



HEMATOLOGICAL MANIFESTATIONS OF CELIAC DISEASE AMONG CHILDREN: A SINGLE CENTER STUDY FROM SOUTH PUNJAB, PAKISTAN

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ABSTRACT

OBJECTIVE: To find out various hematological manifestations among children from South Punjab, having confirmed celiac disease (CD).

METHODS: This case-control study was done at The Institute of Child Health, Multan, Pakistan, from 1st February 2019 to 31st July 2019. We enrolled 139 children having CD, ranging in age from 1-12 years. An equal number of age and gender matched controls were also enrolled. Haematological parameters were compared between cases and controls.

RESULTS: Majority (n=83/139; 59.7%) of children with CD were male. Mean age was 8.78±2.4 years. The common hematological manifestations among children with CD were anemia (n=127; 91.4%), thrombocytosis (n=104; 74.8%); leucopenia (n=10; 7.2%) and coagulopathy (n=13; 9.4%). Anemia alone was present in 20 (14.4%) children, anemia plus thrombocytosis in 91 (65.5%) cases, anemia plus leucopenia in 7 (5.0%) cases and anemia along with thrombocytosis and coagulopathy in 9 (6.5%) cases. Out of 127 cases of anemia, iron deficiency anemia (IDA) was noted in 96 (75.6%) cases, vitamin B₁₂ and folate deficiency anemia in 14 (10.1%) cases whereas double deficiency anemia was seen in 17 (13.4%) cases. According to Modified Marsh Scoring, majority (n=46; 33.1%) of children had Type 3a CD. When compared to controls, CD cases had significantly lower haemoglobin, raised platelet count, lower mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) levels (p value<0.0001).

CONCLUSION: In children having CD, hematological manifestations are common. IDA is the most frequent hematological abnormality observed along with thrombocytosis in children with CD. Hematological parameters were significantly impaired among children with CD.

KEYWORDS: Anemia (MeSH); Celiac Disease (MeSH); Thrombocytosis (MeSH).

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INTRODUCTION

Celiac disease (CD) is described as the immune mediated enteropathy because of sensitivity associated to gluten in individuals who have genetic susceptibility.^{1,2} CD appears when individuals are exposed to dietary gluten in wheat, rye or barley. Some of the most frequent forms of presentations in children are diarrhea which is usually recurrent, weight loss and poor growth.³ More recently, lots of work has been

done regarding non-gastrointestinal (GI) manifestations of CD like anemia, coagulopathy or peripheral neuropathy.⁴

Diagnosis of CD is based on demonstration of enteropathy in small intestinal biopsies while histology evaluation exhibit villous atrophy, crypt hyperplasia as well as intraepithelial lymphocytosis.⁵ Circulating CD specific antibodies to tissue transglutaminase (tTG) are also found along with deamidated gliadin peptides (DGP) and endomysium

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(EMA).^{2,6} Children who show symptoms of CD, small intestinal biopsies may not be needed for diagnosing CD where a strong positive tTG antibody titre and a CD linked human leukocyte antigen (HLA) genotype are present. Gluten was noted as the reason of CD trigger in 1950s, and since then, lifelong gluten free diet has always been the foundation of CD treatment.¹

CD is estimated to affect 1% population globally whereas in Europe its prevalence has been between 1 to 3%. Prevalence of CD among children have been reported as 0.5 to 1% while 90% of children having CD are thought to be undiagnosed that raise serious concerns regarding timely diagnosis of CD for its treatment.⁷⁻¹⁰ In Pakistan, not many studies have been conducted amongst children having CD while among children having persistent diarrhea along with poor growth, 61% of the cases had CD in a study from Karachi.¹¹

Anemia is known to be the most frequent hematological finding in CD affecting 86% of cases.¹² Malabsorption associated with iron, folic acid and vitamin B₁₂ could be contributing to anemia. Researchers have reported around 90% of the cases with CD to have anemia.¹³ Coagulopathy is known to be present in about 20% of the cases,¹⁴ thrombocytosis affect 60% while leucopenia is noted in around 9% of cases who have CD.¹²

Data regarding hematological manifesta-

TABLE I: HEMATOLOGICAL MANIFESTATIONS AMONG CHILDREN WITH CELIAC DISEASE (n= 139)

Hematological Manifestations	Frequency	Percentage
Anemia alone	20	14.4
Leucopenia alone	5	3.6
Thrombocytosis alone	4	2.9
Coagulopathy alone	4	2.9
Anemia plus thrombocytosis	91	65.5
Anemia plus leucopenia	7	5.0
Anemia plus thrombocytosis and coagulopathy	9	6.5

tions of CD is scarce, worldwide. In a country like Pakistan, such data is very difficult to find. Hematological spectrum of CD is thought to be an indicator for early diagnosis and treatment of CD whereas better understanding about these could lead to less burden of morbidity related to CD. This study was planned to find out hematological manifestations among children having confirmed CD in our setup.

