Prothrombin Time and Activated Partial Thromboplastin Time in Children with Newly Diagnosed Coeliac Disease

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ABSTRACT

Introduction: Coeliac disease is a systemic disorder with protean manifestations. It can be associated with abnormalities in coagulation factors resulting in an abnormal bleeding tendency. Only a few studies have been done to evaluate coagulation profile in coeliac children. Objective of this study was to estimate Prothrombin Time, International Normalised Ratio and Activated Partial Thromboplastin Time in newly diagnosed coeliac disease and to correlate it with Anti Tissue Trans-Glutaminase antibody titres, and histopathological grading assuming this knowledge will help in deciding whether we should include testing coagulation profile assays routinely in all patients diagnosed with coeliac disease.

Material and methods: In this cross-sectional observational study, 32 children with confirmed diagnosis of coeliac disease were enrolled after applying the inclusion and exclusion criteria. All clinical, demographic details and investigations available were noted. Blood samples were analysed. Appropriate statistical tests were used and analysis was done using Statistical Package for Social Sciences version 21.0.

Results: Mean age distribution in study subjects was 8.33 ± 4.6 years. Mean age at onset of symptoms was 6.52 ± 4.53 years and Mean duration of illness prior to diagnosis was 1.92 ± 2.87 years. Gastro-Intestinal symptoms and Extra-intestinal symptoms were present in 90.63% and 87.50% patients respectively. Activated Partial Thromboplastin Time was deranged in 31.25% of patients and both Prothrombin Time & International Normalised Ratio were deranged in 9.38% of patients. Non significant mild positive correlation was seen between Anti Tissue Trans-Glutaminase antibody titres with Prothrombin Time & Activated Partial Thromboplastin Time and No significant association was seen in Prothrombin Time & Activated Partial Thromboplastin Time with histopathological grading.

Conclusion: Coagulation abnormalities are frequently present in childhood coeliac disease. Both Prothrombin Time & International Normalised Ratio were deranged in 9.38%; and Activated Partial Thromboplastin Time was deranged in 31.25% patients. Prothrombin Time and Activated Partial Thromboplastin Time showed no significant correlation with Anti Tissue Trans-Glutaminase antibodies titre and histopathological grading.

Keywords: Coeliac Disease, Anti-TTG, INR, Coagulopathy, Vitamin K, Paediatrics.

INTRODUCTION

Coeliac disease (CD), or gluten-sensitive enteropathy, is a systemic disorder with protean manifestations.Anaemia secondary to malabsorption of iron, folic acid, and/or vitamin B_{12} is a common complication of coeliac disease and many patients have anaemia at the time of diagnosis. Coeliac disease may also be associated with thrombocytosis, thrombocytopenia, leukopenia, venous thromboembolism, hyposplenism, coagulopathy and IgA deficiency.[1]

CD can be associated with abnormalities in coagulation factors resulting in an abnormal bleeding tendency. Malabsorption of vitamin K is common in chronic gastrointestinal disorders. A decrease in K vitamin–dependent coagulation factors results in prolongation of coagulation assays such as the prothrombin time (PT), international normalised ratio (INR), and the activated partial thromboplastin time (APTT).[1]

Only a few studies have been done to evaluate coagulation profile in coeliac children. This study was done to estimate prothrombin time (PT), INR and activated partial thromboplastin time (APTT) innewly diagnosed coeliac disease and to correlate it with antiTissue Trans-Glutaminase (TTG) antibodies titres, and histopathological grading assuming this knowledge will help in deciding whether we should include testing coagulation profile assays routinely in all patients diagnosed with coeliac disease.

MATERIAL AND METHODS

This cross sectional observational study was conducted at the Department of Paediatrics in ABVIMS & Dr. RML Hospital, New Delhi, India from 1st November 2018 to 31st March 2020 after obtaining institutional ethical committee clearance.

Sample Size: Coagulation abnormalities in children with Coeliac disease was observed by Shyam Sundar Sharma,

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et al.[2] The study observed 27% had deranged prothrombin time. Taking this value as reference, the minimum required sample size with 20% margin of error and 5% level of significance was 20 patients. We recruited 32 patients with newly diagnosed coeliac disease.

