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CHRONIC DIARREHA: FREQUENCY OF CELIAC DISEASE IN CHILDERNS AT TEATIARY CARE HOSPITAL

Ameer Ali Jamali[1], Bella Shaikh[2], Anwar Ali Jamali[3], Ghulam Mustafa Jamali[4], Iqrar Ali Kanhar[5], Bhojo Mal Tanwani[6].

[1] MBBS, FCPS. Assistant Professor, Department of Pediatrics Medicine, Peoples University of Medical and Health Sciences for Women, Nawabshah, Sindh, Pakistan.

[2] MBBS, (post graduate FCPS). Department of Pediatrics Medicine, Peoples University of Medical and Health Sciences for Women, Nawabshah, Sindh, Pakistan.

[3]MBBS, MD, FCPS. Assistant Professor, Department of Medicine, Peoples University of Medical and Health Sciences Nawabshah Sindh, Pakistan.

[4] MBBS, MD, Senior Registrar, Department of Medicine, Peoples Un iversity of Medical and Health Sciences Nawabshah Sindh, Pakistan.

[5] MBBS, (post graduate FCPS). Department of Pediatrics Medicine, Peoples University of Medical and Health Sciences for Women, Nawabshah, Sindh, Pakistan.

[6] MBBS, M.Phill Department of Physiology, Peoples University of Medical and Health Sciences for Women, Nawabshah, Sindh, Pakistan.

Abstract:

Introduction: Celiac disease (CD) is an autoimmune disease of chronic origin affecting children as well adults and characterized by an unusual response towards gluten present in diet particularly in subjects who are genetically vulnerable. This leads injury to small intestinal mucosa and may be capable of various systemic effects. Objective: To determine the frequency of celiac disease in children presenting in the course of chronic diarrhea by using serological markers. Study Design: This study was Cross sectional. Setting: Pediatrics department, Peoples Medical College and Hospital (PMCH) at Nawabshah. Duration of Study: January 2017- December 2017. Subject and Methods: After fulfilling the inclusion criteria, 260 subjects with signs and symptoms of celiac disease visiting the department of Pediatrics, Peoples Medical College Hospital, Nawabshah were recruited in research. Results: Celiac Disease was diagnosed in 32 (12.3%) subjects with chronic diarrhea. Conclusion: Celiac Disease is commonly seen amongst subjects of chronic diarrhea and gluten-free diet is associated with considerable improvement in clinical features of Celia Disease. All subjects with chronic diarrhea must be evaluated routinely for celiac disease.

***Keywords**: Chronic Diarrhea, Celiac Disease, Tissue Transglutaminase autoantibodies*

Corresponding author:

Anwar Ali Jamali,

MBBS, FCPS. Assistant Professor,
Department of Pediatrics Medicine,
Peoples University of Medical and Health Sciences for Women,
Nawabshah, Sindh, Pakistan
*Email: *jamalianwarali@gmail.com*

QR code

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INTRODUCTION:

Celiac disease (CD) an autoimmune disease of chronic origin presenting in children as well adults, influencing approximately 1% of populace. The occurrence of Celiac disease is considerably variable in different populations [1][2][3]. Celiac disease is a chronic autoimmune disease of children characterized by an unusual response towards gluten present in diet particularly in subjects who are genetically vulnerable. This leads injury to small intestinal mucosa and may be capable of various systemic effects [4][5][6]. It was previously thought that celiac disease is limited to infants and children with malabsorption, but it is now considered that this disease affects all age groups even the elderly [7].

Celiac disease was regarded as a disease of western society in 20th century. The prevalence of celiac disease is variable ranging between 0.14% to 1.17% and 2.4% to 4.4% (in low and high risk groups) as shown in data from Middle East, India, and North Africa [8][9]. In general populace the pervasiveness of celiac disease ranges from 0.5% to 1.0% as observed in different studies [8] [10]. The prevalence rates are 0.33% to 1.5% in Europe and 0.7% to 1.3% in the United States [11]. In Indian children the occurrence of celiac disease was noted as 1% [12]. However incidence varies in different ethnic, racial and geographical parts of the world. The celiac disease affects pediatric as well as adult Pakistani populations but there are no definite renowned data concerning its prevalence [8].

