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CELIAC DISEASE;
A MEDLEY OF CLINICAL FEATURES A TERTIARY CARE HOSPITAL EXPERIENCE.

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ABSTRACT... Background: Celiac disease (CD) is an immune-mediated enteropathy stimulated by intake of gluten, rye and barley in genetically prone persons. In children, gastrointestinal symptoms are usual if disease is diagnosed in first two years of life but as the age at onset of the illness advances to late years, extra-intestinal manifestations have been increasingly recognized affecting almost all organ systems. **Objectives:** To determine the prevalence of varied clinical manifestations of CD in children. To assess classical and non-classical features in patients with CD. **Study Design:** Cross sectional study. **Setting:** Nishtar Hospital Multan. **Period:** July 2016 to July 2017. **Material & Methods:** Ninety-six patients with celiac disease were analyzed. The diagnosis was confirmed by serological antibodies and positive biopsy wherever needed. All the cases were evaluated for different intestinal or extra-intestinal features. Also the cases were categorized based on their primary clinical features into two groups. The classical group had CD patients with usual symptoms. The non-classical group had atypical symptoms. **Results:** The mean age of CD patients at the time of diagnosis was 5.98 ± 3.19 years. Median value for duration of clinical symptoms was 24 months. The common typical clinical presentations included failure to thrive 86 (89.6%), short stature 86 (89.6%), diarrhea 78 (81.3%), unexplained anemia 78 (81.3%) and clubbing 41 (42.7%). The atypical features noted in our study were constipation 21 (21.9%), hypertransaminasemia 38 (39.6 %) and neurological symptoms like irritability/ behavioral changes 41 (42.7%). Family history of gluten allergy or other autoimmune diseases was present in 29 (30.2%) of patients. Children presented with non-classical symptoms were older than 2 years of age and they showed high prevalence of associated immune and non immune diseases compared to those in classical group. **Conclusion:** The knowledge of varied behavior of CD may prevent delay in diagnosis. CD must be particularly screened in patients with unexpected anemia, rickets, clubbing, short stature and in cases with positive history in family.

Key words: Celiac Disease, Clinical Features, Extra-intestinal Features, Gluten-sensitive Enteropathy, Anemia.

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INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy stimulated by intake of gluten, rye and barley in genetically prone persons of all ages. Damage to small intestinal mucosa can cause defective absorption of many important nutrients including folic acid, iron, vitamins and calcium.[1] Exact prevalence of CD in Pakistan is not known. However extrapolated undiagnosed prevalence in Pakistan is 36 / 10000 population.[2]

It has extremely varied clinical presentation. In children, gastrointestinal symptoms are usual if disease is diagnosed in first two years of life but as the age at onset of the illness advances to late years, extra-intestinal manifestations have been increasingly recognized affecting almost all organ systems.[3] Classical symptoms are chronic diarrhea, abdominal distention, failure to thrive and irritability while common extra-intestinal features of CD is iron deficiency anemia (which does not respond to iron therapy) and osteoporosis.[3]

A 30 year study done in Athens, Greece published in 2009 shows that group 1(1978-1987) and 2(1988-1997) had below two and seven percent of patients with non-classical symptoms respectively. This proportion was

increased to 36% during later years (1998-2007) of the study. During initial years of the study, majority of patients had gastrointestinal symptoms. While significant (23%) patients had no gut symptoms after 1998.[4]

Out of a total of 6653 patients of chronic diarrhea presented in Children Hospital Lahore over a period of 7 years from 2003-2010, 2861 patients were diagnosed to have celiac disease (43%). Mode of presentation was with classic symptoms of diarrhea, malabsorption and abdominal distension in 1485 (51%), constipation 429 (15%), failure to thrive 383 (13.4%), vomiting 240 (8.4%), generalized edema 86(3%), isolated refractory anemia 74 (2.6%).[5]

ESPGHAN new guidelines offer the option of omitting biopsies in selected cases with symptoms suggestive of CD.[6] Antibodies of IgA tissue transglutaminase (TTG) & IgA endomysial are used as usual serological marker for diagnosis.[7] More than 95% sensitivity and specificity for these antibodies has been reported in many studies previously.[8]

