ORIGINAL ARTICLE

IRON DEFICIENCY ANAEMIA IN PAKISTAN: CELIAC DISEASE AN UNDERLYING CAUSE

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Background: Iron deficiency anaemia (IDA) is common in Pakistani population and an important cause of morbidity. Celiac disease (CD) is an important contributor and its diagnosis is frequently missed especially if present in atypical/non-diarrhoeal form. Non-responders to iron replacement therapy typically raises suspicion of celiac disease as underlying cause. Aim of this study is to determine the frequency of CD in patients with IDA. **Methods:** A cross sectional study was conducted at tertiary health care centre Islamabad from 12th March to 12th September 2016. Two hundred & ninety patients of newly diagnosed IDA age more than 12 years, including both genders were selected trough non-probability purposive method. Patients with overt Blood loss (gastrointestinal, genitourinary, Pulmonary, recent Trauma or Surgery) were excluded. Active worm infestation and inadequate iron intake were also excluded. After informed consent, all the enrolled patients were investigated for presence of Anti-Tissue tansglutaminase antibody (Human Anti TTG IgA type) by ELISA in their serum at pathology laboratory of PIMS. **Results:** Out of 290 patients of IDA 32 (11%) had celiac disease (p=0.0002), more common in younger age <40 years 24 (75%), predominantly in female 22 (68.75%), more prevailing in Kashmiri population 9(28.12%). **Conclusion:** Celiac disease is common in patients who present with IDA. Diagnosis of CD is frequently missed in the absence of classic features and IDA may be the only manifestation of CD.

Keywords: Celiac disease; Iron Deficiency anaemia; Celiac Serology; Anti endomyseal antibodies; Anti Tissue Trans glutamines antibodies

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INTRODUCTION

Celiac disease (CD) also called as non-tropical sprue, or gluten-sensitive enteropathy is a common gastrointestinal problem and about 1% of adult population is being affected worldwide.[1] It is considered as antibody mediated immune disorder in which small intestinal mucosa becomes hypersensitive to gluten a protein present in food like wheat, rye and barley, causing mucosal damage especially of proximal small intestine which results in ineffective digestion and absorption of most of nutrients. Classic celiac present with chronic or recurrent diarrhoeal illness and manifestations of various nutritional deficiencies. While non-classic or atypical forms present invariably. It can affect any age group.[2] Previously it was thought that celiac was a disease of infants and young children but in recent year's older children and adults are frequently diagnosed with CD. The peak age in adults is considered as 3rd and 4th decade of life, however it is may also appear in 6th decade of life and may directly present with complications. It affects female twice has males.[3] A number of hypothesis are generated regarding aetiology and pathogenesis of CD. Environmental, Genetic and Immunologic factors contribute in development of CD. Environmental factors include types of wheat protein based on its solubility (Prolamins, glutenins, globulins and Albumin soluble in ethanol, diluted acid or alkali, 10% sodium chloride and water respectively).[4] Gluten comprises of both Prolamins and glutenins present in various types of wheat, rye and barley and responsible for antigenicity and damage to Small intestinal mucosa. Grains that do not cause CD include rice, corns, Sorghum and millet. Age at which gluten is introduced in diet of infants is also important. According to a study if gluten is introduced with in first 3 months of life, risk of CD increases by 5 folds.[5] according to another study delayed introduction of gluten in diet (after 7 months of life or more) also increases risk of CD. Role of genetic factors is established by evidence that in first degree relatives incidence of CD ranges from 8–18% and in homozygotes it reaches up to 70%. Further evident that CD is associated with HLA-DQ2 haplotypes. Immunologic factors also play an important role and high titers of Anti-Tissue tansglutaminase (Anti-TTG) antibodies, Anti Endomyseal antibodies (Anti-EMA) and Anti Deaminated Gliadin (DGP) are found in patients of CD. IgA type is more specific than IgM and IgG types.[6] These Antibodies are not only used for the

