Section: Paediatrics

Original Research Article

PROPORTION OF CELIAC DISEASE IN CHILDREN WITH RICKETS

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Abstract

Background: Celiac disease is an immune-mediated, gluten-induced enteropathy in genetically susceptible individuals.Clinical manifestation of celiac disease exhibits a wide spectrum, which includes a combination of gastrointestinal symptoms and extra-intestinal symptoms. Celiac disease can be present as a typical disease containing typical symptoms like chronic diarrhea, malabsorption, failure to thrive or it can present as an atypical disease. **Materials and Methods:** The enrolment of the children in our study, was done in the Department of Pediatrics, GTB Hospital, between November 2019 to October 2021 from the Paediatric outpatient/inpatient/emergency. Thirty children with clinical and radiological evidence of rickets were enrolled in the study. **Result:** Out of 30 children, 1 child had a positive IgA-tTG level. The child with positive serology underwent upper gastrointestinal endoscopy followed by a biopsy which was equivocal (Marsh type). **Conclusion:** By this study, we conclude that although it is known that rickets is one of the presentations of celiac disease, celiac disease as such is less likely to be present in patients with rickets.

INTRODUCTION

Celiac disease is also known as gluten-sensitive enteropathy is one of the most common malabsorption in children.[1] Ingestion of gluten in genetically susceptible individuals leads to immune-mediated mucosal damage of the small intestine which in turn causes malabsorption. The prevalence of celiac disease in north India according to one community-based study is 1.04%.[2] The classical symptoms of celiac disease include abdominal pain, diarrhea, and growth failure. Other nonspecific symptoms are anemia, fatigue, constipation, short stature, osteoporosis, rickets, etc. In some cases, rickets may be the only presenting feature in celiac disease.

The major cause of rickets is the nutritional deficiency of vitamin D, though some studies have shown dietary calcium deficiencies may also lead to rickets. Diseases causing malabsorption like celiac disease leads to rickets by decreasing absorption of vitamin D or calcium. Clinical features of rickets are widening of wrists and ankles, bowing of legs, craniotabes, rachitic rosary, and Harrison sulcus.[3,4] Diagnosis of rickets is made based on history, physical examination, biochemical testing and is confirmed by radiograph.

In a retrospective study conducted by Assad Assiri et al. prevalence of celiac disease was 38.4% in patients with unexplained rickets.[5] Another study conducted by R. Philip et al. from India found 8% of celiac disease patients had rickets.[6] Very few studies were conducted for establishing the prevalence of celiac disease in rickets.

MATERIALS AND METHODS

The enrolment of the children in our study, was done in the Department of Pediatrics, GTB Hospital, between November 2019 to October 2021 from the Paediatric outpatient/inpatient/emergency. Thirty children with clinical and radiological evidence of rickets were enrolled in the study. Detailed history, anthropometry, and clinical examination as well as biochemical investigations including blood hemoglobin, and serum levels of calcium, phosphate, and alkaline phosphatase were done. All cases were then screened for celiac disease using serum levels of IgA-tTG. Those children with a positive serum IgA-tTG underwent upper GI endoscopy and biopsy to confirm the diagnosis of celiac disease.

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Study Subjects

Inclusion Criteria

Children aged between 1 year to 12 years with rickets based on history, examination, and radiological features.

Exclusion Criteria

1. Already diagnosed with celiac disease
2. Rickets due to drugs known to cause metabolic bone disease e.g. - steroids, anticonvulsants, chemotherapy, etc.

Methodology: The screening was done in the Department of Pediatrics, University College of medical sciences and Guru Teg Bahadur Hospital between November 2019 to October 2021 from outpatients/inpatients/emergency. A total of 37 children aged between 1 year to 12 years were screened for cases on the basis of history, clinical examination, and radiological evidence suggestive of rickets. Five children were excluded from the study as they were on chronic anticonvulsant and parents of 2 children did not give consent to enroll the children in the study. A total of 30 children were included in the study and clinical predictors of celiac disease, such as short stature, anemia, failure to thrive, abdominal distension, chronic diarrhea, etc., were enquired. All patients were tested for IgA-tTG antibodies by ELISA kit, and a duodenal biopsy was done in patients who had positive levels of IgA-tTG.