A study conducted at Bahawal Victoria hospital Bahawalpur from 2007-2010, evaluated children presenting with malabsorption by serological markers for celiac disease. The serology was positive for the celiac disease in 228 (70.58 %) out of 323 patients.[9]

Withdrawal from gluten diet for whole life is treatment of CD. Symptoms in patients with CD who remain on gluten-free diet strictly typically disappear after short period of time; these patients also observe improvement in growth and their hematological profile and biochemistry also becomes normal.[10]

MATERIAL & METHODS

We reviewed 96 consecutive children between 1-12 years of age diagnosed with Celiac Disease (CD) between duration of July 2016-July 2017 at pediatric medical unit of Nishtar University Hospital, Multan. The clinical presentation, epidemiological & laboratory parameters of the children with CD were reviewed. Record obtained from follow up clinic included age at the time of presentation, duration of symptoms before diagnosis, anthropometric measurements, hemoglobin level and serum anti – tissue transglutaminase levels (done from single reference laboratory). Patient's siblings with history of other autoimmune disorder like Type 1 Diabetes Mellitus were also screened with TTG levels. The TTG levels of ten times more than the upper limit of normal (>180u/ml) were taken as diagnostic and those patients who had inconclusive levels of TTG (i.e. 18-180u/ml) were confirmed by gut biopsy. Patients having no abnormality of villous architecture were excluded. Also patients with Giardiasis, Immunodeficiency, Inflammatory Bowel Disease, Abdominal Tuberculosis, Cystic Fibrosis, Infective Gastroenteritis and other known causes of failure to thrive (e.g. primary malnutrition, chronic kidney disease) and short stature (e.g. Familial, Growth Hormone Deficiency) were also excluded.

All the cases were categorized based on their primary clinical features. The classical group had CD patients with usual symptoms like chronic diarrhoea and abdominal distention. The non-classical group had atypical symptoms e.g. failure to thrive, anemia, abdominal pain, constipation, alopecia, short stature, rickets and recurrent oral ulcers. This non-classical group never had diarrhea and abdominal distention.

All collected data was analyzed using SPSS version 20. The research proposal got approval by Ethical Review Committee of the institute.

RESULTS

We included 96 children diagnosed with CD in our study. Mean age was 5.98 ± 3.19 years and females were 51%. Mean weight and height z-scores were -3.70 ± 2.22 and -3.14 ± 1.81 respectively. Median duration of symptoms was 24 months before the diagnosis. Intestinal biopsy was done in 12.5% cases to confirm the diagnosis. Consanguinity was present in 52.1% cases and family history suggestive of celiac disease or other autoimmune illness was positive in 30.2% cases (Table-I).

Age (In years) (mean ± SD)	5.98 ± 3.19
≤ 2 years	13 (13.5 %)
> 2 – 5 years	43 (44.8 %)
6 – 10 years	33 (34.4 %)
> 10 years	07 (07.3 %)
Gender (n, %)	
Male	47 (49 %)
Female	49 (51 %)
Weight (z-score) (mean ± SD)	-3.70 ± 2.22
Height (z-score) (mean ± SD)	-3.14 ± 1.81
Duration of symptoms (months, median, IQR)	24 (IQR – 29)
TTG IgA levels (IU/ml, median, IQR)	300 (IQR – 94)
Intestinal biopsy (positive, n, %)	12 (12.5 %)
Consanguinity (Yes, n, %)	50 (52.1 %)
Family history (Yes, n, %)	29 (30.2 %)

Table-I. Demographic features (N=96)

On diagnosis, 89.6% patients presented with failure to thrive, 81.3% had history of chronic diarrhoea and 81.3% cases were found to be anemic. Abdominal distention was present in 65.6% cases. Significant percentage was noticed to have unusual presentation rickets, electrolyte imbalance, alopecia and constipation (66.7%, 53.1%, 33.3%, and 21.9% respectively). (Table-II)