The clinical presentation of celiac disease remains variable all through life, during infancy it usually presents with GIT symptoms, malnutrition and survival failure. In untreated subjects celiac disease is related with increased mortality and morbidity [13][14]. Stringent gluten-free diet is the most important management option of this condition [1][2].

The occurrence of CD (celiac disease) in a study series was 1.3% [15]. The selective serological screening of 198 symptomatic school children in a study showed prevalence of 0.322% celiac disease [4]. In another study, the prevalence of celiac disease by serological markers was 2.2%[1]. Imanzadeh F et al observed celiac disease in 6.5% of subjects of chronic diarrhea in their research [16].

Rationale

In pediatric populace of our country, Celiac disease is not uncommon condition. Clinically it presents with a wide range of features. Facilities of diagnosis with duodenal biopsy are not present widely. However, existing literature regarding the frequency of celiac disease by serological markers revealed that no local data is available in Pakistan. Due to this ambiguity, current study was planned. Therefore, the aim of current research was to determine the frequency of celiac disease in symptomatic pediatric population with chronic diarrhea by using serological markers. This will help to recommend serological markers for diagnosis of clinically suspected cases of celiac disease in centers where biopsy facilities are lacking.

Objective: To determine frequency of the celiac disease in children presenting through chronic diarrhea by using serological markers in a tertiary care hospital.

Operational Definitions:

Chronic Diarrhea: Diarrhea defined as the presence of ≥5 watery stools per day for more than 14th days.

Celiac Disease by serological markers

For the diagnosis of celiac disease blood tests for specific antibodies were done and values of Anti-tTG (Anti-Tissue Transglutaminase antibodies) >10 U/ml were considered diagnostic for celiac disease.

Anemia: Referred to hemoglobin level less than 11gm/dl in age range of 6-48 months and less than 11.5 gm/dl in the age range of > 48 months.

MATERIAL AND METHODS:

Study Design: This study was Cross sectional.

Setting: Pediatrics department, Peoples Medical College and Hospital (PMCH) at Nawabshah.

Duration of Study: January 2017- December 2017.

Sample Size: By taking prevalence of celiac disease with serological markers in children using P=6.5%[16], d=3% the calculated sample size was 260 patients with the help of WHO software for sample size calculation with confidence level 95%.

Sampling Technique: Non probability consecutive sampling.

SAMPLE SELECTION

Inclusion and Exclusion criteria: Children of either gender presenting with history of chronic diarrhea as per operational definition between the ages from 6 months to 12 years were included. Children with diseases like Giardiasis (diagnosed by examination of stool under the microscope for cysts), Irritable bowel syndrome diagnosed on the basis of Visual Analogue Scale (VAS) for at least 3 days per month during the previous 3 months, Cystic fibrosis (on the basis of sweat chloride test level ≥ 60 mmol/L).

DATA COLLECTION PROCEDURE:

This study was conducted after approval of hospital ethical review committee. After fulfilling the inclusion criteria, 260 subjects with signs and

symptoms of celiac disease visiting the department of Pediatrics, Peoples Medical College Hospital, Nawabshah were recruited in research.

Informed written consent was obtained from care takers of children. Patient's demographics and clinical history for symptoms of celiac disease were taken by the researcher. Serum Anti-tTG (anti-tissue transglutaminase antibodies) was done in all selected subjects as a serological marker. After all specific measures 4 ml of venous blood was drawn. Chemiluminescence immunoassay technique was used to analyze the IgA specific antibodies for Anti-tTG (anti-tissue transglutaminase). Anti-tTG (Anti-tissue Transglutaminase) antibodies >10 U/ml were considered diagnostic for celiac disease.

The results were finalized by the experienced consultant pathologist having more than five years of experience. The effect modifiers and biasness were controlled strictly by following the inclusion and exclusion criteria.

