CELIAC DISEASE AMONG CHILDREN PRESENTED WITH UNEXPLAINED SHORT STATURE

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ABSTRACT

Introduction: *Celiac disease is a chronic autoimmune condition, in genetically susceptible persons, perpetuated by the ingested gluten from cereals, wheat and barley, its clinical spectrum is broad, varies from absence of symptoms to gastrointestinal (classic) and/or extra intestinal (non-classic) symptoms, patients without symptoms may have latent or silent celiac disease, because celiac disease can be atypical or even clinically silent, many patients remain undiagnosed and at risk for the long-term, sometimes serious complications of untreated celiac disease. Short stature is the most commonly encountered extra-intestinal (non –classical) symptoms of CD in children, being found in roughly one-third of all new pediatric celiac diagnoses, while it can be directly related to malabsorption of nutrients, it should completely reverse once a child is strictly adherent to Gluten free diet.*

Aim of the work: *The goal of this study was to screen for coeliac disease in Egyptian children with unexplained short stature by estimating serum level of total IgA and tissue transglutaminase IgA.*

Methodology: *Cross sectional analytical study for 100 child with short stature (males and females), attended the pediatric out-patient clinics of AL-Sayed Galal and Alhussen university hospitals in Cairo during the period from April 2017 to march 2019, any child aged 2- 18 years with undetectable cause of short stature whose Z score for height was less than -2 SD for the age and sex according to the WHO charts (WHO, 2006), not previously screened for Celiac disease was enrolled in the study, after approval of his care-giver, the medical records of patients evaluated for short stature include a proper detailed history and physical examination, growth analysis, followed by radiological (bone age), and Laboratory screening (including celiac serological screening and Growth hormone evaluation) , chromosomal analysis were performed when appropriate, followed by small intestinal biopsy for celiac seropositive patients and Growth hormone stimulation test was performed in suspected patients.*

Results: *The demographic characteristics of all 100 cases regarding mean age in months was 80.85 ± 33.55 with range 36 – 179, Sex distribution of all cases was 52 (52.0%) female and 48 (48.0%) male, mean height in cm for all cases was 102.04 ±*

13.48 with range 84 – 141 and median height Z score for all study group was -3.4 (-3.6 – -3) with range -4.6 - -2.6.

The results showed that 11(11%) cases were positive for TTG IgA antibodies with normal level of total IgA Identified celiac cases with mean age in months was 86.91 ± 37.58, female cases were 7 (63.6%) and 4 (36.4%) cases were males, mean Height in cm was 102.18 ± 14 and median height Z score was -3.6 (-4.3 – -3.4).

Keywords: *Short stature; Celiac disease; Children; Anti-tissue transglutaminase antibody, Idiopathic short stature.*

INTRODUCTION

Celiac disease is a chronic autoimmune condition, in genetically susceptible persons, perpetuated by the ingested gluten from cereals, wheat and barley.[1]

Classic symptoms include gastrointestinal problems such as chronic diarrhea, abdominal distension, malabsorption, loss of appetite, and among children failure to grow normally. This often begins between six months and two years of age. Non-classic symptoms (eg, short stature, delayed puberty, epilepsy, peripheral neuritis and iron defiency anemia) are the most common, especially in people older than two years.[2]

The standard method of diagnosing celiac disease in symptomatic persons older than 2 years is the tissue transglutaminase (tTG) IgA test, followed by intestinal biopsy for histologic confirmation.[3]

Short stature is the most commonly encountered extra-intestinal manifestation of CD in children, being found in roughly one-third of all new pediatric celiac diagnoses. While it can be directly related to malabsorption of nutrients, it should completely reverse once a child is strictly adherent to a Gluten free diet (GFD).[4]

Around 2.5-3% of the children worldwide are short, 5 The Egyptian Demographic and Health Survey of 2008 (EDHS 2008) revealed that the prevalence of stunting among children under 5 was 28.9%2, while that of the EDHS 2014 was found to be 21% while the prevalence of stunting among children aged 1-12 years attending the outpatient Pediatric clinic of Al-Azhar University

Hospital (Al-Hussein), Cairo was 15.8%.[6]

Endocrinological causes of short stature accounted for 26% while celiac disease (CD) constituted 6.6% of children with short stature in Egypt.[7]

In Egypt celiac disease is a frequent disorder among children, both in the general population (0.53%) and in at-risk groups (6.4%).[8]

The only known effective treatment is a strict lifelong gluten-free diet, which leads to recovery of the intestinal mucosa, improves symptoms, and reduced risk of developing complications in most people,[9] If untreated it may result in cancers such as intestinal lymphoma and a slight increased risk of early death.[10]

Ethical consideration:

1- The ethical committees of Al-Azhar faculty of medicine & pediatric department approved the study.

