Spectrum of Atypical Celiac Disease in North Indian Children

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Atypical celiac disease (ACD) presenting in childhood has rarely been documented from India. The present retrospective study analyzed features of atypical celiac disease over a 5-year period. Patients were diagnosed to have Celiac Disease (CD) as per the standard ESPGHAN criteria. The biochemical and hematological parameters of the cohort of children presenting with atypical features (ACD) were compared with children presenting as typical diarrheal CD. Twelve children were diagnosed to have CD. Seven of them presented with ACD. The two groups did not differ significantly in their age of presentation, hematological and biochemical profile. Osteoporosis as documented on bone mineral densitometry was present in all 6 patients of ACD in whom BMD was done. Short stature (4) and refractory iron deficiency anaemia (3) was the commonest modes of presentation of ACD. Occurrence of these conditions either singly or in combination warrants exclusion of celiac disease in children.

Key words: *Atypical celiac sprue, Gluten sensitive enteropathy.*

Pediatric celiac disease (CD) is increasingly being reported from India(1-4). The clinical manifestations of CD vary with the age of the patient, the duration and extent of disease, and the presence of extra-intestinal complications. Reports over the last two decades have focused on classical CD in which diarrhea is the predominant symptom. Atypical celiac disease (ACD) that presents with extra-intestinal manifestations in the absence of diarrhea is well recognized in the West (5,6).

In absence of typical diarrheal presentation, many cases of CD remain undiagnosed due to lack of awareness regarding its varied presentation. To the best of our knowledge there is no published data on spectrum of ACD in childhood from the Indian subcontinent. To highlight this fact we present our experience of 7 children with ACD at a tertiary referral center. The clinical and laboratory parameters of patients with ACD were compared with the typical (diarrheal) variety of the disease.

Material and Methods

Our department maintains an ongoing database since 1998 of CD patients, both adults and children. Retrospective analysis of mode of presentation of children diagnosed to have CD in a single unit of Department of Gastroenterology, at GB Pant Hospital, New Delhi, over a period of 5 years from 1998-2002 was done. Patients were labeled as having CD as per the standard ESPGHAN criteria(6). Clinical response to gluten free diet (GFD) was assessed after 6-8 weeks of starting the exclusion diet. Detailed history and physical examination with special reference to anthropometric assessment was done in all children at the time of diagnosis. As per the initial presentation patients were

divided into two groups viz diarrheal or non-diarrheal.

The non-diarrheal group was further sub classified based on the predominant symptom at presentation. Children were labeled to have short stature if their height was less than 5th percentile against the expected height for the age and in the presence of normal height of both parents. The second subgroup was characterized as refractory anemia if the patients were referred to us for investigation of low hemoglobin (<10 g/dL) unresponsive to oral iron and folic acid therapy for atleast 6 months. Detailed workup for anaemia was done in all patients at entry. Serum iron estimation and total iron binding capacity were done in all patients prior to starting GFD. Biochemical tests *viz.*, serum calcium, serum phosphorous and alkaline phosphatase and skeletal radiographs were done in all patients when presumptive diagnosis of CD was made on clinical and histological data prior to starting GFD. For those patients suspected to have metabolic bone disease on the basis of physical examination or biochemical abnormalities, estimation of bone mineral densitometry and intact parathormone (iPTH) levels was also included in the database from January 2001 if patients could afford them. Metabolic bone disease was classified as per WHO classification *viz.*, osteopenia defined as z score between –1 and –2.5 whereas osteoporosis defined as a z score less than –2.5(7). As a part of the database preparation at least one serological marker *viz.*, IgA anti-gliadin antibody, IgA anti-endomysial antibody or tissue transglutaminase antibody was determined if clinical picture and duodenal biopsy was suggestive of CD prior to initiation of GFD. Follow up of all patients diagnosed to have CD was done initially on a monthly basis for 3 months followed by evaluation at 6 monthly intervals thereafter.

Wilcoxan rank sum test was used to compare the means between the two groups. A p value of less than 0.05 was considered statistically significant.

Results

Over a 5 year period starting from 1998, 34 patients were diagnosed to have CD at our center as per the ESPGHAN criteria. Twenty-two of these 34 were adults whereas the remaining were children (<15 years). The pediatric group comprised of 12 children, 7 males and 5 females in the age range of 4-15 years. In seven of these 12, the presentation was with non-diarrheal disease and they were labeled as having atypical celiac disease (ACD)(8). In contrast only four of the 22 (18%) adults had ACD. The mean age of the children with ACD and typical CD was 10.8 and 8.9 yr. respectively. The mean duration of diarrhea at presentation in typical CD children was 3.3 yrs (range 2 to 4.5 yr). None of the children with ACD had a past history of chronic diarrhea.

