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Celiac Disease Occurrence with Autoimmune Infertility in Infertile Men

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Abstract

Objectives: The aim of the present study was to determine the prevalence of celiac disease (CD) among unexplained infertile men and determine the association of CD autoantibodies with antisperm autoantibodies (ASA) as diagnostic tool for Immunological Infertility.

Materials and Methods: One hundred and sixty six male patients were suffering from primary unexplained infertility were chosen to diagnose CD. Three autoantibodies (AD) were detected by performing enzyme linked immunosorbent assay (ELISA), deamidated gliadin peptide/tissue transglutaminase (DGP/tTg-IgA), tTg-IgG, and IgA. Other two autoantibodies were detected by ASA, IgG and ASA-IgA to diagnose immunologic infertility. All serologic procedures and seminal fluid examinations were done on unexplained infertile men in Basrah Governorate, South of Iraq.

Results: Out of 166 participants with unexplained infertility, 15 participants (9%) have been diagnosed as immunological infertile. Thirteen participants (7.8%) have silent CD. Only seven (4.2%) have both immunologic infertility and CD. Statistically significant association between CD and immunological infertility (OR)>20 with (95%CI) between 7.2-58. Significant correlation ($p<0.05$) was resulted between the five autoantibodies and grade A+B motility parameter of seminal fluid analysis.

Conclusion: Screening for CD should be part of the diagnostic work-up of unexplained infertile men, and immunological infertility should be considered as additional AD associated with CD in infertile men.

Keywords: Autoimmune diseases; Antisperm antibody; Celiac disease; Infertility

Introduction

Autoimmune diseases (ADs) tend to occur as: clusters, coexistences, and overlaps among affected individuals and/or their family member, and among population. The numbers of documented cases of a co-occurrence of different ADs in the same patient have increased in recent years [1]. Recently, the documented cases of a co-occurrence of different autoimmune diseases in a single patient in addition to studies investigating the possible common etiopathogenesis of these diseases have increased [2-4].

Celiac disease (CD) is an example of these ADs, characterized by a chronic inflammatory state of the proximal small bowel mucosa accompanied by structural and functional changes, it is triggered by the ingestion of gluten-containing grains in genetically susceptible individuals [5]. People who have CD are at greater risk than the general population for developing one or more of the associated ADs. This association is typically immune-based [6], such as: type 1 diabetes mellitus [7], autoimmune thyroid diseases [8,9] and Addison's disease [10,11]. Association of CD with atopy has also been described [12] but this has been disputed [13]. Other disease associations of uncertain pathogenesis such as: epilepsy with cerebral calcification [14], neurological disorders [15] and infertility [16]. The etiology of infertility among celiac patients seems to be related to many mechanisms of action, mostly studied in infertile women [17-19], while such type of studies were sparse among infertile males. Although, nutritional deficiencies [20], reversible androgen resistance [21] and hyperprolactinaemia [22] have been described in infertile men with CD, the pathophysiological mechanisms involved were undetermined. Furthermore, they ignored the immunological infertility as autoimmune disease. The main cause of immunological infertility is the formation of antisperm antibodies (ASA), which affects the capability of fertilization of spermatozoa [23]. As far as our search, no previous studies considered the association between ASA with CD autoantibodies.

The aims of the present study was to determine the prevalence of CD among unexplained infertile men and determine the association of CD autoantibodies with ASA as diagnostic tool for immunological infertility.

Materials and Methods

Study population

Cross sectional studies were conducted on one hundred and sixty six male patients, suffering from primary unexplained infertility, when they failed to conceive from at least two years of their marriage. Their age ranged between 19-55 years (34.93 ± 9.03 years). They referred to the Basrah Infertility and *In Vitro* Fertilization Center, Basrah, Iraq, from August 2015 to July 2016.

Inclusion criteria

Agreements were obtained from all participants to be included in the study. All of them have unexplained infertility after workup includes hormonal (FSH, testosterone, and LH), and urogenital exam (no hypospadias, no varicocele and normal testes) diagnosed by gynecologists and andrologists who were consultants in Basrah Infertility Center.

Exclusion criteria

Subjects with varicocele, hydrocele, undescended testis, any structural abnormality were excluded. Any apparent causes of infertility (including azoospermia) were excluded from the study. Receiving medicine (corticosteroids, NSAIDs or hormonal replacements) and history of surgical intervention in the genitourinary tract, acute febrile illness was excluded as well.

Seminal fluid (SF) analysis

After three to five days of abstinence, SF specimens were collected by masturbation in sterile container. After the fluid liquefied, SFs were analyzed according to WHO guidelines [24]. Only the sperm concentration (million/ml) and the progressive sperm motility (A+B grades) (linear progressive motility) were checked to exclude the azoospermic patients.

Antisperm antibodies autoantibodies (ASA)

Sperm MAR IgA test (Fertipro NV industriepark Noor Beemem, Belgium) direct qualitative beads test for detection of sperm antibody of the IgA. According to manufacturer's instructions, equal amounts (ten microliters) of fresh semen and sperm MAR latex particles were mixed. The mixture was observed after two minutes under a light microscope at 40x magnification at the edge of a cover glass. The results were documented as: agglutinated sperms> 10%=normal; 10% to 40%=suspected; >40% positive.

