

A prospective study of catch-up growth among Indian children with celiac disease

Madhavi Bharadwaj², Ashish Jain³, Anand Prakash Dubey²,
Avinash Lomash^{1,2}, Seema Kapoor^{1,2}

¹Division of Genetics, ²Departments of Pediatrics and ³Neonatology, Maulana Azad Medical College, Bahadur Shah Zafar Marg, New Delhi, India

ABSTRACT

Objectives: The study was done to investigate the response of the gluten-free diet (GFD) on growth and other biochemical parameters in newly diagnosed children with celiac disease (CD). We also determined the association of Marsh biopsy classification and the response in haematological parameters among the children with GFD over the follow-up time. **Methods:** A prospective observational study was conducted for 1.5 years where children aged 1–10 years with newly confirmed CD (as per Marsh classification) without pre-existing chronic disease were enrolled. Individual anthropometry, biochemical and haematological parameters were recorded on enrolment and compared with 1, 3 and 6 months (follow-up) after initiating GFD (as per World Health Organization growth charts). **Statistical Analysis:** The data were entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences version 21.0. A *P* value of < 0.05 was considered significant. **Results:** A total of 51 (out of 55) children with CD completed 6-month follow-up. A significant improvement in the growth and biochemical parameters was seen at 6-month follow-up with the GFD (*P* < 0.05). There was a significantly decreasing Hb (at enrolment and at 3 months) with increasing Marsh biopsy grade—it was significantly less with Marsh 3C and more with Marsh 3A. A significantly better %Hb improvement was seen in children with Marsh biopsy 3C as compared to 3A and 3B (*P* < 0.05). We found no significant association of Marsh biopsy with Malabsorption, type of anaemia and Serum ferritin levels (*P* > 0.05). **Conclusions:** GFD showed significant improvement in the growth and development of the child with a significant reduction in anaemia at 6 months. With increasing grade of Marsh biopsy, the severity of anaemia increases but after the initiation of GFD, such children show significantly better improvement in %Hb over time.

Keywords: Anthropometry, celiac disease, gluten-free diet, growth

Introduction

The genetic predisposition and immune mediation play an important role in the pathogenesis of celiac disease (CD). It affects 1% of the people worldwide^[1] and in India as well.^[2] The diverse clinical presentations of paediatric CD make it an unusual diagnosis at presentation by the primary care physicians.^[3,4] The continuous search for the non-invasive testing and diagnosis

of this disease^[5] has led to the review of the old protocols and now the latest guidelines advise the diagnosis based on serology, particularly tissue transglutaminase (TTG)-immunoglobulin A (TG2-IgA) and IgA testing supported by histopathology of duodenal biopsy.^[6]

Opting for the single easily modifiable factor, that is gluten-free diet (GFD), from the pathological triad of genetic, immunological and diet seems the only effective way of its treatment/remission.^[7-9] The life-long adherence to a strict GFD, comprising complete elimination of products derived from wheat, rye, and barley and products processed from these cereals and replacing

Address for correspondence: Dr. Ashish Jain,
Boys Hostel, MAMC, New Delhi, India.
E-mail: neoashish2008@gmail.com

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them with naturally gluten-free products (maize, rice, oats, buckwheat, lamb, meat, fish, vegetables, fruit) or by-products from which gluten has been removed,^[10] can help prevent stimulation of autoimmune antibodies, thereby maintaining the normal healthy flora and good absorption of the nutrients.

Usually, the effect of the GFD on growth in children shall begin immediately with the better absorption, but it may take as long as 6–24 months due to the regenerating intestinal villi and other associated factors.^[11] A meta-analysis identified young age as a significant factor affecting the outcome in the children with CD.^[11] One of the studies identified that the concurrent presence of *Helicobacter pylori* can prevent the complete recovery of mucosa in such children.^[12] Literature review shown that previous studies have been conducted on the western population,^[1,13,14] and Saudi children^[4] with sparse research on Indian children.^[14]

Thus, we conducted this research with an aim to study the effects of the GFD on growth and biochemical parameters of Indian children with CD over a 6-month follow-up period. The study shall help in raising concern over early diagnosis of CD and strict nutritional monitoring of such children for their better growth and development.

Methods

A prospective observational study was done from October 2014 to March 2016 in the Department of Pediatrics, where 55 children of age 1–10 years and diagnosed with CD were included. The diagnosis of CD was based on (1) confirmation by duodenal biopsy (endoscopically) as per modified Marsh criteria dividing it into inflammatory damage of infiltrative (I), infiltrative-hyperplastic (II), destructive (III) and hypoplastic (IV) type^[6] and (2) positive serum anti-tissue TTG IgA antibody.