Definition of Disease for purpose of study

Coeliac disease was defined on the basis of ACOG clinical guidelines 2013 for children: Children with clinical symptoms or asymptomatic with family history, positive serology and positive biopsy findings were considered to have coeliac disease. In children with IgA deficiency, alternative serological evidence of IgG anti DGP antibodies was considered positive.

Inclusion criteria

Children in the Paediatric age group (<18 years) presenting to the Paediatrics department with confirmed diagnosis of coeliac disease as decided in ACOG clinical guidelines 2013 were enrolled for the study.

Exclusion criteria

Children diagnosed with any other associated known chronic infections or inflammations.

Children who had received gluten free diet or vitamin K therapy during the past 6 months.

Children who were on any medication which could alter coagulation profile, such as heparin, warfarin, enoxaparin, etc.

All the consecutive children fulfilling the case definition were enrolled for the study. Informed written consent was obtained from parents or guardians. All clinco-demographic details were noted in a predesigned proforma. Anthropometric measurements including weight, height and BMI were recorded using standard methods. Other investigations viz TTG IgA, Histology, Haemogram, LFT, KFT available with the patients were also noted. After obtaining details, a total of 3 ml of venous blood from a peripheral vein was drawn taking all standard aseptic measures after an overnight fasting and preserved in Sodium citrate vial. The samples were analysed for PT, INR and APTT using ACL elite, fully automated coagulation analyzer.Normal values taken for INR : <1.4Prothrombin time : 11.5(control) +/- 4 seconds APTT : 28-34 seconds.[3,4]

STATISTICAL ANALYSIS

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then a non parametric test was used.

Statistical tests were applied as follows-

1. Quantitative variables were compared using Mann-Whitney Test (when the data sets were not normally distributed) between the two groups and ANOVA/ Kruskal Wallis test was used for comparison between more than two groups.
2. Spearman rank correlation coefficient was used to assess the correlation of various parameters with INR, APTT and PT.

A *P* value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

In this cross sectional observational study thirty-two children in the Paediatric age group (<18 years) presenting to the Paediatrics department with confirmed diagnosis of coeliac disease as decided in ACOG clinical guidelines 2013 were enrolled for the study. Investigations wererecorded in case proforma. Following were the results pertaining to the study. In our study, Mean age distribution in study subjects was 8.33 ± 4.6 years.Male: Female ratio in the study population was 1:1.Among the subjects, Mean age at onset of symptoms was 6.52 ± 4.53 years and Mean duration of illness prior to diagnosis was 1.92 ± 2.87 years. GI symptoms were present in 90.63% patients. In majority (65.63%) of patients, pain abdomen was present followed by diarrhea (56.25%) and abdominal distension (53.13%).In 87.50% of patients, Extra-intestinal symptoms were present. In majority (81.25%) of patients, weakness was present followed by easy fatigability (78.13%) and short stature (40.63%).

	Prothrombin time (PT)	International normalised ratio (INR)	APTT
Percentage(%) of subjects with deranged values	9.38%	9.38%	31.25%
Mean ± SD	12.81 ± 2.46 seconds	1.13 ± 0.24	31.39 ± 5.62 seconds
Median(IQR)	12.2(11.3-13.625) seconds	1.05(0.99-1.16)	31.1(28.85-33.325) seconds
Range	9.5-20.6 seconds	0.86-1.92	13.8-42.8 seconds
Normal values taken for INR : <1.4Prothrombin time : 11.5(control) +/- 4 seconds APTT : 28-34 seconds[3,4]			

Table-1: Distribution of coagulation profile in study subjects.

Variables	Prothrombin time (seconds)	APTT (seconds)
Anti TTG titre(IU/mL)		
Correlation coefficient	0.085	0.165
P value	0.64	0.36

Table-2: Correlation of Prothrombin time(seconds) and APTT with Anti TTG titre.

