PREVALENCE OF CELIAC SPRUE AMONG PATIENTS SEEKING THE GASTROENTEROLOGY HOSPITAL AND CORRELATION WITH CERTAIN SOCIODEMOGRAPHIC FACTORS

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Abstract:

Celiac sprue, also known as celiac disease and gluten-sensitive enteropathy, is characterized by malabsorption resulting from inflammatory injury to the mucosa of the small intestine after the ingestion of wheat gluten or related rye and barley proteins. There is clinical and histologic improvement on a strict gluten-free diet and relapse when dietary gluten is reintroduced.[1]

Keywords: Gluten, Celiac Serological Tests, Transglutaminase Antibody, Antigliadin Antibody, Antiendomysial Antibody, Duodenal Biopsy, Villous Atrophy, Chronic Diarrhea, Malabsorption,

Introduction:

Epidemiology and Pathogenesis:

The true prevalence of celiac sprue is difficult to ascertain, because many patients have atypical symptoms or none at all. A large, multicenter Italian study identified seven new cases of celiac sprue in children for each patient with established disease.[4] The highest reported prevalence is in Western Europe and in places where Europeans emigrated, notably North America and Australia.[2-5] Celiacsprue is also found in parts of northwest India, and it may be underdiagnosed in South America, North Africa, and Asia.[6] It is rare among people from a purely African-Caribbean, Chinese, or Japanese background. In most series there is a slight female preponderance.

Celiac sprue results from an inappropriate T-cell–mediated immune response against ingested gluten in genetically predisposed people.[7] The importance of genetic factors is supported by the approximately 10 percent prevalence of the disease among first-degree relatives.[8] Over 95 percent of patients with celiac sprue express the HLA-DQ(α1*501,β1*02) heterodimer (HLA-

DQ2), which preferentially presents gluten-derived gliadin peptides on its antigen-presenting groove to stimulate intestinal mucosal T cells.[9,10] The enzyme tissue transglutaminase is one of the targets of the autoimmune response in celiac sprue.[11] The modification of gliadin by host tissue transglutaminase has a key role in enhancing the gliadin-specific T-cell response,[12] and a single tissue transglutaminase–modified peptide is the dominant α-gliadin T-cell epitope [13] and may be a target for antigen-specific peptide therapy.

Clinical Manifestations:

Celiac Sprue in Children:
Classically, infants with celiac sprue present between the ages of 4 and 24 months with impaired growth, diarrhea, and abdominal distention.[14] Vomiting is common in young infants, as are pallor and edema. The onset of symptoms is gradual and follows the introduction of cereals into the diet. The velocity of weight gain slowly decreases before weight loss ensues. Some children present with constipation, although diarrhea is more typical. Patients with severe, untreated celiac sprue may present with short stature, pubertal delay, iron and folate deficiency with anemia, and rickets. Atypical celiac sprue is usually seen in older children or adolescents, who often have no overt features of malabsorption.

Celiac Sprue in Adults:
The diagnosis of celiac sprue is increasingly being made in adults. About 20 percent of cases occur in patients who are older than 60 years of age.[15] Some patients are short or have symptoms dating back to childhood. However, many have no history of symptoms, suggesting that celiac sprue can develop in adulthood.[16]

Many adults present with episodic or nocturnal diarrhea, flatulence, and weight loss. Enteropathy often results in symptomatic lactose intolerance. Steatorrhea is associated with severe, extensive enteropathy, but it is often absent in patients whose disease is limited to the more proximal portion of the small intestine. Abdominal discomfort and bloating are common and often lead to a mistaken diagnosis of irritable bowel syndrome.

Approximately 50 percent of adult patients do not have clinically significant diarrhea. Iron-deficiency anemia is now the most common clinical presentation in adults with celiac sprue. Other laboratory abnormalities include macrocytic anemia due to folate (or, rarely, vitamin B_{12}) deficiency, coagulopathy resulting from vitamin K deficiency, or vitamin D deficiency leading to hypocalcemia and an elevated alkaline phosphatase level.[17] Other increasingly recognized extraintestinal manifestations include bone fractures,[18] infertility,[19] psychiatric syndromes,[20] and various neurologic conditions, including peripheral neuropathy, ataxia, and seizures.[21]

Associated Conditions:
Many conditions occur in association with celiac sprue[22]. Dermatitis herpetiformis is characterized by intensely pruritic papulovesicular lesions that occur symmetrically over the extensor surfaces of the arms and legs as well as the buttocks, trunk, neck, and scalp. The diagnosis requires the demonstration by immunofluorescence studies of granular deposits of IgA in an area of normal-appearing skin.[23] A small-bowel biopsy in patients with dermatitis herpetiformis demonstrates a mild and patchy gluten-sensitive enteropathy. The skin lesions respond to the withdrawal of gluten from the diet or to treatment with dapsone.