Any children with pre-existing heart disease, chronic pulmonary disease, chronic renal disease, CNS disease, chronic liver disease and any endocrine disorders based on history and clinical examination were excluded from the study. Informed consent was taken from caregivers of the children before enrolment. Ethical clearance was obtained from the Institutional Ethics Committee, New Delhi (EC/MAMC/2011/147).

The sample size calculation was based on the study of Radlović *et al.*^[13] who observed increase in BH percentiles from 37.62 ± 26.26 to 57.22 ± 25.29 . Taking these values as reference, the minimum required sample size with 99% power of study and 1% level of significance is 42 patients. To reduce margin of error, total sample size taken is 51. In our study among the 55 children selected for CD, 4 were lost to follow-up; hence, the data were analysed for 51 patients only.

After a detailed talk with parents, all the children underwent a complete clinical examination, HLA typing (also for siblings and parents) and relevant laboratory investigation and baseline growth, and biochemical parameters were recorded which were compared with growth catch-up in the follow-up period.

Clinical examination: The anthropometric measurements included weight, height, mid-upper arm circumference, head circumference and BMI; the obtained values were then matched to the corresponding age and gender. Height/Length for age, weight for age, weight for height/length and head circumference were assessed using WHO standards.^[15]

Laboratory investigations: Four millimetres of venous blood sample was drawn for estimation of total protein and lipid profile. Three millimetres blood was taken in EDTA vial for haemoglobin (Hb), ferritin and plasma amino acid measurement using the principle of high-performance liquid chromatography. Hb in blood, as a laboratory parameter of nutritional status, was determined by the automatic cell counter Sysmex XP 100. Children aged below 5 years were considered anaemic if Hb in blood was < 110 g/l, and for those aged above 5 years if Hb was < 115 g/l.^[4]

At disease diagnosis and outpatients' check-ups, a counselling session was arranged for parents with the dietician for explaining the GFD, wherein food type allowed and to be avoided were explained. Possible maize flour, rice flour and other options were explained with the help of a diet chart.

Follow-up: After completed hospitalization, all the children were under follow-up as outpatients over 1, 3 and 6 months. The check-up examinations involved compliance with GFD, possible presence of difficulties and a complete examination including accurate weight, height, BMI, Hb and ferritin measurements.

The outcome parameters were (1) change in anthropometric parameters (height/length, weight, mid-upper arm circumference, head circumference), (2) change in biochemical parameters (Hb, serum ferritin, lipid profile, total protein/serum albumin/plasma amino acids, and (3) association of Marsh biopsy features with the catch-up growth.

Statistical analysis

Quantitative variables were compared using the paired *t*-test/Wilcoxon Ranked sum test. Qualitative variables were compared using Chi-square test/Fisher's exact test. The data were entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences version 21.0. A *P* value of < 0.05 was considered significant.

Results

The mean age of presentation of children was 6 years and 2 months \pm 2 years and 4 months. Majority, that is 72.55% (*n* = 37), of children, were >5 years of age, and only 27.45% (*n* = 14) were \leq 5 years of age, with the youngest participant being 19 months of age. The ratio of boys and girls was 2:3 with 31 girls and 20 boys.

Clinical Features: Almost half of the study patients (*n* = 26) presented with classical symptoms of CD (chronic diarrhoea,

abdominal distension and pain abdomen) and others presented with atypical features like refractory anaemia, short stature or was diagnosed on screening.

After GFD, clinically, 70% (n = 36) patients showed improvement in terms of resolution of diarrhoea, abdominal distension, increased appetite, improved activity etc.

Genetic analysis: Eighty-two per cent (n = 42) patients were positive for both HLA-DQ2 0201/0501 alleles, 13.7% (n = 7) patients were positive only for HLA-DQ2-0201, and only 2 patients (3.9%) had only HLA-DQ2-0501 allele. A total of 128 relatives, including parents and siblings, were screened and 15% (n = 20) were found to have silent CD.

Growth parameters: There was a significant improvement in the weight, height and BMI over a period of 6 months as compared to the baseline (P < 0.05), as shown in Tables 1–3.

Haematological and biochemical parameters: We found a significant improvement in Hb (anaemia) and ferritin levels with GFD among the study patients [Table 4 and Figure 1].

At the end of 6 months, the mean Hb significantly increased from 8.61 to 10.72 g/dl (P = 0.045); the mean ferritin increased from 15.12 to 32 ng/dl (P = 0.0001); the total protein increased from 6.07 to 7.09 mg/dl (P = 0.002); HDL increased from 31.72 to 33.08 (P = 0.02); the mean total cholesterol level fell from 130.39 to 124.34 mg/dl. We observed significant (P = 0.006) increase in plasma citrulline levels and significant fall in alanine (P < 0.0005), valine (P < 0.0005), proline (P = 0.0005) and lysine (P = 0.004) levels at the end of 6 months of follow-up.