Diagnosis but monitoring of CD as well. After advancements in celiac serology, the epidemiology of CD has greatly changed and large numbers of previously undiagnosed CD cases are being identified who were Asymptomatic or presented with atypical course. Sensitivity and Specificity of Anti-TTG type A performed by ELISA (enzyme Linked Immuno-sorbent assay) is 95–98% and 97–100% respectively.[7] It is considered as single most useful test for diagnosis and monitoring of CD. There are two variants of Anti TTG, Guinea Pig variant which may have false positive results in presence of autoimmune disorders, congestive cardiac failure and Liver disease while other variant is Human Anti TTG, which doesn't show such false positive results.[7] Another immune marker in CD is Anti-EMA and its 85–98% sensitive and 97–100% specific.[7] IgA DGP is 75–90% sensitive and 82–95% specific.[7] Classic CD presents with chronic diarrhoeal illness, failure to thrive, anaemia, rickets and poor growth in children. In growing age, it may present with short stature. In adults, its presentation is variable and diarrhoeal illness is less frequent. Extra intestinal manifestation, other autoimmune conditions and malignancies especially GI related may accompany CD at first presentation. Anaemia is a common symptom in at least 10–20% of CD patients, and IDA is the major cause of anaemia, although other nutrient deficiency like folic acid and vitamin B_{12} may also plays a role in pathogenesis of anaemia in CD. IDA in CD results from poor iron absorption from inflamed and damaged small intestinal mucosa despite of adequate oral iron intake. The Diagnosis of IDA is made when there is microcytic haemolytic anaemia with low iron and raise Total Iron binding capacity.[8] About 700–800 million people worldwide and 56% pregnant women in under developed countries are suffering from IDA.[9] Most of Pakistani population is suffering from IDA especially high prevalence of IDA has been observed in pregnant women and nursing mothers. Prevalence of IDA among females of reproductive age exists up to 50%.[9]

IDA in CD has its own importance and it may be the only manifestation of CD. Patient of IDA if fails to respond on Oral Iron supplementation in the absence of any active blood loss also raises the suspicion of CD.

This study was conducted because the local data on this subject is insufficient. Celiac disease is frequently missed in the differential diagnosis of IDA so by doing this study we will be able to determine the frequency of CD in our patients with IDA and once confirmed, it can easily be corrected by strict gluten free diet in this way not only anaemia can be corrected in additions those patients can also be prevented from further Autoimmunity, other nutritional deficiencies and a number of CD associated malignancies.

MATERIAL AND METHODS

This cross-sectional study was conducted at tertiary health care centre, Islamabad (both in patient and outdoor, department of Medicine and gastroenterology) from 12th March to 12th September 2016 after approval from hospital ethical committee. Newly diagnosed patients of IDA were selected. Sample size was calculated using WHO (world health organization) sample size calculator. Values considered were Confidence level 95%, Absolute precision 2.5%, prevalence of CD in iron deficiency anaemia of 4.7 %. Sample size calculated was 290. Sampling technique used was non-probability purposive. Two hundred & ninety patients with established iron deficiency anaemia were selected. Operational definition of IDA was taken as patient having Hemoglobulin <14 g/dl in males and< 12 g/dl in females, mean corpuscular volume (MCV) <78 fl, Mean corpuscular haemoglobin (MCH) <26 pg, Serum ferritin <20 ng/ml, Iron <75 µg/dl, Total iron binding capacity (TIBC) >300 µg/dl., Transferrin saturation %: <20%.) Patients of both genders of age more than 12 years were included. All the patients with overt Blood loss (gastrointestinal, genitourinary, Pulmonary, recent Trauma or Surgery) were excluded. Patients with active worm infestation, and inadequate oral iron intake in the form of food also excluded. Informed consent was taken from all enrolled patients.

All the selected patients were investigated for presence of Anti-TTG antibodies IgA via ELISA method in their serum at pathology laboratory of PIMS, Islamabad. Results of Anti-TTG antibodies IgA types were recorded on the *pro forma*.

Data was analysed by using SPSS (version 16). Mean and standard deviation were used for quantitative variables such as age, haemoglobin, MCV, MCH, Iron, TIBC Serum ferritin, and Transferrin saturation. Frequency and percentages were used for qualitative variables such as gender, and presence or absence of IgA Anti-TTG antibodies. *p*-value of > 0.05 was considered as significant.