Autoimmune diseases occur more commonly in patients with celiac sprue, especially type 1 diabetes mellitus [24,25] and autoimmune thyroiditis.[26] The prevalence of celiac sprue in patients

with type 1 diabetes is approximately 3 to 8 percent.[24,25] Unexpected episodes of hypoglycemia or diarrhea should alert clinicians to the possibility of coexisting celiac sprue in patients with type 1 diabetes. The duration of gluten exposure is associated with the prevalence of associated autoimmune diseases, which is additional rationale for early diagnosis and treatment of celiac sprue.[27]

Diagnosis:

Serologic Tests:
The availability of highly sensitive and specific serologic markers greatly facilitates the diagnosis of celiac sprue. These serologic tests are used to evaluate patients with suspected disease, monitor adherence and response to a gluten-free diet, and screen patients with atypical, extraintestinal manifestations.[6] IgA antiendomysial antibodies are usually detected by indirect immunofluorescence with the use of sections of human umbilical cord or, less commonly, monkey esophageal smooth muscle.[31] The reported sensitivity and specificity of antiendomysial antibodies are 85 to 98 percent and 97 to 100 percent, respectively.[6,31-32] Tissue transglutaminase is the autoantigen recognized by antiendomysial antibody.[11] An IgA enzyme-linked immunosorbent assay that uses guinea pig tissue transglutaminase is now widely available and is cheaper, easier to perform, and more sensitive but less specific than the antiendomysial antibody assay.[28,29] A simple dot blot test that uses human recombinant tissue transglutaminase may be more specific than the assay that uses guinea pig tissue transglutaminase.[30] Although false positive results are rare, false negative antiendomysial and tissue transglutaminase antibody results can occur in mild enteropathy, in children under two years of age, and especially in patients with IgA deficiency.
Tests for IgA and IgGantigliadin antibodies have moderate sensitivity but are far less specific than tests for IgA antiendomysial antibodies.[6,34,35] Many normal persons as well as patients with gastrointestinal inflammation from other causes test positive for antigliadin antibodies.[35] Consequently, the positive predictive value of antigliadin antibody tests in a general population is poor. However, IgA antigliadin antibody is the most useful serologic marker in symptomatic children younger than two years of age. A test for IgGantigliadin antibody is useful in the 2 to 10 percent of patients with celiac sprue who have coexisting IgA deficiency. Levels of IgA antigliadin, IgA antiendomysial, and IgA tissue transglutaminase antibody all become undetectable in patients who are on a strict gluten-free diet. Tests for IgA antigliadin antibody are useful to monitor dietary compliance, since levels of this antibody are the easiest to quantify.[36] Levels of IgA antigliadin antibody gradually become undetectable within three to six months after gluten is withdrawn from the diet.

BIOPSY OF THE SMALL INTESTINE:
Histologic examination of a biopsy specimen of the small intestine remains the diagnostic gold standard for celiac sprue. In current practice, most biopsies in children and adults are performed during upper endoscopy. Endoscopy is more reliable than previous capsule-biopsy techniques, because it allows multiple specimens to be obtained, thus reducing sampling error, and because, in many cases, examination of the upper gastrointestinal tract may in itself be indicated (e.g., in iron-deficiency anemia).[37] Specimens should be obtained from the distal duodenum (second or third part) to avoid the architectural distortion produced by Brunner's glands or peptic duodenitis. Absent, flattened, or scalloped duodenal folds are not specific for celiac sprue.[38]

The classic lesion in patients with untreated celiac sprue is characterized histologically by striking mucosal architectural changes, with absent villi and hyperplastic crypts.[39] There are increased numbers of intraepithelial lymphocytes and of plasma cells and lymphocytes in the lamina propria. The severity and extent of the histologic abnormalities in celiac sprue vary widely. Patients who have mild, focal abnormalities confined to the proximal small intestine are likely to have fewer symptoms and less malabsorption than patients with severe, extensive enteropathy.

