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Prevalence of Celiac Disease in Patients with Nutritional Anemia in Western Part of India

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Abstract: ***Background: Around 1.6 billion people worldwide are affected by nutritional anemia. A small percentage of nutritional anemia cases are attributed to celiac disease (CeD). However, data on the prevalence of CeD among individuals with nutritional anemia in the Western part of India is scarce. Patients and methods: Individuals with nutritional anemia were prospectively investigated for the presence of CeD through the detection of immunoglobulin A (IgA) antitissue transglutaminase antibodies (anti-tTG Ab). Those who had a positive antibody result proceeded to have an upper gastrointestinal endoscopy, accompanied by a duodenal biopsy. The diagnosis of CeD was confirmed following Indian guidelines. Results: A total of 116 patients, including 96 females, were screened, with a mean age of 37 ± 17.8 years. Among them, 19 patients (16.3%) were positive for IgA anti-tTG antibodies. Fifteen of these antibody-positive patients agreed to undergo a duodenal biopsy, which showed villous abnormalities of modified Marsh grade 2 or higher in 11 cases. The overall seroprevalence of CeD was 16.3%, while the biopsy-confirmed prevalence stood at 9.3%. Moreover, an additional four patients (3.4%) were identified as having potential CeD. Chronic diarrhea and short stature emerged as significant predictors of CeD among patients with nutritional anemia. Conclusion: Even in the Western part of India, approximately one in 10 patients with nutritional anemia have CeD, reflecting similar findings across the country. Consequently, we should screen all patients with nutritional anemia for CeD through antitissue transglutaminase antibody testing. This is especially crucial for those with unexplained, persistent nutritional anemia that does not respond to oral iron therapy.***

Keywords: celiac disease, anemia, antitissue transglutaminase antibody

1. Introduction

Celiac disease (CeD) is an immune- mediated disorder that affects the small intestine, triggered by the ingestion of gluten—a protein found in wheat, barley, and rye—in people who are genetically susceptible.[1] Although once thought to be uncommon, CeD exhibits a wide spectrum of clinical manifestations, from cases with no symptoms at all to those with symptoms.[2,3] "classical CeD," characterized by gastrointestinal symptoms, comprises 50–60% of cases, whereas "nonclassical Ce D," marked by nongastrointestinal symptoms, makes up 40 –50% of these cases.[4] Anemia, short stature, dyspepsia, infertility, or hypertransaminasemia, which are not the usual presentations, can be the sole indicators of CeD, even in the absence of gastrointestinal symptoms, making the clinical diagnosis challenging.[1,4] Due to its varied manifestations, patients with CeD may seek medical attention from healthcare professionals across various specialties other than gastroenterologists or pediatricians. For example, patients may seek care from hematologists (for anemia), endocrinologists for short stature or type I diabetes, or gynecologists for concerns related to infertility.[5] Consequently patients with atypical features without gastrointestinal symptoms are often not screened for CeD.[6]

In 2013, approximately 1.9 billion individuals, representing 27% of the world's population, were affected by anemia.[7] According to the National Family Health Survey released in November 2021, anemia is prevalent among both women and men across all age-groups in India.[8]

Anemia is a common manifestation of CeD. Around 12–69% of individuals with CeD have anemia in Western countries, while as many as 85–90% of patients with CeD have anemia in India.[8–10] In certain instances, iron deficiency might be the sole sign of CeD, even in the absence of diarrhea, making it the most common type of anemia associated with the condition.[4,8–10]

Our study sought to assess the prevalence of CeD among patients with nutritional anemia at a tertiary care center in this region.

Patients and Methods

We conducted a prospective, cross-sectional study at a tertiary care hospital. Patients,>12 years of age, with nutritional anemia were recruited. Criteria for anemia was taken as per the World Health Organization (WHO) criteria as males having hemoglobin <13 gm/dL and females having hemoglobin <12 gm/dL.

Patients with other hematological dis- eases (such as aplastic anemia, thalassemia, hemolytic anemia, and myelodysplasia), advanced malignancies, and chronic conditions (including chronic infectious diseases, chronic renal failure, severe cardiac and respiratory diseases, chronic liver disease, and collagen vascular disease), as well as pregnant patients and those with obvious blood loss (including menorrhagia), were excluded from the study. All of them underwent a complete evaluation for demographics, clinical manifestations, and dietary history. Patients underwent a com- prehensive hematological workup, which included complete blood counts, peripheral blood smear analysis, RBC indices, serum iron studies, serum B12 levels, and additional investigations based on clinical indications.

Screening for Celiac Disease
All patients recruited for this study underwent testing for CeD using the immunoglobulin A (IgA) antitissue transglutaminase antibodies (anti-tTG Ab) conducted by a local commercial laboratory. The anti-tTG Ab value was recorded along with the cutoff value prescribed by the manufacturer.

Upper Gastrointestinal Endoscopy and Duodenal Mucosal Biopsies
Patients with positive IgA anti-tTG antibodies were subsequently asked to undergo an upper gastrointestinal endoscopic examination. During the endoscopy, all findings in the esophagus, stomach, and duodenum were recorded on a case record form. Between four and six biopsy samples were collected from the second portion of the duodenum. Features indicative of CeD, such as scalloping of folds, absence of mucosal folds, a mosaic rank sum test was applied to nonparametric data to assess statistical significance. Bivariable logistic regression was done for association and to study the predictors of the disease. Penalized logtic regression was employed to calculate the odds ratio for variables excluded from the bivariable regression due to collinearity (where one stratifying group had 0 participants). The association between predictors and CeD was represented as a crude odds ratio. A *p*-value below 0.05 was considered indicative of statistical significance.