Constitutional symptoms	
Failing to thrive	86 (89.6 %)
Clubbing	41 (42.7 %)
Edema	25 (26.0 %)
Dental enamel defects	20 (20.8 %)
GIT symptoms	
Recurrent diarrhea	78 (81.3 %)
Abdominal distension	63 (65.6 %)
Abdominal pain	52 (54.2 %)
Vomiting	51 (53.1 %)
Abnormal LFT's	38 (39.6 %)
Constipation	21 (21.9 %)
Aphthous ulcers	16 (16.7 %)
Hematological symptoms	
Anemia	78 (81.3 %)
Microcytic	70
Macrocytic	05
Hemolytic	03
Thrombocytopenia	02 (2.1%)
Endocrine symptoms	
Short stature	86 (89.6 %)
Rickets	64 (66.7 %)
Alopecia	32 (33.3 %)
Metabolic disturbances Electrolyte imbalance (Na, K, Mg, Ca, PO)	51 (53.1 %)
Central nervous symptoms Irritability, Seizures, Intracranial calcification	41 (42.7 %)

Table-II. Clinical presentation (N=96)

Demographic characteristics & anthropometric measurements of both groups are demonstrated in Table-III. In non-classical group, there was no patient reported below 2 years of age. Consanguinity was commonly found (55.1%) in classical group. In classical group, family history was positive in 33.3% cases. Median duration of symptoms before diagnosis was more (30 months) in non-classical group. Mean value for TTG IgA levels was high (300) in classical group. Mean z-scores for weight & height in classical group were -3.67 and -2.95 respectively.

Table-IV shows comparison in clinical manifestations in both of the groups. In non-classical group where recurrent diarrhoea and abdominal distention were absent, patients were failing to thrive, short stature, anemic and had findings of rickets.

Iron deficiency anemia was more commonly found in non classical group while deranged liver enzymes were present more commonly in classical group. (Table-V)

Associated diseases e.g. Type 1 diabetes mellitus (Type1 DM), autoimmune thyroiditis (AIT) & epilepsy were more prevalent in non classical group as shown in Figure-1.

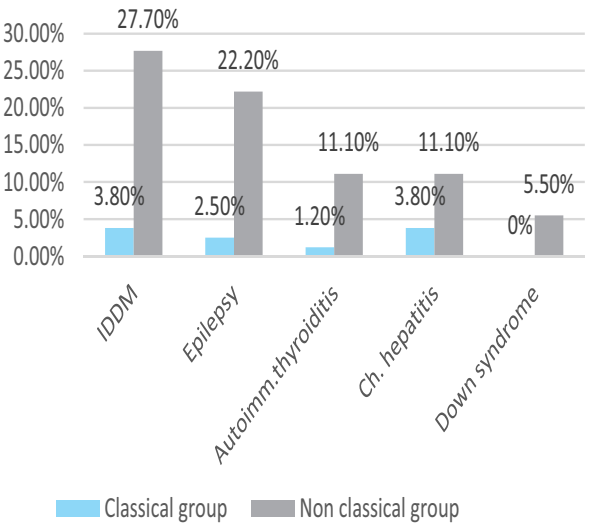

Figure-1. Associated disorders in patients with classical and non-classical celiac disease groups (N=96)

Variables	Classical group (n=78)	Non-classical group (n=18)	p-value
Age (mean, SD)	5.8 (3.2)	6.7 (3.1)	0.313
Age distribution ≤ 2 years > 2 – 5 years 6 – 10 years > 10 years	 13 (16.7 %) 33 (42.3 %) 26 (33.3 %) 06 (07.7 %)	 00 (00%) 10 (55.5%) 07 (38.9%) 01 (05.5%)	0.25
Gender (male)	39 (50 %)	08 (44.4 %)	0.67
Consanguinity (yes)	43 (55.1%)	07 (38.8%)	0.24
Family history (yes)	26 (33.3%)	03 (16.6%)	0.17
Duration of symptoms (months) [median, IQR]	24 (31)	23 (18)	0.67
Weight (z-score) [mean, SD]	- 3.67 ± 2.27	- 3.84 ± 2.07	0.77
Height (z-score) [mean, SD]	- 2.95 ± 1.48	- 3.94 ± 2.76	0.15
TTG IgA (IU/ml) [median, IQR]	300 (84)	217 (69)	0.06