Treatment:

Because a gluten-free diet represents a lifetime commitment, is more expensive than a normal diet, and may limit patients socially, especially children and teenagers, it should never be recommended unless the diagnosis of celiac sprue is firmly established. There is no role for an empirical therapeutic trial of gluten withdrawal because a patient's response is often equivocal and because the abnormal findings on both the serologic tests and small-bowel biopsy may revert to normal, making subsequent definitive diagnosis difficult.

Approximately 70 percent of patients have symptomatic improvement within two weeks after starting a gluten-free diet.[40] The speed and eventual degree of histologic improvement are unpredictable [41] but invariably lag behind the clinical response and may not be evident on repeated biopsy for two to three months.

In addition to a gluten-free diet, all patients with newly diagnosed celiac sprue who have clinically evident malabsorption should initially receive a multivitamin preparation and appropriate supplements to correct any iron or folate deficiency. Patients with steatorrhea, hypocalcemia, or osteopenic bone disease should receive oral calcium and vitamin D supplementation. Patients with hyposplenism should receive prophylactic antibiotics before undergoing invasive manipulations and may benefit from pneumococcus vaccination.

Aim of the study:

- To see the Prevalence of Celiac disease among Patients attending gastroenterology hospital in Baghdad.
- To see the Correlation with Certain Demographic Factors.

Materials and methods:

Participants and study design:

The study is hospital based cross sectional descriptive analytic study conducted from the start of 2018 to the mid of2019 in gastroenterology teaching hospital in Baghdad. Patients were sent for serology and endoscopy for duodenal biopsies for confirmation of diagnosis of celiac disease.

Subjects and sampling methods:

After Full history and examination of the patients referred to thesehospitals due to variable clinical symptoms, samplearecollected according to convenient sampling methods and a convenient sample of 140 patients was studied.

Sample calculation:
It will be according to the following equation: [42]

$$\frac{Z_{1-\alpha/2}{}^2 p(1-p)}{d^2}$$

Here:
$Z_{1-\alpha/2}$is the standard error of normal variant at 5% type 1 error (p<0.05) which is 1.96 and at 1% type 1 error (p value < 0.01) which is 2.58. Majority of studies regard p value significant below 0.05 so the no. 1.96 is used in formula.
p = is the proportion expected in population based on previous literatures
d = absolute error that to be decided by the researcher
Sample size = $(1.96)^2$ X 0.1 X (1-0.1) / $(0.05)^2$
            = 138 as a minimum sample
According to prevalence of 10 %

Investigation:
        Serology test resultsregarded negative if < 12 IU/mlTest regarded equivocal if 12-18 IU/mlTest regarded positive if > 18 IU/ml.
        Duodenal biopsies were taken through upper endoscopies with histology were interpreted in the pathology department by specialized pathologist.
        According to our clinical routine, a minimum of 3-4 representative small-bowel mucosal biopsies are taken upon esophagogastroduodenoscopy from the distal duodenum. Samplesare embedded in preserve tube and sent for pathology department which is stained and read by pathologist under a light microscope.

Ethical aspects:
        The Institution's Ethical Committee approval was obtained prior to the enrolment of subjects. The objectives and the detailed procedures of blood taking and endoscopy involved in the study were explained to all eligible subjects for this study. The patients were informed that they can voluntarilyparticipate in this study.

Data Collection:
        The questions focused on sociodemographic data (age, sex) and background characteristics of type 1 DM, other autoimmune diseases and family history.

Statistical analysis:
        Data wereanalyzed by the statistical package of social sciences version 25. Statistics of the variables was expressed as medians, ranges, frequencies and percentage, as appropriate and calculatedby chi-squared test. Odds ratio (OR) and the 95% confidence interval of OR were calculated, it is worth mentioned that value of OR below one indicated that the factor is protective factor while an OR of more than one indicated that the factor is risk factor. Value of OR of one indicated no difference in the risk, however, if the 95% CI of OR involves the value

of one, then the association considered not significant. Level of significance of ≤ 0.05, considered as significant difference or association.

Results:

The mean age was 18.91 ranging from 2 – 60 years. **Figure 1**

There were 140 patients participated in the study, 90 of them were confirmed to have CD (positive serology and positive histology) and 50 patients who were confirmed that they have no CD diagnosis (negative serology and negative histology). **Figure 2**

Statistically significant association had been found in the baseline of some of demographic characteristics of the studied groups regarding age, gender, family history and association with diabetes type one.

