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Chapter 4

Management of Celiac Patients with Growth Failure

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Abstract

Celiac disease (CD) may be considered as a systemic immune-mediated disorder that is triggered by dietary gluten in genetically susceptible subjects. CD children and adolescents show typical intestinal symptoms such as diarrhea, loss of weight and abdominal distension, or extraintestinal signs, the so-called nonclassical CD, such as short stature and delayed puberty. An endocrinological investigation including an evaluation of growth hormone (GH) secretion should be performed in CD subjects who show no catch-up growth after at least 1 year on a strict gluten-free diet (GFD) in the presence of a seronegativity of anti-transglutaminase and/or antiendomysial antibodies. When the diagnosis of GH deficiency is formulated, a substitutive therapy with GH must be promptly started to obtain a complete catch-up growth. The long-term effects of GH therapy in CD children who follow a strict GFD are comparable to those found in children with idiopathic GHD. A widely documented association has been observed between CD and type I diabetes mellitus and/or Hashimoto thyroiditis and/or Addison's disease. During follow-up, pediatricians should check antibody serology, thyroid and adrenal function and glucose-metabolic profile in order to verify the compliance with both diet and GH treatment. Adherence to a strict gluten-free diet promotes regular linear growth and may prevent CD complications as well as the onset of other autoimmune diseases.

Keywords: celiac disease, short stature, growth failure, growth hormone deficiency, growth hormone therapy

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1. Introduction

Celiac disease (CD) may be considered as a systemic immune-mediated disorder that is triggered by the ingestion of dietary gluten in genetically susceptible subjects, resulting in various degrees of small intestinal damage.

Celiac disease affects approximately 1% of the population of Europe and North America, but it is estimated that the number of undiagnosed cases is currently far greater than that of diagnosed cases because of the presence of prevalent forms with nonspecific symptoms including short stature and delayed puberty [1, 2].

The clinical manifestation of celiac disease in children has changed over the last few years. The classic symptoms including diarrhea, growth failure and abdominal distension are becoming less common, and nonspecific signs and symptoms have become more frequent.

The various presentation of celiac disease ranges from typical gastrointestinal symptoms to extraintestinal signs, thus presenting the physician with a challenge in making an early diagnosis. It has been postulated that the diagnosis of celiac disease may be delayed by 3.5 years on average in patients who have extraintestinal symptoms [3].

Early diagnosis, especially in children, helps to reduce the impact of comorbidities and to increase final adult height [4, 5].

2. Celiac disease and short stature

Diagnosis of CD is based on serological testing for specific markers, such as circulating anti-transglutaminase and antiendomysial 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. Full compliance to gluten-free diet reduces the risk of malignancy including T-cell lymphoma and non-Hodgkin's lymphoma [6].

When evaluating a child with short stature, the first step is to rule out celiac disease as short stature may be the only presenting symptom of the disease [7]. Between 8 and 10% of children with apparently idiopathic short stature have serologic evidence of celiac disease, i.e., positive IgA antibodies against tranglutaminase and anti-endomysium [8–11].

The probability of celiac disease in children with short stature of nonendocrinological cause is reported to be very high [12, 13].

For this reason, growth monitoring is very important for all children and, in particular, for those individuals with a higher risk of developing celiac disease. Population-based screening for celiac disease can be performed fairly accurately when several screening parameters for abnormal growth are used simultaneously, and combined with the use of longitudinal growth data [13].

The pathogenesis of growth failure is unclear. It is probably multifactorial and can be due to malabsorption, abnormalities in the endocrine hypothalamus-pituitary axis or growth hormone resistance [14].

Growth monitoring is a standard practice for a pediatrician. A child's height or length should be evaluated using specific devices. Children's length (for children less than 2 years old) is measured using a Harpenden infantometer. After the age of 2 years, height measurement requires the Harpenden stadiometer and the orthostatic position.

Growth percentile can be determined by correlating the child's height with their age on a growth chart. This practice is useful in comparing a patient's height to the expected parameters for children of the same age and sex. National and international growth charts report auxological parameters of a normal population from birth to adult age.

Growth charts are also useful in determining growth deceleration. Growth rate can be calculated using the difference between two height measurements detected in an at least period of 6–12 months. Growth rate below 10th percentile (or 25th for other authors) requires further diagnostic examinations.