DATA ANALYSIS PROCEDURE:

Computer based software SPSS (Statistical Package for Social Sciences) version 20.0. was applied on collected data. Qualitative variables such as gender, anemia, and Celiac disease were analyzed for frequency and percentages. Mean ±SD was calculated for quantitative variable i.e. age, weight, anti-tTG antibodies titers at the time of diagnosis and duration of diarrhea. Stratification was done on gender, age, weight, anemia and duration of diarrhea to see the effect of these modifiers on outcome. Chi-square tests with P≤0.05 were regarded as remarkable.

RESULTS:

Total 260 patients with chronic watery diarrhea who were enrolled in this study, Mean age were 5.97 years (range, 6 months to 12 years). Serum anti-tTG antibodies titers mean was 7.9+/-3.1 in patients. Mean weight of patients was 13.5 kg with standard deviation 5.36kg. There were 122(46.9%) girls and 138(53.1%) boys who participated in the study. Anti-tTG antibodies titers was positive (CD) in 32 (12.3%) patients. **Table 1.**

Laboratory findings revealed anemia in 135 patients (51.9%), stratification was done, celiac disease was diagnosed in 20(16.4%) girls and 12(8.7%) male gender showed significant effect on the celiac disease with p-value 0.05. **Figure 1**

In **Table 2** stratification was done, celiac disease was diagnosed in 21(14.9%) patients had age < or equal to 5 years of age and 11(9.2%) patients who had age more than 5 years, showed non-significant effect on the celiac disease with p-value 0.16. In stratification of underweight was presented, celiac disease was diagnosed in 26(14.4%) underweight patients and 6(7.5%) in normal weight patients, it showed non-significant effect on the celiac disease with p-value 0.08.

In stratification was done, celiac disease was diagnosed in 5(6%) patients had duration of diarrhea < or equal to 25 days and 27(15.3%) patients who had duration of diarrhea for more than 25 days, it showed significant effect on the celiac disease with p-value 0.03. In stratification was done, celiac disease was diagnosed in 25(18.5%) patients were anemic and 7(5.6%) patients who anemic, it showed significant effect on the celiac disease with p-value 0.002.

Table 1: Descriptive statistics of quantitative variables. (n=260)

Variables	Number	Minimum	Maximum	Mean	Std. Deviation
Age	260	6 month	12 years	5.97	2.38
Weight	260	5	35	13.5	5.36
Anti-TTG Antibodies titers	260	6.5	13.4	7.9	3.1

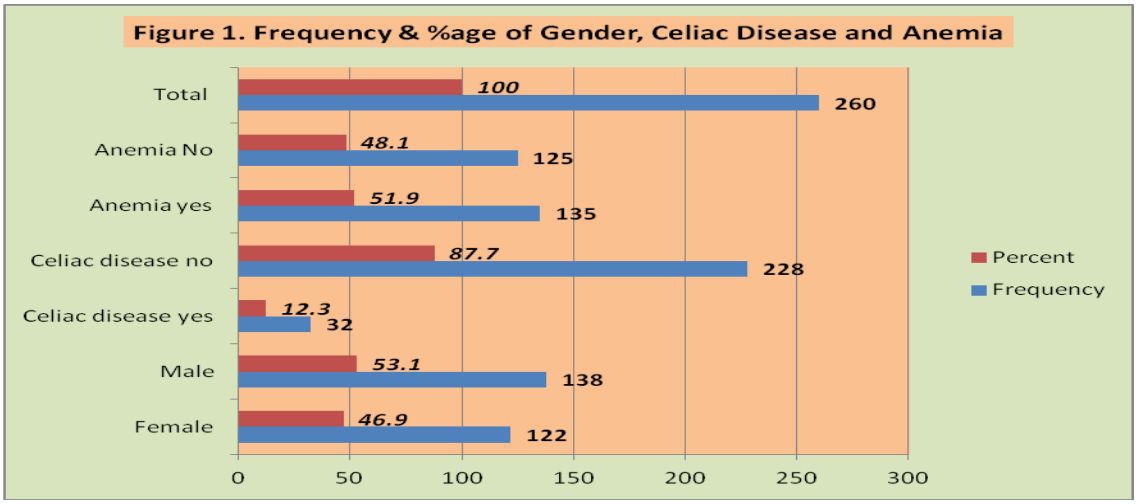

Table 2. Stratification for Celiac disease with regards to gender, age, weight, duration of diarrhea and anemia. n=260

