Anemia and Celiac Disease-Experience At Tertiary Care Center of Northern India

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Abstract: *Background:* Celiac disease (CD), is a chronic immune-mediated disorder of small intestine that occurs in genetically predisposed populations. It is characterized by permanent intolerance to wheat gliadins and other cereal prolamins. The epidemiology of CD has iceberg characteristics with more undiagnosed cases. The diagnosis of CD is currently based on both typical small bowel biopsy findings with clinical and serological parameters. Anemia secondary to iron, folic acid and vitamin B12 malabsorption is a common complication of celiac disease. Patients can also present with thrombocytosis, thrombocytopenia, leukopenia, venous thromboembolism, hyposplenism and IgA deficiency.

Aims: This study conducted with aims to study presenting complaints of suspected cases of celiac disease and further correlate endoscopic duodenal biopsies with various clinical and serological parameters.

Materials and Methods: The detailed clinical history and physical examination was done and then duodenum biopsies in hundred cases of suspected CD (on the basis of clinical and serological profile) were taken. Histopathological diagnosis was established on routine hematoxylin and eosin stained sections. The histopathological grading was performed as per modified Marsh grading. Representative section was also subjected for immunohistochemically staining with antihuman CD3 antibody for evaluating intraepithelial lymphocytes. Comparison of these grades with the serological (anti tTG levels) and other clinical parameters (symptoms, weight, endoscopy and hemoglobin levels) were done. These data were subsequently analyzed using SPSS 20.0 software. Chi square test and other relevant statistics were used to assess the relationship between two variables. P-value less than 0.05 was accepted as statistically significant.

Results and Conclusions: Majority of patients presented with typical gastrointestinal symptoms and anemia and significantly correlated with higher Marsh grades (p=0.0326) but atypical symptoms can be the primary presentation of the disease. Patients with higher serum anti-tTG levels, have a high-degree probability of duodenal damage. Anti-tTG levels have conclusively been proven to correlate with increasing histological grades (p=0.005).

Keywords: Celiac disease, anemia, gluten.

1. INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated disorder of small intestine that occurs in genetically predisposed populations [1]. The pathogenesis entails a T cell□mediated immune response with production of autoantibodies directed against tissue transglutaminase or endomysium. Wheat, rye, oat and barley prolamins are toxic for celiac patients due to their high glutamine and proline content [2]. Initially the suspicion of CD was based on clinical gastrointestinal (GI) symptoms. Subsequently, the disease has been found with variety of atypical symptoms and even in asymptomatic subjects [3]. Celiac disease affects people in all parts of the world. Originally thought to be a rare childhood syndrome, but it is now known to be a common genetic disorder. While celiac disease is estimated to affect about 1% of the world's population, it is thought to be uncommon not only in India but in Asia also. Screening studies in different populations have shown that the prevalence of the disease is much higher than previously thought, 1% or more in both the United States and Europe. The prevalence of detected cases of celiac disease is much lower, from 0.27% to 0.02%. 4. There is a general perception that celiac disease is uncommon in India. As the origin of north Indians is Indo-European, it is likely that celiac disease would be more common in north India than previously thought.

The histologic changes in CD vary from severe villous atrophy to more subtle changes (with or without increased density of intraepithelial lymphocytes and crypt hyperplasia). Although villous atrophy is not specific to CD. Serology has become increasingly relevant to CD diagnosis. Anti-tissue transglutaminase antibodies) are the most sensitive test for CD [2].

2. MATERIAL AND METHODS

Biopsies from a total of 100 consecutive cases of suspected CD formed the study group. Various symptoms considered for clinical suspicious of CD including GI symptoms (diarrhea, vomiting and pain abdomen), Anemia and other atypical symptoms. Complete history and clinical examination was done to rule out other causes of malabsorption.

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The biopsy was taken from second part of duodenum through eosophagoduodenoscopy with the assessment of duodenal endoscopic markers including scalloping of folds, grooving, and nodularity of mucosa. Histopathological diagnosis was established on routine hematoxylin and eosin stained sections [4].

Immunohistochemical (IHC) staining [5] with antihuman CD3 antibody was done for evaluating intraepithelial lymphocytes (IELs) with positive (tonsillar tissue) and negative (substituting the primary antibody with an antibody of irrelevant specificity) controls. The histopathological grading was performed as per modified Marsh grading [6].