2- Informed consent was obtained from parents of all included children.

3- The research protocol did not interfere with any medical recommendations or prescriptions.

4- The aim of the study & all investigations as well as the risks & benefits of study have been explained to parents of the patients.

5- The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

6- All data of patients & results of study are confidential & patients have the right to keep it.

7- The patient has the right to withdraw from the study at any time.

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PATIENTS AND METHODS

This study is a cross sectional study that was carried out on 100 children with short stature (males and females), The cases were attending the pediatric out-patient clinic off AL-Sayed Galal and Alhussen university hospitals in

Cairo, any child fulfilled the inclusion criteria was enrolled in the study after obtaining a written consent from the care giver during the period from April 2017 to march 2019.

Inclusion criteria:

1- Age 2 - 18 years with undetectable case of short stature whose Z score for height was < -2 SD for the age and sex according to the WHO charts.[11]

2. Not previously screened for Celiac disease.

Exclusion criteria:

Short children with demonstrable cause such as;

1) Familial and constitutional short stature.

2) Chronic illness.

3) Disproportionate short stature.

4) Short stature of endocrinal origin (eg, growth hormone deficiency).

5) Turner syndrome.

6) Short stature with significant congenital anomalies.

7) Patients on gluten free diet.

Each child enrolled in the study was subjected to the following:-

1) Prestructured questionnaire.

2) Anthropometric measurements.

3) Detailed history (eg: personal, dietetic, familial, gastrointestinal symptoms).

4) Complete physical examination.

5) Radiological investigation: Antero-posterior plain X-ray film of left wrist was taken, and bone age was determined according to Greulich and Pyle atlas.[12]

6) Laboratory investigations

- Complete blood count by using cell counter (Diagon D cell 60, Hungary).
- Liver ((SGOT, SGPT) and renal (Blood urea and creatine) using biochemical auto-analyzer (BT 1500, Rome, Italy
- Total serum IgA by nephlometry using a Behring BNII nephelometer (Dade Behring, Milton Keynes, UK).level below10mg/dl considered deficient.[13]
- IgA class serum human tissue transglutaminase antibody

(IgA-TTGA) by enzyme linked immunosorpant assay (ELISA):

Used kits: Enzyme-linked Immunosorbent Assay Kit for Tissue transglutaminase IgA (INOVA Diagnositics Inc., USA).

Results: The result was considered weak positive if the sample demonstrates 20–30U/ml or moderate to strong positive if the sample demonstrates >30U/ml.[14]

- **Thyroid profile:** TSH was estimated by immunoradiometric assay (IRMA), while FT3 and FT4 were estimated by radioimmunoassay kits from Diagnosis Product Corporation (Los Angeles, CA, USA).[15]
- **Growth hormone evaluation** (IGF-1 and growth hormone provocation test for cases with low level of IGF-1), **IGF-1** was determined at diagnosis using solid phase IRMA, using kits from Diagnostic System Laboratories Inc., Texas, USA., Patients were considered not to be GH deficient when the peak GH value during the stimulation test was equal to or higher than 7 ng/ml
- **KARYOTYPING** for all female patients with undetectable cause of short stature to exclude turner syndrome

7) **Upper gastrointestinal endoscopy for duodenal biopsy:** was done for the study group subjects who will have positive values on anti-tissue transglutaminase (IgA) antibody estimation, Four to six biopsy specimens were taken from the bulb and second parts of the duodenum. Formalin-fixed biopsy specimens stained with hematoxylin and eosin will be studied with the use of light microscopy, mucosal lesions were classified according to the criteria of modified Marsh (Dr. Michael Marsh introduced the classification system to describe the stages of damage in the small intestine as seen under a microscope).[16]

Statistical analysis:

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY,

USA).Continuous numerical variables were presented as mean and standard deviation (SD). *: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

RESULTS

Our results are demonstrated in the following tables:

Table (1): Age and sex distribution of all cases with unexplained short stature

		Total cases
		No. = 100
Age (months)	Mean ± SD	80.85 ± 33.55
	Range	36 – 179
Sex	Female	52 (52.0%)
	Male	48 (48.0%)

Table (2): celiac serological screening of studied population

		Total cases
		No. = 100
Total IGA	Normal	100 (100.0%)
	deficient	0 (0.0%)
Tissue Transglutaminase IgA	positive	11 (11%)
	Negative	89 (89%)

This table shows Celiac disease present in 11% of cases with unexplained short staure.