Short stature and refractory anemia were the mode of presentation in 4 and 3 children respectively. In five of these 7 children the height was less than the fifth percentile of the expected height according to the age. Significant anemia was present in 6 of these 7 children and the mean hemoglobin was 7.9 g/dL. Anemia was suggestive of iron deficiency in all 6 children with low serum iron levels and elevated total iron binding capacity. The mean levels of serum calcium, alkaline phosphatase and transferrin saturation index in the ACD group were 8.7g/dL, 758 IU/mL and 9.8% respectively.

Skeletal radiographs were normal in all patients except one, which showed radiographic features of rickets. Bone mineral densitometry showed osteoporosis in each of the 6 patients in which this test was

performed. The z score ranged between –4.08 to –5.51. Since BMD estimation was done in only 2 patients with typical CD (z score –2.78 and –3.89), no meaningful comparison could be made between the two groups. Secondary hyperparathyroidism was detected in 3 of the 4 patients in the ACD group in whom this test was done. Serum iPTH levels were more than 95 pg/mL (normal range 7-53 pg/mL) in each of these 3 patients. Four patients tested positive for IgA antiendomysial antibodies whereas 2 and 1 showed elevated titres of tissue transglutaminase antibody and IgA antigliadin antibody respectively. Histopathological examination of duodenal biopsy specimens showed severe villous atrophy, crypt hyperplasia with increase in intraepithelial lymphocytes in six patients whereas in one patient there was moderate villous atrophy (*Table I*).

Follow up data was available in all 7 children. The mean follow up period was 19 months (range 4-36 mo). During the follow up period there was an impressive gain in height and hemoglobin (*Table I1*) in all the children.

Discussion

Although CD was once thought to be rare in India, several recent reports have cleared this misconception(1-4). However all of these reports deal with typical (diarrheal) variety of CD although passing reference has been made about the presentation of atypical disease(3,4).

The corner stone for diagnosis of CD is the revised ESPGHAN criteria which are based on demonstration of characteristic small intestinal mucosal abnormality on histological examination when the patient is consuming a normal diet(6). The second requirement is a clear cut remission on strict GFD with relief of all symptoms within few weeks. The second requirement poses difficulties in patients suspected to have ACD. Unlike in typical CD, where remission in diarrhea occurs within 2-4 weeks of excluding gluten from diet, patients with ACD who present with refractory anaemia, growth failure or metabolic bone disease take significantly longer to show a clinical improvement. In these patients the presence of serological markers adds

TABLE I–*The clinical, laboratory and histological data of children with atypical celiac disease.*

S. No.	Age / sex (yr)	Presentation	Baseline Ht (cm)	Hb (g/dL)	Follow-up Ht (cm)	Hb (g/dL)	BMD z score (L1-4)	Duration of follow up (mo)	Serological marker	Duodenal Biopsy
1	6/F	Short Stature	108	11	121	12	– 4.87	36	EMA	SVA
2	12/F	Anemia	132	9.4	138.5	12.4	– 5.43	10	EMA	SVA
3	12/M	Anemia	133	8.0	140	11.7	– 5.03	12	AGA	SVA
4	15/F	Anemia	142	5.9	152	12	– 4.08	18	TTG	SVA
5	8/M	Short stature	111	7.5	123	11	– 3.48	33	EMA	SVA
6	9/F	Short stature	110	7.5	112.5	10.9	– 5.51	4	TTG	MVA
7	11/M	Short stature	118	7.0	131	11.4	Not done	18	EMA	SVA

M: Male, F: Female, EMA: endomysial antibodies, AGA: anti gliadin antibodies, TTG: tissue transglutaminase antibodies, SVA: Subtotal villous atrophy, MVA: moderate villous atrophy.

TABLE II–*Comparison of Clinical and Biochemical Parameters in Typical and Atypical Celiac Disease.*

Parameter	Typical celiac disease (n = 5) Mean ± S.D.	Atypical celiac disease (n = 7) Mean ± S.D.	p value
Age (yr)	8.9 ± 4	10.8 ± 2.2	n.s.*
Hemoglobin (g/dl)	9.4 ± 1.6	7.9 ± 1.8	n.s. *
S. Calcium (mg/dl)	9.8 ± 0.9	8.7 ± 1.0	n.s. *
S. Alkaline Phosphatase (IU/l)	447 ± 206	758 ± 198	0.05
Transferrin Saturation Index (%)	16.5 ± 5.6	9.8 ± 4.1	n.s. *

* n.s. = (not significant).

weightage to the diagnosis in the initial period till clinical improvement becomes manifest. A repeat duodenal biopsy to demonstrate improvement of villous atrophy on gluten free diet is advisable for confirmation of diagnosis in ACD cases in whom the clinical improvement is subtle and equivocal(6). All the children with ACD in our study had a good response to GFD, thus obviating the need for a repeat biopsy to demonstrate improvement of duodenal villous atrophy.