Variables		Celiac disease		Total	p-value
		Yes	No		
	Female	20	102	122	**0.05 (Significant)**
		16.40%	83.60%	100.00%	
	Male	12	126	138	
		8.70%	91.30%	100.00%	
Total male and female		32	228	260	
		12.30%	87.70%	100.00%	
Age	< or 5 years	21	120	141	**0.16 (Non-significant)**
		14.90%	85.10%	100.00%	
Age	>5 years	11	108	119	
		9.20%	90.80%	100.00%	
Total		32	228	260	
		12.30%	87.70%	100.00%	
Underweight	Yes	26	154	180	**0.08 (Non-significant)**
		14.40%	85.60%	100.00%	
Underweight	No	6	74	80	
		7.50%	92.50%	100.00%	
		32	228	260	
		12.30%	87.70%	100.00%	
Total Underweight		Yes	No		
Duration of diarrhoea	<25 days	5	78	83	**0.03 (Significant)**
		6.00%	94.00%	100.00%	
Duration of diarrhoea	≥25 days	27	150	177	
		15.30%	84.70%	100.00%	
		32	228	260	
		12.30%	87.70%	100.00%	
Total Duration of diarrhoea		Yes	No		
Anemia	Yes	25	110	135	**0.002 (Significant)**
		18.50%	81.50%	100.00%	
Anemia	No	7	118	125	
		5.60%	94.40%	100.00%	
Total Anemia		32	228	260	
		12.30%	87.70%	100.00%	

DISCUSSION:

Index series is one of the largest compilations of children referred to pediatric hematology services with hematological abnormalities and subsequently diagnosed to have CD. Though gastrointestinal (GI) complaints were frequent, they were subjectively less annoying. The foremost symptoms were related to anemia. Regional distribution of patients in the study represents predominantly wheat-consuming north Indian population.
Society of European Pediatric (Gastroenterology and Nutrition) had given guidelines for diagnosis of CD. Histological confirmation is mandatory and remains the gold standard of diagnosis. We have swayed from the standard guidelines, as the diagnosis was made in a large majority by serology alone. Biopsy was performed in 31 cases; the findings were not in conflict with the diagnosis of CD in any of the symptomatic, sero-positive cases. This gave us confidence in initiating Gluten Free Diet in symptomatic cases following a positive Anti tTG antibodies. With the introduction of highly specific and sensitive serological tests, there is increasing discussion on avoiding duodenal biopsy in selected, overtly symptomatic, serologically positive cases. This is particularly true in tropical countries where histological changes consistent with CD may not be pathognomonic of the disease.

Several conditions may lead to villous atrophy that is indistinguishable from CD; such as persistent enteric infections, parasitic infestation with Giardia lamblia, small bowel bacterial overgrowth or tropical sprue, severe malnutrition and rotavirus enteritis [17][18].

A biopsy may in fact be misleading in such cases. In popular flow-charts for the diagnosis of CD, cases with a clinical probability of CD and positive serology are shown to have a 'dead-end' option of a positive biopsy [19]. The occurrence of circulating anti-endomysial or anti-tTG antibodies is extremely predictive (97%-100%) with the biopsy changes of Celiac Disease in subjects with clinical features of CD [20]. Need for intestinal biopsy in every case has been questioned by Scoglio et al, [21] though their conclusions were criticized as being flawed [22]. Murdock et al [23] had raised the issue of diagnostic criteria for CD as well. It has been suggested that a biopsy may not be required in symptomatic children with a high titer of tTGA [24].
Previously this was false impression that celiac disease was infrequent in Indian population but it is frequent as proved by many newly reports [25][26]. Conversely, the entire of these reports is related with subjects of diarrhea (typical variety) of Celiac Disease, while passing reference had existed on the subjects presenting of unusual variety of illness [27].
In current research, 260 children having chronic diarrhea of small intestinal origin were evaluated for the occurrence of Celiac Disease. All the subjects with diagnosis of Celiac Disease were put on gluten free diet and followed for six months. We analyzed that celiac disease is regular diagnosis in children with chronic diarrhea in Pakistani population. Current study results are similar with findings as well as occurrence of Celiac Disease in indoor subjects of chronic diarrhea in a hospital at Middle East [28]. In Kuwaiti children occurrence of CD was noted as 18.5% in subjects who presented with chronic diarrhea [29].