Table (3): Histopathological evaluation of celiac group

		Celiac group
		no. = 11
Marsh classification of celiac group*	II	2 (18.2%)
	IIIA	3 (27.3%)
	IIIB	6 (54.5%)

*Marsh II: Lymphocytic enteritis with crypt hyperplasia
Marsh IIIA: Partial villous atrophy
Marsh IIIB: Subtotal villous atrophy

Table (4): Intestinal and extra intestinal symptoms of celiac and non-celiac groups

		Non-celiac group	Celiac group	Test value	P-value	Sig.
		No. = 89	No. = 11			
Gastro-intestinal symptoms	Diarrhea	1 (1.1%)	5 (45.5%)	34.113	0.000	HS
	Vomiting	13 (14.6%)	4 (36.4%)	3.284	0.070	NS
	Constipation	15 (16.9%)	6 (54.5%)	8.383	0.004	HS
	Abdominal pain	8 (9.0%)	7 (63.6%)	22.931	0.000	HS
	Abdominal distension	1 (1.1%)	4 (36.4%)	25.595	0.000	HS
	Hematemesis	1 (1.1%)	0 (0.0%)	0.125	0.724	NS
	Oral ulcers	4 (4.5%)	2 (18.2%)	3.252	0.071	NS
	Rectal prolapse	2 (2.2%)	1 (9.1%)	1.576	0.209	NS
	Dental enamel hypoplasia	3 (3.4%)	3 (27.3%)	9.917	0.002	HS
Skin symptoms	Alopecia	2 (2.2%)	1 (9.1%)	1.576	0.209	NS
Chest symptoms	ASTHMA	11 (12.4%)	4 (36.4%)	4.424	0.035	S
	Recurrent pneumonia	4 (4.5%)	0 (0.0%)	0.515	0.473	NS
Skeletal symptoms	Rachitic symptoms	8 (9.0%)	4 (36.4%)	6.947	0.008	HS
	Cong anomaly	2 (2.2%)	0 (0.0%)	0.252	0.616	NS
CNS symptoms	Head ache	4 (4.5%)	2 (18.2%)	3.252	0.071	NS
	Epilepsy	5 (5.6%)	0 (0.0%)	0.651	0.420	NS
	Hearing loss	2 (2.2%)	0 (0.0%)	0.252	0.616	NS
	Developmental delay	3 (3.4%)	0 (0.0%)	0.382	0.536	NS

This table shows that, the commonest gastrointestinal symptom in celiac group was chronic abdominal pain followed by chronic constipation then chronic diarrhea, Results showed highly significant difference in gastrointestinal symptoms in celiac cases compaired to non-celiac cases in chronic abdominal pain, chronic diarrhea, chronic constipation, abdominal distention and dental enamel hypoplasia with P value (0.00).

Table (5): Anthropometric measurements of celiac and non-celiac groups

		Non-celiac group	Celiac group	Test value	P-value	Sig.
		no. = 89	no. = 11			
Height (cm)	Mean ± SD	102.02 ± 13.48	102.18 ± 14.14	-0.037•	0.971	NS
	Range	84 – 141	84.5 – 129			
Height z-score	Median (IQR)	-3.3 (-3.6 – -3)	-3.6 (-4.3 – -3.4)	- 3.000≠	0.003	HS
	Range	-4.1 – -2.6	-4.6 – -3.2			
Weight (Kg)	Mean ± SD	17.99 ± 5.33	17.12 ± 5.8	0.505•	0.615	NS
	Range	10.7 – 34	11 – 31			
Weight z-score	Median (IQR)	-1.7 (-2.5 – -1.1)	-2.6 (-3.1 – -2.2)	- 3.021≠	0.003	HS
	Range	-3.5 – 1.2	-3.2 – -1.7			
BMI Kg/M(2)	Mean ± SD	17.01 ± 2.08	15.97 ± 1.15	1.610•	0.111	NS
	Range	14.1 – 24.2	14.9 – 18.6			
BMI z-score	Median (IQR)	0.6 (-0.3 – 1.4)	-0.1 (-0.4 – 0.6)	- 1.681≠	0.093	NS
	Range	-2 – 5	-0.9 – 1.5			
Head circumference (cm)	Normal	81 (91.0%)	11 (100.0%)	1.075*	0.300	NS
	Microcephaly	8 (9.0%)	0 (0.0%)			
Tunner stage	Normal	78 (87.6%)	9 (81.8%)	0.293*	0.588	NS
	Delayed	11 (12.4%)	2 (18.2%)			
Bone age	Normal	70 (78.7%)	9 (81.8%)	0.059*	0.808	NS
	Delayed	19 (21.3%)	2 (18.2%)			