The age of the patients in both study groups showed significant association between those who are CD positive and those with CD negative, 71.1% of CD patients were children vs. 54% in CD negative groups respectively. In CD groups there were 28.9 % adults vs. 46% in non CD groups. (P=0.041), (OR=2.09) with CI 95% of OR= (1.02 to 4.30).

The gender of patients showed significant association, female represent 72.2% of CD group versus 27.8% male patients, in corresponding female represent 48% of non CD group versus 52% male patients. Statistically significant difference had been found (P= 0.004) (OR=2.81). CI 95% of OR= (1.36 to 5.79).

Positive Family History was significantly associated between studied groups, 18.9% in CD group and 4% in non CD group, (P=0.025), (OR=5.58). CI 95% of OR= (1.23 to 25.29).

Type 1 DM was significantly higher in CD group than non CD group, (P=0.02) where 22.2% of patients in CD group had Type 1 DM compared to only 6% in the non CD group. (OR=4.47), CI 95% of OR= (1.25 to 15.91).

All findings regarding the demographic data and its association with celiac disease of the studied groups are demonstrated in (Table 1 & 2).
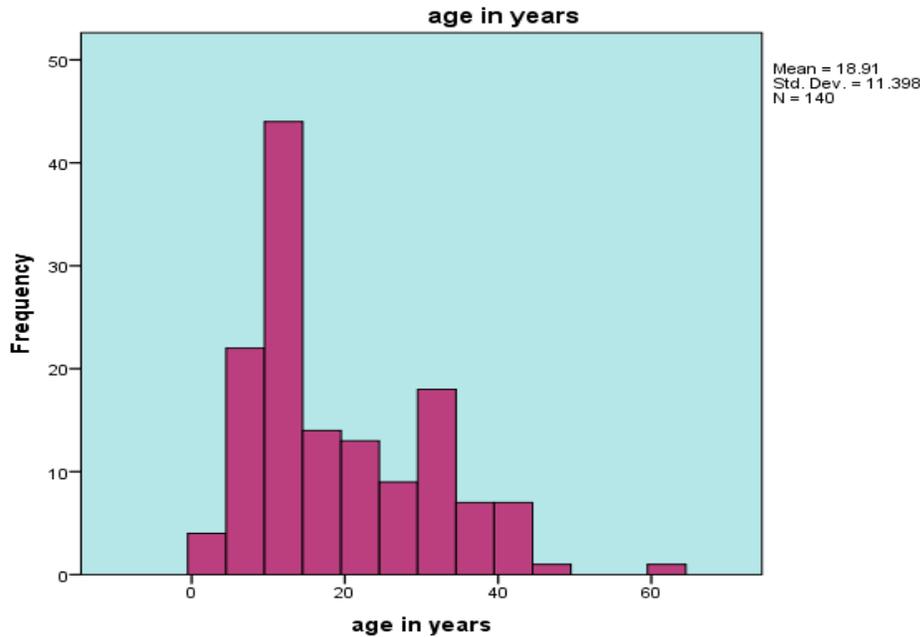
Figure 1: Histogram show the frequency of ages in study group patients

Table 1. Demographics and clinical parameters of suspected celiac disease patients (n=140)

|			Number		Percentage	
Sex	**Female**	89	**Children**	56	40 %	63.6%
			Adults	33	23.6 %	
	Male	51	**Children**	35	25 %	36.4 %
			Adults	16	11.4%	
Family History of Celiac Disease	**No**		121		86.4 %	
	Yes		19		13.6 %	
Associated Autoimmune Diseases	**Non**		111		79.3 %	
	Type 1 DM		23		16.4 %	
	Thyroid Diseases		3		2.1 %	
	AIH		1		0.7 %	
	Addison Disease		1		0.7 %	
	Vitiligo		1		0.7 %	
Presentation	**Short Stature**		50		35.7 %	
	Diarrhea		36		25.7 %	
	Wt. Loss		24		17.1 %	
	Bloating		19		13.6 %	
	Anemia		10		7.1 %	
	Constipation		1		0.7 %	
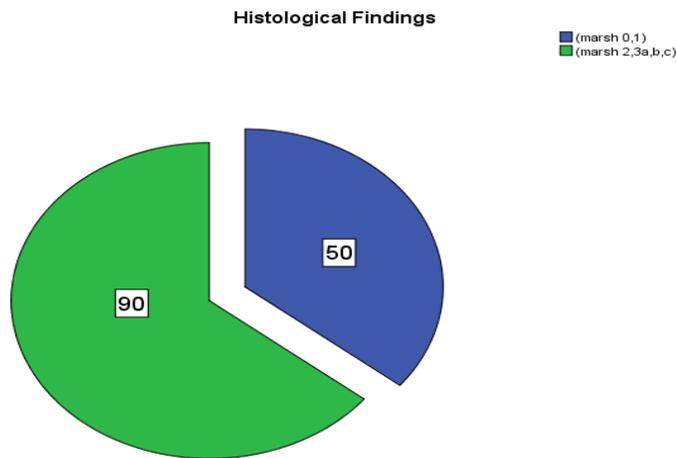
Figure 2 : Pie chart show the frequency of histological findings after endoscopic examination

