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PREVALENCE OF CELIAC DISEASE AMONG CHILDREN WITH SHORT STATURE IN A TERTIARY CARE HOSPITAL: A CROSS-SECTIONAL STUDY.

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Abstract

Background

Celiac disease (CD), triggered by gluten and tissue transglutaminase, commonly affects the small intestine, with extra-intestinal manifestations like short stature emerging, prompting this study to assess its prevalence among patients with short stature.

Objectives of the Study

(1) To show the prevalence of celiac disease among children with short stature. (2) To show the effect of dietary restrictions in children with celiac disease on height.

Methods

A retrospective cross-sectional study included children assessed for short stature, whose medical records were analyzed. IgA tTG levels were determined using enzyme immunoassay, with concentrations >20U/mL considered positive. Those with positive results underwent standard celiac disease investigations, including endoscopy and biopsy.

Results

Medical documents of 103 patients with short stature were evaluated. 40 of them were included in the study according to inclusion criteria; 26(65%) were female and 14 (35%) were male. Median age was 9 years (from 2 - 18 years). The anti-tTG assays were positive in 20% of patients (8/40). Out of 8 patients who had positive titers of anti-tTG, 6 (75%) were diagnosed with celiac disease by endoscopy and biopsy according to the modified Marsh classification. All children diagnosed with celiac disease were kept on a gluten-free diet. Follow-up anthropometric data for six months as recorded in medical documents were analyzed and showed improvement in growth rates.

Conclusion

Celiac disease is a cause of short stature that should be included in diagnostic investigations of short stature.

Recommendations

Routine screening for celiac disease in children with short stature, even without digestive symptoms, is essential, as evidenced by a 20% prevalence rate in this study. Implementing a gluten-free diet resulted in improved growth rates, emphasizing the importance of dietary management in associated conditions.

Keywords: *Celiac Disease, Short Stature, anti-tTG antibody, Gluten-Free Diet, Pediatric Health*
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Introduction

Celiac disease (CD) is the most common genetically related food intolerance worldwide. It is a multifactorial, autoimmune disorder that occurs in genetically susceptible individuals and is triggered by a well-identified environmental factor (gluten and related prolamines present in wheat, rye, and barley), and the autoantigen is also well-known (i.e., the ubiquitous enzyme tissue transglutaminase) (John et al. 2011). The disease primarily affects the small intestine, where it progressively leads to flattening of the small intestinal mucosa. 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). The genetic susceptibility to celiac disease is conferred by well-identified haplotypes in the human leukocyte antigen (HLA) class II region (i.e., DR3 or DR5/DR7 or HLA DR4) (Branski et al 2006). Gluten is the single major environmental factor that triggers celiac disease, which has a narrow and highly specific association with class II haplotypes of HLA DQ2 (haplotypes DR-17 or DR5/7) and, to a lesser extent, DQ8 (haplotype DR-4) (Rudolph, 2003). Scientific knowledge on the pathogenesis of celiac disease has markedly increased in the past few years; the combined roles of innate and adaptive immunity are now better understood (Dubois and Van Heel, 2008). Altered processing by intraluminal enzymes, changes in intestinal permeability, and activation of innate

immunity mechanisms may be involved and precede the activation of the adaptive immune response. Environmental factors might affect the risk of developing celiac disease or the timing of its presentation (Nicholas,2011). 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. The American Association of Clinical Endocrinologists defines "short stature" as height more than 2 standard deviations below the mean for age and gender. The Centers for Disease Control and Prevention growth charts use the 3rd percentile of the growth curve as the lower limit (Hill et al. 2005).

Objectives of the Study:

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

(2) To show the effect of dietary restrictions in children with celiac disease on height.

Patients and Methods:

Study design

A cross-sectional retrospective study was carried out.

Study setting

The study was carried out at the upgraded department of pediatrics, Sheikh Bhikhari Medical College (SBMC), Hazaribagh, Jharkhand, India, between November 2021 and October 2023.

Participants

A total of 103 children and adolescents aged range from 2 to 18 years were evaluated.