This table shows highly significant difference in height Z score and weight Z score between celiac and non-celiac groups with P value (0.003)

Table (6): Comparison between celiac and non-celiac groups as regard C.B.C.

		Non-celiac group	Celiac group	Test value	P-value	Sig.
		No. = 89	No. = 11			
Hb	Mean ± SD	10.01 ± 0.98	7.48 ± 0.85	8.159	0.000	HS
	Range	7.9 – 12.1	6.4 – 8.9			
MCV	Mean ± SD	73.45 ± 5.5	57.45 ± 5.85	9.044	0.000	HS
	Range	59 – 89	49 – 68			
MCHC	Mean ± SD	28.99 ± 2.43	23.55 ± 2.34	7.039	0.000	HS
	Range	24 – 34	21 – 29			
	Range	0.2 – 0.7	0.3 – 0.6			

This table shows high significant difference in Hb, MCV and MCHC between celiac and non-celiac groups with p value (0.000).

Table (7): Growth hormone evaluation of celiac and non-celiac groups

		Total cases	Non celiac group	Celiac group	Test value*	P-value	Sig.
		No. = 100	No. = 89	No. = 11			
ILGF1	**Normal**	79 (79.0%)	70 (78.7%)	9 (81.8%)	0.059	0.808	NS
	Low	21 (21.0%)	19 (21.3%)	2 (18.2%)			
GH provocative test	**No**	0 (0.0%)	0 (0.0%)	0 (0.0%)	21.000	0.000	HS
	Normal response	19 (90.5%)	19 (100.0%)	0 (0.0%)			
	Deficient	2 (9.5%)	0 (0.0%)	2 (100.0%)			

This table shows Cases of celiac disease with low level of ILGF-1 showed low level of GH after provocation test and diagnosed as Growth hormone deficiency, while non-celiac

group with low level of ILGF-1 showed normal GH response after provocation test and this consistent with ISS.

Table (8): Marsh classification and level of Hb, ILGF-1, height and weight Z scores

		Marsh classification			Test value	P-value	Sig.
		II	IIIA	IIIB			
ILGF1	Normal	2 (100.0%)	2 (66.7%)	5 (83.3%)	0.917*	0.632	NS
	Low	0 (0.0%)	1 (33.3%)	1 (16.7%)			
Height z-score	Median (IQR)	-3.4 (-3.4 – -3.4)	-3.5 (-4.5 – -3.2)	-3.9 (-4.3 – -3.6)	3.819≠	0.148	NS
	Range	-3.4 – -3.4	-4.5 – -3.2	-4.6 – -3.5			
Weight z-score	Median (IQR)	-2.6 (-2.7 – -2.5)	-2.2 (-3.1 – -1.9)	-2.65 (-3.1 – -2.5)	0.565≠	0.754	NS
	Range	-2.7 – -2.5	-3.1 – -1.9	-3.2 – -1.7			
HB	Mean ± SD	7.70 ± 1.56	8.13 ± 0.75	7.08 ± 0.51	1.913•	0.209	NS
	Range	6.6 – 8.8	7.4 – 8.9	6.4 – 7.9			

This table shows no significant relation betweenlevel of Hb, ILGF-1, height and weight Z scores and MARSH classification.

DISCUSSION

This study is a cross sectional study that carried out on **100** children with proportionate short stature who attended the pediatric out-patient clinics of ALSayed-Galal and Alhussen university hospitals in Cairo, our objective was aimed to find out celiac disease among children presented with unexplained short stature.

The results showed that **11 (11%)** cases from the total 100 (100%) cases with unexplained proportionated short stature were positive for Tissue

transglutaminase (TTG) IgA antibodies with normal level of total IgA identified as positive serological test for celiac disease with mean age in months was **86.91 ± 37.58** and range 48 – 168 and female cases were **7 (63.6%)** and **4 (36.4%)** cases were males.

