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RESEARCH ARTICLE

A disease to consider in the differential diagnosis of lower back pain: Celiac disease and related autoimmune disorders

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Abstract

Introductıon: Celiac disease (CD) is an autoimmune disease caused by gluten ingestion in genetically susceptible individuals. Although gastrointestinal system symptoms are common, extraintestinal symptoms may be seen during the disease course. Due to similar genetic features and pathogenetic pathways for autoimmunity, increasing rheumatological diseases have been reported in CD in recent years. In this study, we aimed to evaluate patients with CD in terms of musculoskeletal symptomatology and presence of rheumatic disease and autoantibody positivity.

Methods: The study was designed as a cross-sectional, retrospective cohort study. Between January 2020-2022, 65 patients with CD who were followed-up in the gastroenterology clinic of our hospital and consulted to the rheumatology outpatient clinic for any reason were included in the study. Medical records were reviewed, laboratory and imaging results were recorded.

Results: Admission to the rheumatology clinic, the most common symptoms were inflammatory back pain(IBP) (43.1%) followed by xerophthalmia (15.4%). None of the patients with IBP had radiographically active sacroiliitis. In total, concomitant rheumatological diseases were 6 (9.2%): 2 patients (3.1%) had Sjögren's syndrome and one undifferentiated connective tissue disease, systemic lupus erythematosus, psoriatic arthritis and familial Mediterranean fever. Except for the CD autoantibodies, the frequency of anti-nuclear antibodies (ANA) was 38%, and the most common extractable nuclear antigen (ENA) patterns were DFS-70 and SSA.

Conclusion: Although the most common symptom is IBP, the absence of radiographic findings of spondyloarthritis in CD patients suggests these to be a non-rheumatological cause associated with CD. On the other hand, CD patients with xerophthalmia and/or ANA positivity may need to be evaluated for connective tissue diseases, especially SjS.

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Introduction

Celiac disease (CD) is a chronic autoimmune disease with multisystem involvement that arises due to gluten intake in genetically predisposed individuals. Its prevalence in the general population is around 1%.[1] The common symptoms of the disease are directly associated with the gastrointestinal system (GIS). GIS symptoms include diarrhea, loss of appetite, abdominal bloating, and failure to thrive, and they are more commonly observed in the pediatric population.[2] Less frequently, CD can also manifest with a systemic course with extraintestinal symptoms. Extraintestinal symptoms are common in both children and adults.[2] In 40% of cases, microcytic anemia due to iron deficiency [3] (caused by malabsorption of iron or chronic inflammation) or, more rarely, macrocytic anemia due to folate and/or B12 vitamin deficiency can be observed. Changes in the absorption of calcium and vitamin D3 are associated with osteopenia and osteoporosis.[4]

Gluten is a commonly used term for the insoluble protein complex derived from wheat, rye and barley.[5] It is poorly digested in the human intestine. Gluten peptides pass through the submucosa of the small intestine without being fully broken down. In genetically susceptible individuals (90-95% HLA, the remaining portion HLA-DQ8), this leads to the development of an immune (anti-deamidated gliadin antibodies - DGP) and autoimmune (anti-endomysial antibodies - EMA, anti-tissue transglutaminase antibodies - tTG) reaction. In patients, the adaptive immune system is more dominant, leading to the production of anti-EMA and anti-tTG antibodies, lymphocytic infiltration in the intestinal mucosa, and destruction of villus architecture.[6]

The increased prevalence of autoimmunity and rheumatic diseases in CD can be explained by shared genetic characteristics, common triggers, or compromised intestinal permeability. Similar to CD, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients have been found to exhibit mild inflammation in the small intestinal mucosa along with an increased number of intraepithelial lymphocytes (IELs).[7] On the other hand, symptoms related to joint and muscle involvement have been described in individuals with CD.[8] In conclusion, while initially considered a homogeneous disease, it is now acknowledged that CD encompasses a broader clinical spectrum. The relative risk of associating one or more autoimmune pathologies is approximately three times higher in individuals with CD compared to the general population.[9] Furthermore, about 30% of CD patients also have another accompanying immune pathology.[10] In recent years, systemic involvement in CD has been studied further, and musculoskeletal symptoms have also been described. In a study conducted by Jericho et al,[11] a significant number of adult patients exhibited musculoskeletal symptoms: arthralgia (16%), arthritis (15%), and myalgia (8%). Similarly, various studies have suggested associations between CD and back pain, sacroiliitis,[12] RA, SLE, vasculitis, polymyositis, and CD.[13] However, there are different results in the literature as well. A different study conducted by Shor et al.[14] İndicated that among the frequently detected autoantibodies in CD, anti-gliadin immunoglobulin G (IgG) antibodies were only observed in 12 out of 186 patients with RA. Similarly, another study has reported that RA is observed in CD patients at a lower rate compared to controls.[15]

Due to the conflicting results in the literature, more research is needed on this topic. So, in this study, we aimed to evaluate patients with CD in terms of rheumatological symptomatology and presence of rheumatological disease and autoantibody positivity.

Material and Methods

Study design

This study was designed as a cross-sectional, retrospective cohort study with approval by Ankara City Hospital ethics committee dated 07/09/2022, numbered E1-22-2862 and was therefore performed in accordance with the ethical standarts laid down in the 1964 Declaration of Helsinki and its later amendments. The study included patients who were under follow-up at the Gastroenterology Clinic of Ankara City Hospital with a diagnosis of CD and had sought care at the Rheumatology outpatient clinic for any complaints. For this purpose, the patients' medical records were reviewed. Additionally, patients were contacted or their information was gathered when they attended follow-up outpatient appointments.

Main outcomes and other variables

Demographic characteristics, medical treatments, laboratory and imaging results were also collected from the hospital database. Musculoskeletal complaints of the patients, rheumatological diseases and other comorbidities were also recorded separately. All evaluated autoantibodies of the patients were recorded. Except for celiac disease-related au-

toantibodies, antinuclear antibodies (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) and extractable nuclear antigen (ENA), which are used in the diagnosis of rheumatologic diseases, were recorded. Laboratory upper limits for antibodies used in the diagnosis of rheumatological diseases were considered positive as follows: ANA >1/100 U/mL, RF >20 IU/mL , anti-CCP>5 U/mL. Antibody titers were indicated in patients with ANA positivity. If there is any subgroup antibody positivity in the ENA test, the ENA test was considered positive and the subgroup antibody was also specified. MEFV and HLA-B27 genetic test results performed in patients deemed necessary according to rheumatological symptomatology were also recorded.

Statistical analysis

Data are analyzed using Statistical Package for the Social Sciences (SPSS) 22.0 software (SPSS.Inc., Chicago, IL). Normality of continuous variables is evaluated with Shapiro–Wilk test and with plots and histograms visually. Continuous variables are presented either with median (minimum–maximum, min-max) or mean±standard deviation, according to normality. Categorical variables are presented with numbers and percentages.

Results

Our study included 65 patients who were under follow-up in the gastroenterology clinic with a diagnosis of CD. Forty-seven patients (72.3%) were female and the median age of these patients was 31 years (min-max: 18-70). The demographics features and comorbidities of CD patients are presented in Table 1. The median duration of diagnosis for the patients was 3 years (min-max: 0-20). In CD related autoantibodies, the most frequently detected autoantibody was anti-tissue transglutaminase IgA (64.6%), followed by anti-endomysial IgA (53.8%), and anti-gliadin IgA (40%). Interestingly, 21.5% (n=14) patients had negative CD related autoantibodies; they were diagnosed with CD according to endoscopic biopsy.

The most common rheumatological complaint was inflammatory back pain (43.1%, n=28), followed by dry eyes (xerophthalmia) in 10 patients (15.4%), hip pain in 8 patients (12.3%), and oral ulcers (aft) in 8 patients (12.3%). Among patients describing inflammatory back pain, direct radiographs were evaluated and an enthesitis-like appearance was observed in 7 patients (10.5%). Similarly, irregularities and grade 1 sacroiliitis were found in 7 patients (10.5%) on sacroiliac direct radiographs. Eight patients underwent magnetic resonance imaging (MRI), but none of them showed active sacroiliitis.

Table 1. Demographic and clinical characteristics of patients followed up with celiac disease

Age, year, meadian (min-max)	31 (18-70)
Female, n (%)	47 (72.3)
Comorbidities, n (%)	
Autoimmune hypothyroidism	7 (10.8)
Diabetes mellitus	4 (6.2)
Sjogren's syndrome	2 (3.1)
Undifferentiated connective tissue disease	1 (1.5)
Systemic lupus erythematosus	1 (1.5)
Psoriatic arthritis	1 (1.5)
Familial Mediterrean fever	1 (1.5)
Disease duration, year, median (min – max)	3 (0-20)
Reasons for referral to rheumatology clinic, n (%)	
Inflammatory back pain	28 (43.1)
Xerophtalmia	10 (15.4)
Hip pain	8 (12.3)
Oral aphthae	8 (12.3)

In the evaluation of concomitant rheumatological diseases, Sjögren's syndrome (SjS) was present in 2 patients (3.1%), undifferentiated connective tissue disease (UCTD) in 1 patient (1.5%), systemic lupus erythematosus (SLE) in 1 patient (1.5%), psoriatic arthritis (PsA) in 1 patient (1.5%), and familial Mediterranean fever (FMF) in 1 patient (1.5%). The most common non-rheumatological comorbidity accompanying CD was autoimmune hypothyroidism, which was present in 7 patients (10.8%), followed by DM in 4 patients (6.2%). Among these 4 DM patients, 3 (75%) were being followed up for type 1 DM.

