Araştırma Makalesi (Research Article)

İç Anadolu Bölgesinde Çölyak Hastalığının İdiyopatik İnfertilite ile İlişkisi

The Association of Celiac Disease with Idiopathic Infertility in Central Anatolia Region

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Amaç: Çölyak hastalığı (ÇH) genetik predispozisyonu olan bireylerde gluten alımı sonrası ince barsaklarda ortaya çıkan inflamatuvar bir hastalıktır. ÇH birçok jinekolojik ve obstetrik probleme yol açar. Biz İç Anadolu bölgesinde idiyopatik infertilitesi olan hastalarda çölyak hastalığı prevalansını araştırmayı amaçladık.

Gereç ve Yöntemler: Erciyes Üniversitesi Tıp Fakültesi Jinekoloji ve Obstetrik kliniğinde idiyopatik infertilite tanısı ile izlenen 30 hasta ile en az 1 gebelik öyküsü olan 33 sağlıklı kadın çalışmaya dahil edildi. Tüm hastaların Antigliadin antikor (AGA) Ig G ve Ig M seviyeleri, Antiendomisyal antikor (AEA), Anti doku Transglutaminaz antikoru (tTG) ve Ig G/M antikorları ölçüldü. Test sonucu pozitif gelen hastaların üst gastrointestinal endoskopi ve duodenal biyopsileri yapıldı.

Bulgular: Gruplar arasında anemi varlığı, yaş ve vücut kitle indeksi (VKİ) açısından fark yoktu. Hasta grubunda dört hastada AGA Ig A ve yalnızca 1 hastada AGA Ig G pozitif iken kontrol grubunda 3 hastada AGA IgA pozitifti. EMA testi kontrol grubunda yalnızca 1 hastada pozitifti ancak hasta grubunda hiçbir hastada pozitif değildi. tTG Ig A antikorları her iki grupta da negatifti. Kontrol grubunda 2 hastada tTG Ig G pozitifti. Serolojik testler açısından her iki grup arasında anlamlı istatistiksel farklılık yoktu.

Sonuç: İdiyopatik infertilite hastalarında ÇH prevalansı kontrol grubunda benzerdi. Bu hasta grubunda bu ilişkiyi değerlendirmek için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Antikorlar, Çölyak hastalığı, İnfertilite

Abstract

Objective: Celiac Disease (CD) is an inflammatory autoimmune disease that occurs in the small intestine of genetically predisposed individuals after gluten intake. CD leads to several gynecological and obstetrical problems. We aimed to investigate the prevalence of CD in patients with the diagnosis of idiopathic infertility in Central Anatolia.

Material and Methods: The study included 30 female patients who had been diagnosed with idiopathic infertility in the Erciyes University Faculty of Medicine, Gynecology and Obstetrics clinic and 33 healthy women with at least one healthy pregnancy. The levels of antigliadin antibody (AGA) IgG/IgM, anti-endomysial antibody (EMA), anti-tissue transglutaminase antibodies (tTG) and IgG/IgM antibodies were measured in all patients and the study group. Upper gastrointestinal endoscopy and duodenal biopsy were performed for the individuals with a positive test result.

Results: There was no significant difference in the presence of anemia, age, and body mass index between the groups. While AGA IgA was positive in four patients and AGA IgG was only positive in one patient in the patient group, AGA IgA was positive in three patients in the control group. In the control group, only one patient had a positive EMA test result; however, there was no positive result in any of the patients in the study group. tTG IgA antibodies were negative in both groups. Two patients had positive test in terms of tTG IgG in the control group. There was no statistically significant difference in terms of serological tests in both groups.

Conclusion: The prevalence of CD in idiopathic infertile patients was similar to the control group. Further studies are needed to evaluate this relationship in this cohort.