Marsh classification for celiac cases was Marsh class II in **2 (18.2%)** cases, IIIA in **3 (27.3%)** cases and IIIB in **6 (54.5%)** cases.

The low percentage of celiac cases may be related to wide range of age group of studied population **(2-18years)**, low socioeconomic standard of most of studied population which contributed to lack of early medical advice and lack of specific nutritional institutions for celiac disease.

Our finding is consistent with other studies in Saudi Arabia and India, in Kingdom of Saudi Arabia studies showed that the percentage of celiac disease among children with short stature is approximately 10%, [17] nearly 11% of patients presenting with short stature in India have coeliac disease, in these patients chronic diarrhea and anemia were significant predictors of coeliac disease, [18] while in our study chronic abdominal pain and anemia were the significant predictors of celiac disease.

In Egypt a study by **El Dayem et al., 2010** [19] showed that celiac disease in non-endocrinal short stature account for (34.3%), these result agreed with **De Lecea et al., 1996**, [20] who reported the percentage of CD in short children ranging from 25 to 33.8%. In **2017** a study by **Hussein et al.,** [21] for etiological factors of short stature in children and adolescents (experience at a tertiary care hospital) showed that celiac disease constituted 6.6% of children with short stature.

Our data revealed the demographic characteristics of all **100** cases with unexplained short stature regarding mean age in months **80.85 ± 33.55** with range **36 – 179** while mean age for celiac cases **86.91 ± 37.58** with range **48 – 168** and for non-celiac cases was **80.1 ± 33.17** with range **36 – 179**, with no significant difference between celiac and non-celiac groups The mean age for celiac group **86.91 ± 37.58** can be explained by the age of asking medical advice for children with short stature due to comparing with other children during entry the nursery or primary school.

A study by **Savage et al** identified the age of diagnosis of celiac disease to be 6 years for girls and 7 years for boys. [22]

In Egypt a study by **ELrefai et al, 2009** [23] defined the average age for diagnosis of Celiac disease by **5.5** years, while another study **El Dayem et al., 2010** [16] defined the mean age for diagnosis of celiac disease in non-endocrinal short stature by **7.9 ± 3.9** years.

Sex distribution of all cases was **52 (52.0%)** female and **48 (48.0%)** male, while in celiac group **7 (63.6 %)** female and **4 (36.4%)** male and non-celiac group **45 (50.6 %)** female and **44 (49.4%)** male, with no significant difference between celiac and non-celiac groups.

A study by **Rubio-Tapia et al., 2016** [24] showed that the clinical presentation of celiac disease is not the same in men and women. The disease is not only more frequent in women than in men but is also more severe and more rapid.

In Egypt a study **by Shehab, 2013** [25] observed equal sex ratio among CD children.

There was significant decrease in celiac cases in height Z score with P value **(0.003)** and weight Z score with P value **(0.003)** compared to non-celiac group, these findings in celiac cases can be explained by the chronic malabsorption state affecting celiac cases which in turn results in various nutritional deficiencies of macro- and micronutrients such as minerals, vitamins, calories, dietary fiber and Hb.

A study Chishty, **Singh, 2017** [26] proved that the mean values of weight z-score, Height z-score and Hb were significantly lower in CD patients compared to non-celiac, another study by **Eren, 2018** [27] performed a comparison for anthropometric measurements in patients who were diagnosed at ≤ 6 years of age and > 6 years of age and proved that the height and weight z-scores of the patients who were diagnosed at > 6 years of age were significantly lower than the younger group which mean the celiac disease is a progressive chronic malnutriting disease and only the Gluten free diet (GFD) compliance will positively affect the patients' all growth parameters.

Bone age for all cases was normal in **79 (79.0%)** cases and delayed in **21 (21.0%)** cases, in celiac cases bone age delayed in **2 (18.2%)** cases and normal in **9 (81.8%)** cases while in non-celiac cases normal bone age found in **70 (78.7%)** and was delayed in **19 (21.3%)**.