Antibodies associated with rheumatological diseases are presented in Table 2. RF positivity was detected in 2 patients (3.1%). In these patients, the positivity was at a low titer (>20 IU but <60 IU) (1st patient RF: 19, 2nd patient RF: 36). Anti-CCP positivity was observed in only 1 patient. ANA positivity was more common, found in 25 patients (38.5%). Among these patients, ANA titers were 1/100 in 15 patients (23.1%), 1/320 in 7 patients (10.8%), while the remaining 3 patients showed higher titers of ANA positivity (1/1000-1/3200). In the ENA tests, dense fine speckled (DFS) positivity was observed most frequently (6 patients, 9.2%). Additionally, an-

ti-SSA positivity was detected in 4 patients (6.1%). Other autoantibodies with positive findings were anti-SSB, anti-Ro52, anti-Mi2, anti-Ku, anti-Scl70, and anti-histone antibodies. Genetic mutation analysis for Familial Mediterranean Fever (FMF) was conducted on 7 patients. Among these patients, 1 (14.2%) had the M694V heterozygous mutation, 1 (14.2%) had the E148Q heterozygous mutation, and in the other 5 patients (71.4%), no mutation was detected. Genetic analysis for HLA-B27 was performed on 7 patients. Among the tested patients, 1 (14.2%) was positive, and the remaining 6 (85.8%) were negative for HLA-B27.

Table 2. Commonly Detected Autoantibodies Positivity in Patients Followed with Celiac Disease

RF, n (%)	2 (3.1)
Anti-CCP, n (%)	1 (1.5)
ANA, n (%)	25(38.5)
1/100	15 (23.1)
1/320	7 (10.8)
1/1000-1/3200	3 (4.5)
ENA, (%)	
DFS	6 (9.2)
SS-A	4 (6.1)

Discussion

With improved diagnostic methods and comprehensive screening of individuals considered at risk, Celiac disease has seen a significant increase in prevalence over the past 50 years.[16] In Western countries, the prevalence of histologically confirmed CD patients is around 0.6%, while the prevalence of serological screening in the general population is approximately 1%. The female-to-male ratio varies between 1:3 and 1.5:1. The disease is known to affect all age groups, with over 70% of patients being diagnosed after the age of 20.[17] CD may present with a variety of different symptomatology. Traditionally, patients present with symptoms like diarrhea, steatorrhea, and weight loss. However, CD can manifest with a wide range of symptoms and findings including anemia, reflux esophagitis, eosinophilic esophagitis, neuropathy, ataxia, depression, short stature, osteomalacia, osteoporosis, and unexplained elevated liver transaminases.[11,13,18,19] Gluten is a significant trigger factor in CD. The term "gluten" refers to a mixture of proteins from wheat, including gliadin and glutenin, as well as similar proteins from other grains.[20] Prolamins, a complex group of alcohol-soluble lectins, constitute important seed proteins in grains. The most abundant gluten prolamins (gliadin and glutenin) are primarily found in wheat. However, other grains such as barley (known as hordeins), rye (secalins) and oats (avenins) also contain substantial amounts of prolamins.[21] The pathophysiology of CD arises from a complex interplay between genetic and environmental factors that lead to an inappropriate immune response in affected individuals.

Gluten may trigger other autoimmune processes beyond CD. In a study, it was demonstrated that gluten has effects on spontaneous autoimmunity in non-obese diabetic mice.[22] When exposed to dietary gluten, these mice exhibit high levels of mucosal proinflammatory cytokines and develop minor intestinal enteropathy. The abnormal immunological response triggered by proteins derived from gluten can lead to the production of different antibodies affecting various systems. Most commonly, in CD, antibodies are produced against members of the transglutaminase (TG) family, particularly IgA-class antibodies targeting transglutaminase 2 (TG, also known as protein-glutamine γ-glutamyltransferase),[23] in dermatitis herpetiformis against TG2 and TG3, and in gluten ataxia against TG6.[24]

There are two significant questions in the relationship between CD and autoimmunity. First, "does CD directly lead to other autoimmune diseases?", second, "can the clinical course of autoimmunity be altered in CD patients by adopting a gluten-free diet?". There are various studies in the literature addressing these questions. For instance, there are numerous studies regarding the relationship between CD and RA, one of the most common rheumatological diseases.[25,26] In those studies, there can be conflicting results regarding the prevalence of CD in patients with RA. For instance, in a study by Elhami et al,[27] the estimated rate of CD among RA patients is approximately 3%, which is three times higher than the healthy population. However, in another study, a lower association between RA and CD was found compared to control groups.[28] In our study, we did not observe any cases of RA in individuals with CD. When considering the other results of our study, we found a frequency of 3.1% for SjS among individuals with CD. According to the 2020 European League Against

Rheumatism (EULAR) SjS guidelines, the prevalence in European countries ranges from 1 to 23 individuals per 10,000 people (0.01% - 0.23%).[29] When comparing these frequencies, our study suggests a higher prevalence of SjS in individuals with CD.

The literature has demonstrated through various studies that extraintestinal manifestations are frequently observed in CD.[30,31] Rheumatological symptoms are frequently encountered in CD patients, mainly musculoskeletal symptoms. Myalgia, a common symptom of CD, can be associated with nutritional deficiencies or systemic inflammation.[11] Arthralgia and arthritis, which are reported to occur in approximately 20-30% of cases, are also common musculoskeletal symptoms.[32] In patients with CD, excessive vitamin D and calcium malabsorption due to villous atrophy leads to secondary hyperparathyroidism, dramatic decrease in bone mineralization, and osteomalacia.[33] This condition is one of the important causes of arthralgia and myalgia seen in patients. In our study, similar to the data in the literature, musculoskeletal symptoms were quite common in CD. A recent meta-analysis, despite an increase in the frequency of arthralgia, indicated that the frequency of arthritis does not increase in CD.[32] Our study also found that the frequency of inflammatory arthritis did not increase. Xerophthalmia, the second most common extraintestinal complaint in our study, is also commonly seen in CD, consistent with the literature. The prevalence of SjS in CD varies between 1% and 14.7% in various studies.[34,35]

Our study has certain limitations. The most important limitation is the relatively small number of CD patients. Another significant limitation is the retrospective nature of our study. Evaluating patients based on their presenting complaints and conducting assessments and investigations prospectively might yield different results.

Conclusion

In our study, rheumatological symptoms, especially musculoskeletal symptoms, were quite common in patients with CD. Although IBP is the most common rheumatological symptom in CD, we did not find evidence of spondyloarthritis confirmed by radiological imaging. Xerophthalmia was the second most common rheumatologic symptom and an increased prevalence of SjS was found similar to some studies in the literature. According to our findings, CD patients with xerophthalmia and/or ANA positivity may need to be evaluated for connective tissue diseases, especially SjS. However, larger and more comprehensive studies are needed to better show the relationship between rheumatological diseases and CD.

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Conflicts of interest:

The authors declare no conflicts of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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RESEARCH ARTICLE

Correlation between Helicobacter pylori and serum levels of ghrelin, obestatin, leptin and motilin in hyperemesis gravidarum

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Abstract

Introductıon: Hyperemesis gravidarum (HEG) is the severe form of nausea and vomiting seen in pregnancy. Many factors are thought to affect the development of the disease however, the pathogenesis of HEG has not been clearly revealed yet. In this study, we aimed to evaluate serum ghrelin, obestatin, leptin, motilin levels and their relationship with Helicobacter pylori (H.pylori) in the patients diagnosed with HEG.

Methods: A total of 160 patients including 48 HEG patients, 57 asymptomatic pregnant women, and 55 healthy non-pregnant women aged between 18-40 years, who were admitted to our tertiary research hospital were included in the study, Gastrointestinal hormone levels compared between three groups and the HEG group divided by the H.pylori seropositivity and hormone levels were compared between H.pylori positive and negative patients.

Results: In the HEG group, the mean serum ghrelin level was significantly lower and the mean leptin level was significantly higher than the asymptomatic pregnant and non-pregnant control groups (p=0.0001 and p=0.0001). The mean obestatin level of the HEG group was significantly lower than the non-pregnant control group (p=0.012). The mean motilin level in the HEG group was significantly higher compared to the asymptomatic pregnant control group (p=0.020).

Conclusion: This study suggests a possible role of ghrelin, obestatin, leptin and motilin in the pathology of HEG independent from H.pylori positivity.