Keywords: Antibodies, Celiac disease, Infertility

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INTRODUCTION

Celiac disease (CD) is a disease that develops as a result of hypersensitivity to gluten found in cereals such as wheat, barley, oats, and rye. It may involve the small intestine mucosa and submucosa, often progresses to malabsorption, and clinical manifestations improve by removing the gluten from the diet (1). It is one of the well-known diseases in the world with an average prevalence of 1-2% in recent studies and observed 2-3 times more frequently in women than in men (2-4).

Patients may present with abdominal pain, dyspepsia, or diarrhea, which are classical symptoms of CD, or with symptoms of multisystemic involvement such as growth retardation, anemia, osteoporosis, infertility and recurrent miscarriages. Infertility is defined as the absence of pregnancy despite having unprotected sexual intercourse for at least one year. Infertility affects 10-15% of couples in the reproductive age group (18-45 years) (5). The infertility ratio is 8-12%, and the ratio ranges from 10% to 20% in Turkey (6).

Some studies have showed the relationship between idiopathic infertility and reproductive problems and CD. They also reported improved fertility after celiac diet in infertile females (7-10).

A study has been investigated association between CD and fertility in infertile North American women and found the prevelance as 5.9% in infertile population. The mechanism of reproductive problems in CD is still unclear.

However, nutritional problems and autoimmune mechanisms are generally the most overrated reasons to explain this relationship.

Anti-TG antibodies that are thought to be present in endometrial endothelial cells, are assumed to bind to these cells. Thus these antibodies may affect the embryo implantation and result in infertility (12).

This study aimed to investigate the persistence of these serological tests for CD in infertility for the first time in our country. We evaluated infertility in CD patients by analiyzing three different antibody titers.

MATERIAL and METHODS

The study was carried out in the Department of Internal Medicine in Erciyes University Faculty of Medicine. Before conducting the study, we received Academic Committee approval, as well as Ethics Committee approval (Ethics Committee decision number: 2013/562, Date: 20.08.2013). The study was planned according to the principles of the Helsinki Declaration. All patients included in the study were informed about the tests to be performed. Their written consent form was obtained to perform the tests and the necessary physical examination.

Idiopathic infertility was diagnosed based on the absence of a reason to explain infertility as a result of the examinations in the obstetrics and gynecology clinic. Spermiogram, hysterosalpingography (HSG), display of ovulation (with progesterone level on the 21st day of the cycle), pituitary hormones (FSH, LH), and thyroid function tests were evaluated in couples with infertility. Laparoscopy had been performed in some cases, when as needed (when tubal patency could not be monitored in hysterosalpingography (HSG) and pathology of tuba uterina was considered). Idiopathic infertility was diagnosed when these tests resulted in normal values.

The study included primary infertile women (18-40 years of age) who did not have any pathology in HSG and hormone tests, were not diagnosed with CD previously, and whose partners had normal spermiogram results. Those with known pituitary or hypothalamic disease, DM, HT, hypothyroidism, hyperthyroidism, polycystic ovarian syndrome (PCOS), or hyperandrogenemia were excluded.

The study involved 30 female patients who met the inclusion criteria and were diagnosed with infertility, and 33 women with fertility, between the ages of 18 and 40.

Serological Evaluation

Venous blood samples were taken from all individuals in the patient and control groups, and EMA IgA, AGA IgG, and IgA were examined using the micro Enzyme-Linked Immunoabsorbent Assay (ELISA) method in the serology laboratory of our hospital. Values

>25 IU/ml for AGA antibodies, and >20 for EMA IgA were considered positive. ELISA BioTek microplate reader and Elx50 microplate washer devices, Sunred human t reader and Elx50 microplate washer devices, Sunred human tTG IgA kit, and Sunred human tTG IgG antibody-ELISA test kits were used for the tTG. Values > 300 ng/ml for tTG IgA and values > 10 µg/ml for tTG IgG were considered positive.