RESULTS

The studied group included 30 cases (with rickets). Amongst the enrolled children, 19 (63.3%) were males and 11 (36.7%) were females (Figure 1). The age of the patients ranged from 1 to 7 years with the mean (SD) age of presentation being 2.55 ± 1.64 years and median (IQR) age being2.00 (1.38-3.00). The age distribution is shown in Figure 2.

1. Presenting complaints:

Amongst the enrolled subjects, cough was the most common presenting complaints (76.7%, n=23) followed by fever (66.7%, n= 20), coryza (13.3%, n=4), and fast breathing (6.7%, n=2). Other presenting complaints were seizure, carpopedal spasm, dribbling of urine, poor development, poor growth, loose stool, decreased food intake, loss of milestones, pain abdomen, and respiratory distress. One patient visited the hospital for vaccination. [Table 1, Figure 3]

2. Clinical History

A detailed clinical history of enrolled participants was taken including the clinical predictors indicating celiac disease. History of constipation was present in two (6.7%) of the enrolled participants, history of diarrhea in seven (23.3%), abdominal pain associated with the change in stool frequency or consistency was present in one patient (3.3%). No participant had any history of abdominal distension, a family history of known celiac disease, or any malignancy. History of consanguinity (third-degree) was present in two patients (6.7%).

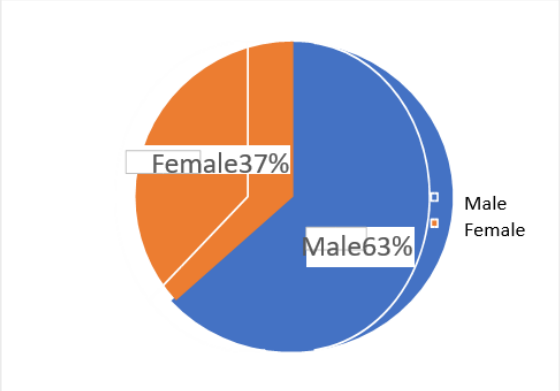

Figure 1: Distribution of gender among the enrolled participants

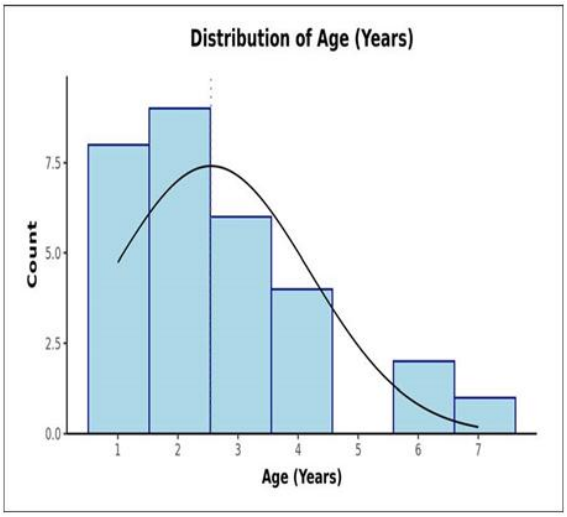

Figure 2: Distribution of age among the enrolled participants

Table 1: Summary of presenting complaints.

Presenting Complaints	n
Loss Of Milestones	1 (3.3%)
Seizure	1 (3.3%)
Cough	23 (76.7%)
Coryza	4 (13.3%)
Decreased Food Intake	1 (3.3%)
Pain Abdomen	1 (3.3%)
Carpopedal Spasm	1 (3.3%)
Poor Growth	1 (3.3%)
Fever	20 (66.7%)
Fast Breathing	2 (6.7%)

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Acute Gastroenteritis	1 (3.3%)
Respiratory Distress	1 (3.3%)
Dribbling Of Urine	1 (3.3%)
Poor Development	1 (3.3%)
Vaccination	1 (3.3%)