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Introduction

Hyperemesis gravidarum (HEG) is the severe form of nausea and vomiting during pregnancy and it affects almost 3 percent of all pregnancies.[1] HEG is mainly seen in the first half of the pregnancy period but rarely it can continue until the end of the pregnancy. In individuals afflicted with severe symptoms, a spectrum of adverse outcomes may ensue, including but not limited to weight loss, fluid-electrolyte imbalances of a severity warranting hospitalization, nutritional deficiencies, esophageal damage, and a notable diminution in the quality of life experienced by both the patient and their caregivers.[2,3] Some patients may want to terminate their pregnancy because of the severity of the disease.[4] While an increase in adverse obstetric outcomes such as low birth weight has been reported in pregnant women experiencing significant weight loss, particularly, the literature presents conflicting data on this matter.[5,6] Many factors like Helicobacter pylori (H.pylori), pregnancy hormones, corrupted gastrointestinal motility, immune factors and changes in autonomic nervous activity are blamed for the pathogenesis of the disease.[7] However, the exact effect of any factor has not been revealed.

Ghrelin, leptin, obestatin and motilin are hormones that play a major role in regulating appetite and gastrointestinal function. Ghrelin is a peptide hormone that increases appetite, induces growth hormone synthesis and weight gain in case of negative energy balance.[8] Obestatin is synthesized by the stomach and small intestine. It's encoded by the same gene as ghrelin but its effect becomes opposite of ghrelin by posttranslational modification.[9] Leptin is a peptide hormone that is produced by many tissues. The primary resource of leptin is adipose tissue as well as placenta is one of the tissues that synthesize leptin.[10] It has roles in the regulation of appetite, energy regulation and reproductive functions. Leptin synthesis increases with satiety and increased levels of this hormone makes suppression in appetite.[11] Motilin is secreted from the M cells located in the proximal small intestine.[12] It stimulates gastrointestinal motility and fastens gastric and gallbladder emptying.[13]

H.pylori is a well known gram negative bacteria and it is one of the most common bacterial infections in human beings.[14] Humans are the primary reservoir of the pathogen and it transmits fecal-oral and oral-oral way.[14] H.pylori infection is mainly associated with gastric peptic ulcer and is thought to be associated with other several gastrointestinal tract problems (eg. gastritis, gastric adenocarcinoma, lymphoma).[15]

In this study, we aimed to analyze serum ghrelin, obestatin, leptin, and motilin levels, which have important effects on appetite, gastrointestinal motility, and energy metabolism in our patients diagnosed with HEG, and to evaluate their relationship with H.pylori, to understand the role of these markers in the pathogenesis of the disease.

Material and Methods

Patient selection

The patients with severe nausea and vomiting that cause weight loss of 5% or more of their pre-pregnancy period or with a modified Pregnancy-Unique Quantification of Emesis (PUQE) score of 12 or more were accepted as HEG (n=48). For the control group, completely healthy pregnant women at similar gestational weeks (n=57) and healthy non-pregnant women (n=55) in similar age groups and BMI were included in the study. Exclusion criteria were set as follows; the presence of chronic liver or kidney disease, chronic gastrointestinal system diseases, hypertension, cardiovascular diseases, metabolic diseases, endocrine diseases such as thyroid diseases or diabetes mellitus, multiple pregnancies, and patients who achieved pregnancy with assisted reproductive techniques. Informed consent was obtained from all participants and the study was approved by the local ethics committee. The trial registration number is 2011-KAEK-27/2018- E.1800075891 and the registration date was 27/06/2018.

Measuring leptin, obestatin, ghrelin, motilin, and H.pylori

Venous peripheral blood samples were taken from study participants to measure hormone levels. Samples were taken at 09.00 a.m., following 12-hour fasting, then they were centrifuged for 10 minutes, at 3000 rpm. The serum extract was stored at -80 °C. Fine test human LEP (leptin), GHRL (ghrelin), OB (obestatin) and MTL (motilin) ELISA kits (Fine Biotech, Wuhan, China) were used to identify serum hormone levels. Gastric hormone measurements were conducted in a specialized private diagnostic laboratory. H.pylori IgG Enzyme Immunoassay ELISA kit (Diagnostic Bioprobes, Sesto San Giovanni (MI), Italy) was used to determine the presence of antibodies against H.pylori.

Statistical Analysis

For the statistical evaluation of the results, we used SPSS Package Program version 20.0. To present the descriptive data, number, percentage, mean, standard deviation (SD), median, minimum and maximum were used. We used the Chi-square test to compare categorical variables. The Kolmogorov-Smirnov test was used to analyze whether the variables were normally distributed, and the Shapiro-Wilk test was used to test for subgroup normality. One-Way ANOVA test was used to compare the variables with normal distribution, and post hoc comparisons with Bonferroni correction were made for variables that were found statistically significant. Kruskal Wallis analysis and Mann Whitney U test were used to compare the variables that did not fit the normal distribution, and Dunn-Bonferroni corrected pairwise comparison was made for statistically significant variables. P<0.05 was accepted for statistical significance.

Results

The mean age of the asymptomatic pregnant group was 28±5.5 years, the HEG group was 29.8±5.4 years, and the non-pregnant controls was 27.7±7.6 years. Table 1 shows the demographic and clinical data of the patients who participated in the study.

Table 1. Obstetric and demographic characteristics of study groups

	HEG	Asymptomatic pregnant	Non-pregnant control	
	Mean ± SD	Mean ± SD	Mean ± SD	p
Age (years)	29,8±5,4	28±5,5	27,7±7,6	0,088
BMI (kg/m²)	23,9±3,5	24,3±2,5	23,4±2,7	0,089
Gravida	2,1±1,1	2,3±1,4	1,0±1,3	**0,0001**
Parity	0,7±0,7	0,8±0,8	0,9±1,2	0,549

When the study groups were evaluated based on laboratory values, there were statistically significant differences in hemoglobin (p=0.0001), hematocrit (p=0.0001), urea (p=0.0001), and creatinine (p=0.0001) levels between the nonpregnant control group and the other two groups. Comparing the groups for white blood cell (WBC) and C-reactive protein (CRP) levels, the mean of the non-pregnant control group was found to be significantly lower than HEG and asymptomatic pregnant groups (p=0.0001 and p=0.0001, respectively). We found no other significant difference in terms of laboratory parameters between the three groups (Table 2).

Table 2. Evaluation of the laboratory results of study groups

	HEG	Asymptomatic pregnant	Non-pregnant control	
	Mean ± SD	Mean ± SD	Mean ± SD	p
Hgb (g/dl)	13,1±1,1	12,6±0,9	12,4±0,9	**0,0001**
Htc (%)	38,5±2,9	36,9±2,2	35,9±2,7	**0,0001**
WBC (/uL)	7196,4±15425	8873,7±2119,8	8731,3±23251	**0,0001**
CRP (mg/dl)	0,4±0,4	0,9±1,1	0,6±0,6	**0,0001**
ESR (mm/s)	17,8±11,7	27,8±12,9	31,4±16,1	**0,0001**
TSH (uIU/mL)	1,9±1,1	2,0±1,2	1,6±1,1	0,064
ALT (U/L)	18,3±16,9	14,8±9,5	17,2±15,4	0,643
AST (U/L)	23,7±45,2	16,1±3,9	19,1±20,1	0,074
Urea (mg/dl)	22,5±6,6	15,1±3,7	15,8±4,8	**0,0001**
Creatinin (mg/dl)	0,7±0,1	0,5±0,1	0,5±0,1	**0,0001**
Glucose (mg/dl)	97,1±12,6	94,9±19,6	93,6±14,5	0,074

Hgb: hemoglobin; Htc: hematocrit; WBC: white blood cell; CRP: C-reactive protein; ESR; eritrosit sedimentation rate; TSH: thyroid stimulating hormone

Thirty two (56,1%) of the asymptomatic pregnant group, 24 (43,6%) of the non-pregnant group and 32 (66,7%) of the HEG group were H.pylori immunoglobulin positive. The differences between groups were not statistically significant (p=0.063). The mean serum ghrelin level of the HEG group was significantly lower than the other two groups (p=0.0001 and p=0.0001, respectively). The mean serum obestatin level was found to be significantly lower in the HEG group compared to the non-pregnant control group (p=0.012). The mean serum leptin level in the HEG group was significantly higher than both the means of the asymptomatic pregnancy group and the non-pregnant controls (p=0.0001). The mean serum motilin level of the HEG group was statistically significantly higher than the mean of the asymptomatic pregnant control group (p=0.020). Table 3 shows a detailed comparison of hormone levels between the study groups.

Table 3. Comparison of the hormone levels of three groups

	HEG	Asymptomatic pregnant	Non-pregnant control	
	Mean ± SD	Mean ± SD	Mean ± SD	p
Ghrelin (pg/ml)	1178±588,1	5365,6±4697,1	5225,1±5232,5	**0,0001**
Obestatin (pg/ml)	40,2±32,5	42,2±25,8	52,3±30	**0,012**
Leptin (pg/ml)	3612,7±721,9	3105,3±771,4	3044,9±896,1	**0,0001**
Motilin (pg/ml)	12,2±4,4	11,9±7,2	11,6±3,7	**0,020**

In the HEG group, there was no statistically significant difference in terms of serum Leptin, Motilin, Ghrelin and Obestatin parameters between H.pylori positive and negative patients (p=0.325, p=0.412, p=0.406, and p=0.734, respectively) (Table 4).