Our report of seven patients is the first to focus on the atypical presentation of CD in children from India and compares the clinical presentation of the two groups. As expected the mean age of children with ACD was nearly 2 years more than the other group. This is mainly because diarrhea is a more alarming symptom for which parents are likely to seek early medical attention. On the other hand, growth failure or anemia are more subtle in presentation and may escape the attention of parents for considerable time resulting in a delayed presentation. On the basis of this logic we hypothesized that hematological and bone biochemistry parameters are likely to show more derangement in the ACD group than in the typical CD by virtue of the longer time required to reach the diagnosis in the former group. On comparing the various parameters between the two groups we found that despite the lower values of hemoglobin, calcium and transferrin saturation index in the ACD group none of these differences were statistically significant. However since our sample size is small it is possible that this is a type 2 error and larger studies need to be done to address this issue.

The widespread availability of highly sensitive and specific serological markers has resulted in changing the spectrum of CD in the West as atypical and early disease is being recognized more frequently(8). This is perhaps not true for India as at least three studies from north India have recorded that more than 93% of Indian children still present with classical type of disease(1-3). Our data is definitely skewed as there is a very high percentage of ACD at our center. The skewness in our data is due to the fact that it is from a tertiary referral center; only cases that remain undiagnosed in primary and secondary health centers are referred to us. We do not suggest that majority of CD in north India presents with atypical disease.

Of the several atypical presentations of CD the commonest are short stature and refractory anemia. Other less common manifestations are unexplained metabolic

Key Messages

- The diagnosis of atypical celiac disease is frequently missed as it presents sans diarrhea.
- Short stature and refractory iron deficiency anemia are the commonest modes of presentation.

bone disease, infertility and idiopathic epilepsy(8). Short stature and refractory anemia are not mutually exclusive as both features may co-exist. In fact all three patients with refractory anemia had significant growth retardation and conversely severe anemia was present in three of the four children with short stature. Thus it would appear that both these modes of presentation go hand in hand with each other. It is believed that as many as 9%-10% of those with "idiopathic" short stature have CD(9,10).

Prevalence of metabolic bone disease in Indian children with CD is not known. There was a high frequency of metabolic bone disease and secondary hyperparathyroidism in this cohort that appears to be at least at par with the figure of 50% reported in untreated celiac disease children from Turkey(11). All children with ACD in our study showed normal levels of serum calcium and skeletal radiographs were also normal in all but one and yet BMD showed significant changes of metabolic bone disease. These data underscore the need for adding calcium and vitamin D supplemen-tation to gluten free diet at least in this subgroup even though they may be asymptomatic or show no biochemical or radiological evidence of bone disease.

To summarize, the diagnosis of ACD is frequently missed as it presents sans diarrhea. This is probably the reason that these children are likely to be diagnosed at tertiary referral centers. The commonest modes of presentation of ACD are refractory anemia and/or short stature. Positive serology is helpful in this subgroup as clinical improvement may take longer time. With increasing awareness and widespread availability of serological markers for celiac disease, its clinical spectrum in India is likely to undergo a change with greater proportion of atypical and asymptomatic patients being diagnosed early.

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Serum Prolactin in Seizure Disorders

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This study aimed to determine the post-ictal prolactin (PL) response in different types of seizures and seizure-like events in children, and correlate with the post-ictal duration. Patients were divided into group I (generalized tonic-clonic seizures, complex partial seizures or simple partial seizures), group II (febrile convulsions) and group III (conditions mimicking seizures). Group IV consisted of 25 controls. Blood was collected within 2 hours of the seizure and PL levels assayed. PL levels were significantly high only within group I; highest and baseline levels were attained within 10 minutes and by 100 minutes respectively. The sensitivity and specificity of elevated PL for epileptic seizures were 64% and 98% respectively. It is concluded that a high prolactin level within 100 minutes of a seizure is suggestive that a generalized or complex partial seizure has occurred.

Key words: *Prolactin, Seizures.*

An elaborate history and accurate description is necessary for making correct diagnoses of seizures. Uncertainty arises when it has occurred in isolation or the description is unreliable. The repertoire of seizures is so extensive that even physicians find it difficult to distinguish between seizures and similar conditions(1). Jeavons, *et al*,