Statistical Methods

The data were evaluated in the IBM SPSS Statistics 21.0 statistics package program. The number of units (n), percentage (%), and mean ± standard deviation were given as summary statistics. The normal distribution of numerical variables was analyzed with the Shapiro-Wilk test. Independent samples t-test was used for two-group comparisons. The exact method of the chi-square test was used to compare categorical variables. P value <0.05 was considered statistically significant.

RESULTS

The mean age was 28.4 years in the patient group and 29.3 years in the control group. The body mass index was 22.6 km/m^2 in the patient group and 22.17 km/m^2 in the control group. There was also no significant difference between biochemical parameters. Clinical and biochemical characteristics, and blood pressure monitoring of study participants are summarized in **Table 1**.

Table 1. Clinical and biochemical characteristics and blood pressure monitoring of infertile patients and healthy controls

Variables	*Infertile patients (n=30)*	*Healthy controls (n=33)*	*P*
Age, (years)	28.4±4.5	29.3±3.28	Ns
Systolic blood pressure (mmHg)	120± 8.5	122 ± 9.0	Ns
Diastolic blood pressure (mmHg)	75± 6.0	74± 5.5	Ns
eGFR* (ml/min/1.73 m^2)	83.9 ± 5.8	85.4 ± 3.6	Ns
BMI (kg/m^2)	22.6±2.30	22.1±2.43	Ns
Hemoglobin (g/l)	13.1 ± 1.9	13.5 ± 2.1	Ns
Platelet count (x1,000/mm^3)	228 ± 44	256 ± 49	Ns
White blood cell count (10^3/uL)	6.5 ± 3.2	5.8 ± 2.3	Ns
Smoking status	2 (6%)	3(9%)	Ns
Biochemical parameters			
Plasma fasting glucose (mg/dl)	88.0 ± 8.5	86 ± 9.0	Ns
Creatinine (mg/dl)	0.89 ± 0.21	0.84 ± 0.15	Ns
Fasting total cholesterol (mg/dl)	182± 32.5	177.9 ± 29.9	Ns
Fasting HDL- cholesterol (mg/dl)	42.2 ± 11.9	43.1± 7.1	Ns
Fasting LDL- cholesterol (mg/dl)	112.4± 27.1	113.6 ± 22.7	Ns
Fasting triglyceride (mg/dl)	143± 98	138± 81.9	Ns
Hs-CRP (mg/l)	5.4 ± 2.1	5.1 ± 1.9	Ns

Ns: Not significance statistically difference, BMI: Body mass index

All patients were given a detailed physical examination and system query in terms of CD. No patients had symptoms of chronic diarrhea, abdominal pain, and weight loss. One patient in the infertile group and two people in the control group had occasional complaints of abdominal distention. However, no organic pathology was detected in these individuals.

AGA IgG/IgM, EMA, and tTG IgG/IgM were tested in all patients. AGA IgA was detected in four patients and AGA IgG in one patient in the patient group. In the control group, AGA IgA was positive in three patients, and none of them had AGA IgG positivity. There was no statistically significant difference between the two groups (p> 0.05) **(Table 2)**.

EMA was positive in one patient in the control group, and none in the patient group. The difference was not statistically significant (p> 0.05). That patient did not accept the upper endoscopy procedure for diagnostic purposes **(Table 2)**.

TTG IgA antibodies were negative in all patients in both groups. Two people in the control group had tTG IgG positivity. All patients in the patient group were negative. There was no statistically significant difference between the groups (p> 0.05) **(Table 3)**.