Table 4. Comparison of hormonal parameters according to the presence of H.pylori in the Hyperemesis Gravidarum group

	H.pylori IgG (-)	*H.pylori* IgG (+)	
	Mean ± SD	Mean ± SD	p
Ghrelin (pg/ml)	1253,8±434,8	1140,2±654,5	0,325
Obestatin (pg/ml)	36,4±24,7	42±35,9	0,412
Leptin (pg/ml)	3519±747,6	3659,4±716,2	0,406
Motilin (pg/ml)	11,7±2,9	12,4±4,9	0,734

Discussion

The factors that are emphasized today for the development of HEG have a multifactorial etiology that has psychological, hormonal, infectious (H.pylori etc.), genetic and environmental origins. In this study, we investigated several hormonal factors, especially of gastrointestinal origin, which are thought to be important in the pathophysiology of HEG and also their relationship with H.pylori.

Ghrelin has an important effect on energy metabolism and appetite. Because of that, several studies investigate the difference in serum ghrelin levels between HEG patients and healthy pregnant women. The data is conflicted about serum ghrelin levels in HEG patients. Some studies reported both higher and not significantly different ghrelin levels in the HEG patients in the literature.[16,17] Öztürk et al. showed statistically significantly lower ghrelin levels in HEG patients.[18] Our study found that serum ghrelin levels were significantly lower in the HEG group compared to asymptomatic pregnant and nonpregnant controls. In the pathogenesis of a disease in which the appetite is severely reduced and the energy balance becomes negative, such as HEG, a decrease in ghrelin synthesis may have an effect. The fact that ghrelin levels were also lower in the HEG group compared to the non-pregnant control group supports this theory.

There are only a few studies evaluating the relationship of obestatin with HEG. In a study that included 30 HEG and 30 healthy pregnant women, higher serum obestatin levels were observed in the HEG group but the difference was not statistically significant.[19] Other studies have not found significant differences in terms of obestatin levels between the same groups.[18,20] Our study found significantly lower serum obestatin levels in the HEG group compared with the nonpregnant group, while no significant difference was found between the HEG group and the asymptomatic pregnant control group. Our findings are compatible with current literature data in this respect. In the light of these findings, it can be said that the changes in the obestatin hormone do not contribute to the development of HEG.

It has been thought that leptin, which has important effects on appetite and energy metabolism, may play a role in the development of HEG, like other hormones, and there are many studies in the literature aiming to reveal this relationship. Several studies reported no difference in terms of leptin levels in HEG patients compared to healthy pregnants.[16,21] Another prospective study compared adjusted leptin levels (ALL) (serum leptin level / gestational week) between HEG patients and healthy pregnants and it has shown significantly higher ALL in HEG patients.[22] In the same line Aka et al. stated that serum leptin levels of the HEG patients were significantly higher in their study.[23] In our study, serum leptin levels of the HEG group were significantly higher than both healthy pregnant and non-pregnant control groups. The suppressive effect of leptin on appetite suggests that the high level of this hormone may contribute to the development of HEG.

It has been shown that gastric emptying time increases and gastric motility decreases during early and late pregnancy periods and mechanical compression of the gravid uterus and hormonal changes during pregnancy are thought to be responsible.[24] There are a few studies that investigated motilin levels during pregnancy and changes in motilin levels in HEG patients. These studies showed lower motilin levels in pregnant women but there were no significant differences between HEG patients and healthy pregnants.[25,26] In our study, the mean motilin level in the HEG group was significantly higher than in the asymptomatic pregnant group. However, there was no significant difference between the non-pregnant control group and the HEG or healthy pregnant control groups in terms of motilin levels. The determination of high motilin levels in the HEG group can be explained by the assumption that it is

a consequence of the disease rather than its cause. Many studies that examine the relationship between HEG and H.pylori, which is associated with gastritis, peptic ulcer, gastric adenocarcinoma and lymphoma. In a study that enrolled 247 pregnant women with gastric complaints and 27 pregnant women without gastric complaints, H.pylori seropositivity was significantly higher in the gastric complaint group.[27] In another study in which HEG patients and asymptomatic pregnant women were examined in terms of seropositivity, the rate of seropositivity was found to be significantly higher in the HEG group.[28] In a study by Grooten et al., 5549 patients were evaluated and the HEG patients were grouped according to their weekly vomiting frequency. It was reported that the frequency of daily vomiting increased in patients with H.pylori seropositivity, while in this group maternal weight gain was decreased, and the incidence of delivering low birth weight and small for gestational age (SGA) infants was slightly increased.[29] In Jacobson et al. study in which 53 HEG patients and 153 asymptomatic pregnant women were included, HEG patients were evaluated in terms of H. pylori seropositivity and no significant difference was found between the two groups in terms of H.pylori IgG seropositivity.[30] A systematic review reported conflicting data regarding the relationship between HEG and H. pylori infection. The authors suggested that additional studies of higher quality could be helpful in identifying predictive factors for HEG.[31] In our study, no significant difference was observed between the three groups in terms of H.pylori IgG positivity. This condition is partially compatible with the literature, while it presents contradictions in some aspects.

Conclusion

In conclusion, we observed lower ghrelin and obestatin levels and higher leptin and motilin levels in the HEG group compared to the asymptomatic pregnant group. This could be a contribution to the literature about the pathogenesis of HEG and its relationship with gastrointestinal hormones. Through this means, acquiring additional knowledge about the pathogenesis of the disease could facilitate advancements in the prevention and treatment of this condition, particularly during the early stages of pregnancy, wherein it exerts a substantial negative impact. Serum hormone levels did not differ between HEG patients that were grouped as H.pylori positive and negative. Moreover, our study is the first in the literature to make this comparison in HEG patients. The number of studies evaluating the relationship between H.pylori and gastrointestinal system hormones is limited and the data are inconsistent. Therefore, further studies on the subject, especially in the pregnant population, could help understanding the effect of H.pylori infection on gastrointestinal system hormone levels and the relationship between HEG.

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RESEARCH ARTICLE

The Relationship of Cases with Isolated Proteinuria in Pregnancy with Maternal and Perinatal Outcomes

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Abstract

Introductıon: There are a limited number of studies in the literature on the obstetric consequences of isolated gestational proteinuria (IGP) disease and the progression of preeclampsia (PE). It has been stated that gestational proteinuria may be a risk factor for PE. With this study, we aimed to determine the risk factors for the development of PE in cases with isolated proteinuria during pregnancy and to compare the maternal and perinatal outcomes of the cases.

Methods: The study was designed as a retrospective cross-sectional study. Pregnant women over the 20th gestational week and diagnosed with proteinuria by 24 hour urine analysis were included in the study. Patients who were diagnosed with gestational proteinuria and did not develop PE during their follow up were classified as IGP and patients who developed PE.

Results: The average time between the detection of proteinuria and the development of PE was calculated as 16 days. Week of gestation at delivery(p<.001)and the time between proteinurine detection and delivery(p=.002) were significantly lower in the PE group. In 52 of 185 patients with gestational proteinuria in total, proteinuria was detected an average of 32w 5d, and increased blood pressure and development of PE occured at an average of 35 weeks of gestation. NB intensive care requirement, preterm delivery and IUGR rates were found to be significantly higher in the group with PE. Ceserean delivery rate in IGP was calculated as 54.14%,ceserean delivery rate in PE was 78.85%. A significant correlation was found between the history of preeclampsia in the development of preeclampsia in IGP patients(OR: 11,000 (1,199-100,883), p=0.034) and increased urine proteinuria(OR: 1,0001 (1,000-1,001),p=0.007).

Conclusion: Patients who have had preeclampsia before and who have a high 24 hour urine value are more likely to return to PE. IGP has a more benign prognosis in terms of maternal and fetal compared to PE.

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Introduction

Preeclampsia (PE) is defined as hypertension that starts after the 20th gestational week in a pregnant woman with a normal blood pressure before, and proteinuria or multiple organ damage accompanying it. PE is a multi-systemic disease that affects the cardiovascular, hepatic and renal systems and is associated with increased maternal and perinatal morbidity and mortality.[1-4] The prevalence of PE has been found to be 2.7–8.2% worldwide.[5] Approximately 10--15% of maternal deaths due to obstetric complications have been shown to be associated with PE.[2]

Proteinuria is a pathological condition frequently observed in PE disease and indicates endothelial damage in glomerular tissue.[6] In a normal pregnancy, urinary protein excretion increases as the gestational week progresses and is accepted as a physiological change up to a certain level. However, with dipsticks +1 and above proteinuria (30 mg / dL), protein / creatinine ratio (PCR) 0.3 mg protein / mg creatinine or higher in spot urine sample, or presence of 300 mg / day and above protein in 24-hour urine sample It is considered pathological for all gestational weeks.[7, 8] Although proteinuria is still used in the diagnosis of PE, it has ceased to be an indispensable criterion in diagnosis, and no relationship has been shown between the amount of proteinuria and the severity of PE.[9] In addition, isolated gestational proteinuria (IGP) without PE is observed in some of the cases, starting from the 20th gestational week and returning to normal within the postpartum twelve weeks.[10] It is observed that it is clear whether IGP is a part of the disease spectrum and that PE may develop at varying rates of 33-51% in cases with IGP in studies. In addition, perinatal results of pregnant women with IGP were found to be similar to healthy pregnant women.[10] In biochemical studies, it was found that placental growth factor (PIGF) and soluble-FMS-like tyrosine kinase 1 levels (sFlt-1) in pregnant women with IGP were lower than preeclamptic pregnant women and higher than healthy pregnant women.[11] There are a limited number of studies in the literature on obstetric results of IGP and PE progression.[12,13] However, some authors state that gestational proteinuria may be a risk factor for PE.[12]

With this study, we aimed to determine the risk factors for the development of PE in cases with isolated proteinuria during pregnancy and to compare the maternal and perinatal outcomes of the cases.

