# Percentage of Patient with Celiac Disease among Children with Short Stature

## نسبة المرضى المصابين بحساسية الحنطة لدى الأطفال قصار القامة

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**الخلاصة:**

**خلفية الدراسة** :الأعراض السريرية لمرض حساسية الحنطة تتباين كثيرا .الأعراض الهضمية تكون اكثر شيوعا خلال السنتين الأولى من العمر وكلما تقدم العمر تظهر أعراض جديدة ومنها قصر القامة .يتم في هذه الدراسة تحديد نسبة المرضى المصابين بحساسية الحنطة لدى الأطفال قصار القامة.

**الهدف** : (اولاً) لمعرفة نسبة المرضى المصابين بحساسية الحنطة لدى الاطفال قصار القامه.(ثانياً) تأثير مرض حساسية الحنطة على علاج الاطفال قصار القامه.

**المنهجية** : تم إجراء دراسة من نوع المقطعية المستعرضة، 167 شخصا من الأطفال والمراهقين الذين تتراوح أعمارهم بين 2-18 سنه المراجعين لعيادة الغدد الصماء واضطرابات النمو في مستشفى الزهراء التعليمي للفترة من بداية كانون الأول 2013 إلى نهاية تشرين الثاني 2013 للتحري عن قصر القامة، ادخل في الدراسة 91 شخص وفقا لمعايير الاشتمال. تم استخدام طرق الإنزيمات المناعية لتحديد تركيزمضادات (TTG) في الدم للتحري عن حساسية الحنطة. وقد اعتبرت العينات بتراكيز اكثر من ( 20مل/وحدة) بأنها إيجابية. تم إحالة حالات المرضى الموجبة إلى مركز الجهاز الهضمي لإجراء التنظير واخذ الخزعة المعوية.

**النتائج**: تراوحت أعمار المرضى بين 2-18 سنه؛ منهم 59 ( 65 ٪ ) من الإناث و 32 ( 35 ٪ ) من الذكور. وكان متوسط العمر (9) سنوات. كانت فحوصات مضادات( TTG) إيجابية في 15 (16.5) ٪ من المرضى. تم إجراء خزعة الأمعاء للحالات الموجبة للتحري عن حساسية الحنطة. كانت نتيجة الخزعة موجبة عند 11 شخصا ( 73 ٪ ) حسب تصنيف مارش المعدل لتشخيص حساسية الحنطة .تم وضع جميع الأطفال المشخصين على نظام غذائي خال من الغلوتين و متابعة المرضى لمدة ستة أشهر، و أظهرت تحسنا في معدل الطول. وقد تم تحليل البيانات عن طريق برنامج SPSS من IBM الإصدار 20 باستخدام مربع كاي و إقران T- الاختبار.

**الاستنتاج**: حساسية الحنطة هو سبب مهم لقصر القامة، ويجب أن يوضع في الاعتبار أثناء الاختبارات التشخيصية للأطفال قصار القامة.

**التوصيات**: 1. تضمين تحديد تركيز مضادات (TTG) في الدم كاختبار روتيني للتحري عن حساسية الحنطة لدى الاطفال قصار القامه. **2**. كل المرضى الذين يعانون من قصر القام مجهول السبب ولديهم نتيجة ايجابيه لتركيز مضادات (TTG) مع مستوى طبيعي من IgA يجب أن يخضع لخزعة الأمعاء لإثبات تشخيص مرض حساسية الحنطة.

**Abstract:**

**Back ground:** Clinical features of celiac disease vary considerably. Intestinal symptoms are common in children whose disease is diagnosed within the 1st 2 years of life. As the age at presentation of the disease shifts to later in childhood, and with the more liberal use of serologic screening tests, extra-intestinal manifestations and associated disorders, without any accompanying digestive symptoms, have increasingly become recognized, including short stature. We aim in this study to determine the percentage of celiac disease among patients with short stature.

**Objectives of the Study**: (1) to show the percentage of patient with celiac disease in short stature children. (2) to show the effect celiac disease on treatment of short stature children.