No investigation of children's growth can be separated from the analysis of target height, which is determined by the measurement of the parents' height and the evaluation of pubertal development.

Weight evaluation and determination of BMI (body mass index) are essential in order to analyze children's growth. Weight and BMI should be reported on a specific growth chart [15].

In a celiac child with a stature below the 3rd percentile or below the percentile related to target height, a diagnostic work-up should be undertaken to investigate GH secretion. Diagnostic evaluation should be started immediately, without waiting for growth failure, if a CD subject shows the first pubertal signs, i.e., development of bud breast in females or increased testicular volume in males.

However, it is an accepted practice to rule out CD before evaluating GH secretion, since false GH responses to pharmacological stimuli have been observed, followed by their normalization after starting a GFD. It has been reported that 0.23% of children with short stature shows an association between CD and GH deficiency [10].

On the other hand, CD patients show catch-up growth generally after beginning the GFD and usually return to their normal growth within 1–2 years [16, 17].

Therefore, a careful follow-up is mandatory in order to verify the normal growth progression, as well as annual evaluation of serology negativity. If the CD subject does not show catch-up growth, and tests negative for "celiac" antibodies, an evaluation of GH secretion is mandatory [17].

In the event of GH deficiency confirmed by 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, substitutive GH therapy should be started.

GH basal levels are normally very low and they are not useful in confirming GH deficiency.

GH secretion may be not so easy to measure because it is regulated by different peptides and neurotransmitters, such as GHRH and somatostatin, and it is pulsatile throughout the day. Given the poor reproducibility and accuracy of these tests, clinicians should bear in mind that GHD diagnosis is based on clinical and auxological findings that suggest a hypothesis of GHD [18].

The results of stimulation tests serve merely to confirm the clinical diagnosis.

Spontaneous and stimulated GH secretion is variable. Levels vary significantly according to gender, age, weight and pubertal status [19].

Moreover, spontaneous GH secretion progressively decreases with age, and this trend is more pronounced in males. During the pubertal period, there is a marked increase in GH secretion, which is directly influenced by sex steroids. Where there is an increase in body mass index, a decreasing trend of GH peak values after stimulation tests has been observed.

However, in clinical practice, a specific range based on age, sex, weight and pubertal stage does not exist.

Serum GH cut-off values for pharmacological stimulation tests depend on the type of stimulus and the method used for determining serum GH.

For this reason, there are specific recommendations within guidelines aimed at standardizing GH assays [20].

In clinical practice, stimulation tests include different pharmacological stimuli. Given the poor reproducibility of these tests, it has been established that two provocative tests are required for a diagnosis of GH deficiency.

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.

The insulin tolerance test (ITT) is considered the gold standard in evaluating GH secretion. Insulin-induced hypoglycemia acts as a stimulus for GH secretion. Insulin is administered intravenously (0.1 unit/kg in children over 4 years of age and 0.05 unit/kg in younger children). Then blood samples are collected to measure GH, glucose and cortisol levels, at 0, 30, 60, 90, 120 minutes after insulin injection. This test requires careful observation by experienced staff because of the risk of hypoglycemia. If the blood glucose level decreases by 40–50% of basal value or reaches less than 40 mg/dl, the test is considered effective. Usually, GH peak occurs 15–30 minutes after glucose nadir.

Glucagon induces GH secretion by stimulating endogenous insulin secretion following an increase in blood glucose level. It is administered intramuscularly (0.03 mg/kg, maximum 1 mg). Measurements of GH, cortisol and glucose are carried out after 30, 60, 120, 150, and 180 minutes after glucagon administration. GH peak is usually observed after 2–3 hours (concurrently with hypoglycemia).

Arginine inhibits somatostatin release. The arginine provocative test consists of IV infusion of arginine hydrochloride (0.5 g/kg, maximum 40 g) over a 30-minute period. Blood samples should be collected at baseline and after 30, 60, 90, and 120 minutes after infusion. GH peak is expected to occur 60 minutes after arginine administration.

