

Short children with impaired growth hormone secretion

Do they have celiac disease?

Omar I. Saadah, MRCP, CABP

ABSTRACT

الأهداف: تحديد مدى انتشار الداء الزلاقي لدى الأطفال الذين يعانون من قصر القامة الناتج عن نقص هرمون النمو.

المنهجية: تم من خلال هذه الدراسة الاستيعابية مراجعة السجلات الطبية للمرضى الذين يعانون من قصر القامة ونقص هرمون النمو ممن تم تشخيصهم في مستشفى جامعة الملك عبد العزيز بجدة خلال الفترة 2002-2016م، وتم تسجيل نتائج إجراء تحليل مضادات الترانسقلوتامينيز للكشف عن احتمالية الداء الزلاقي ومن ثم تأكيد التشخيص عن طريق أخذ خزعة من الغشاء المبطن للاثني عشر. تم تسجيل البيانات السريرية والمخبرية وقياسات النمو لجميع المرضى.

النتائج: من بين 351 مريضاً تم تحديدهم ممن لديهم نقص في هرمون النمو، منهم 199 من الذكور (56.7%). متوسط أعمارهم 9.0 ± 3.7 سنوات (المدى، 2-17.6 سنة)، ومتوسط الانحراف المعياري للطول -2.9 ± 1.3 . منهم 42.2% نقص هرمون النمو الجزئي و57.8% لديهم نقص كلي. وكان متوسط الذروة لهرمون النمو 5.8 ± 3.9 نانوغرام/مل. كما بلغ معدل الامصال الإيجابية للداء الزلاقي 13.4% منهم 4% تم تأكيد التشخيص عن طريق فحص الخزعة. تم تحديد مستوى مضادات الترانسقلوتامينيز كمحدد وحيد لاحتمالية الداء الزلاقي.

الخلاصة: بلغت نسبة مضادات الترانسقلوتامينيز الإيجابية 23% ونسبة الحالات الموكدة بفحص الخزعة 4% من الأطفال ممن يعانون من قصر القامة ونقص هرمون. وعليه فإن تشخيص نقص هرمون النمو لا يمنع البحث عن الداء الزلاقي المصاحب، لأن العلاج عن طريق الحمية الخالية من الجلوتين قد يحسن النمو.

Objectives: To determine the prevalence of celiac disease (CeD) in children with short stature (SS) and growth hormone deficiency (GHD).

Methods: This is a retrospective study of patients with isolated SS and GHD, diagnosed during the period 2002 to 2016. Their medical records were reviewed and serum tissue transglutaminase (tTG) antibody results retrieved. Patients with positive serology results underwent upper gastrointestinal endoscopy and small bowel biopsy to confirm the diagnosis of

CeD. Clinical, anthropometric, and laboratory data were recorded for all patients.

Results: Of the 351 patients identified with GHD, 199 (56.7%) were male. The mean age \pm SD was 9.0 ± 3.7 years (range: 2-17.6 years), and the mean \pm SD height-for-age z score was -2.9 ± 1.3 . Partial GHD constituted 42.2% and severe GHD constituted 57.8% of GHD diagnoses. The mean growth hormone (GH) peak level was 5.8 ± 3.9 ng/ml. Forty-seven patients (13.4%) had positive serology, and 14 (4%) had biopsy-proven CeD. No predictors could be identified through binary logistic regression analysis.

Conclusion: A prevalence of CeD seropositivity was found in 13.4% and overt CeD in 4% of children with GHD. The finding of GHD should not preclude the search for CeD, because the majority will potentially improve on a gluten-free diet (GFD).

Keywords: celiac disease, short stature, growth, children, Saudi Arabia

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From the Pediatric Gastroenterology Unit, Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Omar I. Saadah, Pediatric Gastroenterology Unit, Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia. E-mail: osaadah@kau.edu.sa
ORCID: <https://orcid.org/0000-0002-3744-9907>

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Celiac disease (CeD) is an autoimmune-mediated enteropathy, triggered by dietary gluten and related polyamines in individuals with genetic susceptibility who carry the HLA-DQ2 or HLA-DQ8 haplotype; it manifests in various clinical presentations and with a number of CD-specific antibodies.¹ Celiac disease may present itself through classical symptoms of malabsorption, including chronic diarrhea, abdominal distention, and poor weight gain, and commonly with extraintestinal manifestations, including short stature (SS), delayed puberty, osteopenia/osteoporosis, dental enamel defects, iron deficiency anemia, infertility, and arthropathy.² Short stature can be the only sign of CeD in children, without associated gastrointestinal (GI) symptoms.² The prevalence of CeD in SS has been reported in 2-8% of participants in several studies.^{3,4} This significant risk justifies the routine screening of all children with SS for CeD. The growth impairment associated with CeD is usually a result of either malnutrition, impairment of the growth hormone (GH) axis, or insensitivity to GH.^{3,5} Moderate SS occurs in 11.3% and severe SS occurs in 1.8% of Saudi boys, and moderate SS occurs in 10.5% and severe SS occurs in 1.2% of girls.⁶ Isolated GHD was partly responsible for 21.8% of cases of SS in Saudi children.⁷ The reported prevalence of CeD in Saudi children with isolated SS after excluding endocrinology causes, chronic illnesses, and genetic and chromosomal abnormalities was 9.5-10.9%.^{8,9}