RESULTS

In this study 290 patients presenting with IDA were investigated for presence of Anti-TTG IgA antibodies. Presence of antibodies confirmed CD. Minimum age was 12 years and maximum was 60 years. The mean age of study patients was 36±24 years. Out of 290 patients, 256 (88.3%) were below 40 years of age, while 34 (11.72%) were of above 40 years. Age was further divided into 5 groups. Fifty-six (19.3%) patients were in age group 12–20 years,

110 (37.9%) patients in group >20–30 years, 90 (31%) patients in group >30–40 years, 28 (9.65%) patients in group >40–50 years and 6 (2%) patients in age group > 50–60 years. Out of 290 patients 140 (48.2%) were males and 150 (51.8%) were females. (Table-1)

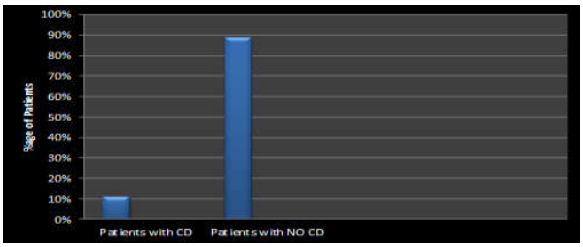
In this study, we found that out of 290 patients of IDA, Anti TTG (type A) was present in 32 (11%) patients serum (p=0.0002), and thus labelled as having CD. (Graph 1)

Age distribution of CD patients was analyzed. Four (7.1%) patients were in age group 12–20 years, 13 (11.8%) patients in group >20–30 years, 7 (7.7%) patients in group >30–40 years, 8 (28.5%) patients in >40–50 years age group. None of the patient's CD in age more than 50 years. Twenty-four (75%) of CD patients were young of age less than 40 years. (Table-2)

Celiac disease was twice more common in females 22 (68.75%) than in males 10 (31.25%). Distribution of celiac disease patients with respect to place was also analyzed. Maximum number of patients belong to Kashmir, i.e., 9 (28.12%), 8 (25%) patients belong to Peshawar, 6 (18.75%) belong to Rawalpindi, 5 (15.62%) belong to Islamabad, and 4 (12.5%) belong to other areas of Pakistan. (Table-3)

Table-1: Age and Gender distribution of study patients (n=290)

	Number of patients	%age patients
Age (years)		
Mean±SD	36±24	
Range (min-max)	12–60	
Age categories (years)		
12–20	56	19.31
>20–30	110	37.93
>30–40	90	31
>40–50	28	9.65
>50–60	6	2
Gender		
Male	140	48.27
Female	150	51.72



Graph-1: Prevalence of CD in Iron deficiency anaemia

Table-2: Distribution of CD according to age groups (n=290)

Age in years	Number of Patients n = 290	Number of Patients Having CD	%age of patient
12–20	56	4	7.14
>20–30	110	13	11.81
>30–40	90	7	7.77
>40–50	28	8	28.5
>50–60	6	0	0

Table 3: Distribution of CD according to place/ area (n=32)

Area Distribution	Number of Patients n=32	%age of patients
Islamabad	5	15.62
Rawalpindi	6	18.75
Kashmir	9	28.12
Peshawar	8	25.0
Others	4	12.5

DISCUSSION

Celiac disease is a chronic condition, affects small intestine through immune mediated mechanisms activated by gluten containing food in genetically predisposed individuals. Spectrum of celiac disease varies from asymptomatic to clinically overt disease that present with both Gastrointestinal and extra-gastrointestinal manifestations. Previously it was thought that it's the disease of infants and children but now it is frequently being identified in adult population. The advancements in serologic tests have dramatically changed the epidemiology of CD worldwide by revealing the higher incidences of silent or atypical CD. The current standards of care is to adopt the policy of case finding approach in targeted populations that include high risk subjects, asymptomatic or minimum GI manifestations including close relatives of CD or atypical presentations. As anaemia, especially IDA, is a frequent feature present in CD and may be the only manifestation that 'why its presence in the absence of any other obvious cause raises a strong suspicion of CD. As the single most useful test used for diagnosis and monitoring of CD is Anti-TTG Ig A type its presence eliminates the need for Small bowel biopsy through highly technical and invasive upper GI endoscopy. It is very easy to treat IDA in CD by dietary modification with strict gluten free diet. Not only this but this intervention causes reversal of previously unexplained nutritional deficiencies, resolution of GI symptoms, marked reduction in autoimmunity and risk of malignancies including GI related like T Cell Lymphoma. Studies on prevalence of CD in newly diagnosed IDA has shown different results. Corazza *et al* performed celiac serology in 200 patients with IDA and he found that 5% IDA had celiac disease. According to Howard et al the prevalence of CD in 333 anaemic patients with IDA with or without concomitant folate deficiency was 4.7%. Zamani *et al.* [10] conducted a similar study and they revealed that 14.6% patients with IDA of unknown origin had actually CD. In the study conducted by Unsworth *et al.* 6% females who donates blood and presented with IDA had CD. Annibale *et al*. from Italy performed a prospective study on 71 patients of obscure IDA and concluded that treatment failure in obscure IDA raises a