GHRH can directly assess pituitary gland capacity to secrete GH. The GHRH test (alone or in combination with arginine administration) is useful in diagnosing hypothalamic defects. A dosage of 1 mcg/kg of GHRH is administered intravenously. Serum samples are collected at baseline and 15, 30, 45, 60, 90, and 120 minutes after GHRH administration (frequently with concurrent infusion of arginine hydrochloride). GHRH plus arginine stimulates GH secretion to a greater extent than GHRH alone. The GHRH plus arginine test is useful for identifying false-positive GH deficiency in children with blunted GH secretion after the classic pharmacological provocative tests [21] (**Table 1**).

IGFs (insulin-like growth factors) are GH-dependent peptides that mediate many of the anabolic and mitogenic actions of GH. IGF-1 and IGF-binding protein-3 (IGFBP-3) levels depend on GH secretion. Given the stability of its serum levels during the day, the measurement of serum IGF-1 should be a useful tool in evaluating GH secretion, bypassing provocation tests and their poor reproducibility. IGF-1 levels are influenced by age and pubertal development and, although age and puberty-corrected IGF-1 reference values have been generated, an overlap between IGF-1 values for normal and GHD children still exists, particularly in children younger than 5 years of age. Serum IGF-1 levels can vary between laboratories due to the different assay methods used. Most investigators have used cutoffs of either the 5th percentile or less than −2 SD to define subnormal levels of IGF-1 [22].

Guidelines consider a value of IGF-1 below 0 SD as an indication to undergo provocative tests. In fact, individuals with idiopathic GHD and a serum IGF-1 level of greater than 0 SD for age are highly likely to have normal provocative tests [20].

IGF-1 levels are also influenced by nutritional conditions: reduced IGF-1 levels may occur in children with malnutrition. Low IGF-1 serum values are described in case of hypothyroidism, hepatic disease and diabetes.

IGFBP-3 values are also used in the diagnostic approach to GHD, but no correlation has been found between GH levels and serum levels of IGFBP-3 in assessing GHD.

Although low serum levels of IGF-1 and IGFBP-3 would suggest a diagnosis of GH deficiency (given the mechanism of action of GH), normal levels do not rule out the possibility of GHD. Therefore, we should perform a provocative test as recommended by the guidelines of the Pediatric Endocrine Society [20].

Low levels of insulin-like growth factor 1 and insulin-like growth factor binding protein (IGFBP) are reported in patients with CD [23].

Stimulus	Dosage
Insulin (ITT) IV	0.05–0.1 U/kg (max 4 U)
Glucagon IM	0.03 mg/kg (max 1 mg)
Arginine hydrochloride IV	0.5 g/kg (max 40 g)
GHRH IV	1 mcg/kg

ITT: insulin tolerance test; IV: intravenously; IM: intramuscular; GHRH: growth hormone-releasing hormone.

Table 1. Growth hormone provocative tests.

Treatment with rhGH should be started as soon as possible after the diagnosis, with a view to obtaining normalization of height during childhood and a better adult height.

Before starting GH treatment, it is necessary to check glucose tolerance (by performing an oral glucose tolerance test, named OGTT) because growth hormone may contribute to insulin resistance.

Especially in cases of total deficiency (GH peak <4 ng/ml), possible deficiencies of other pituitary hormones including TSH, ACTH, FSH, LH should be investigated.

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

A deficiency in pituitary gonadotropins, LH and FSH, can be assessed only during puberty when an increase in pubertal gonadotropin occurs.

Brain magnetic resonance may be required to rule out morphological hypothalamus-pituitary region abnormalities.

CD patients with GHD should be treated with the same GH dosage utilized in patients with idiopathic GHD. Substitutive therapy should be started at the weekly dosage of 0.25 mg/kg divided in six daily subcutaneous injections administered in the evening before sleeping to mimic the physiological night-time elevation of spontaneous GH [24].

International protocols suggest increasing the dosage and/or administering therapy every day during puberty, without a weekly rest, to maximize growth during this period [20].

Subcutaneous administration is the best delivery procedure due to ease of execution and good patient compliance. It is necessary to vary the injection site to avoid lipodystrophy, which may prevent GH absorption. If properly motivated and instructed, the child may administer the GH therapy himself.

GH treatment should be monitored every 6 months by evaluating the biomarkers of thyroid function such as FT4 and TSH, adrenal function such as cortisol basal values, and the glucose-metabolic profile including blood glucose, glycated hemoglobin and insulin basal levels.