Characteristic features of classic celiac disease are chronic diarrhea, anorexia, distension of abdomen, muscle wasting and malnutrition and are usually observed in children between the ages of 06 months to 18 months. After the availability of diagnostic serological tools for Celiac Disease, it was proved that many atypical forms of this disease exist and these atypical forms are more common than the typical forms and also that CD is present not only in children but is also seen in all age groups [30]. The diagnosis of CD has been reported at the age of 67 years in an old woman [31]. Current study revealed an interesting finding in 03 subjects, they were IgA EMA positive with normal duodenal biopsy (Marsh 0), and their symptoms i.e. diarrhea resolved completely with gluten free diet. The normal duodenal biopsy does not exclude the CD, because this may be related with the patchy involvement of the duodenum by disease. The other likelihood may be that subjects have latent Celiac Disease along with a small degree of gluten sensitivity. Subjects with diarrhea dominant IBS (irritable bowel syndrome) having antibodies related to celiac disease responded well to gluten free diet [32].

Idiopathic enteropathy and Crohns disease of small bowel origin were frequent and ought to be regarded in differential diagnosis of chronic diarrhea of small bowel nature [33]. Most of the infectious causes of chronic diarrhea other than tuberculosis were less common. The celiac disease is under diagnosed disease as shown by this population- based research. In a study conducted in schoolchildren with non-invasive serological screening detected disease in those who were not previously diagnosed.

Clinically the celiac disease presents as tip of iceberg. Genetically remarkable increased risk of celiac

disease may be the reason of increased prevalence. Human Leucocyte Antigen genotypes allocation in population matches with genotyping of Finnish population. Factual occurrence of the CD expected to be still greater than 1per 99. Individuals with normal biopsy of small bowel, consuming regular amounts of gluten, they show consequent mucosal changes and CD as evidenced by presence of gluten-induced antibodies. At the beginning of study, we observed that 5 patients were serologically positive for CD but with follow up screening inspite of taking regular diet they became sero-negative for CD, current feature supports to the natural history of a minor variant of CD in that gluten sensitivity rises and falls in due course [34].

Earlier it was suggested that cereals intolerance was not a definite feature of CD, subjects who reported with abdominal complains after taking cereals only 10% of them had CD [35]. HLA-DQ2 or DQ8 molecules are found in nearly all subjects of sero-positive celiac disease. IgA endo-mysial (indirect immunofluorescence) antibodies screening, authenticated in Europe was used to discover the untreated CD subjects. The negative aspect of this test remains its bias (subjectivity). Later on, a non-observer dependent ELISA test was introduced to detect antibodies against tissue transglutaminase. It was observed that this screening test was consistent and susceptible same as endomyseal antibodies screening test.

Subjects with clinically silent CD and genetically inherited intolerance to gluten must go through these simple and reliable screening tests before they develop the features of malabsorption. One third of patients with confirmed CD in current study were without symptoms and had no any risk factors. Osteoporosis and other complications are the risk of undetected CD. On the other hand, particularly in asymptomatic subjects the permanent requirement to pursue a GFD (Gluten Free Diet) is troublesome. Before suggesting for population-based screening for CD, the consequences of CD in asymptomatic subjects must be reviewed. Nevertheless, specified findings of this study with the intention of celiac disease show CD as under diagnosed. Multifaceted clinical picture of the CD must be kept in mind by clinicians along with elevated index of doubt and a small threshold for arranging serological screening.