Celiac disease can be complicated by metabolic bone diseases like osteoporosis, secondary hyperparathyroidism, and osteomalacia even without gastrointestinal complaints, these bone disorders explained by both local and systemic mechanisms started with calcium malabsorption due to mucosal atrophy, therefore, to avoid hypocalcemia parathyroid hormone increases substantially (secondary hyperparathyroidism) and stimulates osteoclasts mediated bone degradation, calcium is then obtained from the skeleton reservoir, but this high remodeling state can lead to osteopenia and osteoporosis, altering bone microstructure and increasing fracture risk. 28

In celiac group **2 (18.2%)** cases had delayed bone age diagnosed later with dealing with a short child must be the exclusion of CD, which may be responsible for growth failure. In particular, before evaluating Growth Hormone (GH) secretion in a short child in whom 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. 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.[29]

In non-celiac group **19 (21.3%)** cases had delayed bone age and low level of ILGF-1 with normal Growth Hormone level on provocation test, these cases diagnosed as Idiopathic short stature (ISS).

Tanner staging for all cases was normal in **87 (87.0%)** cases and delayed in **13 (13.0%)** cases,

in celiac cases only **2 (18.2%)** cases had delayed tanner staging, aged 11 years (male with tanner stage I) and 14 years(female with tanner stage II) and **11 (12.4%)** cases in non-celiac cases had delayed tanner staging

The clinical findings can be explained by the lack effect of CD, deficient ILGF-1 and growth hormone in the development of secondary sexual characters

Delayed puberty affecting roughly 10% of newly pediatric celiac patients, delayed puberty is defined by lack of physical or hormonal signs of puberty at the age of usual onset. Visible secondary sexual development usually begins when girls achieve a bone age of 11 years and boys achieve a bone age of 12 years. In girls, a lack of breast development by 13 years, or a lack of menarche within three years after breast development or by 16 years is considered to be abnormal. For boys, no testicular enlargement by 14 years or a delay in development for five years or more after onset of genitalia enlargement is considered abnormal. In the case of CD, this delay in puberty is directly related to malabsorption, malnutrition and the disruption of the hypothalamic control of growth hormone secretion which should be resolved on a GFD, which should prevent any long-term complications and restore normal maturation.[30]

The commonest gastrointestinal symptom in celiac group was chronic abdominal pain **7 (63.6%)** cases followed by chronic constipation **6 (54.5%)** cases and only chronic diarrhea present in **5 (45.5%)** cases, Rectal prolapse found in one female case aged 11ys.

Results showed significant increase in the percentage of gastrointestinal symptoms in celiac cases compaired to non-celiac cases in chronic abdominal pain with P value (0.000), chronic diarrhea with P value (0.000), chronic constipation with P value (0.004), abdominal distention with P value (0.000) and dental enamel hypoplasia with P value (0.002), chronic diarrhea in celiac disease is due to the maldigestion and malabsorption of nutrients. The stools might be watery or semi formed, light tan or gray and oily or frothy. The stools have a characteristic foul odour. In

infants and young children, malabsorption of ingested fat (steatorrhea) results in the delivery of excessive dietary fat to the large bowel. This results in the production of hydroxy fatty acids by bacteria, which causes secretion of fluids into the intestinal lumen.

Celiac disease causes damage to the intestinal villi that are responsible for absorbing nutrients, as food travels through the digestive tract, the intestinal villi are unable to fully absorb nutrients and may often absorb extra moisture from the stool instead. This leads to hardened stool that is difficult to pass, resulting in constipation

Chronic abdominal pain in celiac disease is common and maybe explained by the affection of intestinal microbiota on the complex gut-brain axis along with the enteric nervous system, immune system and external environment, and alterations in this axis predispose to chronic pain in celiac disease, maldigestion and bloating can cause abnormal swelling and feeling of a full or tight abdomen and accompanied by abdominal pain. [31]

Rectal prolapse in celiac disease occurred as a result of chronic constipation and increased of intra-abdominal pressure with weak pelvic floor muscles, [32] these findings consistent with findings of Guandalini and Discepolo, 2016 study. [33]

Results showed significant increase in the percentage of extra-intestinal symptoms in celiac cases compaired to non-celiac cases in asthma with P value **(0.035)** and rachitic symptoms with P value **(0.008)**, The frequency of asthma increases in celiac patients, possibly due to common genetic or environmental factors contribute to the risk for both and nutritional deficiencies occurring due to celiac may help incite asthma. [34]

Rickets in celiac disease is explained by the loss of villous architecture leads to malabsorption of calcium and vitamin D leading to hypocalcemia and secondary hyperparathyroidism. In addition, the release of proinflammatory cytokines, activating osteoblast represents the main locally acting mechanisms responsible for bone derangement, this result agreed

with the study by **Assiri et al., 2016**. [35]