Material and Methods

The study was designed as a retrospective cross-sectional study. The data of pregnant patients whose follow-up and treatment was continuing between 2010-2019 in the Department of Obstetrics and Gynecology, Faculty of Medicine, Selcuk University, were analyzed. Approval was obtained from the local ethics committee of Selçuk University for the study (Reg. No=2019/257).

The pregnant women who were above the 20th gestational week and whose diagnosis of proteinuria were confirmed as a result of 24 hour urine analysis were included in the study. Patients with renal and autoimmune diseases, chronic hypertension, pre-gestational diabetes and urinary tract infection were not included in the study.

Patients who were diagnosed with gestational proteinuria and did not develop PE during their follow up were classified as IGP and those who developed as preeclampsia. Demographic and laboratory factors between these two groups; age, gravida, parity, body mass index (BMI), urine dipstick result, spot urine P / K ratio, protein level in 24-hour urine, gestational week in which proteinuria was first detected, gestational week at which delivery takes place, and time between detection of proteinuria and the time of delivery, from perinatal and maternal consequences; maternal intensive care need, neonatal intensive care need, newborn birth weight, PPROM, preterm delivery, IUGR, C / S ratios and APGAR 1st and 5th minute scores were compared.

The diagnostic criteria for PE were determined according to the criteria defined by the American College of Obstetrics and Gynecology Association.[14]

Statistical Analysis

SPSS 21 (Statistical Package for Social Sciences) program was used for statistical analysis while evaluating the findings obtained in the study. Descriptive statistical methods (mean, standard deviation, frequency) were calculated while evaluating the study data. Student t test was used for comparing parameters showing normal distribution between two groups and Mann Whitney U test was used for comparing parameters that did not show normal distribution between two groups. The Chi-Square test was used to compare qualitative data. Univariate and multivariate binary logistic regression analysis were used to predict preeclampsia. Results were evaluated at 95% confidence interval and significance level of $p < 0.05$.

Results

Records of 66604 pregnant patients were reviewed. It was found that 1808 pregnant women were followed up and treated with dipstick method, 1011 pregnant women with PCR and 206 pregnant women with a pre-diagnosis of proteinuria in 24-hour urine. 21 of the 206 patients were excluded from the study because of additional systemic diseases. The frequency of gestational proteinuria in the study was found to be 0.28% (185/66604). PE development was observed in 52 (28.11%) of 185 pregnant women with gestational proteinuria included in the study. The mean age of the patients included in the study was calculated as 28.69 ± 5.68 years. The average time between the detection of proteinuria and the development of PE was calculated as 16 days. Accordingly, between the two groups; while there was no significant difference in terms of age, gravida, parity, BMI and first week of gestation in which proteinuria was detected ($p<.05$); dipstick urine result ($p<.001$), spot urine PCR ($p = .046$) and 24 hour urine protein values ($p = .001$) were found to be significantly higher in the PE group. Week of gestation at delivery ($p<.001$) and the time between proteinurine detection and delivery ($p = .002$) were significantly lower in the PE group (Table 1).

Table 1. Comparison of demographic data of the groups

	Isolated proteinuria (n=133)	Preeclampsia (n=52)	p-Value
Age	28,20 ± 5,40	29,94 ± 6,24	0,061
Gravida	2,18 ± 1,35 (1-7)	2,50 ± 1,48 (1-7)	0,149
Parite	0,94 ± 1,09 (0-6)	1,12 ± 1,22 (0-6)	0,452
BMI (kg/m²)	32,51 ± 3,71	33,00 ± 4,30	0,446
The result of dipstick	1,19 ± 0,8	1,33 ± 0,94	**< 0,001**
Protein/kreatinin (mg/g)	0,61 ± 0,67	0,96 ± 1,08	**0,046**
Proteinuria in urine for 24 hours (mg/day)	691,78 ± 909,63	1431,48 ± 2071,75	**0,001**
The first detection of gestational week	33 (20-39)	33 (20-38)	0,668
Gestational week of birth	38 (26-41)	37 (20-39)	**< 0,001**
The time between the first detection and birth (day)	38,96 ± 35,52	24,29 ± 30,49	**0,002**

Data were analyzed by independent sample t-test, Mann-Whitney U test, Pearson Chi-square.
Data were given as mean ± standard error, median (min-max) or as n (%)
BMI, body mass index.

In 52 of 185 patients with gestational proteinuria in total, proteinuria was detected at an average of 32w 5d, and increased blood pressure and development of PE occurred in the 35th gestational week. Birth took place when the average was 36w 1d. In the remaining 133 IGP patient group, the average week of proteinuria onset is 32w 2d, and the average week of gestation at birth is 37w5d (Figure 1).

Figure 1.

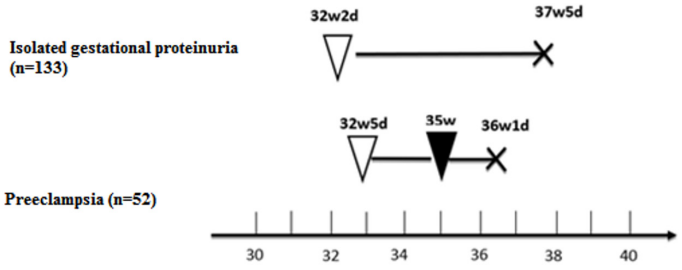

Figure 1. The development of PE with the occurrence of hypertension in the period from the time of detection of proteinuria to then birth.

Perinatal complications and fetal results of the patients are shown in Table 2. While there was no significant difference between the two groups in terms of PPROM development and the baby's first and fifth minute Apgar scores at birth, maternal intensive care requirement, NIC intensive care need, preterm delivery and IUGR rates were found to be significantly higher in the group with PE. In parallel with this result, HF birth weight was found to be significantly lower in the group with PE.

Table 2. Comparison of between perinatal complications and fetal deciency groups

	Isolated proteinuria (n=133)	Preeclampsia (n=52)	P-value
Mother intensive care (n,%)	1 (%0,75)	2 (%3,85)	**< 0,001**
PPROM (n,%)	2 (%1,5)	1 (%1,92)	0,749
Preterm birth (n,%)	19 (%14,29)	26 (%50,00)	**< 0,001**
Neonatal intensive care (n,%)	15 (%11,28)	17 (%32,69)	**< 0,001**
IUGR (n,%)	10 (%7,52)	17 (%32,69)	**< 0,001**
APGAR 1	7 (5-9)	7 (5-9)	0,461
APGAR 5	9 (6-10)	9 (6-10)	0,915
Neonatal weight	3080,70 ± 627,78	2504,75 ± 734 ,00	**< 0,001**
Caesarean section rate (n,%)	72 (%54,14)	41 (%78,85)	**0,001**
Gender boy	68 (%51,1)	31 (%59,6)	0,298
girl	65 (%48,9)	21 (%40,4)	

Data were analyzed by independent sample t-test, Mann-Whitney U test, Pearson Chi-square. Data were given as mean ± standard error, median (min-max) or as n (%). BMI, body mass index. PPROM : Preterm prematür membran.

When the IGP and PE patient groups were compared in terms of delivery type, a statistically significant difference was observed, and the rate of cesarean delivery was found to be higher in the group with PE (Cesarean delivery rate in IGP is 54.14%. Cesarean delivery rate in PE is 78.85%). When a comparison was made in terms of newborn gender in both patient groups, it was observed that the rate of male babies was higher.(59.6% in the PE patient group, 51.1% in the IGP patient group).

Variables for the prediction of preeclampsia in patients with isolated gestational proteinuria were examined by univariate and multivariate regression analysis. In univariate analysis, it was shown that preeclampsia history (OR: 11,000 (1,199-100,883), p = 0.034) and increased proteinuria in 24-hour urine (OR: 1,001 (1,000-1,001), p = 0.007) were found to be independently significant in the development of preeclampsia in IGP patients. In the multivariate analysis, a history of preeclampsia (OR: 12.675 (1.374-116.948), p = 0.025) and increased proteinuria in 24-hour urine (OR: 1.00 (1,000-1.001), p = 0.005) were shown to be statistically significant (Table 3).