Coagulation profile	1(n=2)	2 (n=1)	3A (n=7)	3B (n=14)	3C (n=8)	Total	P value	Test performed
Prothrombin time (seconds)								
Mean ± SD	12.45 ± 0.35	14.1 ± 0	13.03 ± 3.4	11.74 ± 1.25	14.41 ± 2.88	12.81 ± 2.46	0.13	Kruskal Wallis test; Chi square = 6.964
Median(IQR)	12.45 (12.325-12.575)	14.1 (14.1-14.1)	11.7 (11.4-12.6)	11.65 (11-12.35)	14.2 (12.375-15.75)	12.2 (11.3-13.625)		
Range	12.2-12.7	14.1-14.1	10.9-20.6	9.5-14.3	10.9-19.1	9.5-20.6		

Table 3:- Association of Prothrombin time with histopath grading (Marsh grade).

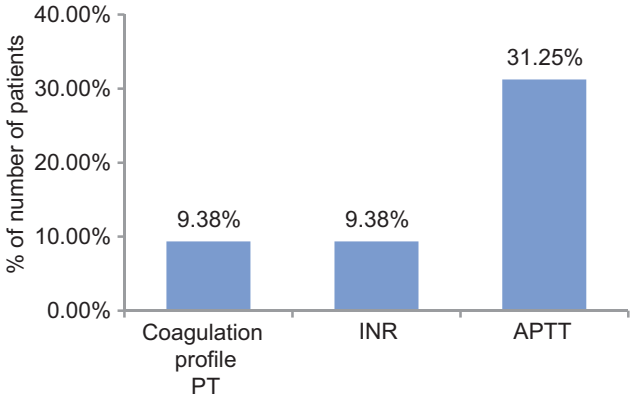

Figure-1: Percentage of patients with abnormal coagulation profile among study subjects.

Mean value of anti TTG IgA titre (IU/mL) of study subjects was 224.38 ± 216.69.In majority (43.75%) of patients, histopathgrading (Marsh grade) was 3B followed by 3C(25.00%), 3A(21.88%), grade 1(6.25%) and grade 2(3.13%).

Mean value of weight (kg) amongst study subjects was 19.67 ± 8.65 and height (cm) was 115.87 ± 23.5. Mean value of body mass index (kg/m²) amongst study subjects was 13.96 ± 1.98.

On examination, pallor was present in 71.88% of patients followed by dental caries (34.38%), poor oral hygiene(18.75%), glossitis (15.63%), cheilosis (12.50%) and stomatitis (9.38%).

In present study, APTT was deranged in 31.25% of patients and both prothrombin time(seconds) and international normalised ratio were deranged in 9.38% of patients. (Table-1 and Figure-1)

Non significant mild positive correlation was seen between anti TTG titre(IU/mL) with prothrombin time(seconds), APTT(seconds) with correlation coefficient of 0.085, 0.165 respectively. (Table-2) No significant association was seen in prothrombin time(seconds) and APTT(seconds) with histopathological grading (Marsh grade). (Table-3 and 4)

DISCUSSION

In our study mean value of age of study subjects was 8.33 years; Mean age of onset of symptoms amongst study subjects was 6.52 years. Mean duration of symptoms prior to diagnosis was 1.92 years. In a previous study by Sharma SS et al[2], the mean age of coeliac children at presentation was 5.5 years, which was less than that of our study and in the study by Ertekin V et al[5], the mean age in their study population was 8.774.3 years, which was similar to that reported in our study.Higher mean age was reported by Fisgin et al[6], where the mean age of the female and male was 11.2 years and 11.4 years, respectively. Meena DK et al[7], reported that mean age of children at diagnosis of CD was 7.05±4.4 years and the mean age of onset of symptoms in study subjects was 5.4±3.8 years.

In our study 50% of patients were males and 50% were females. In a previous study by Sharma SS et al[2], out of 111 children, 65 were boys and 46 were girls. Meena DK et al[7], reported that out of the 66 children included in their study, 53% were males and 47% females. Ertekin V et al[5] found predominance of females as 52.6% were girls and 47.4% were boys. Also in the study by Fisgin et al[6], more females were in the study with 68.1% females and 31.8% males. The demographic distribution of our study is comparable to other previous studies.