Inclusion criteria

Children and adolescents were included in this study according to the criteria below:

1. Children with height less than third centile for age and gender.

2. Normal endocrine work-up (e.g. normal GH response, normal Thyroid profile).

3. No evidence of chronic disorders.

4. Normal karyotype for females.

5. Negative history of genetic short stature.

Exclusion criteria

The exclusion criteria for the study on celiac disease among children with short stature include:

1. Children above the third percentile for age and gender according to NCHS growth charts.

2. Diagnosed endocrine disorders or other hormonal imbalances affecting growth.

3. Chronic systemic diseases or genetic conditions known to impact stature.

4. Previous diagnosis of celiac disease or children already on a gluten-free diet.

5. History of gastrointestinal surgery, medication influencing growth, or incomplete medical records.

Sample size: To calculate the sample size for this study, the following formula was used for estimating a proportion of a population:

$$n = \frac{Z2 \times p \times (1-p)}{E2}$$

Where:

- n = sample size

- Z = Z-score corresponding to the desired level of confidence

- p = estimated proportion in the population

- E = margin of error

Bias

There was a chance that bias would arise when the study first started, but it was avoided by giving all participants identical information and hiding the group allocation from the nurses who collected the data.

Data collection

The aim and the objective of the study were conveyed to patients as well as their parents.

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For each patient, the following points were evaluated by review of medical documents- weight and height, 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. Medical documents were reviewed for fields 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) assessments was performed. Patients were considered not to be GH deficient when the peak GH value during the stimulation 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 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 gastroenterologist to continue the investigation of celiac disease by endoscopy and biopsy.

Statistical analysis

The data obtained from the study was arranged in a tabulated manner in an Excel sheet, and the data was then subjected to statistical analysis using SPSS version 21.0.

Ethical considerations

The study protocol was approved by the SBMC Ethics Committee and written informed consent was received from all the participant's parents.

Results:

A total of 103 patients were evaluated between November 2021 to October 2023; 40 of them were included in the study according to inclusion criteria; 26 (65%) were female and 14(35%) were male. Median age was 9 years (from 2 - 18 years). The anti-tTG assays were positive in 20% of patients (8/40). Out of 8 anti-tTG-positive patients, 6(75%) have been diagnosed with celiac disease by endoscopy and biopsy. All patients showed significant improvement in their growth when follow-up anthropometry measures were reviewed.]

Table (1) Demographic characteristics

Variable	Total Participants (n=40)	Celiac Disease Positive (n=6)	Celiac Disease Negative (n=34)
Age			
- Median (Range)	9 years (2-18 years)	8 years (2-15 years)	9 years (3-18 years)
Gender			
- Female	26 (65%)	4 (67%)	22 (65%)
- Male	14 (35%)	2 (33%)	12 (35%)
Socioeconomic Status			
- Low	20 (50%)	4 (67%)	16 (47%)
- Middle	12 (30%)	1 (17%)	11 (32%)
- High	8 (20%)	1 (17%)	7 (21%)
Family History of CD			
- Positive	12 (30%)	5 (83%)	7 (21%)

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Table (2) Clinical characteristics

Symptoms and Characteristics	Total Participants (n=40)	Celiac Disease Positive (n=6)	Celiac Disease Negative (n=34)
Abdominal Pains	28 (70%)	6 (100%)	22 (65%)
Flatulence	24 (60%)	5 (83%)	19 (56%)
Recurrent Aphthous Ulcers	20 (50%)	5 (83%)	15 (44%)
Difficulty Gaining Weight	18 (45%)	5 (83%)	13 (38%)
Irritability	16 (40%)	4 (67%)	12 (35%)
History of Anemia	22 (55%)	6 (100%)	16 (47%)

Table (3) The number of tTG positive and biopsy positive among total number of patients.

Serology (tTG) negative	Serology(tTG) positive	
32	Biopsy Positive	6
	Biopsy Negative	2

Table (4) The mean of height, age and gender distribution of patients included in study.