METHODS

This case-control study was conducted at The Children's Hospital and The Institute of Child Health, Multan, Pakistan, from 1st February 2019 to 31st July 2019. By considering 95% confidence interval, margin of error as 5% and prevalence of anemia as 90% in children with CD,¹³ a sample size of 139 was calculated for this study. Approval from institutional ethical and research committee was taken. Informed consent from all the parents/guardians was also taken. We enrolled 139 children from The Department of Paediatric Gastroenterology, Hepatology & Nutrition, who had CD, with age ranging from 1-12 years. Confirmation of CD was made after small intestinal biopsy exhibiting mucosal alterations according to "Modified Marsh Criteria" which involves partial to full villous atrophy, crypt elongation and/or increase in intraepithelial lymphocytes. All cases who were having liver disease (depicted by ALT > 40 IU/L) or intestinal tuberculosis were excluded from this study.^{6,15} An equal number of age and gender matched controls (n= 139) were also enrolled.

According to institutional protocol, all important laboratory studies including complete blood count, prothrombin time (PT) and activated partial thromboplastin time (APTT) were done.

Anemia was labeled as hemoglobin less than 10 g/dL and all those children who had anemia, serum iron, serum ferritin, serum red cell folate and serum vitamin B₁₂ were investigated.

Pre-designed proforma was used to record study data. SPSS version 20.0 was adopted for data analysis. Gender, residential status, hematological manifestations of CD and disease type were represented as frequencies and percentages whereas age was calculated as mean along with standard deviation. Independent sample t-test was used to compare hematological parameters between cases and controls considering p value <0.05 as significant.

RESULTS

Among patients with CD, 83 (59.7%) were male and 56 (40.3%) were female. Male to female ration was found to be 1.48:1. Majority (n=65; 46.8%) of the children with CD, were less than 5 years of age while 42 (30.2%) were in age range from 5 to 8 years and 32 (23.0%) were more than 8 to 12 years of age. Mean age was recorded as 8.78±2.4 years.

The common hematological manifestations among children with celiac disease were anemia (n=127; 91.4%) and thrombocytosis (n=104; 74.8%). Anemia alone was present in 20 (14.4%) children, anemia plus thrombocytosis in 91 (65.5%) cases, anemia plus leucopenia in 7 (5.0%) cases and anemia along with thrombocytosis and coagulopathy in 9 (6.5%) cases (Table I).

Out of 127 cases of anemia, iron deficiency anemia was noted in 96 (75.6%) cases, vitamin B₁₂ and folate deficiency anemia in 14 (10.1%) cases whereas double deficiency anemia was seen in 17 (13.4%) cases.

According to Modified Marsh Scoring in children with CD, Type 3a, Type 3b, Type 3c, Type 2 and Type 1 were found in 46 (33.1%), 38 (27.3%), 35 (25.2%), 17 (12.2%) and 3 (2.2%) cases respectively.

When compared to controls, CD cases had significantly lower haemoglobin (%), raised platelet count, lower MCV femoliter (fl) and MCH picograms (pg) levels (p value <0.0001). Haematological parameters among both study groups are shown in Table II.

DISCUSSION

CD is considered a systemic disease having numerous hematological patterns.¹² In the past, hematological manifestations of CD like anemia has been explained but we noted other features like thrombosis and coagulopathy were also present in children having CD.