**Method:** A cross sectional study that carried out at the Endocrine Pediatrics Clinic at A Zahraa Teaching Hospital for a period from 1st of January 2013 to end of October 2013; a total of 167 children and adolescents, aged range from 2 to 18 years were registered with short stature . 91 children of them only have been enrolled in this study according to inclusion criteria. Enzyme immunoassay (Biosystems, Spain) was used to determine IgA tTG using microplate tests. Samples with concentrations >20U/mL were defined as positive. Patients with positive anti-tTG serology were referred to the gastroenterology clinic to continue investigation of celiac disease by endoscopy and biopsy. Data were analyzed by SPSS software from IBM version 20 using chi square and paired T-test.

**Result:** A total of 167 patients were evaluated 91 of them only have been enrolled in our study according to inclusion criteria; 59 (65%) were female and 32 (35%) were male. Median age was 9 years (from 2 - 18 years).The anti-tTG assays were positive in 16.5% of patients (15/91). Out of 15 patient whose diagnosed as anti-tTG positive, 11 (73%) have been diagnosed as celiac disease by endoscopy and biopsy according to

modified marsh classification. All children diagnosed to have celiac disease were kept on a gluten-free diet. Patients were followed-up for six months and showed improvement in growth rate.

**Conclusion:** Celiac disease a cause of short stature that should be included in diagnostic investigations of short stature.

**Recommendation** anti-tTG antibody as routine test recommended for all patients with short statures. All patients with idiopathic short statures and anti-tTG test positive with normal IgA level should be subjected to intestinal biopsy to prove the diagnosis of celiac disease.

**Keywords: Celiac Disease, Short Stature, anti-tTG antibody.**

# INTRODUCTION:

Celiac disease is an immune-mediated disorder elicited by the ingestion of gluten in genetically susceptible persons and characterized by chronic inflammation of the small intestine. It is considered an autoimmune condition because of the presence of anti–TG2 antibodies and the association with other autoimmune diseases (thyroid, liver, diabetes, adrenal) [(1)].

Celiac disease is triggered by the ingestion of wheat gluten and related prolamines from rye and barley. In most studies oats proved to be safe; however, a few celiac patients have oats prolamine–reactive mucosal T cells that can cause mucosal inflammation [(2)].

Celiac disease is a common disorder (1% prevalence of biopsy-proven disease). It is thought to be rare in Central Africa and East Asia. Environmental factors might affect the risk of developing celiac disease or the timing of its presentation. Prolonged breastfeeding has been associated with a reduced incidence of symptomatic disease. Less clear is the effect of the time of gluten introduction in the infant diet; the ingestion of increased amounts of gluten in the 1st year of life can increase the incidence [(3)].

Infectious agents have been hypothesized to play a role because frequent rotavirus infections are associated with an increased risk. It is plausible that the contact with gliadin at a time when there is ongoing intestinal inflammation, altered intestinal permeability, and enhanced antigen presentation can increase the risk of developing the disease, at least in a subset of persons [(4).]

Short stature (SS) refers to a height of a human being which is below expected. Shortness is a vague term without a precise definition and with significant relativity to context. Because of the lack of preciseness, there is often disagreement about the degree of shortness that should be called *short*[(5)].

The American Association of Clinical Endocrinologists defines "short stature" as height more than 2 standard deviations below the mean for age and gender, which corresponds To the shorter 2.3% of individual[(1).]The Centers for Disease Control and Prevention growth charts use the 3rd percentile of the growth curve as the of the lower limit[(6).]

# OBJECTIVES OF THE STUDY:

(1) To show the percentage of patient with celiac disease among short stature children.

(2) To show the effect celiac disease on treatment of short stature children.

# PATIENTS AND METHODS:

A total of 167 children and adolescents aged range from 2 to 18 years were registered at the Endocrine Pediatrics Clinic at A Zahraa Teaching Hospital in An Najaf city defined as short stature when their heights were below the third percentile for their age and sex

according to the height/age curves published by the National Center for Health Statistics (NCHS), 2000. Children and adolescent were included in this study according to criteria**:**

1. All short children, height less than third centile for age and gender.
2. Normal endocrine work-up (e.g. normal GH response, normal TF.
3. No evidence of chronic disorders.
4. Normal karyotype for female.
5. Negative history of genetic short stature.