Table 2. AGA IgA, AGA IgG, and EMA Levels of the Patient and Control Groups

		Patient		Control		P
		n	%	n	%	
AGA IgA	Positive	4	13.3	3	9.1	0.7
	Negative	26	86.7	30	90.9	
	Total	30	100	33	100	
AGA IgG	Positive	1	3.3	0	0	0.476
	Negative	29	96.7	33	100	
	Total	30	100	33	100	
EMA	Positive	0	0	1	3	0.98
	Negative	30	100	32	97	
	Total	30	100	33	100	

Table 3. TTG IgA and tTG IgG Levels of the Patients and Control Groups

			Patients	Controls	Total
tTG IgA	Positive	n	0	0	0
		%	0	0	0
	Negative	n	30	33	63
		%	100	100	100
	Total	n	30	33	63
		%	100	100	100
tTG IgG	Positive	n	0	2	2
		%	0	6.1	3.2
	Negative	n	30	31	61
		%	100	93.9	96.8
	Total	n	30	33	63
		%	100	100	100

There was no significant difference between the groups in terms of anemia. Eight people in the control group and seven in the patient group had hemoglobin <12 g/dl. Their anemia was compatible with iron deficiency anemia. Folic acid and B12 levels were normal in all patients.

DISCUSSION

CD is a chronic and inflammatory small bowel disease that is triggered by gluten in individuals with a genetic predisposition. This clinical situation occurs with T cell-mediated immune mechanism and causes malabsorption. The prevalence of CD seropositivity was determined as 1/130-1/300 in adults patients in Europe (2, 12-15). Gürsoy et al. found that its prevalence was 1% in Kayseri which located Central Anatolia (16).

In our study, we aimed to investigate CD associated with idiopathic infertility by using multiple tests in this location.

The infertility rate was found 0.2% in Italy in the general population. However, infertility was found 1.2% in a study conducted in CD patients who were between the ages of 15-49 (17). Hussein Shamaly et al. showed that the CD rate was found 2.65% in the 192 patients with idiopathic infertility group while only 0.5% ratio was found in the 210 healthy volunteers aged 18-44 years. In addition, another study showed that the CD was found 1.5% in the 100 couples with idiopathic infertility group whereas this ratio was 0.25% in the 200 healthy couples (18,19).

Contrary to these studies, several studies have demonstrated that there was no association found between CD and infertility. Also, no relationship was found between infertility and pregnancy complications in this study involving 5000 cases with CD (19).

A study by Rita Sharshiner et al. compared tTG and EMA IgA and IgM antibody titers in 116 patients with idiopathic recurrent miscarriages with healthy pregnancy controls. However, no statistical difference was found between the two groups and the authors suggested that such screening was not required in the infertile group in terms of CD antibodies (20). A study by Kolho et al. performed a study included 47 cases with unknown infertility, 63 cases with recurrent miscarriages, and 51 healthy women and they suggested that the CD prevalence was not different from a normal population (21). Similarly, other studies have shown that the CD prevalence is similar in healthy controls with infertile women (22-24).

Currently, studies on CD and infertility have examined presence of antibodies generally. There have been serious researches on the immunological origin of this association in recent years especially. AGA can also be found positive in atopic eczema, pemphigus, sjögren's syndrome, and rheumatoid arthritis in the literature (25).

Kumar et al. performed a large-scale study for a subclinical celiac in the obstetrics clinic. AGA IgA IgG, tTG IgA, and EMA IgA were tested for the patients with reproductive problems and the control group. TTG IgA was positive in 6.7% of those with recurrent miscarriages, 5.7% of those with stillbirths, 5.6% of the infertile group, 9.3% of those with intrauterine growth retardation and in 1.3% of the control group. The seroprevalence of tTG and EMA was similar in each group when compared to the control group. Therefore, the authors suggested serological evaluation should be performed in people with idiopathic reproductive problems in terms of subclinical CD (26).

Unlike previous studies, we evaluated the relationship between infertility and CD in patients with idiopathic infertility by using multiple serological tests. There was no statistically significant difference in terms of serological tests in both groups.

In conclusion, the importance of this study is the first controlled study investigating the association of infertility and CD in our country using by analyzing several antibodies. We suggest that new markers are needed to investigate autoimmunity which is one of the causes of infertility in women.

Conflicts of interest

The authors declare that they have no conflict of interest.

Research Contribution Rate Statement Summary: The authors declare that, they have contributed equally to the manuscript.

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