Table 3. Prediction of preeclampsia of isolated gestational proteinuria patients

	Preeclampsia			
	Univariate		Multivariate	
Parameters	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.056 (0,997-1,119)	0,063		
Gravida	1,173 (0,938-1,467)	0,163		
BMI	1,033 (0,951-1,122)	0,444		
Preeklampsia history (yes)	11,000(1,199-100,883)	**0,034**	12,675 (1,374-116,948)	**0,025**
The first week of diagnosis	1,025 (0,956-1,099)	0,485		
Proteinuria in 24 hour urine	1,001 (1,000-1,001)	**0,007**	1,001(1,000-1,001)	**0,005**
Multiple pregnancy (yes)	0,850 (0,086-8,359)	0,889		
Fetal sex (boy)	1,411 (0,737-2,703)	0,299		

Univariate and multivariate logistic regression analysis was performed. BMI, body mass index, CI, confidence interval; OR, odds ratio. Bold values refer to statistical significance ($p < .05$)

Discussion

In our study, data of 185 patients who received proteinuria with 24-hour urine analysis during pregnancy were analyzed. PE development was observed in 52 (28.11%) of these pregnant women. The frequency of gestational proteinuria in the study was found to be 0.28% (185/66604). The average time between the detection of proteinuria and the development of PE was calculated as 16 days. Maternal and fetal outcomes were worse in the PE group. High 24-hour urine output and a history of preeclampsia were also found to be independent risk factors in the transition to preeclampsia.

PE is a multisystemic syndrome that affects the cardiovascular, hepatic and renal systems, associated with increased maternal, perinatal morbidity and mortality.[1-4] Many risk factors associated with preeclampsia have been identified. Obesity, nulliparity, multiple pregnancy, maternal age of more than 35, a mother's history of preeclampsia in a previous pregnancy, hyperhomocystinemia, metabolic syndrome and pre-pregnancy diabetes mellitus increase the risk of developing preeclampsia.[15,16] The presence of a previous history of preeclampsia increases the risk of preeclampsia by 8 times compared to those who do not have such a history.[17,18] Despite many studies conducted, the pathophysiology of preeclampsia is still not clearly understood today. Many theories have been put forward to explain the cause of preeclampsia. What is considered important today:[19] 1)Placentation with abnormal trophoblastic invasion of uterine vessels. 2)Immunological tolerance deconformity between maternal, paternal(placental) and fetal tissues. 3)Systemic endothelial dysfunction. 4) Inflammation/Infection. 5)Genetic, nutritional and environmental factors.

A normal pregnancy causes many anatomical and physiological changes in the urinary system. During pregnancy, the kidney size grows by approximately 1 ~ 1.5 cm and an increase in weight is observed.[11] Renal plasma flow (RPF) begins to increase in the early weeks of pregnancy and this increase is shown as one of the causes of renal hyperfiltration. The glomerular filtration rate (GFR) also increases, as does RPF. This increase is 50% more at the end of the first trimester than in the pre-pregnancy period, and this condition persists until the end of pregnancy. Around in the third moon after giving birth returns to normal levels.[7] In the studies conducted, the mechanisms underlying the significant increase in RPF and GFR have been examined. It has been observed that relaxation is important in the increase of GFR and RPF during pregnancy.[8] Relaxin increases the production of endothelin and nitric oxide in the renal

circulation. As a result, it leads to a decrease in renal afferent and efferent arteriole resistance with renal vasodilation, thereby increasing renal blood flow and GFR.[19] Failure in this critical adaptation is associated with poor pregnancy outcomes such as preeclampsia and intrauterine growth retardation.[20] Protein secretion secondary to the physiological changes of pregnancy increases from the kidneys during pregnancy and is considered a normal finding up to a certain level. However, the presence of 300mg or more protein in a 24-hour urine sample is considered pathological for all gestational weeks.[8,19] Proteinuria indicates endothelial damage. Although proteinuria is not an indispensable criterion for the diagnosis of PE, screening for proteinuria still has an important place, since most of the pregnant women who develop PE in the clinic are diagnosed with the presence of proteinuria. Another debate on proteinuria is IGP, and there are limited data in current guidelines on the subject of diagnosis and treatment of hypertension in pregnancy.[20,21] IGP frequency and pathogenesis have not been clearly elucidated. In some studies on the presence of proteinuria in preeclampsia, vascular endothelial growth factor and increased soluble tyrosine kinase 1 levels are held responsible for the pathogenesis of proteinuria.[22-26] Studies on IGP also support these results. However, it should be noted that placental growth factor (PIGF) and soluble-FMS-like tyrosine kinase 1 levels in pregnant women with IGP were found to be lower than preeclamptic pregnant women and higher than healthy pregnant women.[11] In the light of this information, IGP, PE diagnosis should PE be positioned as a criterion within the spectrum of disease or whether PE could be an early form of the disease spectrum .

IGP frequency is not known exactly like its pathogenesis. There are two prospective studies in the literature that state it as 4%.[27,28] Ekiz et al. This rate was reported as 0.33%, while this rate was found to be 1.4% in a multi-center observational study.[22,29] In our study, the frequency of IGP was found to be 0.28% in our patient group, where 66604 patients were screened and 185 patients were included in the study over a 10-year period. It is known that the risk of developing PE increases in IGP cases. In our study, it was found that 28.11% (52/185) of pregnant women with IGP developed PE in the following weeks of gestation. Considering that proteinuria is a late clinical manifestation of preeclampsia and that it can sometimes occur without any symptoms or high blood pressure, this is an important rate. Erkenekli et al.[30] Found the rate of patients who progressed from IGP to Preeclampsia as 35%, while Ekiz et al. Similarly found this rate as 33.7%.[22] Yamada et al,[29] this rate was given as 25% in a multi-center study. Morikawa et al.[31] Showed in their study that isolated proteinuria developed in the second half of pregnancy, and that PE developed in 51% of the cases. These studies have shown that after the detection of IGP, the frequency of development of PE may vary depending on the variety of environmental factors exposed, the difference and number of patient groups included in the study, but it can be said that approximately 25% to 50% of these patients will develop PE.

The average time from the detection of isolated gestational proteinuria to the development of PE was found to be 16 days in our study. In another study on this subject, it was reported that this period ranged from 3 days to 20 days and was 10 days on average. [32]

In our study in which there were 185 IGP patients in total, blood pressure increased in an average of 35 weeks of gestation in 52 patients and PE developed. While the mean onset week of proteinuria in 52 patients with PE was 32w5d, the week of delivery was 36w1d. In the remaining 133 isolated proteinuria patients group, mean proteinuria detection week was 32w2d and the week of delivery was 37w5d. In the light of these findings, it was found that proteinuria occurred at the same time in the patient group with PE (n = 52) and in the isolated proteinuria patient group (n = 133), while it was found that delivery occurred earlier in the patient group with PE. In a study conducted by Akaishi et al. On this subject, it was shown that the onset of proteinuria and delivery were earlier in the group with PE.[28] Our study findings support the study of Akaishi et al. In terms of timing of delivery. Proteinuria first detection week was found to be similar in the PE patient group and the IGP patient group in our study. In addition, when the first detected dipstick urine result, spot urine protein / creatinine ratio and 24-hour urine proteinuria were examined in the IGP and PE patient groups, it was observed that each of them was high in the PE developing group, and the repeated 24-hour urine proteinuria measurements during pregnancy also tended to increase in the group developing PE.

Since the possibility of developing PE in pregnant women with IGP is high, it is extremely valuable to determine the risk factors that predict

PE development. However, there is not enough data about this in the sources. Macdonald-Wallis et al. In a study they conducted with 11,651 cases, they found that pre-gestational BMI, young age, twin pregnancy and nulliparity, among the defined risk factors for PE, were associated with proteinuria occurring in normal term pregnancy.[33] In our study, it was found that having a history of preeclampsia (OR: 11,000 (1,199-100,883), p = 0.034) and increased proteinuria in 24-hour urine (OR: 1,001 (1,000-1,001), p = 0.007) predicted the development of preeclampsia.

There are few studies comparing the perinatal outcomes of IGP patients with and without PE in IGP patients. Ekiz et al. in their study, in which they retrospectively scanned 31472 patients and included 157 cases with IGP, it was shown that the week of birth was earlier, birth weights were lower and the need for neonatal intensive care was higher in the group with PE.[22] Our study also supports these findings, and the rate of preterm delivery was found to be significantly higher in the group with PE (50.00% in PE cases). In IGP cases, the preterm delivery rate was found to be 14.29%, and it was similar to the general population rates . In addition, in the group diagnosed with PE, the neonatal birth weight is lower (average newborn weight of IGP is 3080.70 ± 627.78 g, while the average PE weight is 2504.75 ± 734.00 g). while 11.3%, PE neonatal intensive care need was 32.7%) and maternal intensive care need was higher. There was no significant difference between the two groups in terms of PPROM, newborn 1st and 5th minute Apgar scores, and the amount of proteinuria observed in the postpartum period.

In some studies examining the gender distribution of babies of mothers with PE, the rate of male babies is high, in line with our results, and the reason is not known exactly.[34,35] When the sex ratios of newborn babies with and without PE were examined, it was found that the rate of male babies was higher in both patient groups (male babies rate in IGP 51.1% and male babies in PE 59.6%). In addition, in the univariate regression analysis, although it was not statistically significant, it was found that having a male baby increased the risk of developing PE (OR: 1.411 (0.737-2.703), p = 0.299).

The limitation of the study is that it is a retrospective study and the number of patients is small. The advantage is that there are not many studies on this subject in the literature.