CONCLUSION:

Among subjects presenting with chronic diarrhea, celiac disease is a frequent cause. Noteworthy improvement noted in clinical features after gluten free diet. All subjects with chronic diarrhea must go through routine screening for the celiac disease.

Healthcare segment must arrange for attentiveness of public for celiac disease. Celiac disease apparently seems to be less frequent in populations, recent facts specifies that burden of disease may be more, thorough investigations had positive value in the enhanced management and decreasing the mortality and morbidity associated with celiac disease in pediatrics population.

To conclude, hematologists need to be aware of the extra-intestinal manifestations of CD. Serological tests for CD should be requested in children presenting with Iron Deficiency Anaemia that is refractory to hematinics or who have coexisting growth retardation. Whether duodenal biopsy can be avoided in selected, overtly symptomatic, sero-positive cases, needs deliberation. Prolonged duration of symptoms and diagnosis at an older age indicates that awareness for CD needs to be broadened. Abatement of symptoms and improvement in growth parameters following GFD are gratifying for patient, family, and the physicians alike.

Those subjects, who are at risk of CD, need serologic screening for the alleviation of ailment, preventing disease related complications and to get improved quality of life.

REFERENCES:

1. Ivarsson A, Myleus A, Norstrom F, van der Pals M, Rosen A, Hogberg L, et al. Prevalence of childhood celiac disease in and changes infant feeding. Pediatr. 2013;131(3):687-94.
2. Green PH, Cellier C. Celiac disease. N Engl J Med. 2007;357(17):1731–43.
3. Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med. 2010;42(8):587–95.
4. Deora NS, Deswal A, Dwivedi M, Mishra HN. Prevalence of coeliac disease in india:a mini review. Int J Latest Res Sci Technol. 2014;3(10:58-60.
5. Lauret E, Rodrigo L. Celiac disease and autoimmune-associated conditions. Biomed Res Int. 2013;2013:127589.
6. Cataldo F, Montalto G. Celiac disease in the developing countries: a new and challenging public health problem. World J Gastroenterol. 2007;13(15):2153.
7. Al Saidi SS, Al Harthi SO, Mula-Abed WAS. Diagnostic utility of coeliac disease: a