Anti-tTG levels were performed by enzyme-linked immunosorbent assay (ELISA). Patients with anti-tTG>15 U/ml were considered to be suspicious even the absence of clinical symptoms. These patients were again divided into two groups, including 15-99U/ml and ≥100U/ml. complete hematologic work-up was performed to classify anemia. Reference range for anemia for age was taken from WHO guidelines [7]. Reference range for weight for age was as per Advanced Pediatric Life Support guidelines [8]. All patients were started on gluten-free diet (GFD) along with hematinic. Celiac status of a patient was confirmed by clinical response to GFD, defined as improved symptoms such as weight gain, and increase in hemoglobin concentration at 4 and 24 weeks. Comparison of these histological grades with the anti-tTG levels and other clinical parameters (symptoms, weight, endoscopy and hemoglobin levels) were done using SPSS 20.0 software. Chi square test and other relevant statistics were used to assess the relationship between two variables. P-value less than 0.05 was accepted as statistically significant.

3. RESULTS

Biopsies from second part of duodenum of 100 consecutive cases of suspected CD formed the study group. Maximum number of the cases (71%) lied in age group 11-30 years. Mean age of study group was 21.16 year.

Children and adolescents (<18 years) constituted 40% while adults (≥18 years) constituted 60% of study group. Maximum number of the cases among children and adults were belong to age group 11-17 (26) and 21-30 (32) years respectively. Female patients constituted 54% of total study group. Out of 40 children, 23 were females and 17 were males. Out of 60 adults, 31 were females and 29 were males.

Histologically, 87 cases were positive for CD. Most of them belonged to grade IIIa (36 cases). Remaining 51 cases were distributed as follows: Grade I (13), grade II (10), grade IIIb (16), grade IIIc (10) and grade IV (02).

Maximum number of patients (82%) presented with typical/gastrointestinal symptoms (including diarrhea, abdominal pain and vomiting). Among these, 20 cases presented with all the three GI symptoms. Diarrhea (85.36%) was the most common complaint. Other 18 cases had atypical symptoms, in which short stature (07), hypothyroidism (03), and diabetes (03) were predominant in study group. Difference in presentation of GI symptoms between children and adult groups was statistically insignificant (p=0.339). Preponderance of GI over atypical symptoms was statistically significant (p=0.0001). Gastrointestinal and atypical symptoms predominated in higher modified Marsh grades (III and IV), but this was significant statistically (p=0.0326) for GI symptoms only.

Anemia was diagnosed in majority of our cases (90%). Anemia was observed more in adults (93.33%) than children (85%) which was statistically insignificant (p=0.161). There was a fall in hemoglobin levels with higher grades in both children and adults, but this was statistically insignificant (p=0.729 and 0.726 respectively). Sixty three cases were underweight. Underweight were seen more in children (70%) than adults (58.33%) and difference was statistically insignificant (p=0.117). There was a decrease in weight with higher Marsh grades in both children and adults but not significant statistically (p=0.189 and 0.40 respectively).

Endoscopic findings (nodularity, granularity and scalloping) were present in 45% of the cases. Maximum endoscopically positive cases had scalloping (88.89%). Distribution of endoscopic findings in children and adults was not significant (p=0.682). Increasing severity of endoscopic damage had been found with increasing Marsh grades, but was statistically insignificant (p=0.431). The sensitivity, specificity, positive and negative predictive value for endoscopic finding in relation to CD were 47.13%, 69.23%, 91.11% and 16.36% respectively.

On the basis of serum tTG levels, cases were categorized into two groups with cut off value of 15U/ml. Sixteen cases had tTG level <15 U/ml. Eighty four cases had serum tTG levels (≥15U/ml); among these 53 cases had serum tTG ≥100 U/ml.

We found a statistically significant increase in anti-tTG values from histologically milder forms of the disease to more severe forms (p=0.005). Though 16 cases had tTG <15 U/ml, but histologically different grades of CD was seen in 14 cases, of which grade IIIa was predominated. Out of rest 84 cases with tTG ≥15 U/ml, 11 cases were histologically negative. The sensitivity, specificity, positive predictive value and negative predictive value for serum tTG levels in relation to CD were 83.91%, 15.38%, 86.90% and 12.50% respectively. Fifty three cases with higher tTG level (≥100 U/ml) predominated in higher grades, which was statistically significant (p=0.009).

4. DISCUSSION

The insight into CD has undergone a revolutionary development regarding epidemiology, diagnostics and treatment. CD also known as intestinal infantilism, idiopathic steatorrhea, non-tropical sprue, and gluten-sensitive enteropathy [9]. Various etiological factors are considered for CD including genetic (HLA class II antigen) and environmental risk factors [9] including GI infections [10].

