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Original Article

Demographic and Clinical Profile of Celiac Disease in Kashmiri Children: An Observational Study

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Abstract

Introduction: Celiac disease is a common disorder in North India. No study is available regarding its clinicopathological profile in Kashmiri children. Kashmir valley is abode to three different ethnicities principally constituted by Kashmiris and small population of Pahari and Gujjar.

Aims and Objective: This study aims to study demographic and clinical profile of celiac disease in Kashmiri children.

Materials and Methods: The current study is hospital-based descriptive observational study conducted over $1_{1/2\ year}$. All patients in the age group of 6 months–12 years presenting with chronic diarrhea and unexplained failure to thrive were evaluated for celiac disease. A total of 62 patients were evaluated during the study period and 12 came positive for celiac disease (19%).

Results: Mean age of presentation is 6 years. Regarding principal modes of presentation, chronic diarrhea is observed in 10 (83%), unexplained failure to thrive 2 (16%), short stature 4 (33%), 7 out of 12 with wasting (58%), anemia 6 (50%), electrolyte disturbance like hypokalemia in 7 (58%), with severe hypokalemia (k+<2) in three patients, and isolated hypertransaminasemia in 4 (33%). Majority of the patients are Pahari/Gujjar (66%) despite constituting very little of whole population. This means that a case of chronic diarrhea and unexplained failure to thrive is more likely to be celiac if belonging to this section of society.

Conclusion: Celiac disease is well present in Kashmiri children with case positivity rate among chronic diarrhea and unexplained failure to thrive comparable to rest of North India and clinical spectrum shows malnutrition, anemia, and dyselectrolytemia in majority of patients. Its prevalence varies between different ethnic groups being more in Pahari and Gujjar children as compared to ethnic Kashmiri population.

Key words: Anemia, Chronic diarrhea, Failure to thrive, Malabsorption

INTRODUCTION

Celiac disease is a chronic systemic autoimmune disorder triggered by ingestion of dietary gluten and is characterized by small intestinal inflammation and villous atrophy.[1] It was not until the middle of the 20th century that a link between certain cereals and celiac disease was made by William Karel Dickle, a Dutch pediatrician. He became convinced that the consumption of bread and wheat floor was directly responsible for deterioration in patients suffering from this condition.[2] Subsequent work by Van de Kamer showed that it was the water insoluble portion or gluten moiety of wheat that produced intestinal injury in patients with celiac disease.[2] Since the 1980s, we have seen substantial advances in our understanding of genetic, immune, and molecular mechanisms fundamental to pathogenesis of celiac disease. In 1986, Howell *et al.* observed that celiac disease was associated with human leukocyte antigen (HLA)-DQ2 haplotypes. In 1993, Lundin *et al.* demonstrated that DQ2 gene products preferentially present gluten-derived gliadin peptides to intestinal mucosal T-cell in celiac disease. Subsequently, the enzyme Ttg type 2 was identified as a celiac autoantigen, leading to more accurate serological diagnostic tests. Celiac disease exhibits a spectrum of clinical presentation. Atypical celiac is fully expressed gluten sensitive enteropathy manifest only by extraintestinal symptoms and signs including short stature, anemia, osteoporosis, and infertility. Silent celiac

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is fully expressed gluten-sensitive enteropathy usually found after serological testing in asymptomatic patients. The atypical and silent variants are more common than classical or typical celiac which is fully expressed gluten-sensitive enteropathy found in association with classic gastrointestinal (GI) symptoms of malabsorption. This combination of serologic, genetic, and histologic data also led to the identification of two other types of celiac disease. Patients with latent celiac disease have normal villous architecture on a gluten containing diet but at another time have had or will have gluten-sensitive villous atrophy. Patients with potential celiac disease have never had a biopsy consistent with celiac disease but show immunological abnormality consistent with disease like positive immunoglobulin (Ig)A Ttg2.

Clinical features of celiac disease vary considerably. Intestinal symptoms are common in children whose disease is diagnosed within the first 2 years of life, failure to thrive, chronic diarrhea, vomiting, abdominal distention, muscle wasting, anorexia, and irritability which are present in most cases. Occasionally, there is constipation rectal prolapsed or intussusception.[1]