The exact mechanism by which CD leads to headaches in is unclear, but it is speculated that it may be secondary to a lack of vitamins, macro elements, such as magnesium, low levels of serotonin, which are the direct result of the celiac associated malabsorption. An alternate hypothesis is that the impaired immune response results in an imbalance of pro-inflammatory cytokines in response to ingested gluten, leading to altered vascular tone, and subsequently, the onset of the headache. [27]

While alopecia has an association with pediatric CD, it is one of the less common extra-intestinal manifestations seen, occurring in roughly 1% of patients. It is presumed to occur through an autoimmune reaction involving T-cell dysregulation and autoantibodies directed against anagen-stage hair follicle structures and a direct association with the human leukocyte antigen (HLA)-DQB1*0201 allele, these results consistent with the study done by **Laurikka et al., 2018**. [36]

Lower levels of mean hemoglobin concentration, MCV and MCHC were more prominent in celiac group than non-celiac group with P value **(0.000)** for all means, and this can be explained by (1) iron is predominantly absorbed in the first portion of the small bowel, the duodenum, which is the main portion of the bowel affected by CD resulting in duodenal inflammation which subsequently leads to the malabsorption of iron and resultant iron-deficiency anemia, (2) occult blood loss in the gastrointestinal (GI) tract, occult gastrointestinal bleeding was detected in 25% to 54% of patients with CD, depending on the degree of villous atrophy, (3) Anemia of chronic disease, defined by anemia with high ferritin levels and inflammatory syndrome, has been also described in CD, associated aplastic anemia has also been reported in isolated cases. Vitamin B12 deficiency was considered theoretically to be less common in CD, as its absorption takes place in the terminal ileum, which is infrequently involved. However, studies have reported significant proportions for B12 deficiency also, [37] these finding

consistent with the study in Egypt done by **Abd El-Shaheed et al., 2018**. [38]

The level of ILGF-1 for all cases was normal in **79 (79.0%)** cases and low in **21 (21.0%)** cases, but in celiac group **2 (18.2%)** cases showed low level and in non-celiac group **19 (21.3%)** cases showed low level, these results contrasted with other study done by **Giovenale et al., 2006** [39] who found that 0.23% of celiac cases had GH deficiency and these children did not grow after 1 year of GFD

Cases of celiac disease with low level of ILGF-1 showed low level of GH after provocation test and diagnosed as Growth hormone deficiency, while non-celiac group with low level of ILGF-1 showed normal GH response after provocation test and this consistent with ISS.

The presence of anti-pituitary autoantibodies (AAPs) is reported in children with CD and GH deficiency, **Iughetti et al., 2006** [40] found four out of five CD children with GH deficiency that resulted positive at high titers for AAPs, they also detected the presence of both anti-pituitary and anti-hypothalamus antibodies in seven CD children who did not show catch up growth after at least 12-months on a GFD, suggesting an autoimmune involvement between the two entities, and these findings agreed with **Nardecchia et al., 2019**. [41]

CONCLUSION

- Celiac disease is important cause for unexplained short stature
- Celiac disease could be associated with GH deficiency

RECOMMENDATIONS

1. Paediatricians and other health care professionals should strive to make celiac disease screening readily available to all children with short stature within their community, especially for those infants most at risk.

2. Educational programs focused on non-classic presentation of celiac disease.

3. All short stature children should be screened for celiac disease whether they are males or females, had GIT symptoms or not, had delayed or normal bone age and had already diagnosed cause for short stature or not.

4. Idiopathic short stature should be considered in cases with low

level ILGF-1 and normal Growth hormone stimulation test.

STUDY LIMITATIONS

The current study had the following limitations:

- The results were from a single medical Centre.
- The sample size was rather small.
- Refusal of some patients to enter the study.

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المرض القللي (السيلياك) في الأطفال الذين يعانون من قصر قامه غير معلوم السبب

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الهدف من الدراسة:

دراسة المرض القللي(السيلياك) في الأطفال المصابين بقصر قامه غير معلوم السبب.

مواد وأساليب الدراسة

الإعتبارات الأخلاقية:

تمت الموافقة على الدراسة من جانب لجنة الأخلاقيات بكلية طب الأزهر بنين بالقاهرة. وتم الحصول على موافقة مكتوبة باللغة العربية من جميع المشاركين .وتضمنت هذه الموافقة كل تفاصيل الدراسة (العنوان ،الأهداف، الأساليب، الفوائد المتوقعة وخصوصية البيانات).