Gliadin is a glycoprotein extract from gluten, directly toxic to the enterocytes of individuals with CD. Transglutaminase enzyme crosslinks gliadin and causes specific deamination of glutamine into glutamic acid. With such deamination, the gliadin peptides are able to be more efficiently presented to gliadin-reactive CD-4 T cells. Without Transglutaminase, it is believed that gliadin is less immunogenic. Thus Transglutaminase autoantibodies play a role in disease pathogenesis, but lacks sufficient supportive evidence [11].

The epidemiology of CD has iceberg characteristics as there are more undiagnosed cases. The female-to-male ratio is 2:1. The prevalence of CD is globally 1%. The prevalence of CD in India is nearly the same as that in Western Caucasian populations [12].

The clinical presentation of CD depends on the severity of small intestine damage. Depending on the clinical, histopathological and immunological features, CD can be classified into the following forms: classical (typical), subclinical (atypical or mono-symptomatic), silent (asymptomatic) and potential/latent. A number of idiopathic neurological disorders associated with atypical CD such as epilepsy, cerebellar ataxia, intellectual deterioration, peripheral neuropathy and multiple sclerosis. Reproductive system dysfunction may be observed in the form of menstrual irregularities, infertility and obstetric complication in females and impotence, infertility and abnormalities of sperm in males [2].

Several disorders are associated with CD. The most well-known association is with dermatitis herpetiformis and other pathological conditions include autoimmune disorders (diabetes mellitus type 1, thyroid disorders, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, alopecia, vitiligo, Addison's disease, Sjogren's syndrome, IgA nephropathy and IgA deficiency), idiopathic disorders (primitive dilated cardiomyopathy, atopy and inflammatory bowel disease) and chromosome disorders (Down, Turner and Williams syndromes) [2, 13, 14]. These associations may be due to common pathogenic basis. Various malignancies have been linked to CD such as enteropathy-associated T-cell lymphoma, multiple myeloma, Hodgkin's disease, gastric cancer, melanoma of the skin, renal cell carcinoma, breast cancer, carcinoid tumour of the pancreas, meningioma, lung cancer, liposarcoma of the abdomen and prostate cancer [13].

In current practice, the diagnostic protocol of CD is based on (1) History and clinical presentation; (2) Serological screening; (3) Histological findings; (4) Obvious clinical and serological response to a gluten free diet; (5) Age >2 years and (6) Exclusion of other clinical conditions mimicking CD [3]. It has been suggested that cases with high celiac autoantibody values might not need histological confirmation. Consensus is needed on the diagnostic criteria for cases with mild mucosal changes or high antibody levels [15].

Auto-antibodies against endomysial (EMA), tissue transglutaminase (tTG), gliadin and deamidated gliadin peptides (DGPs) are measured in serologic tests. All of these antibodies are immunoglobulin A (IgA) or G (IgG) type. Anti-tTG antibodies are highly sensitive and specific for CD. ELISA tests for IgA anti-tTG antibodies are now widely available. But there are still substantial differences between the cut-off points suggested by the manufacturers [15]. The characteristic findings of CD on endoscopy include: (a) Scalloped folds, fissures and a mosaic pattern, (b) Flattened folds, and (c) Smaller size and/or disappearance of folds with maximum insufflation [16].

An intestinal biopsy and serology represents the gold standard in diagnosing CD. It is also essential that biopsy samples are correctly oriented to avoid tangential artifacts and under or over estimation of villi atrophy and counting of IELs. Modified Marsh

classification allows a short and precise classification of the intestinal lesion at the time of first diagnosis and follow up Giardiasis, Tropical/Collagenous/Hypogamma-globulinaemic sprue, autoimmune enteropathy, Infectious gastroenteritis, Intestinal T-cell lymphoma and Food protein hypersensitivity are differential diagnosis of CD [6].

Adult celiac were more than children in our study. In both groups, females were predominant. Maximum number of patients presented with GI symptoms than atypical symptoms in which diarrhea was the most common complaint as seen in other studies in literature [16-21]. Presentation of gastrointestinal symptoms was statistically significant over atypical symptoms (p=0.0001). Typical GI symptoms predominated in higher histological grades, which is statistically significant (p=0.0326). Study by Donaldson *et al*. and other authors suggested that the severity of symptoms followed a linear trend toward more severe histopathological grades [16, 17, 20, 22, 23].