PE is a pregnancy complication associated with increased maternal and perinatal morbidity and mortality worldwide. Since only proteinuria can be detected in some preeclamptic patients at the beginning without developing hypertension, pregnant women with isolated proteinuria should be given consultancy on PE and antenatal follow-up should be done regularly and at frequent intervals. Because PE may develop between 25% and 50% of the patients in the following weeks of gestation, causing both maternal and perinatal unwanted pregnancy complications.

Although pregnancy outcomes of IGP cases have been reported as positive in most of the studies conducted on this subject, there is a considerable possibility of developing preeclampsia in these patients. Although we see that the perinatal outcomes of pregnant women with IGP do not deteriorate in our study, close follow-up of women with a history of PE and high proteinuria in their previous pregnancies is extremely important in terms of PE development.

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RESEARCH ARTICLE

What are the factors affecting the mound displacement detected in endoscopic treatment failure of vesicoureteral reflux

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Abstract

Introductıon: Success rates of endoscopic treatment for vesicoureteral reflux range from 50-100%. Various factors predict outcomes after endoscopic injection. Mound displacement is one of the most critical factors for failure. We observed mound displacement in most of the patients with endoscopic injection failure. We aimed to evaluate predisposing factors for mound displacement in patients with endoscopic injection for vesicoureteral reflux.

Methods: In 2020, operative images were taken and archived in cases where the endoscopic injection was applied due to vesicoureteral reflux. The localization of the bulking agent was evaluated during the redo procedure in 11 patients who were re-admitted due to the failure of the injection procedure. In addition, age, gender, side and degree of reflux, bladder thickness in US, and bladder trabeculation were evaluated.

Results: Local migration of bulking agent was seen in 11 patients at cystoscopy after initial treatment failure. Our repeat endoscopic injection rate was 11/80 (13.75%). Bladder wall thickness and/or trabeculation, constipation, and post-voiding residue (over 20 ml) were significantly higher in patients with mound displacement.

Conclusion: Patients with thick bladder walls with increased PVR and accompanying constipation have the risk of mound displacement. Therefore, we recommend performing a cystoscopy in all cases with recurrence to evaluate the location of the bulking agent. If the mound displacement is noted, we recommend reinjection. Patients with a thick bladder wall, postvoiding residue, and concomitant constipation are at increased risk of bulking agent displacement. If migration of bulking agent is detected, we recommend reinjection with Double HIT or multi-site injection techniques.

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Introduction

Endoscopic vesicoureteral reflux (VUR) treatment has gained popularity as an alternative to open surgeries in the past 30-40 years. It has been widely used since the application materials are easy to use without complication in outpatients.[1-3] Unfortunately, recurrence rates of VUR after endoscopic injection appear to be around 15–20 % .[4]

The efficacy of Dx/HA injection has been difficult to fully define, given that reported success rates range from 50% to 100% .[5,6] Various factors that predict outcome after an endoscopic injection,such as gender,[7] age,[7] preoperative VUR grade,[8-12] renal scarring,[12] surgeon experience,[8,9,13] injected volume,[10,13] mound appearance,[10,14] and dysfunctional voiding,[15] had been determined.

However, in our cystoscopic evaluation of patients who were reoperated for the failure of the STING procedure,we observed mound displacement in most of the patients (figure1).Therefore, this study aimed to determine the factors causing the mound displacement in the cases where reinjection was applied for the failure of the STING procedure.

Figure 1

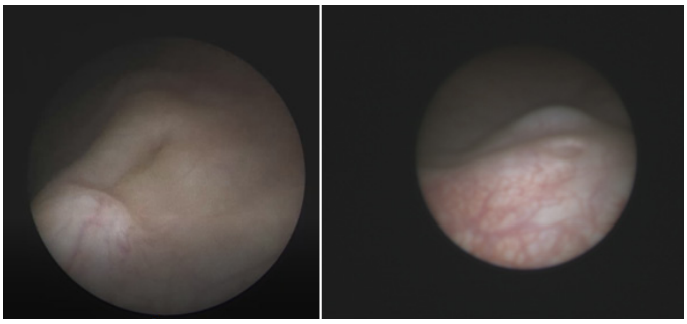


Figure 1.Displacement of the mound in subureteric injection. The mound moved the caudal direction of the orifice and the cranial direction in the left and right images, respectively

Material and Methods

Eighty cases of VUR who underwent subureteric Diethylaminoethyl-Dextran (DEAE-Dextran)+Hyalurinicacid (HA) (Dexell,IstemMedical Ankara Turkey) injection was prospectively evaluated in the study between January 01 and December 31, 2020. The local ethics committee approved this study (ref. No. E2-21-798).

1 ml of the bulking agent was routinely injected with the classical STING method. Additional 1 ml bulking agent was used in cases where coaptation could not be achieved. No routine VCUG was performed in the follow-up after the STING application. Patients who did not experience recurrent urinary tract infections after STING were considered to have had successful treatment, and no imaging was performed to determine the location of the bulking agent in these patients. However, VCUG was performed in cases with recurrent urinary tract infections in the follow-up. In cases with persistent VUR, cystoscopy was performed again, and the location of the injection bulking agent and hydrodistension at the ureteral orifice was evaluated. We only performed repeat cystoscopy on the patients with clinical failure and persistent VUR on cystogram and compared these patients with those with clinical success.

We tried to determine whether the injection was done with the proper technique by comparing the archive images of the interventions belonging to the endoscopic procedures. We compared the reoperation image records of the patients we encountered with recurrence during the follow-up with the image records of the first intervention in which we performed the endoscopic injection. The STING was applied again in cases with local migration of the injection bulking agent and/or ureteral hydrodistention. Open surgery was performed in cases where the bulking agent was found to be in place on cystoscopy, but the VUR persisted despite this.

Cases with secondary VUR, such as neurogenic bladder, duplicated system, or posterior urethral valve, and cases with the first injection performed in another medical center were excluded from the study. We evaluated patients with clinical failure for mound displacement and other cases in terms of age, gender, side and degree of reflux, bladder thickness in ultrasound (US), and bladder trabeculation in cystoscopy. Urinary tract dysfunction was evaluated using the symptom-scoring questionnaire Akbal et al. prepared.[16] Constipation was evaluated according to the ROMA IV criteria.[17] Bladder wall thickness was measured as the ventral wall thickness in the full bladder in US.[18] Two groups were compared by Chi-square test. Statistical significance was considered p b <0.05. The SPSS 17.0 software program was used to perform statistical analysis.

Results

Eighty cases aged between 5 months and 17 years (mean 4.54+3.26 years; median 4.00+3.26 years) were evaluated. Twenty-two of the cases were

male, and 58 were female. In 14 cases referred to our clinic due to unsuccessful STING applications from other medical centers, two cases underwent ureteroneocystostomy, and 9 cases had neurogenic bladder, posterior urethral valve, or duplicated system excluded from the study. Reinjection was performed in 11 cases with persistent VUR among 80 cases whose first injections were made in our clinic. Mound displacement is noted in 7 cases and disappears in 4 cases total of 11 patients (13.75%) who underwent the first injection in our clinic. A total of 11 cases (2 male, 9 female; 2-6.5 years, average 3.86+1.55 years; median 4.00+1.55 years) reinjection was applied.

No statistically significant difference was noted between the ages of the cases with the migration of the bulking agent and the cases without migration (p=0.246). Furthermore, when the two groups were compared in terms of gender, no significant difference was found (p=0.514). Finally, no significant difference was found in comparing the side (unilateral/bilateral) and grade of reflux (p=0.481, p=0.560) (Table 1, 2, 3). A statistically significant difference in terms of symptom score was not detected between the two groups (p=0.472)

Table 1 Gender distrubition of the two groups

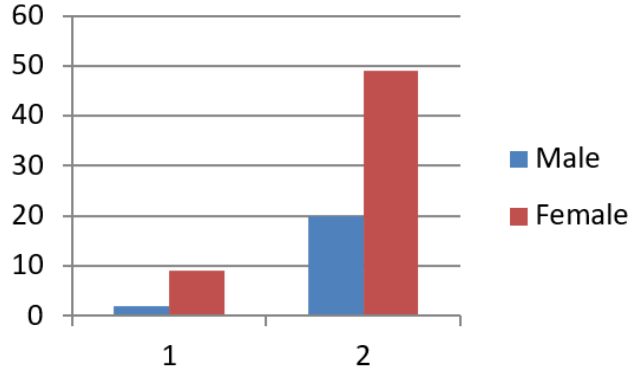


Table 2 Side of the VUR in patients with Redo and first injection

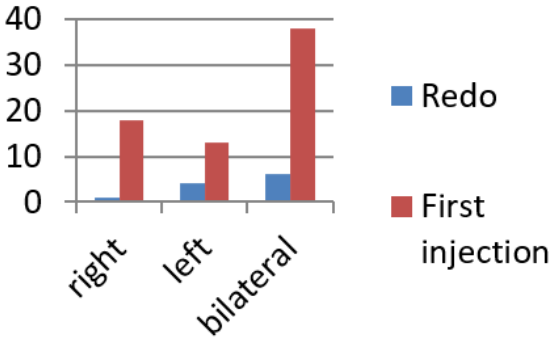
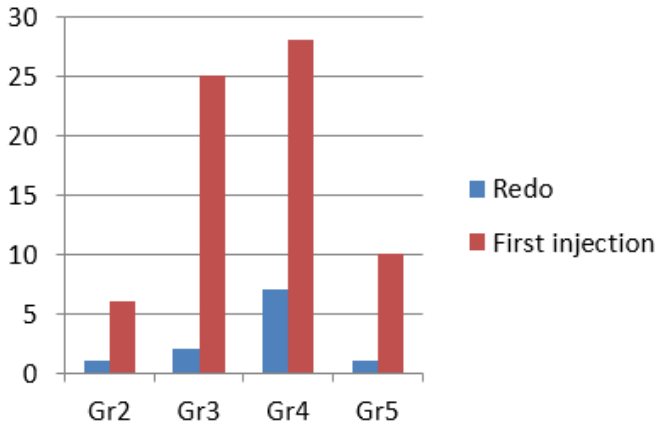