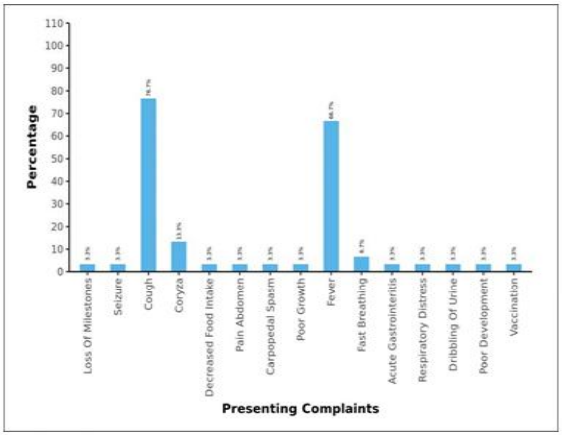

Figure 3: Summary of presenting complaints

3. Dietary history:

History of top feeding in the first 6 months was present in ten (33.3%) of the enrolled participants. Twenty (66.7%) of the patients were exclusively breastfed in the first 6 months. 16.7% (n=5) of children had started complementary feeding before 6 months of age, and 83.3% (n=25) of children were started on complementary feeds after 6 months of age. The mean (SD) and median (IQR) age of starting gluten-containing complementary feeds were 6.57 (2.67) months and 6 (6, 7.5) months respectively.

4. Anthropometric parameters:

The mean (SD) weight of the patients was 10.38 (3.59) kg and the median (IQR) weight was 9.65 (8.00; 11.30) kg. Eight patients (26.7%) were moderately underweight while 6 patients (20%) were severely underweight. The mean (SD) height of the patients was 81.94 (14.64) cm and median (IQR) height was 76.75 (70.25; 86.38) cm. Four (13.3%) were stunted while 11 patients (36.7%) were severely stunted. Wasting was present in 3 patients (11.1%) while 4 patients (14.8%) were severely wasted. The anthropometric details of enrolled subjects are depicted in [Table 2].

Table 2: Anthropometric measurement of enrolled participants

Parameter	Mean (SD)	Median (IQR)
Weight-for-Age (n=30)	10.38 (3.59)	9.65 (8.00, 11.30)
Height-for-Age (n=30)	81.94 (14.64)	76.75 (70.25, 86.38)
BMI-for-Age (n=3)	13.23 (1.09)	12.63 (12.6, 13.56)

5. Physical Examination

Pallor was present in 24 patients (80%) among the enrolled participants. Edema was present in one participant suffering from severe acute malnutrition. Among the signs of rickets, widening of wrist and ankle was present in all 30 (100%) of the enrolled participants. Four (13.3%) had bowing of legs, three (10%) had Harrison sulcus, 26 patients (86.7%) had rachitic rosary and 19 patients (63.3%) had frontal bossing. There were no signs of vitamin deficiency in enrolled participants.

Respiratory system examination revealed crepitations in two patients and bilateral rhonchi in three patients. One patient had a soft ejection systolic murmur (grade 2) likely due to acyanotic congenital heart disease in the patient. Hepatomegaly was present in seven patients. The rest of the systemic examination was normal in all the patients.

6. Laboratory Features

The hemoglobin level in the study subjects varied from 4.2 g/dL to 11.4 g/dL. The mean (SD) value of the hemoglobin was 9.05 (2.05) g/dL and the median (IQR) was9.50 (7.75, 10.60) g/dL. Anemia was defined as a hemoglobin level less than 11 g/dL in the age between 12 and 59 months and less than 11.5 g/dL in the age between 60 and 144 months. Anemia was present in 86.6% (n=26) of enrolled participants.

The serum calcium level in the study subjects varied from 6.3 to 10.5 mg/dL. The mean (SD) and the median (IQR) serum calcium levels were 8.61 (1.04) mg/dL and 8.75 (8.22, 9.39) mg/dL respectively. The serum phosphate levels in the study subjects varied from 2.50 to 12.50 mg/dL. The mean (SD) and the median (IQR) serum phosphate levels were 7.37 (3.31) mg/dL and 6.55 (4.48, 10.07) mg/dL.

The serum alkaline phosphatase levels in the study subjects varied from 131 to 748 IU/L. The mean (SD) and the median (IQR) serum alkaline phosphatase levels were 251.63 (137.55) IU/L and 208.50 (163.25, 260.00) IU/L respectively. Box and Whisker curves of hemoglobin levels and serum levels of calcium, phosphate, and alkaline phosphatase are given in.