All guardians were informed and agreed to participate in the study, and signed a free and informed consent form. For each patient the following points are done, weight and height, were measured with children unclothed, with no shoes or socks, using a digital balance accurate to 0.1kg and a wall-mounted stadiometer accurate to 0.1cm. After measurement, a structured questionnaire was administered covering socioeconomic and demographic aspects as well as complaints related to celiac disease (abnormal intestinal rhythm, abdominal pains, flatulence, recurrent aphthous ulcers, difficulty gaining weight and height, irritability, history of anemia, other cases of celiac disease in the family).

Bone age was determined using the Greulich and Pyle atlas. Pubertal stages were evaluated according to Tanner. Mid-parental height was calculated for each child's parents to exclude genetic causes of short stature, using the standard formula.

All children had undergone an extensive endocrine work-up that included growth hormone (GH), free-thyroxin (FT4), thyroid stimulating hormone (TSH), glucose, electrolytes, venous blood gas, and urine pH assessments. The routine GH stimulation test using two biochemical (either clonidine and glucagon or insulin-induced hypoglycemia as a secretagogue) and two physiological (post-exercise and during sleep) assessments was performed. Patients were considered not to be GH deficient when the peak GH value during the stimulation test or the physiological test was >10 ng/dL. Blood for serology was collected by venous puncture into tubes with no anticoagulant, which were then centrifuged to separate serum. Initial screening was carried out using anti-tTG assays .Enzyme immunoassay (Biosystems, Spain) was used to determine IgA tTG using microplate tests. Samples with concentrations >20U/mL were defined as positive[7].Patients with positive anti-tTG serology were referred to the gastroenterology clinic to continue investigation of celiac disease by endoscopy and biopsy. Data were analyzed by SPSS software from IBM version 20 using chi square and paired T-test.

## RESULTS :

**Table (1) the number of tTG positive and biopsy positive among total number of patients.**

| Serology negative patients | Serology positive patients | |
|---|---|---|
| | Biopsy positive | Biopsy negative |
| 76 | 11 | 4 |

A total of 167 patients were evaluated between January and October of 2013; 91 of them only have been enrolled in our study according to inclusion criteria; 59 (65%) were female and 32 (35%) were male. Median age was 9 years (from 2 - 18 years).The anti-tTG assays were positive in 16.5% of patients (15/91). Out of 15 patient whose diagnosed as anti-tTG positive, 11 (73%) have been diagnosed as celiac disease by endoscopy and biopsy.

**Table (2) the mean of height, age and gender distribution of patients included in study.**

| GROUPS | Ht. Mean (SD) | Age Mean (SD) | Gender female | Male |
|---|---|---|---|---|
| Patients with CD (positive biopsy) | 95.8 cm (12) | 1.7 yrs.(0.4) | 8 | 3 |
| Patients without CD (serology negative) | 120.2 cm (21.5) | 9.6 yrs. (3.5) | 51 | 29 |
| **p-value** | **0.6** | **0.048** | **0.56** | |

Table 2 shows the mean and standard deviation of the height and age of patients enrolled in the study in regard to two groups: those with celiac disease and without; also compare between gender distributions of both groups. There are no significance with height and gender (P-value= 0.6 and 0.53 respectively) but age distribution shows P-value < 0.05.