In this study, we noted that 91.4% children with CD were having anemia. There are variations in terms of figures regarding the presence of anemia amongst children with CD. Data from Finland among children with CD, aged less than 18 years noted 18% of the patients to have anemia at the time of enrollment in the study which is quite contrary to the current findings.¹³ de Vizia B, et al. found 34% of the infants with CD to have anemia.¹⁴ Children with CD are thought to have poor adherence to dietary advice and in a country like Pakistan where nutritional status of healthy children is not up to the desired levels, presence of CD further worsens the nutritional status of these children. Anemia at the time of CD diagnosis is also linked with more severe histology and serology findings among children so very high prevalence of anemia in the present study could be pointing towards more severe presence of disease probably among these children. A local study done from Lahore also noted that 94.2% children with CD had anemia.¹⁵ Early diagnosis of anemia could be critical for good prognosis of CD but it has been found that even with 1 year of gluten-free diet, hemoglobin levels might not improve.¹³ Children with unexplained anemia need to be evaluated for possible presence of CD.

Thrombocytosis was another common

finding among children with CD in our study. Thrombocytosis is noted to be far more common than thrombocytopenia among children having CD.^{16,17} Exact mechanism behind thrombocytosis in the present study could be secondary to inflammatory mediators or iron-deficiency anemia or because of hyposplenism.¹⁸ The exact mechanism behind thrombocytosis in children with CD is not fully understood in the past. Further research is needed to shed light on this important aspect. Thrombocytosis as an alone entity was noted in only 4 (2.9%) of our children which shows that this finding is not very common in children with CD as thrombocytosis usually present with anemia most commonly. Madni B, et al.¹⁵ also noted only 1.7% of the children with CD were having thrombocytosis alone while other researchers¹⁹ also got figures of 2.9%.

Leucopenia is generally described as a rare finding in cases having CD.¹⁷ We observed leucopenia in 7.2% of children with CD. Leucopenia is usually found along with anemia in cases having CD.^{15,19} Deficiency of folate as well as copper in children with CD could be the underlying mechanism behind leucopenia in these children.²⁰

It is important to note that children enrolled in this study did not have any kind of active bleeding. We noted coagulopathy in 9.4% of our cases. In the past, coagulopathy has been found in cases that had CD. A study from Lahore noted 8.3% of their cases to have CD.¹⁵ Coagulopathy alone is an uncommon finding as was found in the present study and by other researchers as it is usually found accompanied with anemia or thrombocytosis.^{15,19} The reason could be low vitamin K synthesis due to malabsorption and diarrhea in such cases.¹⁹ Low levels of vitamin K may aid to decreased vitamin K factors which

in turn could prolong PT and APTT. Intramuscular hemorrhage has also been found in previous studies.^{19,20}

According to Modified March Criteria,²¹ Type 3 disease was noted in majority of the children with CD in the current study. In the present study, we found that hematological manifestations of in children having CD are quite common, so it is proposed that children with recurrent iron deficiency anemia need to be evaluated for CD.

Limitations: Primary nutritional deficiencies could also be a major contributing factor in children having CD, but we were unable to include any nutritional data of our study participants. We could not correlate disease severity with different degree of hematological manifestations. No data about the treatment, outcome or measures adopted for these children at our setting were elaborated so further studies could be planned with follow up data to further highlight compliance, catch up growth as well as outcome of children with CD.

CONCLUSION

In children having celiac disease, hematological manifestations are common. Iron deficiency anemia is the most frequent hematological abnormality noted along with thrombocytosis in children with CD. Haematological parameters were significantly impaired among children with CD. More studies aiming follow up data and compliance to various management strategies are required to shed light on growth outcome of children with celiac disease.

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TABLE II: HEMATOLOGICAL PARAMETERS AMONG CASES AND CONTROLS

Hematological Indices	Celiac Disease Group (n= 139)	Controls (n= 139)	P-Value
Haemoglobin (g/dL)	7.3±2.81	10.2±2.57	<0.0001
Platelet Count (per mm ³)	441x10 ³ ±128x10 ³	293x10 ³ ±92x10 ³	<0.0001
Mean corpuscular volume (fl)	62.5±4.2	81.1±3.8	<0.0001
Mean corpuscular hemoglobin (pg/cell)	19.2±2.5	27.8±4.8	<0.0001
Mean corpuscular hemoglobin concentration (g/dL)	28.6±3.5	32.4±3.7	<0.0001

Values in Mean±SD

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

SJJ: Conception and study design, acquisition of data, drafting the manuscript, critical review, approval of the final version to be published

MTA & IH: Acquisition of data, drafting the manuscript, approval of the final version to be published

HS & GKK: Analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

MAT: Acquisition, analysis and interpretation of data, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.



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