Serum IgA-tTG level was done in all enrolled patients of rickets and was positive in one patient (IgA-tTGtiter of 25.2705 U/mL).

Outcomes

- **Primary Outcome: Proportion of Celiac disease in children with rickets**

Celiac disease was not confirmed in any of the enrolled patients of rickets. Out of 30 children with rickets, serum IgA-tTG level by ELISA was positive (>22 U/mL) in one patient (3.3%) while it was negative in 29 patients (96.7%). Upper gastrointestinal endoscopy and biopsy was done in the patient with positive IgA-tTG and graded as

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Marsh stage I according to modified Marsh grading of Oberhuber& Colleagues.

- **Secondary outcome: Clinical predictors in celiac disease and non-celiac patients with rickets**

Although there were no confirmed cases of celiac disease among the enrolled participants, one patient had positive values of serum IgA-tTG. The patient had anemia, was moderately underweight, and had severe stunting, though there was no history of constipation, chronic diarrhea, or abdominal distension in the patient.

DISCUSSION

Celiac disease, also known as gluten sensitive enteropathy, is a permanent intestinal intolerance to gluten and related proteins that leads to mucosal damage in genetically susceptible individuals. Classical symptoms included growth failure as the main presentation followed by chronic diarrhea, abdominal pain and vomiting. The classical age of presentation of celiac disease is 9 months to 1 year with chronic diarrhea, anorexia, and failure to thrive, muscle wasting and abdominal distension. However, atypical disease with short stature, anemia, constipation, and ataxia has now become more frequent in older children. Rickets is also a common presentation in patients of celiac disease.

This study was a cross-sectional study conducted in the department of Pediatrics, UCMS & GTBH from November 2019 to October 2021. The aim of our study was to determine the proportion of celiac disease in children with rickets. We screened 37 children with clinical and radiological evidence of rickets. Out of 37 screened patients, 7 were excluded from the study (5 were on chronic antiepileptic drugs, and parents of 2 patients gave negative consent for participation in the study). Thirty children aged between 1-12 years with clinical and radiological evidence of rickets were enrolled as cases. Serum IgA-tTG levels were performed to screen the children for celiac disease. Out of 30 cases, one child had positive serum IgA-tTG levels. The child with positive serum IgA-tTG levels was invited for upper gastrointestinal endoscopy and biopsy. Marsh staging was done on the histopathological specimen,[7] and it was concluded to have Marsh stage I. According to ESPGHAN criteria, a confirmation of celiac disease can be done in Marsh stages II and above. Thus, in this study, there was no confirmed case of celiac disease among the children with rickets.

The strengths of this study are (i) Only a few studies were conducted throughout the world for subclinical forms of celiac disease (like rickets). Hence, this study was designed as a cross-sectional study, to give evidence for such association between rickets and celiac disease in children. (ii) Methodology of our study was robust. (iii). The cases of rickets were screened on the basis of both clinical and radiological evidence (iv) Upper GI endoscopy and biopsy was performed on the cases with positive serum IgA-tTG (ELISA based) to confirm the diagnosis of celiac disease. (v) The clinical predictors of celiac disease such as short stature, anemia, failure to thrive, chronic diarrhea, constipation, and abdominal distension were also looked for in this study.

The limitations of our study are (i) This study was a hospital-based study and hence the result obtained in this study might not be representative of the whole population in the community. (ii) In our study, the calculated sample size was 177 cases, but due to the COVID19 pandemic and GTB hospital being converted into a fully dedicated COVID hospital, the sample size was reduced to 30 cases, this might have increased the chances of missing the diagnosis of celiac disease in patients with rickets (iii) There was no follow up included in this study. (iv) Serum IgA levels were not performed in the enrolled participants, so conditions in which IgA deficiency is seen might have given false-negative results in the patients of celiac disease. (v) Other causes of rickets were not explored in this study.

The primary objective of our study was to determine the proportion of celiac disease in children with rickets. In our study, the IgA t-TG was positive in one child with rickets. An upper gastrointestinal biopsy was performed which was equivocal (Marsh I) for celiac disease in children with rickets. Many studies have been conducted previously on the clinical presentation of celiac disease, but very few studies have been conducted to estimate the proportion of celiac disease in patients with rickets in different parts of the world.