**Table (3) Demographic data of age, gender and height of enrolled patients at the initial presentation and follow-up of height, 6 month on a gluten-free diet.**

| Age(years) | Gender | Ht. 1(cm)* | Ht. 2(cm) ** |
|---|---|---|---|
| 4 | M | 98.5 | 106 |
| 5 | M | 95 | 101 |
| 3 | M | 77.5 | 84 |
| 6 | F | 98 | 103 |
| 7 | F | 102 | 107 |
| 6 | F | 103.5 | 110 |
| 5 | F | 102 | 107.5 |
| 5 | F | 100 | 105.5 |
| 2 | F | 75 | 79 |
| 6 | F | 106 | 112 |
| 3 | F | 85 | 89.5 |
| **Mean(SD)** | | **94.7(10.7)** | **95.7(10.3)** |
| **P-Value** | | **0.000*** | |

*** height at presentation.**

****height after 6 months of gluten free diet.**

Table 3 shows that eleven out of 91 short stature child who enrolled in the study have been diagnosed with celiac disease by endoscopy and biopsy. They were followed up for a period of 6 months with gluten free diet; so this table shows that there is significant

improvement in their height mean in comparison the time of registration in the study (P-value=0.000) . They continue on GH treatment for the same period.

## DISCUSSION:

It is important to point out that, to date, diagnosis of celiac disease is still based on observation of histological abnormalities; biopsy is an invasive and expensive method which is not appropriate for initial investigation [8]. Furthermore, the wide spectrum of celiac disease and its nonspecific clinical manifestations make it difficult to identify patients who require biopsy[8]. Over recent years, attempts have been made to find other diagnostic methods with good sensitivity and specificity for the screening and diagnosis of celiac patients .The anti-tTG assay emerged as a great hope for celiac disease screening, since it is an easily-executed test with a relatively low cost and can be used in screening studies [7-9]. The AEA takes longer, costs more and is operator-dependent, which can lead to errors[8,10-12]. Based on the available evidence and on practical considerations, anti-tTG is the primary test recommended for screening[8,11].

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition[9] recommends the anti-tTG as the initial screening test for groups at risk of celiac disease, followed by intestinal biopsy.

In our study; 91 patient who have been enrolled in our study according to inclusion, the anti-tTG assays were positive in 16.5% of cases (15/91). Out of fifteen patient whose diagnosed as anti-tTG positive, 11/15 (73%) – 11/91 (12.1%) have been diagnosed as celiac disease by endoscopy and biopsy. This result is close to that result found by de Lecea et al (1996), Spain[13] 18.6% (22/118) of children with short stature had biopsy proven coeliac disease. However; higher percentage of celiac disease among short stature children had been found by Altuntas et al (1998), Turkey[14] 55.3% (26/47); this may be attributed to smaller population size.

Other studies show much lower percentage of celiac disease as in Rossi et al (1993), USA[15] 1.7% (2/117) which may be explained by different geographical area. Also Knudtzon et al (1991), Norway[16] shows a much less prevalence of celiac disease in short stature children i.e. 2.9% (5/168).

All of these comparable study subject their enrolled population to diagnostic endoscopy and biopsy to roll out celiac disease which is not the case in our study and they did not depend on anti-t TG to select patients for endoscopy because of limited resources in our center and fear of patient from this invasive test.

The mechanism of growth retardation is not clearly understood in patients with CD; nutritional deficiencies especially zinc deficiency, low serum somatomedin activity and defects in growth hormone secretion have been proposed as underlying mechanisms [17]. An association between CD and autoimmune disorders, such as type Ⅰ diabetes, autoimmune thyroid disease, and Sjögren's syndrome, has been well documented in the literature [18]. These conditions were not detected in patients in the present study.

Withdrawal of gluten from diet for a period of six months show marked improvement on patient linear growth this goes with Nemet et al[19].

## CONCLUSION:

Celiac disease is a cause of short stature that should not be forgotten and must be borne in mind during diagnostic investigations. It is important to test all children with short stature for celiac disease by measuring antitissue transglutaminase. Considering that anti-tTG assays identify IgA antibodies, it is important to confirm serum IgA levels in patients with clinical

signs compatible with celiac disease and negative serology. A small intestine biopsy is an indispensable part of the sequence of diagnostic investigation of seropositive patients.

## RECOMMENDATION:

1. Anti-tTG antibody as routine test for all patients with short statures.
2. All patients with idiopathic short statures and anti-tTG test positive with normal IgA level should be subjected to intestinal biopsy to prove the diagnosis of celiac disease.

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