Recently, monitoring IGF-I every 6 months has been suggested since it may evaluate adherence to treatment and help clinicians modify GH dosage in order to optimize growth response.

If serum IGF-1 levels exceed the normal value for age or pubertal stage, reducing the GH dose is recommended [20].

If catch-up growth does not occur, it is necessary to suspend treatment and reconsider diagnosis. Anti-GH antibodies should be evaluated, although their occurrence is very rare in clinical practice.

Both height and growth velocity significantly improves during GH therapy, confirming that catch-up growth following GFD is due to low GH secretion. The growth velocity increases especially during the first year of GH therapy, and subsequently remains constant, although always above pre-treatment values [17].

The long-term effects of GH therapy in CD children who follow a strict GFD are comparable to those found in children with idiopathic GHD. During follow-up, pediatricians should check antibody serology, thyroid and adrenal function and the glucose-metabolic profile in order to verify the compliance with both diet and GH treatment.

The height CD subjects attain in adulthood does not differ from that of idiopathic GHD patients. Adherence to a strict gluten-free diet plays an important role in the management of celiac disease leading to a good response to GH treatment [24].

Patients with GH deficiency in childhood are usually re-tested in late adolescence or young adulthood because GHD may persist into adult life. A provocative test is repeated after at least 1 month of GH-therapy washout. It is possible to use a GHRH plus arginine test (a value >19 ng/ml is considered normal) or insulin tolerance test (ITT), considering a value of up to 6 ng/ml as normal secretion. No other tests have been validated for re-evaluation of the somatotropic axis [25].

When a diagnosis of adult GHD is established, continuation of GH therapy is recommended. The growth hormone is involved in numerous ongoing metabolic processes in adult life.

In the presence of a normal GH response to at least one pharmacological stimulus, the auxological follow-up should continue until adult age. Careful clinical surveillance is mandatory: if patient presents growth failure is necessary to repeat auxological evaluation.

Furthermore, CD must be ruled out also in subjects with delayed appearance of pubertal signs, i.e., in girls over 13 years old with an absence of mammary glands and in boys over 14 years old with a testicular volume of less than 4 ml.

Delayed puberty may be one of the extraintestinal manifestations of celiac disease. Delayed menarche has been documented in girls with CD but not in those on a gluten-free diet.

In males, androgen resistance has been implicated in the development of celiac disease. The exact correlation between CD and delayed puberty is not known. Autoimmunity directed against hormonal axis has been proposed as a causative mechanism. Furthermore, it has been suggested that malabsorption of micronutrients may influence hormone synthesis [26, 27].

Other reasons for nonresponse may be due to less-than-strict adherence to GFD or other underlying comorbidities including diabetes mellitus type I and Hashimoto thyroiditis. Thus, re-evaluation of the compliance to GFD or research for additional underlying comorbidities in CD patients failing to respond to GFD is mandatory.

3. Conclusions

In children presenting with short stature, the first step should be to rule out subclinical hypothyroidism and celiac disease before referring them for other endocrine tests.

On the other hand, careful assessment of growth rate and pubertal development is mandatory in children diagnosed as celiac on the basis of serological testing for specific markers and histological analysis of duodenal biopsies. Normal growth velocity does not require further

endocrine tests. However, in cases of growth velocity deceleration under the 10th–25th percentile, thyroid function must be evaluated to exclude Hashimoto thyroiditis. Subsequently, an evaluation of GH secretion in CD patients should be requested mainly if no catch-up growth is observed within 1 year on a strict GFD and in those whose tests are negative for anti-transglutaminase and anti-endomysium antibodies.

Moreover, in CD subjects with GHD, substitutive GH therapy should be promptly started and administered at standard doses daily in order to achieve complete catch-up growth.

The long-time effects of GH therapy in children who follow a strict diet are similar to those observed in children with idiopathic GHD. Finally, during follow-up, the clinician must carefully verify adherence to GFD and check seronegativity, auxological parameters, thyroid and adrenal function, and glucose-metabolic profile. Before deciding whether to interrupt or continue GH therapy in a patient who has reached definitive stature, hormonal secretion retesting is needed in order to identify patients at risk of developing adult deficiency.

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Conflict of interest

The authors declare no conflict of interest.

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