Table-III. Comparison between classical and non-classical group

Manifestations	Classical group (n=78)	Non-classical group (n=18)	p-value
Recurrent diarrhea	78 (100%)	0 (0%)	< 0.001
Abdominal distention	78 (100%)	0 (0%)	< 0.001
Failure to thrive	69 (88.4%)	17 (94.4%)	0.50
Short stature	69 (88.4%)	17 (94.4%)	0.50
Un-explained anemia	62 (79.4%)	16 (88.8%)	0.36
Rickets	48 (61.5%)	16 (88.8%)	0.03
Dental enamel defect	10 (12.8%)	10 (55.5%)	< 0.001
Aphthous stomatitis	11 (14.1%)	05 (27.7%)	0.16
Constipation	18 (23%)	03 (16.6%)	0.60
Alopecia	26 (33.3%)	06 (33.3%)	1.0
Positive intestinal biopsy	07 (8.9%)	05 (27.7%)	0.03

Table-IV. Comparison of clinical manifestation in classical vs. non-classical groups

Laboratory feature	Classical group (n=78)	Non-classical group (n=18)	p-value
Iron deficiency anemia	56 (71.7%)	14 (77.7%)	0.60
Vitamin B12 deficiency	02 (2.5%)	01 (5.5%)	0.51
Folic acid deficiency	01 (1.2%)	01 (5.5%)	0.25
Hypertransaminasemia	34 (43.5%)	04 (22.2%)	0.09
Hypoproteinemia	20 (25.6%)	05 (27.7%)	0.86

Table-V. Laboratory finding of patients with classical and non-classical celiac disease groups (N = 96)

DISCUSSION

Celiac disease (CD) is immune mediated disease involving gut due to permanent gluten sensitivity in genetically prone persons. 1-2% prevalence of CD has been reported worldwide.[11] But it reaches 40% when CD presents with common symptoms like loose stools.[12] CD is manifested by usual symptoms of diarrhoea, abdominal distention & failing to thrive but it may present with unexplained anemia, rickets, neurological disease and deranged liver enzymes. Our study shows results regarding clinical profile from 96 cases of CD in children visiting pediatric department of this tertiary care hospital. In this study, maximum patients (55.5%) were in the age range of >2-5years with only 13.5% patients

≤ 2 years of age that may be linked to the late introduction of weaning and prolonged breast feeding practice in Pakistani children. Mean age at diagnosis was 5.9 years showing late diagnosis of CD. Male to female ratio was 0.9:1.

In a research conducted in India, cases of CD who were symptomatic before the first two years of age were 45%, and 55% showed symptoms after two years of age while 8.3 years was mean age at diagnosis.[13]

In the present study, mean z-score for weight was less (-3.7 standard deviation (SD) ± 2.2) as compared to mean z-score for height (-3.1 SD ± 1.8) relatable to a study conducted in Norwegian children with CD where they had lower z-scores for height from 12 months (−0.09 SD) and weight from 15 months of life (−0.09 SD) compared with controls.[14]

Our study showed that consanguinity was present among 52% of patients and 32% patients had positive family history of similar or other autoimmune diseases. Results clearly correlate with autoimmunity linked with CD. Sollid LM and Lie BA found DQ2 in >90% patients with CD and DQ8 in 5-10% patients with CD and according to their study, CD can essentially be ruled out if there is absence of any CD related HLA alleles.[15]

Our study showed that failure to thrive (FTT) (89.6%), recurrent diarrhoea (81.3%), anemia (81.3), rickets (66.7%) and abdominal distention (65.6%) were the dominant manifestations while much contribution was found by other uncommon clinical features like abdominal pain (54.2%), vomiting (53.1%), neurological symptoms (42.7%), alopecia (33.3%), constipation (21.9%) and aphthous ulcers (16.7%). Results of our study are comparable to those reported in India where 84% patients presented with diarrhea, 91% with FTT and 84% with anemia.[16]

In 2011, a study conducted at military hospital Kharian showed that diarrhoea, abdominal distension, anemia, FTT, pallor and rickets were present in 73.1%, 57.7%, 55.8%, 53.8%, and 53.8% of patient respectively.[17]

We categorized the diagnosed patients into two groups and comparison of results showed that non classical group (patients without diarrhoea and abdominal distention) had no patient below 2 years of age. Likely reason was delayed presentation in such children. Consanguinity (55.1%) and positive family history (33.3%) was more prevalent in classical group.