تصميم االدراسة:

هذه الدراسة دراسة مقطعية.

الأشخاص المستهدفين والمدة:

أجرى هذا البحث على مائة طفلا وطفلة يعانون من قصر القامة الغير مفسر، تم اختيارهم من عيادات الأطفال الخارجية بمستشفى سيد جلال و مستشفى الحسين الجامعي بالمعايير الأتية:

معايير الاشتمال:

• قصر القامة الغير مفسر.

معايير الاستبعاد:

• الأطفال الذين يعانون من قصر القامة المفسر.

• الاطفال الذين سبق تشخيصهم بمرض بمرض السيلياك.

تم تجميع البيانات عن طريق:

1- موافقه كتابية من القائم على رعاية الطفل.

2- الاجابه علي استبيان منظم مسبقا.

3- أخذ التاريخ الطبي المتعلق بالطفل تفصيليا.

4- القياسات المختلفة لكل طفل من ناحية الطول والوزن ومؤشر الكتلة الجسدية و تناسبات أطوال الجسم.

5- الفحص الطبي الشامل مع التركيز على وجود أى أعراض متعلقه بالجهاز الهضمي.

6- التركيز على وجود أى أعراض ناجمة عن الخلل الوراثي ليتم استبعاها.

7- عمل أشعة سينية على الرسغ الأيسر.

8- فحص عينة من الدم الوريدي لعمل صورة دم كامله وقياس وظائف الكلي والكبد.

9- عمل وظائف الغده الدرقيه.

10- قياس نسبة عامل النمو شبيه الانسولين-1 للإستدلال علي هرمون النمو مع عمل اختبار تحفيزي لهرمون النمو عند الاشتباه في نقص هرمون النمو.

11- فحص عينة من الدم الوريدي لمستوي الاجسام المضاده أ الكليه ومستوي الاجسام المضاده أ للإنزيم ناقل الغلوتامين.

12- التصوير الصبغي الكروموسومي للاطفال الاناث.

13- التنظير العلوي للجهاز الهضمي مع اخذ عينات من الاثني عشر للاطفال ذوي المدلول الايجابي للأجسام المضاده أ للإنزيم ناقل الغلوتامين.

وكانت النتائج كالآتي:

• متوسط عمر الاطفال بالشهور موضوع الدراسه (80,85 ± 33,55) و متوسط الطول (102.04 ± 13.48).

• خلال الدراسه تبين ان عدد الاطفال المصابين بقصر القامه نتيجة الاصابة بمرض السيلياك يصل ال 11%.

• يتراوح متوسط عمر الاطفال بالشهور الاطفال المصابين بمرض السيلياك (86.91 ± 37.58) و متوسط الطول (102.18 ± 14.14).

• تعد الام البطن اشهر اعراض الجهاز الهضمي المنتشره بين الاطفال موضوع الدراسه المصابين بمرض السيلياك ويأتي بعدها الامساك ثم الاسهال.

• بعض حالات الاطفال المصابين بمرض بمرض السيلياك قد تكون مصاحبه لنقص في افراز هرمون النمو.

• خلال الدراسه تبين ان عدد الاطفال المصابين بقصر القامه مع نقص في عامل النمو شبيه الانسولين -1 مع إستجابه طبيعية لتحفيز هرمون النمو يمثل 19%.

وخلصت الدراسة إلى ما يلي :

- بمرض بمرض السيلياك من الاسباب المهمة لقصر القامه الغير المفسر فى الأطفال.

وقد أوصت الدراسة بالآتي:

1- ضرورة أن يكافح الأطباء و غيرهم من العاملين في الرعاية الصحية من أجل توفير الفحوصات الازمه بمرض (السيلياك) للأطفال المصابين بقصر القامه في محيطهم وبخاصة لذوى الاحتياج الخاص له.

2- أهمية التوعية عن الاعراض الغير النمطيه بمرض السيلياك.

3- يجب عمل الفحوصات الخاصة بمرض بمرض السيلياك للاطفال المصابين بقصر القامه مع عدم الاعتبار للجنس او الاعراض او العمر العظمي.

4- قصر القامة مجهول السبب يجب اعتباره في حالات قصر القامه مع نقص في عامل النمو شبيه الانسولين-1 مع إستجابه طبيعية لتحفيز هرمون النمو ويحتاج الي التشخيص بواسطة التحليل الجيني.