Serum separated from blood samples collected from the participants to be used for detection of IgG ASA by using ELISA.

Celiac disease autoantibodies

Serum samples from the participants were collected from venues blood specimens. Directly after collection, tissue transglutaminase (tTg) IgA, tissue transglutaminase (tTg) IgG and tissue transglutaminase/deamidated gliadin peptide (tTg/DGP) ELISA kits QUANTA (INOVA Diagnostics, San Diego, CA, USA) were used for diagnosis of celiac disease. According to the manufacturer's instructions, ELISA microplates were incubated with patients' serums samples. Anti-human tTg-IgA, tTg-IgG, or DGP IgAG antibodies coated to the ELISA wells were detected by labeled with horseradish-peroxidase. From the optical density of the sample, antibody levels were calculated in relation to the reactivity of a positive control and measured as Arbitrary Units (AU). The results were documented as: <20 AU=Negative; 20-30 AU=weakly positive; >30 AU=strong positive (manufacturer's instructions).

Statistical calculation

To analyze the results, SPSS software (version 21) was used. Descriptive statistics was used to describe the distribution of the study population according to morbidity. Then Fisher's Exact test was applied to test the existence of any association between the prevalence of celiac disease and immunological infertility. Odds ratio was measured with 95% confidence interval to determine the strength of association.

Autoantibodies levels were expressed as frequency and percentage values. The correlation coefficients (r values — between five markers of autoantibodies and two parameters of seminal fluid) were examined by Pearson correlation. The correlation is significant at the 0.01 level (2-tailed).

Result

Descriptive table (Table 1) shows the frequency and percentage of autoantibodies in infertile men. Out of 166 participants: tTg-IgA 13 (7.8%) were positive; tTg-IgG 16 (9.6%) were positive; DGP/tTg-IgA 8 (4.8%) were positive; ASA-IgG 36 (21.7%) were positive; and for ASA-IgA 15 (9%) were positive.

Autoantibodies	Negative		Suspected		Positive	
N=166	Frequency	%	Frequency	%	Frequency	%
tTg-IgA	125	75.3	28	16.9	13	7.8
tTg-IgG	124	74.7	26	15.7	16	9.6
DGP/tTg-IgA	135	81.3	23	13.8	8	4.8
ASA-IgG	63	38	67	40.3	36	21.7
ASA-IgA	130	78.3	21	12.7	15	9

Table 1: Description for frequency and percentage of autoantibodies.

Out of 166 participants with unexplained infertility, 15 participants (9%) have been diagnosed as immunological infertile. Thirteen (7.8%) unexplained infertile men have silent CD. Only seven (4.2%) have both Immunologic infertility and CD, while the rest of 166 (131) (78.9%) have neither immunologic infertility nor CD (Table 2).

Category	Frequency	%
Non-immunological infertility+Non CD	131	78.9
Immunological infertility+CD	7	4.2
CD only	13	7.8
Immunological infertility only	15	9.1
Total	166	100

Table 2: Frequency and percentage of immunological infertile, celiac disease and both among 166 infertile men.

Table 3 shows the Fisher's Exact test for association between immunological infertility and CD. Resulted that CD and immunological infertility have strong (significant) association in odds ratio >20 with 95% CI between 7.2-58.

Immunological infertility/CD	Negative	Positive	Total (%)
Negative (%)	131 (91.6)	12 (8.4)	143 (100)
Positive (%)	8 (34.8)	15 (65.2)	23 (100)

Total (%)	139 (83.7)	27 (16.3)	166 (100)
Fisher's Exact Test=0.0001; odds ratio=20.469; 95% CI is 7.220-58.025			

Table 3: Fisher's Exact table for association between immunological infertility and CD patients.

Table 4 shows five autoantibodies correlated significantly (P<0.01) with activity grades (A+B) of seminal fluid with exception to DGP/tTg IgA not significantly correlated. Total sperm count was not correlated significantly with all five autoantibodies.

Autoantibodies	Sperm total count (million/ml)	Activity grade (A+B)
tTg IgA	0.808	0.651*
tTg IgG	o.303	0.802*
DGP/tTg IgA	0.802	0.232
ASA IgG	0.313	0.339*
ASA IgA	0.312	0.253*
*Correlation is significant at the P<0.01 (2-tailed).		

Table 4: Correlation (r value) and the significances between CD and immunological infertility autoantibodies markers with seminal fluid parameters by Pearson correlation.

Symptoms were complained by the patients affected with silent celiac disease ranged from recurrent diarrhea to iron deficiency with other autoimmune and chronic disease (Table 5).