2. Results

Demographic Characteristics
Our study included 116 patients with nutritional anemia, with a mean age of 37.01 ± 17.85 years, and 96 of these patients were women. The most common clinical manifestations among these patients were easy fatigability, weakness, and loss of appetite.

Severity of Anemia
Most of the patients, 97 (83.6%) had severe anemia. Majority of the patients (86.2%), both males and females, had a microcytic type of anemia. Macrocytic anemia was seen in 11/116 patients. Normocytic anemia was seen in five patients. Iron deficiency anemia (IDA) was more prevalent than vitamin B12 deficiency anemia.

Screening Test for Celiac Disease Using Antitissue Transglutaminase Antibody
We screened all patients for CeD using the IgA anti-tTG antibody test. Among them, 19 patients (16.3%) were positive for IgA anti- tTG antibody, indicating a seroprevalence pattern, and nodular mucosa were noted. Duodenal biopsies were preserved in 10% formalin, and villous abnormalities were graded according to the modified Marsh criteria.

Criteria for the Diagnosis of Celiac Disease
Celiac disease was identified in accordance with the guidelines provided by the Indian Council of Medical Research, which included a combination of clinical manifestations, positive serological findings, along with villous abnormalities classified as modified Marsh grade 2 or 3 (3a, 3b, 3c). clinical phenotypes of CeD were defined as per Oslo of CeD in patients with nutritional anemia at 16.3%. The anti-tTG Ab levels were mildly positive (2–5 times the upper limit of normal) in 15 patients and strongly positive (>10 times the upper limit of normal) in four patients.

Upper Gastrointestinal Endoscopy in Patients Who were Seropositive for Celiac Disease
All 19 serological- positive patients were requested to undergo an upper gastrointestinal endoscopic examination, and 15 of them complied. Among these 15 patients, 7 had normal duodenal folds, 6 exhibited scalloping of the duodenal folds, 1 had atrophic folds in the second part of the duodenum (D2), and 1 displayed nodularity of the duodenal folds. Duodenal biopsies were obtained from all 15 patients.

Hematological Parameters in Patients with Positive Anti-tTG Ab. The mean hemoglobin in patients with positive anti-tTG was 6.2 gm/dL. About 15/19 (78.9%) patients had iron deficiency anemia, 2 (10.5%) had vitamin B12 deficiency, and 2 (10.53%) had a mixed deficiency, suggesting that iron deficiency is the predominant type of anemia in CeD. Majority of the patients in this group (16/19, 84.2%) had severe anemia. In patients with IDA, we normally see thrombocytosis, but in 5/19 (26.3%) patients, thrombocytopenia was seen.

3. Discussion

In our study, the seroprevalence of CeD among the 116 patients with nutritional anemia was 16.3%, whereas the biopsy- confirmed prevalence stood at 9.3%. Chronic diarrhea and short stature were identified as key predictors of CeD in these patients. The prevalence of CeD in anemic patients observed in this study is consistent with anemia who were screened for CeD, 19

were positive for anti-tTG Ab, indicating a seroprevalence of 16.3%. Eleven patients exhibited villous abnormalities classified as modified Marsh grade 2 or higher, meeting the criteria for CeD, which suggests a prevalence of 9.4%. Additionally, in four patients (3.4%) with anemia and a positive anti-tTG Ab, intestinal biopsies revealed villous abnormalities of modified Marsh grade 1, indicating a diagnosis of potential CeD, resulting in a prevalence of 3.4% for potential CeD in this cohort. Four patients with anemia had a positive anti-tTG Ab but were unable to undergo endoscopic examination. These patients were labeled as having CeD autoimmunity and are very likely to have CeD, given their symptomatic anemia.

Predictors of Celiac Disease
A significant association was observed between chronic diarrhea and short stature with CeD (*p*-value 0.011 and 0.007, respectively). Chronic diarrhea and short stature can be significant predictors of CeD. The severity and type of anemia were not found to have a significant association with CeD.

In this study, independent predictors of CeD included a younger age at anemia onset, an extended duration of the condition, and the occurrence of diarrhea. The area beneath the receiver operating characteristic (ROC) curve measured 0.86, indicating that these three characteristics could reliably

predict CeD in 86% of patients with nutritional anemia. Therefore, screening for Ce D should be considered in patients with these predictive factors and in those with unexplained, long-standing nutritional anemia that is unresponsive to oral iron therapy.

This is the first study to explore the prevalence of CeD in patients with anemia in the Western part of India. The diagnosis of CeD was made using standard criteria, with the majority of patients undergoing upper gastrointestinal endoscopy and biopsy. We encompassed the full spectrum of CeD, including patients with anemia exhibiting CeD autoimmunity, potential CeD, and confirmed CeD.

While our initial aim was to include 160 patients with anemia, we managed to recruit only 116 due to the COVID-19 pandemic and the resulting diversion of healthcare resources to COVID-19 patient care. Furthermore, the response to a GFD could not be assessed in all patients because of the ongoing pandemic.

In conclusion, approximately 1 in 10 patients with nutritional anemia has CeD even in the Western part of India, as seen elsewhere in India. Therefore, all patients with nutritional anemia should be screened for CeD using antitissue transglutaminase antibody, especially those with unexplained long- standing nutritional anemia unresponsive to oral iron therapy.

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