Anemia secondary to iron, folic acid and vitamin B12 malabsorption is a common complication of celiac disease. Patients can also present with thrombocytosis, thrombocytopenia, leukopenia, venous thrombo-embolism, hyposplenism and IgA deficiency. Celiac disease also predisposes to lymphoma development. The highest risk is for enteropathy associated T-cell lymphoma (EATL), an aggressive lymphoma with poor prognosis, however an increased risk for B-cell lymphomas and extra intestinal lymphomas has been described. Anemia is a frequent finding in patients with celiac disease (CD) and may be the presenting feature. It may also be the only abnormality identified. Anemia was particularly common in patients with untreated CD in the past, but it is still frequently encountered in undiagnosed adults. The etiology of anemia in celiac disease is multifactorial. The anemia is usually hypo proliferative, reflecting impaired absorption of essential nutrients like iron and various vitamins. The overall prevalence of anemia at the time of diagnosis of celiac disease has been estimated between 12 and 69%. Anemias caused by hemolysis are very rarely reported in celiac disease patients. The most obvious cause of anemia in celiac disease is impaired absorption of iron and other nutrients including folate and

Cobalamin. Iron is absorbed in the proximal small intestine and the absorption is dependent upon several factors, including an intact mucosal surface and intestinal acidity. Villous atrophy of the intestinal mucosa is an important cause of abnormal iron absorption, which is reflected as laboratory evidence of iron deficiency anemia (IDA) in most anemic patients with celiac disease. Iron-deficiency anemia can be found even in the absence of diarrhea or steatorrhea. The anemia seen in celiac disease can also result from malabsorption of various micronutrients necessary for normal hematopoiesis which include vitamin B12, folate deficiency and Copper. The treatment of IDA associated with CD is primarily a gluten free diet (GFD) and iron supplementation until the iron stores have been restored. Patients with vitamin B12 deficiency should receive therapy with parenteral vitamin B12 and those with folate deficiency should receive oral supplementation of same.

Anemia was diagnosed in majority of our patients (90%). Prevalence of anemia among celiac patients was also observed in various studies [19, 20]. Anemia was observed more in adults as compared to children. There was a fall in hemoglobin levels with increase in tTG levels and higher grades in both children and adults, which was statistically insignificant. However Dipper *et al.* found significant association between anemia and anti-tTG antibody [24]. This may be due to more specific test was used for diagnosis of anemia like serum ferritin. We observed that 63% celiac patients were underweight and more in children. There was a decrease in weight with increase in tTG levels and higher Marsh grades in both children and adults. This decrease in weight was statistically significant in adults only (p=0.05). Similar association was observed by Dipper *et al*. [24].

Endoscopic findings (nodularity, granularity and scalloping) were absent in 55% cases. Sensitivity, specificity, positive and negative predictive value were 47.13%, 69.23%, 91.11% and 16.36% respectively for the endoscopic findings. Association between endoscopic findings with various Marsh grades was not significant (p=0.431). Similar insignificant observations were found by Oxentenko *et al*. [25]. However in few studies, these endoscopic changes were significantly associated [26, 27]. This may be due to various factors including selection of the patients, sensitivity and specificity of endoscopic method used or histological criteria used for evaluation of duodenal biopsy.

We classified the study population in two groups on the basis of cut off value of tTG (15U/ml). Eighty four cases had serum tTG levels ≥15U/ml, among these 53 cases had ≥100 U/ml. Concordant findings were also observed by Donaldson *et al.* and Kotze *et al*. [20, 28]. Sensitivity, specificity, positive and negative predictive

value were 83.91%, 15.38%, 86.90% 12.50% for serum tTG levels. We found a statistically significant increase in anti-tTG values from histologically milder to severe forms (p=0.005). Similar observations were found in various studies [16, 18, 20, 22, 23-30]. Fourteen case had different grades with tTG <15U/ml. Similar observation was seen by Kalhan *et al*. [16].

Higher tTG level (≥100U/ml) was predominant in higher grades, which was statistically significant (p=0.009). It has been proposed that higher IgA tTG level can be considered diagnostic tool for CD even without biopsy [21, 23, 29]. Allesio and colleagues concluded high probability of duodenal damage if anti-tTG serology ≥7 times the cut-off [30].

5. CONCLUSION

To conclude, majority of patients with CD present with typical gastrointestinal symptoms and anemia but atypical symptoms can be the primary presentation. Endoscopic markers have been predictive of the disease and are guides for directing small bowel biopsies in patients suspected of having CD. Patients with serum anti-tTG levels ≥100U/ml, have a high-degree probability of duodenal damage. So, in selected conditions with strong clinical suspicion and high titers of anti tTG, a duodenal biopsy may be avoided and it could be the basis to prescribe GFD. Celiac disease is having varied manifestations and worldwide distribution, mainly in gluten eating predominant areas. The awareness about this disease is required at every level including the treating physicians, as it is more often missed, mainly due to its atypical manifestations. Hence a strong index of suspicion is required for its early diagnosis and proper treatment.

CONFLICT OF INTERESTS

"The authors declare that they have no conflict of interests."

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