The most common extraintestinal manifestation of celiac disease is iron deficiency anemia,[1] unresponsive to iron therapy. Osteoporosis may be present. There may be short stature, arthritis, arthralgias, endocrinopathies, epilepsies with bilateral occipital calcification peripheral neuropathies, cardiomyopathies, chronic lung disease, aphthous stomatitis, alopecia, and isolated hypertransaminasemia. Some diseases with an autoimmune pathogenesis are found in higher than normal incidence in celiac patients. Among these are type 1 diabetes, autoimmune thyroid disease, Addison disease, Sjogren's disease, autoimmune cholangitis, autoimmune hepatitis, primary biliary cirrhosis, IgA nephropathy, and dilated cardiomyopathy.[1] The mean age of onset of symptoms in Indian children is 2.4 years and mean age of diagnosis is 8.3 years.[3] There is considerable variation in clinical profile of celiac disease in India and west, whereas studies in India show higher prevalence of diarrhea (88%) and failure to thrive (90%),[3] studies in west have shown a low percentage of celiac disease patients suffering from diarrhea.[4-6] Again studies have challenged the symptoms and associated conditions as a tool for case finding and screening.[4-6] Celiac disease is a common disorder with about 1% prevalence of biopsy proven cases in Western countries.[1] The term celiac iceberg was coined to describe the wide variation in nature and intensity of clinical presentation of which overt celiac is only the emerging peak. The discovery of large immersed part of celiac iceberg has transformed the status of celiac disease, long considered a rare disease to that of a common health problem.

The availability of new, simple, very sensitive, and specific serological tests has shown that celiac disease is not only common in Europe but also in developing countries. The prevalence of celiac disease in India is not well documented. Most of the studies in the past two decades in India have focused on classical celiac disease in which chronic diarrhea is a predominant feature. With advent of simple and accurate serological markers, population screening has shown higher prevalence of 1 in 70 to 1 in 250 in North India with diagnosed to undiagnosed ratio of 1:75.

There are limited data on prevalence of celiac disease in India. The majority data are from North India. There are regional variations in prevalence of celiac disease in India due to genetic and dietary factors that are wheat rice shift as we go from north to south in India.[10] It is most common cause of chronic diarrhea in children over 2 years of age in North India.[7] Among adults, it accounts for 26% of chronic diarrhea.[8]

Our study shows demographic and clinical profile of celiac disease in children with:

- Chronic diarrhea and malabsorption
- Unexplained failure to thrive.

MATERIALS AND METHODS

The study was conducted at GB Pant Hospital, Srinagar, an associated hospital of GMC, Srinagar. The study was a hospital-based observational study of admitted patients/children conducted from April 1, 2014, to October 1, 2015.

Inclusion Criteria

Children between 6 months and 12 years both males and females presenting with chronic diarrhea and/or failure to thrive were included in the study. Children were labeled as having chronic diarrhea if they had diarrheal episodes lasting for 14 days or more. Children were labeled as having fat malabsorption if there was a clinical evidence of fat-soluble vitamin deficiency or documented weight loss or wasting or presence of fat globules on stool microscopy. Children with stool positive for reducing substances and PH <5.5 were considered to have carbohydrate malabsorption. Children hospitalized for unexplained failure to thrive formed the second group of patients to be screened for celiac disease.

Children were excluded in which failure to thrive was secondary to chronic systemic disease, chronic infections, child abuse and neglect, children with chronic diarrhea secondary to giardiasis, clinical or laboratory evidence of cholestasis liver disease, cystic fibrosis, abetalipoproteinemia, and patients who have undergone gut resection. Children

fulfilling the inclusion criteria of the study underwent detailed relevant history and clinical examination recorded in a preset pro forma. Anthropometric assessment was done. Dietary evaluation including feeding history, age at introduction of gluten containing diet was done. Other tests such as hemogram, blood chemistry, coagulation profile, stool microscopy, stool for fat, and X-ray wrist were done. Serological testing with IgA TTG was also done. Serology was supplemented with serum IgA levels. If it came positive, children were subjected to small intestinal biopsy. Histopathological examination of biopsy specimen was done and reporting was done according to MARSH grading. Positive cases were followed up after introduction of gluten-free diet.

RESULTS

A total of 62 patients in the age group of 6 months–12 years presenting with either chronic diarrhea or unexplained failure to thrive/gain weight were evaluated for celiac disease in time span of $1_{1/2\ year}$s. Twelve out of 62 study patients came positive for celiac disease with a case positivity rate of 19%. Mean age at presentation was 6 years. Earliest presentation was in one infant presenting at 11 months with chronic diarrhea and failure to thrive, positive for celiac disease both on serology and biopsy. Under nutrition was present in 7 out of 12 (58%). Four patients (33%) were with short stature, anemia was present in 6 patients (50%), and electrolyte abnormalities, especially hypokalemia, were present in 7 patients (58%). The most common presentation seen was chronic diarrhea present in 83% of patients.[10] Unexplained failure to thrive/gain weight without diarrheal disease was present in 2 patients (16%). Upper GI endoscopy was grossly normal in 75% of cases. Only 3 patients (25 %) showed gross changes on upper GI endoscopy. Out of total 62 patients that were evaluated, 27 (43%) were from Pahari/Gujjar population (non-ethnic group) whereas 35 patients (56%) were from ethnic population. Case positivity rate seen was 29% (8 out of 27 study subjects) in Pahari/Gujjar population and 11.4% (4 out of 35 study subjects) in ethnic population.

