone and levothyroxine were administered to subjects with multiple deficiencies, in the same way as for patient with multiple pituitary defects. Both height and growth velocity significantly improved throughout the therapy, confirming that the absence of catch-up growth after a GFD was not due to malnutrition, but to low GH secretion. The growth rate increased significantly during the first year of GH therapy and then tapered, always remaining, however, above pre-treatment values.

In a subsequent study, conducted on ten pre-pubertal children with CD and GHD, and compared with a group of children of the same age with idiopathic GHD, both of whom were treated for five years with the same GH dosages, a similar increase in height and growth velocity was noted [21].

Growth rate increased significantly during the first year of therapy ($p < 0.005$) and subsequently levelled off, however, above the pre-treatment. During the fourth year of therapy, the growth velocity of children with CD and GHD was higher than that of children with only idiopathic GHD (Figure 1).

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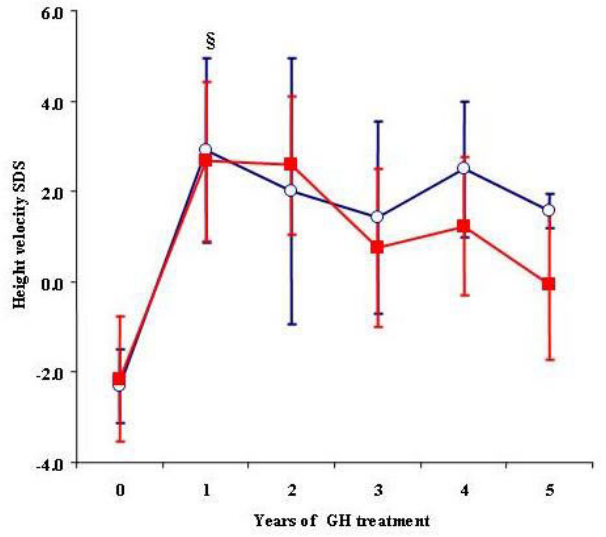

Figure 1: The growth rate before and during the first 5 years of GH replacement therapy in patients with CD and GHD (blue line) and in patients with idiopathic GHD (red line). The data are expressed as the mean and standard deviation § $p<0.05$ time 1 versus time 0 for the corresponding group (t-test for paired samples).

For some subjects in this study, growth velocity was followed until they reached their final adult height (growth velocity < 2 cm/year at the time of the last examination). This stature, considered "near final height", did not differ in the two groups (CD patients with GHD: 0.05±0.56SDS; patients with idiopathic GHD: -0.73±0.81 SDS, p=0.154) (Figure 2).

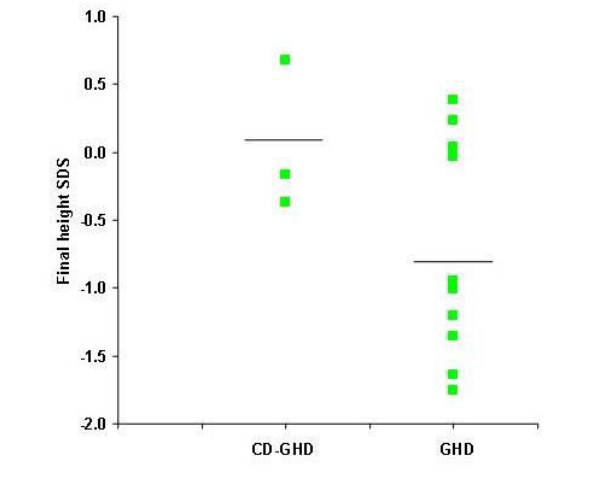

Figure 2: Final height of CD patients with GHD (left) and those with idiopathic GHD (right). The horizontal lines represent the mean value.

In the light of these results, we believe that celiac patients with GHD should be promptly treated with the same GH dosage as patients with idiopathic GHD (0.21-0.25 mg/kg/week s.c.), which should be administered in the evening before bedtime to mimic the physiological night-time elevation of the hormone. In cases of associated hormonal deficiencies, the doses of levothyroxine, hydrocortisone, estradiol, testosterone enanthate and desmopressin are the same as those used in patients without CD.

In celiac patients with GHD who are following a strict GFD, the response to replacement treatment is similar to that of subjects with idiopathic GHD.

Compliance to a GFD is very important in achieving a good response to GH therapy. Clinical results suggest, in fact, that CD patients with GHD do not respond to hormone replacement therapy if they do not follow a strict GFD.

Moreover, we have previously shown that CD children treated for associated GHD can successfully reach normal final height [22] (Figure 3).

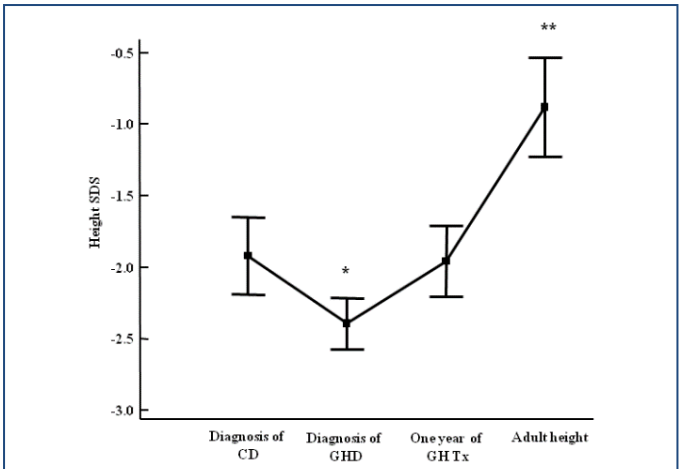

Figure 3: Height Standard Deviation Score (SDS) in CD-GHD patients at CD diagnosis, at GHD diagnosis, after 1 year of GH replacement therapy and at final height.

Conclusions

Before evaluating Growth Hormone (GH) secretion in a short child in whom GHD is suspected, CD must be excluded since false GH responses to pharmacological stimuli have been observed, followed by their normalization after starting a GFD. If CD has already been established, the evaluation of GH secretion should be performed in CD children who show no catch-up growth after at least one year on a strict GFD, after seronegativity of anti-tissue transglutaminase and anti-endomysial antibodies has been confirmed. After the start of a GFD, catch-up growth is generally observed, and the celiac

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child usually returns to his/her normal growth curve for weight and height within 1–2 years.

In subjects with CD and GHD, GH replacement therapy should be promptly started and administered at standard doses in order to reach complete catch-up growth. During follow-up, it is important to verify compliance with the GFD and to check the specific serology, auxological parameters, thyroid and adrenal function, and glyco-metabolic profile. Studies have shown that compliance to a GFD is essential in order to obtain a good response to GH therapy.

The long-term benefits of GH therapy in children who follow a strict GFD are similar to those observed in children with idiopathic GHD.

Finally, in celiac patients, early identification of autoimmune disorders may be useful in the prevention of long-term complications.

This article focuses on the results of research studies carried out by authors in the field of celiac disease.

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