The primary aim of this study is to determine the prevalence of CeD in children with SS due to GHD; the secondary aim is to look for possible predictors of CeD.

Methods. A review of medical records was undertaken with respect to children with isolated SS diagnosed in the period 2002 to 2016. These patients were identified using the hospital medical records in the Health Information Coding System (ICD 09) and through a review of the pediatric clinic patient registry.

The inclusion criteria were the following: Saudi nationality; aged less than 18 years; height-for-age z score (HAZ): ≤ 2 , following the WHO criteria; absence of GI symptoms; abnormal GH provocation test; and CeD serology performed. The exclusion criteria were the following: patients with known chronic illnesses, thyroid problems, and genetic or chromosomal abnormalities.

As noted, SS was defined according to the WHO criteria: only patients with HAZ less than 2 SD below the mean were included in the study. The z score was estimated using an anthropometric software program

(EpiInfo, Centers for Disease Control and Prevention, Atlanta, GA, USA).

Basic information retrieved from medical records comprised demographic data, weight, body mass index (BMI), and blood levels of the following: albumin, hemoglobin, calcium, phosphate, alkaline phosphatase, and vitamin D.

Celiac disease serological screening was performed in the hospital immunology laboratory using an anti-tissue transglutaminase antibody determined by enzyme-linked immunosorbent assay (ELISA), utilizing the Quanta Lit tTG ELISA kit (INOVA Diagnostic Inc., San Diego, CA, USA). A negative result was reported if the tTG level was <20 U/ml, as instructed by the manufacturer. Total serum IgA was also measured for all patients screened using the nephelometry system (Siemens AG, Munich, Germany) to identify patients with IgA deficiency.

The diagnosis of CeD was based on European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria: having positive antibody testing to tTG, followed by small intestinal biopsy obtained through upper gastrointestinal endoscopy to confirm the diagnosis.¹ Biopsy specimens were classified according to the Marsh-Oberhuber classification.¹⁰

The diagnosis of GHD was based on a low GH response (<10 ng/mL) after at least 2 different pharmacological tests in children with SS. Clonidine (150 micrograms/m² BSA orally) and glucagon (15 micrograms/kg, intramuscular) stimulation tests were performed on all patients on 2 different occasions, followed by a collection of blood samples at 0, 30, 60, 90, 120, 150, 180, and 210 minutes after stimulation. The severity of GHD was further categorized into severe GHD, in which the peak GH level was ≤ 5 ng/mL, and partial GHD, in which the peak GH level was >5 and <10 ng/mL.

Serum insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) levels were recorded. Serum insulin-like growth factor 1 was measured in plasma by radioimmunoassay (RIA) after acid-alcohol extraction. IGF-binding protein 3 was measured by RIA in diluted serum.

Bone age was established by performing a plain radiograph of the left hand and wrist using the Greulich and Pyle method.¹¹ The delay in bone age was calculated by subtracting the chronological age from the bone age in months.

Data analysis. Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows, version 22 (IBM Corp., Armonk, NY, USA). Data were expressed as a percentage of the total for categorical

variables and as the mean and standard deviation (SD) for continuous variables. For comparisons, we used a Chi-square test and Fisher's exact test for categorical variables and a 2-sample t-test and the Mann-Whitney U test for continuous variables. Binary logistic regression analysis was performed to identify possible predictors of CeD. A $p < 0.05$ was considered significant.

Ethical considerations were followed in accordance with the Declaration of Helsinki throughout this study, and it was approved by the Research Committee/Biomedical Ethics Unit, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia (Reference No. 497-19).

Results. Of the 700 children identified with SS, 351 (50.1%) fulfilled the inclusion and exclusion criteria within the study period. Partial GHD constituted 42.2% and severe 57.8%. The mean age \pm SD was 9.0 \pm 3.7 years, with a range of 2-17.6 years. There were 199 (56.7%) male patients and 152 (43.3%) female patients, with a male/female ratio of 1.3:1. All patients had serological screening for CeD and assessment for growth hormone deficiency, including the growth hormone provocation test. The baseline clinical and laboratory characteristics are shown in **Table 1**.