Groups	Height	Age	Gender	
			Female	Male
Patients with Celiac Disease (positive biopsy)	95.75 cm	5.17 yrs	4	2
Patients without Celiac disease (serology negative)	120.2 cm	9.6 yrs	22	12

Table (5) Demographic data of age, gender and height of enrolled patients at the initial presentation and follow-up of height, 6 months on a gluten-free diet.

Age (years)	**Gender**	**Ht.1(cm)**	**Ht.2(cm)**
4	M	98.5	102
5	M	95	99
3	M	77.5	82
6	F	98	101
7	F	102	103
6	F	103.5	106
MEAN HEIGHT		**95.75 ± 23.8**	**98.83 ± 32.5**

Ht.1 (cm) : Height at presentation. Ht.2 (cm) : Height after 6 months of gluten free diet.

Discussion

In the study involving 40 patients with short stature, 20% of them had positive anti-tTG (anti-tissue transglutaminase) assays, indicating a potential presence of celiac disease. Among the eight patients with positive anti-tTG titers, 75% were subsequently diagnosed with celiac disease through confirmatory procedures like endoscopy and biopsy.

The percentage of patients diagnosed with celiac disease via biopsy among all children with short stature in the study was 15%. This finding suggests that while a significant proportion of patients tested positive for anti-tTG, a smaller subset had confirmed celiac disease upon further investigation through endoscopy and biopsy. This indicates the importance of confirmatory diagnostic procedures in accurately identifying cases of celiac disease, as not all positive anti-tTG results necessarily translate to a definitive diagnosis. This result is close to that result found by de Lecea et al (1996), Spain 18.6% (22/118) of children with short stature had biopsy-proven coeliac disease. However; a higher percentage of celiac disease among short-stature children had been found by Altuntas et al (1998), Turkey at 55.3% (26/47); this may be attributed to the smaller population size. Other studies show a much lower percentage of celiac disease as in Rossi et al (1993), USA 1.7% (2/117) which may be explained by different geographical areas. Also, studies by Knudtzon et al (1991), and Norway et al show a much less prevalence of celiac disease in short-stature children i.e. 2.9% (5/168).

All of these comparable studies subjected their enrolled population to diagnostic endoscopy and biopsy to rule out celiac disease and they did not depend on anti-t TG to select patients for endoscopy. However, because of certain limitations viz. financial constraints, fear of invasive tests, and limited resources, the endoscopy and biopsy were undertaken only on children who are serologically positive for celiac disease.

The mechanism of growth retardation is not clearly understood in patients with Celiac disease; nutritional deficiencies especially zinc deficiency, low serum somatomedin activity, and defects in growth hormone secretion have been proposed as underlying mechanisms.

An association between Celiac disease and autoimmune disorders, such as type I diabetes, autoimmune thyroid disease, and Sjögren's syndrome, has been well documented in the literature.

Withdrawal of gluten from the diet for six months showed marked improvement in patients' linear growth.

Generalizability

To enhance the generalizability of study results on celiac disease among children with short stature, researchers should strive for a representative sample, clearly define inclusion and exclusion criteria, use standardized diagnostic methods, consider diverse populations, and provide comprehensive follow-up data. These efforts contribute to a more robust understanding of how the findings apply to broader populations beyond the study sample.

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 anti-tissue 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. In many studies done earlier, a small intestinal biopsy was undertaken in all patients with short stature to find seronegative cases of celiac disease.

Limitations

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

Recommendations

Further prospective studies may be undertaken in this regard to have a better understanding of the prevalence of celiac disease.

Acknowledgment

We are thankful to the patients; without them, the study could not have been done. We are thankful to the supporting staff of our hospital who were involved in the patient care of the study group.

List of abbreviations

CD: Celiac Disease
tTG: Anti-Tissue Transglutaminase
NCHS: National Center for Health Statistics
IgA: Immunoglobulin A
FDA: Food and Drug Administration

Source of funding

No funding received.

Conflict of interest

The authors have no competing interests to declare.

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