In our study, GIT symptoms were present in 90.63% patients, and extra intestinal symptoms were present in 87.50% patients. The most common extra intestinal symptoms were weakness (81.25%) followed by easy fatiguability (78.13%), short stature (40.63%), dental caries (28.13%), easy bruisability (21.88%), and muscular symptoms (15.63%). Pallor was present in 71.88% of patients followed by dental caries (34.38%). Oral hygiene was poor in 18.75% of patients. Proportion of patients with glossitis was 15.63% followed by cheilosis (12.50%) and stomatitis (9.38%). Previous studies have also reported frequent presence of extra intestinal symptoms. Fisgin et al[6]reported that 59% of the patients presented with no abdominal symptoms. In study by Meena DK et al[7] the most common GI symptom was abdominal distension (57.5%), followed by chronic diarrhoea (46.9%), abdominal pain (36.3%), vomiting (21.2%), and constipation (1.5%) In extra intestinal symptoms, weight loss/not gaining weight was present in 65.1%, weakness in 33%, and pedal oedema in 15.1%.

Mean anti-TTG titre of study subjects in our study was 224.38 IU/mLwhich was in line with the studies by Meena DK et al[7]who reported that mean value of anti-TTG was 218.9 IU/mL.

Histopathological grading (Marsh grade) in most of the patients (43.75%) in our study was 3B followed by 3C (25.00%), 3A (21.88%) and grade 1 (6.25%). Histopathological grading (Marsh grade) was 2 in only 1 out of 32 patients.However, in a previous study by Sharma SS et al[2], Marsh grade 3c was present in majority (51.35%) patients followed by Marsh grade 3b in 26.12% patients. This difference can be attributed to the larger sample size of 111 patients in the latter study as compared to our study with 32 patients.

We found that PT was deranged in 9.38%; APTT was deranged in 31.25% INR was deranged in 9.38% and platelet counts were deranged in 18.75%.

Among other Indian studies, INR was found to be deranged in higher number of children in study by Sharma SS et al[2] in 2017 at Fortis, Jaipur where 27% children had deranged INR; 73.9% children had normal platelet counts while thrombocytosis was seen in 26.1% children; 19% children had prolonged APTT.

In 2004 Fisgin et al[6] from Turkey observed that out of 22 children, PT and APTT were deranged in only 1 child (4.5%). However in 2006 Ertekin et al[5]from Turkey reported that the PT, PTT and INR of children with CD on admission were 14.3±3.3 s, 31.7±4.4 s, and 1.28±0.38, respectively. Number with INR >1.4 (%) was present in 25.6% patients. Prolonged PT frequency was 25.6%.

According to the results of Cavallaro et al[8] in 2004 in Italy, which was conducted in adults patients, a prolonged PT was found in 72 coeliac patients (18.5%).

In our study, we found a mild positive statistically insignificant correlation between anti-TTG titre(IU/mL) with prothrombin time(seconds), APTT(seconds) with correlation coefficient of 0.085, 0.165 respectively. PT and APTT also showed no significant association with Marsh biopsy grading(P>0.05). On the other hand Sharma et al[2], found that there was an increasing proportion of coagulopathy with progression of Marsh Grade on duodenal histology. This could be because of the difference in sample population in terms of sample size and higher number of patients presenting with severe histopathological grading in the study by Sharma SS et al[2] as compared to our study.

Overall, mild coagulopathy was found to be common among CD patients however no significant association was seen between the deranged coagulation parameters and the severity of CD based on Marsh grading and anti-TTG titres.

One of the limitations of our study was that clinical significance of coagulopathy could not be demonstrated because none of the patients in the study developed overt bleeding. This could be because our study was a cross-sectional study, a follow up of these patients could have incited the actual episodes of bleeding in these patients. Our study was a single centre hospital based study, so its results may not be applicable to all coeliac patients.

CONCLUSION

Coagulation abnormalities are frequently present in childhood coeliac disease. PT was deranged in 9.38%; INR was deranged in 9.38%; and APTT was deranged in 31.25% patients. PT and APTT showed no significant correlation with anti-TTG antibodies titre and histopathological grading (Marsh grading).

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