Feature	Frequency	%
Diarrhea	8	61.5
Constipation	9	69.2
Flatus	7	53.8
Abdominal distention	11	84.6
Weight loss	6	46.1
Autoimmune diseases: IDDM (1); RA (2); IBD (1)	4	30.7
Chronic diseases	4	30.7
Iron deficiency	8	61.5

Table 5: The silent celiac disease symptoms complain by the celiac affected.

Discussion

According to our research, there were rare studies estimating prevalence of male infertility in celiac disease [22]. In the current study, for the first time, the significant association between the ASA as etiological factor for infertility with silent CD was proven. In Basrah (South of Iraq) there is no population-based studies for the prevalence of CD, however, explanation about the prevalence of silent CD among infertile men may be intricate. Although, CD diagnosed by intestinal biopsy, serologic-based diagnosis in our patients was dependent because they refuse endoscopy procedure.

The prevalence of CD in the general population is about 0.5% to 1% with a female predominance (female/male: 3/1). However, it may vary in different geographical areas [25]. That is why, the majority of researches, considering relation of CD with reproductive changes are focused on the female infertility. Only few researches focused on relation of CD with males infertility. In 2003, Fasano et al. [26] studied the prevalence of undiagnosed CD in American patients of both genders. That study reported a 6.25% prevalence of CD in patients presenting with "idiopathic" infertility although, the genders of those patients were not specified. In the current study, the prevalence rate of silent CD among unexplained infertile men was 7.8% (13/166), while it was 4.2% (7/166) silent celiac disease among immunologic infertile men which seems lower than the others. That is may be due to the inclusion criteria which were more specific and only immunological infertility cases were taken in concern. Furthermore, this specification may give possible etiopathogenesis for infertile men to get CD or vice versa. It has been widely observed that disorders with an AD occur with increased frequency in patients with a history of another AD [1-4]. The presence of one AD should alert the clinician to the possibility of another AD. Attention to these potential coincidences and the possible pathoimmunologic linkage between these ADs in a single individual was drawn in the present paper.

Celiac disease may have different presentations: classic, atypical, silent, latent and refractory [5]. To show equivalent diagnostic performance for silent CD in our patients we used DGP (gliadin II) and tTg for serologic testing. Originally, intestinal biopsy is the golden tool to diagnosis of celiac disease and related disorders. Recently, serological testing has been suggested for screening patients with suspected gluten sensitive enteropathy. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHN) [27] has recommended use of serological markers such as gliadin antibodies to reduce the number of intestinal biopsies needed to make a diagnosis. Recent works [28-30] have revealed that gliadin reactive antibodies from celiac patients bind a very limited number of specific epitopes on the gliadin molecule. They resulted that, selective deamidation of gliadin by the tissue tTg might lead to enhancement of binding by anti-gliadin antibodies. Based on these observations, assays using combination assay (DGP/tTg) have been shown to have higher diagnostic accuracy for celiac disease when compared to standard anti-gliadin and tTG assays [31-33]. That is why, we used the combined serologic test to diagnose the CD in infertile men. In addition, they refused the endoscopic procedure, also we were unable to do HLA-DQ2/8. A significant proportion of celiac patients are IgA deficient. In cohort studies, IgA deficient patients have been shown to have a 10 to 20-fold increased risk of developing CD [34]. So, we screened the CD by using IgA further than IgG.

The prevalence of ASA in general population ranges from 0% to 2%, but, it is greatly increased in infertile men, ranging from 7% to 26% [35]. In the present study, ASA detected in 15/166 (9%) of unexplained infertile men. Several risk factors for development of such autoantibodies have been defined such as testicular torsion, varicocele, cryptorchidism, vasectomy and genital tract infections [36]. In the view of exclusion for any other risk factors for development of ASA in our patients, we cannot assure that CD is additional risk factor for ASA development. It needs for further studies among gluten free diet (GFD) immunologic infertile men and its protective effect.

The ADs most associated with CD were: type 1 diabetes (10%) [7], autoimmune thyroid disorders (7%) [8], primary biliary cirrhosis (PBC) was around 3% [37], and autoimmune hepatitis (AIH) had also been reported [38] with rate of 3% to 6%. In the present study, the resulted issue of CD association with Immunological Infertility (4.2%, OR=20.46) was added for the first time to the long list of ADs associated with CD. It has been suggested that these associations may be explained by the sharing of a common pathogenic basis involving similar environmental triggers and the loss of intestinal barrier secondary to dysfunction of intercellular tight junctions with increased intestinal permeability [39,40]. Furthermore, many risk factors for this association have been hypothesized such as genetic susceptibility [39], having a family history of autoimmunity (first degree relatives) [41], presence of other ADs [40]. In the patients of the present study, 30.7% have other ADs and 41% have first degree relatives with CD.

It is recommended that the screening for celiac disease should be part of the diagnostic work-up of infertile men, particularly when no apparent cause can be ascertained after standard evaluation. Screening high risk patients for CD, such as those with other ADs is a reasonable strategy given the increased prevalence. Treatment of CD with GFD should reduce the recognized complications of this disease, provide benefits in both general health and improve their fertility. It probably does not change the natural history of associated autoimmune disorders.

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42.