DISCUSSION

The current study is well-documented account of celiac disease its clinical and demographic profile in Kashmiri children. No study was available regarding celiac disease in Kashmiri children. Public health importance of celiac disease is still underestimated among primary child physicians. The prevalence of celiac disease in Indian children is not well documented. It has been seen that celiac disease is the most common cause of chronic diarrhea in children above 2 years in North India.[7] Among adults, it accounts for 26% of chronic diarrheas.[8] Celiac disease is submerged in an ocean of malnutrition. The limited data on CD in India can be attributed to several factors like common belief like:

1. Celiac disease is uncommon in India
2. Recognition of tropical sprue and GI TB as major causes of chronic diarrhea and malabsorption
3. Non-realization that partial villous atrophy may be a feature of CD
4. More pressing problem of malnutrition and lack of awareness regarding non-diarrheal manifestation of CD.[9-12]

Regarding age of presentation, this varies from late infancy to adolescence in our study, with one infant presenting at 11 months of age, positive for celiac disease on serology and histology. Mean age at presentation is 6 years. This depends on prolonged breastfeeding and other feeding practices and time of gluten supplementation. Delayed onset of disease in other developing countries with similar feeding practices may be due to prolonged breastfeeding and delayed gluten introduction. In our study, principle mode of presentation is chronic diarrhea and failure to thrive. Chronic diarrhea is present in 83% of patients. Two patients presented with failure to thrive without any diarrheal illness. Increased awareness about this disease is thus required for its early diagnosis, particularly in children presenting without diarrheal illness. In Western studies, proportion of patients without diarrhea is up to 20–40%.[13,14] Among the various clinical and biochemical features, anemia, undernutrition, and short stature are very common. Undernutrition in 58%, anemia in 50%, and short stature in 33%. Iron deficiency anemia is the most common extraintestinal manifestation of celiac disease. Dyselectrolytemia, especially hypokalemia, is very common among celiac patients (58%). Most of our celiac patients had abnormalities of fat malabsorption, anemia, short stature, and dyselectrolytemia. The frequency of common features such as chronic diarrhea, failure to thrive, anemia, and fat malabsorption was similar to those reported earlier from both developing and developed countries.[15,16] No gross difference was found in clinical and laboratory features of celiac disease in Kashmiri children and elsewhere. On endoscopy, gross pathological changes are found in some patients of celiac disease. In our study, only three out of 12 showed gross finding on endoscopy, that is, scalloping. In other words, 75% of patients will not have any grossly identifiable finding on endoscopy. The duodenum may be normal or may show findings like scalloped duodenal folds but these findings are not specific for CD17. All patients in our study were biopsy confirmed with different subclasses of Marsh Grade 3, which is consistent with celiac disease.

With the upcoming of new ESPGHAN18 guidelines, biopsy and histopathology are no more required to confirm the celiac disease, provided the serology comes strongly positive that is more than 10 times the upper limit of normal. It is worthwhile to mention that in our study, all of the patients with positive serology had serum antibody levels <10 times of normal value.

In our country, serology and biopsy are simpler, cheaper, widely available, and more reliable method of diagnosing CD as the restricted availability, reliability of reporting, and high cost of HLA and EMA testing limits its universal use. The prevalence of celiac disease may vary among different communities in one particular geographic region depending on difference in genetic makeup and dietary practices.[17-20]

In our study, case positivity rate among Gujjar and Pahari children is much more (3 times) as compared to ethnic Kashmiri children with chronic diarrhea and failure to thrive. This means that a case of chronic diarrhea or failure to thrive is much more likely to be celiac if belonging to this section of society as compared to majority community.

This difference may be attributed to genetic makeup and dietary difference in two groups. Rice is the major staple diet of ethnic Kashmiris followed by wheat. In Gujjar and Pahari, principal staple diet is wheat and maize followed by rice. Principal trigger wheat is consumed by both of the communities. This difference may be more due to difference in genetic makeup. The main genetic factors are HLA-DQ genes that are the genes encoding DQ2 and DQ8 in HLA complex. Adequate data about DQ2 and DQ8 distribution in India are lacking.

CONCLUSION

Celiac disease is well present in Kashmiri children with case positivity rate among chronic diarrhea and unexplained failure to thrive comparable to rest of North India and clinical spectrum shows malnutrition, anemia, and dyselectrolytemia in majority of patients. Its prevalence varies between different ethnic groups being more in Pahari and Gujjar children as compared to ethnic Kashmiri population.

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