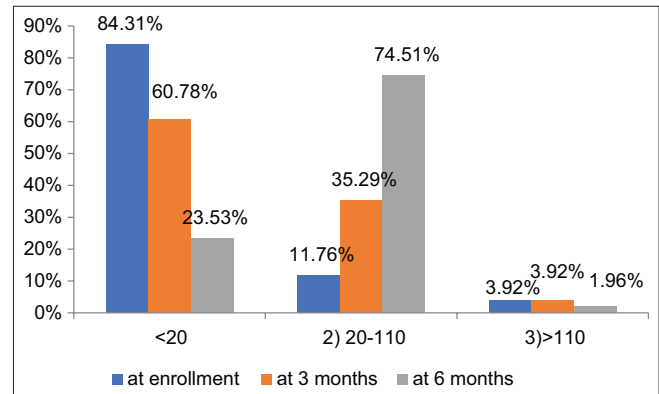


Figure 1: Change in ferritin on follow-up

SD of WT	At enrolment		At 1 month		At 3 months		At 6 months	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
<-3	27	52.94	21	41.18	15	29.41	5	9.80
-3 to -2	12	23.53	15	29.41	12	23.53	14	27.45
-2 to 0	9	17.65	12	23.53	21	41.18	23	45.10
0 to +2	3	5.88	3	5.88	3	5.88	9	17.65
Total	51	100.00	51	100.00	51	100.00	51	100.00
P			0.679		0.0415		<0.0001	

SD of HT	At enrolment		At 1 month		At 3 months		At 6 months	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
<-3	29	56.86	25	49.02	24	47.06	13	25.49
-3 to -2	9	17.65	10	19.61	8	15.69	16	31.37
-2 to 0	9	17.65	12	23.53	15	29.41	16	31.37
0 to +2	4	7.84	3	5.88	3	5.88	5	9.80
>+3	0	0.00	1	1.96	1	1.96	1	1.96
Total	51	100.00	51	100.00	51	100.00	51	100.00
P			0.7504		0.529		0.0252	

SD of BMI	At enrolment		At 1 month		At 3 months		At 6 months	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
<-3	9	17.65	7	13.73	2	3.92	2	3.92
-3 to -2	9	17.65	3	5.88	5	9.80	2	3.92
-2 to 0	26	50.98	32	62.75	30	58.82	22	43.14
0 to +2	7	13.73	9	17.65	14	27.45	25	49.02
Total	51	100.00	51	100.00	51	100.00	51	100.00
P			0.249		0.0417		0.0002	

Table 4: Change in Hb on follow-up

Hb	At enrolment		At 3 months		At 6 months	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
Severe anaemia	16	31.37	7	13.73	1	1.96
Anaemia	27	52.94	36	70.59	38	74.51
Normal	8	15.69	8	15.69	12	23.53
Total	51	100.00	51	100.00	51	100.00
<i>P</i>				0.09		0.0004

The association of Marsh biopsy and the Hb and ferritin has been shown in Tables 5 and 6. Among our study patients, there were 9 children with Marsh 3A, 14 children with Marsh 3B, and 28 children with Marsh 3C. There was a significantly decreasing Hb (at enrolment and at 3 months) with increasing Marsh biopsy grade; it was significantly less with Marsh 3C and more with Marsh 3A. At 6 months of follow-up, the Hb was comparable among the three groups. This was seen due to a significantly better %Hb improvement in children with Marsh biopsy 3C as compared to 3A and 3B ($P < 0.05$). Apart from that, we found no significant association of Marsh biopsy with malabsorption, type of anaemia and serum ferritin levels ($P > 0.05$).

Discussion

CD had been uncommon in Indian children as compared to adult population.^[16] Its increasing prevalence in children currently makes the study important for the general practitioners to screen for CD in any child with stunted growth.^[17]

Our study population showed a female: male sex ratio of 3:2, which was comparable to western reports^[14,18,19] but was unlike Indian studies that showed a slight male preponderance.^[20,21] Since this was a small hospital-based sample ($n = 51$), this finding may not represent the whole population.

The mean age of presentation was delayed and late after the onset of symptoms (6.2 ± 2.4 years) as seen in other Indian studies.^[20,21] This could be due to common ignorance about the disease and inaccessibility to diagnostic services.