One such study was conducted by Asaad Assiriet al. on children with unexplained rickets. In the study, unexplained rickets was defined as ‘no identifiable cause of rickets excluding all those with nutritional, inherited, renal or liver disease’. All children (n=26) had clinical signs of rickets and on radiological examination, they had features of rickets. None of the patients had gastrointestinal symptoms. The diagnosis of celiac disease was confirmed in 10 patients. Serological markers for celiac disease including anti-endomysial antibodies and IgA-tTG were positive in all ten patients and small bowel histopathology showed evidence of celiac disease. Out of 10 patients, seven had MARSH type IIIc, two had type IIIb, and one patient had type IIIa. This study had reported a proportion of celiac disease of 38.4%, among children with unexplained rickets.[5] This high proportion of celiac disease in this study was most likely due to the inclusion of patients of only unexplained rickets, that is, all major causes of rickets had been ruled out. In our study, however, we enrolled all patients with clinical and radiological evidence of rickets irrespective of cause of rickets, and could not find any confirmed case of celiac disease.

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Another study conducted by Nasir A.M. et al. included 81 (47 females and 34 males) children with rickets or osteomalacia aged between 2 to 18 years. The diagnosis of rickets and osteomalacia was based on clinical, biochemical, and radiological data. The commonest cause of rickets was nutritional; either low Vitamin D or low calcium, or both. Five (6.17%) patients were diagnosed to have celiac disease. The diagnosis of celiac disease was based on ESPGHAN criteria. All the diagnosed cases were female.[8] In our study, we included children with rickets aged between 1 year and 12 years of age, and could not find any confirmed case of celiac disease.

There have been many studies to evaluate rickets as the presenting complaint in children with celiac disease. A retrospective study conducted by R. Philip et al. included 36 children with celiac disease. The diagnosis was based on ESPGHAN diagnostic criteria. They found a clinical manifestation of rickets as the presenting complaints in 6% (n=2) patients.[6] In an another retrospective study done by Alvi et al. 46 children with confirmed celiac disease were included and rickets as a presenting complaint was present in 4 patients (8.7%).[9] Similarly, in an another study done by Hussain et al. 52 children with celiac disease were included and frequency of different clinical features of celiac disease were evaluated. Out of 52 children, rickets was present in 28 (53.8%) patients.[10] Imran et al. conducted a prospective study including 90 patients with confirmed cases of celiac disease according to NASPGHAN criteria and rickets was present in 30 (34%) patients.[11] Lomash et al. did a prospective study in patients with celiac disease and found that 58 (18.13%) patients with classical and 52 (26.94%) patients with atypical presentation of celiac disease had rickets.[12] A retrospective study done by Altamimi E et al. included 35 children with celiac disease and signs of rickets was present in 6 (17.1%) patients.[13] There have been many case reports where children presenting with rickets have been diagnosed with celiac disease. One such case reported by Cheguru Sripal Reddy et al. described a case of 4 years, female child, with deformities in the extremities and waddling gait for the last 8 months with failure to thrive. On complete history, examination, and investigation, the child was diagnosed to have rickets. Serological tests were positive for IgA-tTG and anti-endomysial antibodies.[14] Al Sharafi et al. described a case of 13 years old female with an 8 years history of severe rickets causing multiple bone deformities. The patient was also found to have growth failure and anemia.[15]

Thus, rickets as an associated finding is one of the common features in children with celiac disease. However, there have been very few studies estimating proportion of celiac disease in patients with rickets. There are no studies comparing clinical predictors of celiac disease with non-celiac patients in children with rickets. However, there are many studies that have estimated the prevalence of various clinical features in celiac disease.

CONCLUSION

Thus, by this study, we conclude that although it is known that rickets is one of the common presentations of celiac disease, celiac disease as such is less likely to be present in patients with rickets. However looking at various limitations of this study, the major being very small sample size, a definite conclusion can not be made, and further studies with larger sample sizes and more appropriate settings are required to make a definite conclusion.

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