Consanguinity percentage is comparable to 43.9% reported by Butt et al[18] and is in disparity with 30.8% revealed by Hussain et al.[17]

In classical group, median duration of symptoms before presentation was 17 months compared to 30 months in non classical group. Reason was delayed recognition of disease in the latter group. Mean z-score for weight and height was found much less in non classical group representing more compromise on growth in such patients due to delayed diagnosis. Median TTG IgA value was less i.e. 217 in non-classical group compared to 300 in classical group explaining more severity in the latter group.

Our study showed that proportion of failure to thrive, anemia, rickets, dental defects, aphthous ulcers was more (94.4%, 88.8%, 88.8%, 55.5%, 27.7%) in non-classical group compared to those in classical group (88.4%, 79.4%, 61.5%, 12.8%, 14.1%). The difference of dental enamel defects in two groups was statistically significant ($p<0.001$). It represents those patients who are lately diagnosed in non-classical group usually present with more complications. Percentage of biopsy proven cases was more (27.7%) in non-classical group as TTG IgA levels were not relatable to clinical symptoms in such patients.

Steens et al studied increase in changing clinical picture of CD in Netherland where typical gut symptoms were less common and majority children presented with weight less than 10th percentile, lethargy and abdominal pain.[19]

Similarly, changing trend in the clinical profile of CD from classical picture to non-classical findings was reported in Northern Italy[20] and Maryland.[21]

In the present study, Iron deficiency anemia was the usual manifestation of anemia in two groups. Alanine aminotransferase (ALT) levels were high in classical group (43.5%) than in non-classical group (22.2%). This difference between both groups was insignificant (P=0.09).

In 2009, a study was conducted in Turkey which showed almost similar results where iron deficiency anemia was found commonest and nearly equal in typical (60%) and atypical (50%) groups while difference in deranged liver enzymes was significant (p<0.05) in two groups.[22]

Autoimmune disorders i.e. type1 DM & AIT are commonly related with CD.[23] In our study the most commonly found associated disorder was type 1 diabetes mellitus 8 (8.3%) followed by epilepsy 6 (6.2%), chronic hepatitis 5 (5.2%), autoimmune thyroiditis 3 (3.1%), and Down syndrome 1 (1%). All associated diseases were more common in non-classical group rather than classical group. In other words, children in non-classical group who were older in age group and lately diagnosed, more commonly showed related immune and non immune disorders.

Spijkerman et al reported association of type1 DM (4.9%) and AIT (4.1%) with CD in a cohort study.[24] In another study almost 6% prevalence of epilpesy was found in Turkish children with CD.[25]

Many studies report an increased association of autoimmune thyroiditis in children with CD.[26,27] Similarly autoimmune hepatitis (AIH) has been found in pediatric patients with CD with prevalence rate of 13.5%.[28]

CONCLUSION

In some cases of CD, non-gastrointestinal symptoms are the only clinical features without history of malabsorptive stools. Pediatricians must have increased recognition regarding varied behavior of CD to make early diagnosis and prevent treatment delay.

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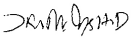
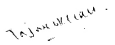
1	Javaria Rasheed	Corresponding author, Conception of idea, writing of manuscript,, literature review, data collection and assembly,drafting of the article.	
2	Tajwer Khan	Data collection, Literature review, Proof reading.	
3	Muhammad Khalid	Data interpretation and analysis statistical expertise, critical revision of intellectual content.	
4	Fauzia Zafar	Final approval and guarantor of article.