We did not find any positive screening in sibling younger to 18 months of age in spite of active screening which was performed on all first-degree relatives: the reason being the practice of prolonged breastfeeding and delayed introduction of gluten in the diet in most of the Indian families. Unlike perceived in earlier studies, only 50% of the patients had classical CD presentation.^[21,22]

The results of the genetic analysis in participants strongly supported the HLA association with CD. We found 15% incidence of CD in first-degree relatives, which is comparable to the worldwide incidence of 15–20%.^[23-25]

In CD, the low weight at presentation is mainly due to decreased absorption of the nutrients and the usual causes of short

stature are many: familial, constitutional, endocrine, renal, gastrointestinal and nutritional disorders. Proposed mechanisms include growth retardation as a result of generalized or selective malnutrition, changes in the insulin-like growth factor-1 system and insulin-like growth factor binding protein 3 during active disease.^[26] We excluded all other diseases and found a significant improvement in the growth and development of the children after 6 months of GFD.

In our study, children with CD had anaemia in 84.3% which was higher than 63% as reported by Rana *et al.*^[27] and it was found that all children had ferritin deficiency (<20 ng/ml). However, Vitamin B12, folic acid and growth hormone level estimation among the other causes of anaemia were not done. After 6 months of GFD, a significant improvement in the Hb (anaemia) and ferritin levels were seen in our study. Without any hematinics, this improvement is remarkable. It emphasizes the role of intestinal malabsorption as a cause of anaemia in children with CD. This fact should be well noted as it may be applied in the general practice for improving the nutritional status of the children.

Among other biochemical parameters, total protein values ($P = 0.002$) and HDL values ($P = 0.02$) increased significantly at the end of 6 months. This result is supported by earlier reports by Capristo *et al.*^[28] and Brar *et al.*^[29] where 1–1.5 years of GFD brought about a significant lowering of cholesterol, LDL and increase in HDL levels and thus signifying the cardioprotective role of GFD in celiac patients with deranged lipid profile.

We had compared the amino acid profile at the end of 6 months with that of enrolment. We observed significant ($P = 0.006$) increase in plasma citrulline levels which is in accordance with the available literature,^[18,22,30] thus strongly supporting citrulline's role as a marker of enterocyte mass recovery during follow-up in patients with CD and thus obviating the need for repeat invasive procedure like an intestinal biopsy. We also observed significant fall in alanine ($P < 0.0005$), valine ($P < 0.0005$), proline ($P = 0.0005$) and lysine ($P = 0.004$) levels during follow-up, cause and clinical application of which need further research and investigation.

Though we found that “6 months” is the optimum scheduling to start to witness the significant effect of the GFD on growth parameters like height and weight for age, and anaemia; however,

Table 5: Association of Marsh biopsy grade with haematological parameters in CD children

	Biopsy-Marsh			Total	P
	3A	3B	3C		
Malabsorption					
–	1 (11.11%)	5 (35.71%)	2 (7.14%)	8 (15.69%)	0.115
+	2 (22.22%)	5 (35.71%)	10 (35.71%)	17 (33.33%)	
++	6 (66.67%)	4 (28.57%)	16 (57.14%)	26 (50.98%)	
Anaemia					
–	3 (33.33%)	5 (35.71%)	8 (28.57%)	16 (31.37%)	0.887
+	6 (66.67%)	9 (64.29%)	20 (71.43%)	35 (68.63%)	
Type of anaemia					
Dimorphic	1 (16.67%)	2 (22.22%)	3 (15.00%)	6 (17.14%)	0.501
MCHC	5 (83.33%)	6 (66.67%)	17 (85.00%)	28 (80.00%)	
Megaloblastic	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (2.86%)	
Haemoglobin at enrolment					
Mean±St. dev.	10.21±2.39	8.98±1.24	7.91±2.16	8.61±2.14	0.012
Median (IQR)	9.8 (8.300-12.025)	8.8 (8-9.800)	7.8 (6.200-9.250)	8.4 (7.050-9.800)	
Haemoglobin at 3 months					
Mean±St. dev.	10.71±1.83	10.11±1.09	9.01±1.66	9.61±1.68	0.01
Median (IQR)	11.2 (9.200-11.650)	10.15 (9.200-11.200)	9.05 (7.850-10.200)	9.4 (8.425-10.775)	
Haemoglobin at 6 months					
Mean±St. dev.	11.13±1.44	10.74±0.61	10.58±1.38	10.72±1.22	0.509
Median (IQR)	10.8 (10.200-11.600)	10.8 (10.300-11)	10.9 (9.800-11.350)	10.8 (10.200-11.300)	
Serum ferritin at enrolment					
Mean±St. dev.	12.01±12.67	15.82±26.08	15.76±32.95	15.12±28.12	0.636
Median (IQR)	6.78 (5.120-13.450)	5.72 (4.630-18.800)	5.4 (3.160-11.610)	5.77 (3.890-11.915)	
Serum ferritin at 3 months					
Mean±St. dev.	15.15±10.56	16.53±9.03	25.98±30.19	21.47±23.59	0.554
Median (IQR)	8.48 (7.235-22.300)	16.16 (10.240-25.110)	15.1 (10.710-24.555)	14.88 (10.075-24.667)	
Serum ferritin at 6 months					
Mean±St. dev.	21.37±11.82	23.91±9.28	39.46±29.2	32±23.98	0.066
Median (IQR)	23.43 (12.745-29.555)	22.95 (16.340-32.460)	30.22 (22.875-38.890)	28 (20.080-34.385)	