Table 2: Relation between sociodemographic factors and celiac disease

		CD Positive(N=90)		CD Negative(N=50)		P Value	OR	CI 95%
		NO.	%	NO.	%			
Age	Children	64	71.1%	27	54%	0.041	2.09	1.02 to 4.30
	Adults	26	28.9%	23	46%			
Gender	Female	65	72.2%	24	48%	0.004	2.81	1.36 to 5.79
	male	25	27.8%	26	52%			
Family History	Yes	17	18.9%	2	4%	0.025	5.58	1.23 to 25.29
	No	73	81.1%	48	96%			
Type 1 DM	Yes	20	22.2%	3	6%	0.02	4.47	1.25 to 15.91
	No	70	77.8%	47	94%			

Discussion:

Celiac disease (CD) is an autoimmune, gluten-sensitive enteropathy where intake of foods containing gluten, result in mucosal damage in the small bowel, leading to malabsorption of nutrients and vitamins.[43]

Serological testing for CD has evolved in recent decades. The most commonly used antibodies are antigliadin antibodies (AGA), endomysial antibodies (EMA) and tissue transglutaminase antibodies (tTG).[44] The tTG test was discovered in the early 1980s, and more recently developed assays may have higher sensitivities and specificities than AGA, which is considered obsolete.[45] The recently introduced deamidatedgliadin peptide antibody (DGP) has shown promising performance as compared to EMA and tTG test results.[46]

All studies used met the requirement that all diagnoses of CD were finally confirmed by a biopsy and not by serologic testing alone, as biopsy is considered necessary by many for diagnosing CD.[46]

In conclusion, tTG IgA and IgG show the best performance from a clinical diagnostic standpoint. It seems as preferable as combining two or more assays tTG (IgA and IgG) or as this shows both very high sensitivities and specificities compared to the single assays as concluded by others.[47]

In the present study Gender distribution of cases showed that the majority of cases that are proved to be celiac disease were females this agrees with Green, when he reported that CD was 2 to 3 times higher in females [48].

In the present study age distribution of cases showed that celiac disease is more in children than in adults. so that, the results of this study are similar to results that obtained by other researchers, especially with results of AL-Kenzawi, when he showed that children account a large number of celiac patients in Iraq countary[49].

In general CD in children is more than other ages, might be attributed to introduction of large amount of gluten or exposure to the gluten without breastfeeding might increase the risk of CD in children [50].

In general, some genetic loci are related to sex, also sex-dependent HLA associations are seen because female patients are carry DQ2 and/or DQ8 molecules while DQ2/DQ8 negative celiac mostly are males [51], or role of sex hormones in immune regulation which may explain sex varieties [52].

In the present study significant numbers of CD patients have positive family history and this agree with the research done India showed that CD prevalence among first-degree relatives was 8.2% (14/169). CD prevalence between siblings is (15.6%) [53].

The present study shows significant association between type 1 DM and celiac disease and this comes in agreement with the results of other research that done in British Columbia who confirmed the prevalence of CD in diabetes type one [54]

Conclusion:

- Assays for the measurement of celiac-related antibodies are widely available but are still of variable accuracy so laboratories should provide the sensitivity and specificity of thetests.
- We recommend the screening for the first degree relatives and patients with type 1 DM with suggestive gastrointestinal symptoms and further studies is required in the future.
- Reliableand applicable markers should beused to monitor patient'scompliance.
- Significant association with type 1 DM

Ethical Clearance: Taken from The Institution's Ethical Committee approval

Source of Funding: Self

Conflict of Interest: nil

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