Celiac screening and evaluation primary outcome. Celiac screening was found to be positive in 47 out of 351 patients with isolated SS, with a mean difference in the tTG antibody titer of 45 IU/mL (95% CI: 28.2-62.3), giving a prevalence of CeD seropositivity of 13.4% in this cohort.

Table 2 compares the demographic, clinical, and laboratory characteristics of patients with CeD-positive and CeD-negative screening. There were no significant differences between the groups. There was a trend towards lower IGF-1 levels in CeD serology-positive patients than in CeD-negative serology patients, but this was not statistically significant ($p=0.10$).

Of the 47 patients identified as positive by screening, only 20 (42.5%) agreed to have an upper endoscopy and a small bowel biopsy. Of the 20 patients who had an upper endoscopy and a small bowel biopsy performed, 14 (70%) were found to have small bowel mucosal villous atrophy compatible with the diagnosis of CeD, giving the prevalence of overt CeD as 4% (95% CI: 1.57-5.54%) of the total cohort. The clinical and laboratory characteristics of patients diagnosed with biopsy-proven CeD are shown in **Table 3**.

Secondary outcome. Bivariate analysis of different variables in patients with overt CeD and patients with normal biopsy showed a significant difference in the mean albumin level ($p=0.02$) (**Table 3**). However, in simple logistic regression analysis, there was no

Table 1 - Clinical and laboratory characteristics of the study cohort.

Characteristics	n	Mean \pm SD
Age (years)	351	9.0 \pm 3.7
tTG titer (U/mL)	351	15 \pm 26
WAZ	351	-1.8 \pm 2.7
HAZ	351	-2.9 \pm 1.3
BMI	351	16.9 \pm 4.1
Bone age delay (months)	75	19.5 \pm 17.6
Hemoglobin (g/dL)	349	12.3 \pm 1.4
Albumin (g/L)	130	38.7 \pm 5.4
Calcium (mmol/L)	131	2.3 \pm 0.12
Phosphate (mmol/L)	127	1.5 \pm 0.25
ALP (U/L)	129	232 \pm 116
GH peak (ng/ml)	351	5.8 \pm 3.9
IGF-1 (ng/ml)	338	140 \pm 149
IGFBP-3 (ng/ml)	295	3133 \pm 1118

tTG: tissue transglutaminase, WAZ: weight-for-age z score, HAZ: height-for-age z score, BMI: body mass index, ALP: alkaline phosphatase, GH: growth hormone, IGF-1: insulin-like growth factor-1, IGFBP-3: IGF-binding protein-3

statistically significant association between celiac disease and age ($p=0.12$), gender ($p=0.06$), weight-for-age ($p=0.46$), height-for-age ($p=0.09$), BMI ($p=0.97$), hemoglobin ($p=0.37$), growth hormone peak ($p=0.78$), IGF-1 ($p=0.96$), IGFBP-3 ($p=0.94$), and albumin in patients with impaired growth hormone secretion.

Discussion. Celiac disease is an autoimmune enteropathy triggered by gluten exposure in genetically susceptible individuals carrying either the HLA DQ2 (95%) or HLA DQ8 haplotype (5%), along with a variety of environmental triggering factors.¹ Celiac disease presents itself in a wide spectrum of intestinal and extraintestinal manifestations. The extraintestinal manifestations involve different body systems, including the central nervous system, endocrine system, and skeletal system.¹² Short stature is considered the second most frequent extraintestinal symptom after iron-deficiency anemia.¹³ The prevalence of clinically overt CeD in children of the general population in Europe and USA is approximately 1% and approximately 2.9-8.3% in children with SS.¹⁴⁻¹⁷

In CeD, an alteration in the circulating IGF system causing lower levels of IGF-1 and IGFBP-3 and higher levels of IGFBP-1 and IGFBP-3 has been reported.⁵ This alteration may be further influenced by the presence of high levels of circulating pro-inflammatory cytokines in patients with CeD.¹⁸ In this study, we found a trend towards lower IGF-1 levels in CeD serology-positive than CeD serology-negative patients

Table 2 - Comparison between patients with a positive and negative CeD screening.