Table 6: Association of Marsh biopsy grade with improvement in the haematological parameters

Percentage change		3A (n=9)	3B (n=14)	3C (n=28)	P
Haemoglobin at 3 months	Mean±St. dev.	6.77±13.35	13.4±11.14	18.14±24.91	0.336
	Median (IQR)	2.66 (–3.104-13.324)	8.98 (6.604-17.582)	11.94 (0.894-30.496)	
Haemoglobin at 6 months	Mean±St. dev.	12.05±16.87	21.28±14.75	40.75±32.76	0.01
	Median (IQR)	7.96 (–1.250-26.618)	22.58 (11.340-29.412)	36.97 (16.274-68.067)	
Serum ferritin at 3 months	Mean±St. dev.	95.64±114.8	233.01±369.37	934.26±2902.37	0.328
	Median (IQR)	100.48 (18.954-142.762)	116.66 (–8.851-377.376)	152.43 (45.566-367.154)	
Serum ferritin at 6 months	Mean±St. dev.	186.72±194.5	378.78±529.57	1253.8±2512.43	0.053
	Median (IQR)	207.4 (–11.121-334.130)	116.4 (61.412-571.863)	443.06 (176.828-901.176)	

the study suffers from the limitation that further follow-up of the patients was not done. Earlier studies have shown that it takes about 1–3 years to complete catch-up growth in children with CD after starting the GFD.^[31,32]

In our study, the severity of CD biopsy as assessed by Marsh criteria showed that Marsh 3C children presented with significantly lower Hb values at enrolment and even at 3 months but showed a significantly better %Hb improvement till 6 months. Ours is one of the few studies to determine the association of Marsh biopsy with various parameters of CD. This stresses on the fact that the severity may be reversed in 6 months of time

with a proper follow-up of the diet. Anaemia in CD has been deemed to be multifactorial and any reduction in Hb should have correlated with ferritin deficiency,^[33] but here we found no significant association of ferritin levels and the change in ferritin levels with Marsh category. The reason can be that CD presents as an inflammatory condition and as serum ferritin is an acute-phase reactant, it may show a false increase. One study has linked the degree of villous atrophy with aetiology of anaemia deciphering that sub-total/total villous atrophy (S/TVA) has lower serum ferritin values than individuals with partial villous atrophy (PVA), reflecting malabsorption of iron. But even they found that despite greater malabsorption of iron in the group

with more severe villous atrophy, the frequency of anaemia was similar in individuals with PVA (20%) and S/TVA (24%).^[34]

The present study suffers from the limitation that deficiency state was assessed by Hb/ferritin levels only. Ferritin suffers from the disadvantage of being an acute-phase reactant and thus it becomes very essential to measure other parameters like serum transferrin receptors, transferrin saturation, and free erythrocyte protoporphyrin while monitoring the response to the therapy and determining any iron deficiency states in CD children.

The results of the study help in recommending future studies based on the biopsy findings and its association with the increasing severity of nutrient deficiencies. It is possible that children with TVA with severe nutrient deficiency show better improvement in the nutritional status in the same time as those with subtotal villous/PVA.

Conclusion

The treatment of CD is life-long GFD. Though this diet is cumbersome, it shows significant improvement in the growth and development of the child with significant reduction in anaemia. The slow or non-improvement in some children is mainly due to poor compliance. With increasing grade of Marsh biopsy, the severity of anaemia increases but after the initiation of GFD, such children show significantly better improvement in %Hb over time.

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Declarations

Ethical Approval: Taken.

Key points

Celiac disease is increasing in the developing countries and the primary care physicians must screen for it in the children with nutritional deficiency and stunted growth. A prompt early diagnosis and compliance with the gluten-free diet may reverse the severity of the disease within a short span of 6 months.

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Conflicts of interest

There are no conflicts of interest.

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