suspicion of CD and 5.7% patients later diagnosed as CD.[11] In a study of 114 patients with IDA, conducted in the United Kingdom, 2.6% patients had CD. In a study from USA, Grisolano *et al*. identified nine cases (8.7%) in 103 patients with IDA. In our study, out of 290 patients of IDA, Anti TTG antibodies (type A) was present in 32 (11%) patients serum (p= 0.0002) and had CD. These results are comparable with other studies as 11% of our study population disclosed as CD. It is also important to highlight here that in all above studies patients with CD had no or minimum GI or extra GI symptoms and only presentation was IDA. As it is proven that celiac can occur at any age but after availability of highly reliable serologic tests for CD, it is more frequently being uncovered in young adults, and elderly. According to available data the prevalence of CD in adults is approximately 1–2% in Europe and 0.4–0.95% in the USA. According to Greetje J *et al.* peak age for CD is early childhood and fourth and fifth decade of life for both women and men. In our study 24 (75%) CD patients presented with CD in age less than 40 years and the highest prevalence of CD was in age group >20–30 years 13 (11.81%) while 8 (28.5%) CD were between 40 and 50 years old. Highest prevalence in age less than 40 years might be because of study sample as 256 (88.3%) patients of IDA belong to age group less than 40 years. However, our study results also favour available data. Whether diagnosing of CD at advanced age is the result of diagnostic delay or of a true late onset of the disease is still debatable because. According to several studies underreporting of CD is actually diagnostic delay in the elderly population.[12]

Like other autoimmune diseases, CD is more common in women, with female to male ratio of between 2:1 and 3:1. In this study we observed similar results and females were twice more commonly affected than males 22 (68.75%) vs 10 (31.25%). Some gender-influenced genetic factors and immunoregulation mechanisms subject to hormones might explain these differences in gender distribution. In contrast, patients diagnosed as CD of age around 60 and above are more frequently male.

Upper GI endoscopy and small bowel biopsy has its own significance in diagnosis and monitoring of CD. Small bowel biopsy also important role especially in degree of villous destruction and identification of complications like malignancies. As anti TTG Ig A type is a most useful single diagnostic test and sufficient enough to establish a diagnosis of CD and thus eliminates the yield for Small bowel biopsy, upper GI endoscopy was not performed in our study. Other reasons included highly technical invasive endoscopic procedure and a number of patients were not willing for it. Anti-EMA antibodies is used relatively less commonly than ant-TTG because indirect immunofluorescence is relatively more complex, need technical expertise and more expensive. That's why this test was not performed in our study and diagnosis of CD was established only on the basis of anti TTG antibody IgA. Another fact is that IG A deficiency is also present in CD and those having deficiency, anti-TTG IgA would be absent and thus may hide the diagnosis of CD, thus by adding serum IgA levels or IgG DGP assay one can expect more rise in prevalence of CD cases in IDA.

As IDA is the most common form of anaemia worldwide as well as in Pakistan [9] treated by Iron replacement. General population responds well on this treatment but suspicion of CD is raised when despite of adequate use of iron supplements anaemia doesn't corrects or recurrent anaemia occurs. Obscure IDA also needs to look for CD. Strict adherence to gluten free diet in CD not only corrects anaemia, but also corrects others nutrients deficiency stats, reduce risk of Malignancies especially GI related, and reduce Autoimmunity.

CONCLUSION

CD is common in IDA patients who were presented to medical OPD, PIMS, and Islamabad. As diagnosis of CD is frequently missed hence this study has given enough evidence that CD should be suspected in all IDA in special situations like; when aetiology is unclear, recurrent IDA or poor response to oral iron replacement therapy. In these patients gluten, free diet not only corrects anaemia but other nutritional deficiencies can also be covered. In addition risk of auto immunity and malignancies can also be minimized.

AUTHORS' CONTRIBUTION

SK: Intellectual concept, study design, data collection, data interpretation, discussion. AA: Data entry, Statistical analysis. SY: Concept, data collection, discussion

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