descriptive study in a tertiary care hospital, Oman. Oman Med J. 2013;28(4):232.
8. Hussain S, Sabir MU, Afzal M, Asghar I. Coeliac disease-clinical presentation and diagnosis by anti tissue transglutaminase antibodies titre in children. J Pak Med Assoc. 2014;64(4):437-41.
9. Barada K, Bitar A, Makadem MA, Hashash G, Green P. Celiac disease in Middle Eastern and North African countries: A new burden? World J Gastroenterol. 2010;16:1449-57.
10. Hill ID, Dirks MH, Liptak GS, Colleti BB, Fasano A. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J PediatrGastroenterol Nutr. 2005;40:1.
11. Koehne VDB, Bahia M, Lanna CCD, Pinto MRDC, Bambirra EA, Cunha ASD. Prevalence of serological markers for celiac disease (IgA and IgG class antigliadin antibodies and IgA class antiendomysium antibodies) in patients with autoimmune rheumatologic diseases in Belo Horizonte, MG, Brazil. Arquivos De Gastroenterol. 2010;47(3):250-6.
12. Bhattacharya M, Dubey AP, Mathur NB. Prevalence of celiac disease in north Indian children. Indian Pediatr. 2009;46(5):415-7.
13. Di Sabatino A, Corazza GR. Coeliac disease.Lancet. 2009;373(9673):1480–93.
14. Tio M, Cox MR, Eslick GD. Meta-analysis: coeliac disease and the risk of all-cause mortality, any malignancy and lymphoid malignancy. Aliment Pharmacol Ther. 2012;35(5):540–51.
15. Carlsson AK, Axelsson IE, Borulf SK, Bredberg AC, Ivarsson SA. Serological screening for celiac disease in healthy 2.5-year-old children in Sweden. Pediatr. 2001;107(1):42-5.
16. Imanzadeh F, Sayyari AA, Yaghoobi M, Akbari MR, Shafagh H, Farsar AR. Celiac disease in children with diarrhea is more frequent than previously suspected. J Pediatr Gastroenterol Nutr. 2005 Mar;40(3):309-11.
17. Levy J, Bernstein L, Silber N. "Celiac disease: an immune dysregulation syndrome". Curr Probl Pediatr Adolesc Health Care (Review). (Dec 2014) 44 (11): 324–7.
18. Montalto M, Gallo A, Ojetti V, Gasbarrini A."Fructose, trehalose and sorbitol malabsorption" (PDF).Eur Rev Med Pharmacol Sci (Review). (2013) 17 (Suppl 2): 26–9.
19. Patwari AK, Anand VK, Kapur G, Narayan S. Clinical and nutritional profile of children with celiac disease. Indian Pediatr 2003;40:337-42.
20. Mohindra S, Yachha SK, Srivastava A, Krishnani N, Aggarwal R, Ghoshal UC, et al. Coeliac disease in Indian children: Assessment of clinical, nutritional and pathologic characteristics. J Health Popul Nutr 2001;19:204-8.
21. Poddar U, Thapa BR, Nain CK, Prasad A, Singh K. Celiac disease in India: Are they true cases of celiac disease? J Pediatr Gastroenterol Nutr 2002;35:508-12.
22. Pooni PA, Chhina RS, Jaina BK, Singh D, Gautam A. Clinical and anthropometric profile of children with celiac disease in Punjab (North India). J Trop Pediatr 2006;52:30-3
23. Kalhan S, Joseph P, Sharma S, Dubey S, Dudani S, Dixit M. Comparative study of histopathological Marsh grading with clinical and serological parameters in celiac iceberg of north India. Indian J Pathol Microbiol 2011;54:279-83.
24. Fasano A. Celiac disease-how to handle a clinical chameleon. N Engl J Med 2003;348:2568-70.
25. Yachha SK, Misra S, Malik AK, Nagi B, Mehta S. Spectrum of malabsorption syndrome in North Indian children. Indian J Gastroenterol 1993;12:120-25.
26. Poddar U. Celiac disease: clinical features and diagnostic criteria. Indian J Pediatr 1999; 66 (suppl); S21-25
27. Kaur G, Sarkar N, Bhatnagar S, Kumar S, Rapthap CC, Bhan MK, et al. Pediatric celiac disease in India is associated with multiple DR3-DQ2 haplotypes. Hum Immunol 2002; 63(8): 677-682.
28. Al-Bayatti SM. Etiology of chronic diarrhea. Saudi Med J 2002;23:675-9.
29. Shaltout AA, Khuffash FA, Hilal AA, el Ghanem MM. Pattern of protracted diarrhea among children in Kuwait. Ann Trop Padiatr 1989;9:30-2.
30. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving
spectrum. Gastroenterology 2001;120:636-51.
31. Siry M, Burges C, Stiens R, Schneider H, Steiff J. First diagnosis of celiac disease in a 67-year old female patient. Dtsch Med Wochenschr 2000;125:932-6.
32. Wahnschaffe U, Ullrich R, Riecken EO, Schulzke JD. Celiac disease-like abnormalities in a subgroup of patients with irritable bowel syndrome. Gastroenterology 2001;121 :1329-38.
33. Nasr K, Haghighi P, Abadi P, et al. Idiopathic enteropathy: an evaluation in rural Iran with an

appraisal of nutrient loss. Am J Clin Nutr 1976;29:169-76.
34. "Symptoms & Causes of Celiac Disease NIDDK". National Institute of Diabetes and Digestive and Kidney Diseases. June 2016. Retrieved 24 April 2017.
35. Lebwohl B, Ludvigsson JF, Green PH."Celiac disease and non-celiac gluten sensitivity". BMJ (Review). Oct 2015,351: h4347.