Variable	Celiac screen positive		Celiac screen negative		P-value*
	n	mean ± SD	n	mean±SD	
Age	47	8.8 ± 3.2	304	9.1 ± 3.8	0.56
Weight-for-age z score	47	-1.9 ± 2.3	304	-1.8 ± 2.7	0.74
Height-for-age z score	47	-2.8 ± 1.3	304	-2.9 ± 1.4	0.51
Body mass index	47	16.6 ± 4.5	304	16.9 ± 4.1	0.59
Hemoglobin (g/dL)	46	12.1 ± 1.7	303	12.3 ± 1.3	0.76
Albumin (g/L)	17	38.8 ± 2.7	113	38.7 ± 5.7	0.98
Calcium (mmol/L)	19	2.3 ± 0.13	112	2.3 ± 0.12	0.09
Phosphate (mmol/L)	19	1.5 ± 0.19	108	1.5 ± 0.26	0.92
Alkaline phosphatase (U/L)	16	229.7 ± 48.4	113	232.4 ± 123.2	0.32
Growth hormone peak (ng/ml)	47	5.8 ± 2.9	304	5.7 ± 4.0	0.61
IGF-1 (ng/ml)	46	106.6 ± 70.3	292	145 ± 157.6	0.09
IGFBP-3 (ng/ml)	46	3081 ± 1100	249	3142 ± 1123	0.65

*Mann-Whitney U-test, IGF-1: insulin-like growth factor-1, IGFBP-3: IGF-binding protein-3

Table 3 - Bivariate analysis of biopsy-proven CeD patients (n=14) vs. normal-biopsy patients (n=6).

Variable	CeD patients (n=14)	Normal-biopsy patients (n=6)	P-value
	Mean±SD		
Age (years)	7.7 ± 2.7	9.8 ± 5.2	0.53*
Female:male ratio	1.2:1	0.2:1	0.3 [†]
Consanguinity, n (%)	4 (28.6)	2 (33.3)	1.0 [†]
Affected family members, n (%)	2 (14.3)	0 (0)	1.0 [†]
<i>Marsh Score, n (%)</i>			
3b	8 (57.1)		
3c	6 (42.9)		
Weight-for-age z score	-1.6 ± 1.6	-1.8 ± 1.1	1.0*
Height-for-age z score	-2.5 ± 0.56	-2.5 ± 0.48	0.98*
Body mass index	16.5 ± 3.2	15.1 ± 1.8	0.40*
Growth hormone peak peak (ng/ml)	6.6 ± 3.4	6.6 ± 3.3	1.0*
IGF-1 (ng/ml)	83.3 ± 47.7	93.4 ± 56.8	0.88*
IGFBP-3 (ng/ml)	3025 ± 1305	2574 ± 735.6	0.32*
Hemoglobin (g/dL)	12.1 ± 0.98	12.4 ± 0.77	1.0*
Albumin (g/L)	37.6 ± 2.7	41.6 ± 0.58	0.02*

IGF-1: insulin-like growth factor-1, IGFBP-3: IGF-binding protein-3. *Mann-Whitney U test, [†]Fisher's exact test. P-value<0.05 is significant.

($p=0.1$), but we did not see any significant difference in the mean IGFBP-3 levels (Table 2). Furthermore, no differences were demonstrated in the IGF-1 or IGFBP-3 levels when patients with overt CeD were compared to patients with normal biopsy.

In the study cohort, 14 (4%) patients had overt CeD. The GHD could be a result of CeD or an association of the 2 conditions. Studies of CeD patients have reported reduced GH secretion after pharmacological stimulation compared with control subjects.¹⁹ The mechanism of impairment of hypothalamic control of GH secretion is

not very clear. Malnutrition resulting from CeD could have a direct effect on the circulating gluten peptides in the brain, affecting the pituitary and hypothalamic control. The presence of circulating antibodies against the pituitary gland and the hypothalamus may suggest an autoimmune mechanism involving the pituitary gland and causing autoimmune hypophysitis that contributes to growth impairment.²⁰ The institution of a strict gluten-free diet (GFD) for 6-12 months usually reverses changes in the somatotrophic axis, allowing normal GH secretion and response, and thereafter

normal catch-up growth for the child. A lack of response after 12 months of a strict GFD raises the possibility of a combined diagnosis of genuine GHD and CeD. The coexistence of the 2 conditions is rare and has been reported in 0.23% of children with SS.²¹ Those patients often require treatment with recombinant GH to improve their linear growth.

The tTG antibody test has been reported to have higher sensitivity and specificity in screening for CeD in the absence of total IgA deficiency, and at higher cutoff values; it correlates with the severity of mucosal damage in patients with suspected CeD.²²

Study limitations. The strengths of our study are: 1) we included a large number of patients with GHD over the study period, and 2) it concerns an aspect of CeD screening in growth hormone impaired children that has not been widely explored. The study, however, is limited by its retrospective nature and design. A prospective study is required to describe the longitudinal growth pattern of children with CeD and GHD after the institution of GFD.

In conclusion, we have shown a prevalence of CeD seropositivity in 13.4% and of overt CeD in 4% of children with isolated SS. However, no predictors were identified for CeD diagnosis. The finding of GHD should not preclude the search for CeD, since the majority of these patients will potentially improve with the institution of a GFD.

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