Table 3 Grade of the reflux in two groups



When the patients were evaluated in terms of bladder wall thickness and/or trabeculation, there was a significant difference (p=0.001). It was determined that the bladder wall thickness was more than 3 mm in cases where the bulking agent was displaced locally, and the trabeculation was more than in the non-displaced group. Also, it was observed that constipation was accompanied significantly more frequently where the bulking agent was changed (p=0.003). In addition, the post-voiding residue (over 20 ml) was significantly higher where the bulking agent was displaced (p=0.001).

Discussion

Cystoscopy was performed in 11 patients (13,75%) with recurrent febrile urinary tract infections and persistent reflux after the first injection in our series. In the cystoscopy evaluation of these eleven cases, it was found that the mound was displaced or not seen. Therefore, we performed the second injection in these 11 cases whose endoscopic treatment was unsuccessful in our series. Mound creation was determined by evaluating the archive images of 11 patients whose first injections were made in our clinic. We observed that it significantly increased the bladder wall thickness and trabeculation of the cases with local migration of the bulking agent compared to the other cases. Again in these cases, PVR was found to be significantly higher, and constipation was more common. With all these findings, it is possible to say that the risk of local migration of the bulking agent increases because of abnormal bladder dynamics in patients with bladder bowel dysfunction, a high amount of postvoiding residual urine, and a bladder thicker than 3 mm.

In a systematic meta-analysis evaluating the endoscopic treatment of pediatric VUR, the estima-

ted success rate for endoscopic therapy after a single injection was 78 % for grades I and II, 72 % for grade III, 63 % for IV, and 50 % for grade V VUR [19] The literature has reported that mound displacement is observed especially in cases with voiding dysfunction. Capozza et al. suggested that voiding dysfunction could contribute to endoscopic injection failure.[15] They theorized that elevated intravesical pressures could displace or shift the injection mound or cause migration from the original site of implantation. They found that a high percentage of those patients who had failed initial endoscopic treatment had evidence of voiding dysfunction on clinical evaluation. Capozza et al. reported on 45 failures with the Dx/HA copolymer and found that 60% had mound displacementand 33% had an absence of the mound on reinspection.[20] They reported a high percentage of their cases with failed dextranomer microspheres and suspected high intravesical pressures noted by voiding diaries. Trsinar et al. also observed displacement of failed injection mounds and theorized that this was due to voiding dysfunction, although no urodynamic studies or voiding diaries were presented.[21] Kirsch et al.[22] reported on 18 patients who underwent reinjection for primary failures and found that 61% had shifting of the mound away from the injection site. In the remainder of the patients, the mound was either absent or present and indeterminate. Higham-Kessleret al. reported a multi-institutional review of failures after Dx/HA injections for VUR.[23] Eighty patients (97 ureters) who failed a single injection underwent mound observation prior to a second injectionor at the time of open surgery. They found that in those with a mound abnormality, 49% of the mound had shifted, 22% of the mound was absent, and 10% there was a significant mound volume loss. In 15%, the mound was in the perfect location despite persistent VUR. Insuch a case, the question of whether the injection was made in the right place in the first application comes to mind. While the first injection images of the cases with VUR recurrence were evaluated in our study, there is no data on the evaluation of the first injection image in all these studies.When the archive images were examined retrospectively, it was determined that the mound was formed by appropriate injection in the first attempts in ourseries. In addition, voiding dysfunction was evaluated clinically in these studies. In such patients, STING and bladder rehabilitation are expected to prevent local migration of the bulking agent and recurrence. Although some studies noted no differences in the ureter or patient resolution between endoscopic Dx/HA injection techniques, the HIT or double HITprocedure is associated with better VUR correction rates.[24,25] In the Double HIT technique, coaptation in the distal of the ureter continues in the local migration that may be to wards the caudal. Therefore, injection with the Double HIT technique should be attempted first in cases with a thick trabeculate bladder wall, high amount of PVR, and accompanied constipation.[26] The most important limitation of our study is that we performed repeat cystoscopy and VCUG only in case of clinical failure. In clinically successful cases, the comparison was not possible since it is not known how the mound created by injection is.

In conclusion, the reinjection rate after the STING procedure is 13.75% in our series. Mound displacement is noted in all of these patients. Bladder wall thickness and/or trabeculation, constipation and post-voiding residue were significant factors for bulking agent displacement.

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RESEARCH ARTICLE

Ultrasonographic Assessment of Median Nerve Cross-Sectional Area in Obstetricians

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Abstract

Introductıon: : We aimed to investigate whether the median nerve cross-sectional area (MNCSA) is affected in obstetricians due to occupational reasons

Methods: In this cross-sectional study, 93 participants were included. The median nerve cross-sectional area was measured by high-resolution ultrasonography, and clinical symptoms of carpal tunnel syndrome were questioned.

Results: The measurements of MNCSA for the right hand were higher in ≥ 8 years of working experience than in < 8 years of working experience (11mm2 vs. 8 mm2, p<0.001). A significant positive moderate correlation was also between right MNCSA and working experience and daily ultrasonography practice (r=0.557; p<0.001, r=0.561; p<0.001, respectively).

Conclusion: This study showed that increased MNCSA was associated with obstetricians' working experience and daily ultrasonography practice. Considering the prevalence of carpal tunnel syndrome in specific occupational groups, MNCSA measurement by ultrasound may contribute to early diagnosis and convenient selection for further diagnostic tests.

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Introduction

Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment in the upper extremity.[1] CTS was related to constitutional, hormonal, musculoskeletal, and work-related factors.[2] A higher incidence of CTS has been reported in the working population than in the general population.[3] Manual loading, including chronic wrist flexion, repetitive movements, firm grip, excessive force, and chronic vibration, has been associated with carpal tunnel syndrome.[2] Work-related carpal tunnel syndrome has also been reported in healthcare workers, including dentists and laboratory technicians.[4,5]

The gold standard for CTS diagnosis is the patient's clinical history and exclusion of other possible causes.[1] Confirmation of diagnosis by nerve conduction study (NCS) is a conventional approach.[6,7] But, NCSs are somewhat invasive, expensive, uncomfortable, and time-consuming procedures. Recently, median nerve cross-sectional area (MNCSA) measurement by high-resolution ultrasound probes has become essential in suggesting CTS when compatible with the patient's clinical history.[8]

We thought obstetricians might be more vulnerable to CTS-related symptoms because they are exposed to repetitive and forceful maneuvers during prolonged ultrasonographic examinations. Based on these, we aimed to investigate whether the MNCSA affected in obstetricians.

Material and Methods

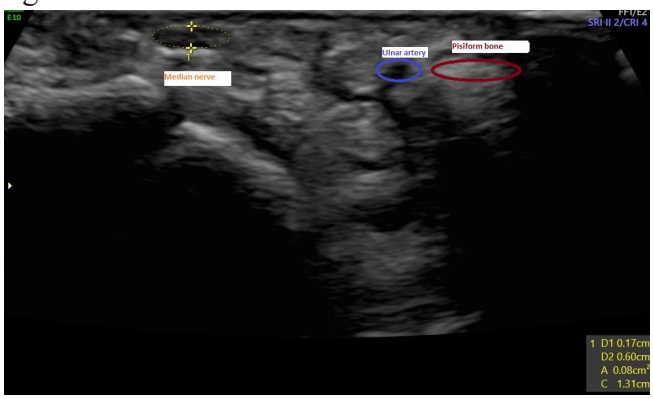
This cross-sectional study was carried out from April 2021 to January 2022 in Ankara City Hospital. Written informed consent was obtained from all participants. The study was approved by the Ministry of Health of the Republic of Turkey and the Medical Research Ethics Department of the hospital and adhered to the Declaration of Helsinki (E2-21-247).

This study included 93 participants. It enrolled obstetricians who had worked for at least one year in the Department of Obstetrics and Gynecology at Ankara City Hospital. The exclusion criteria were diabetes, thyroid diseases, rheumatoid arthritis, pregnancy, smoking, a history of orthopedic trauma in the wrists, and work experience of fewer than 12 months.

All participants replied to a self-administered questionnaire composed of two parts. The first part of the questionnaire included personal data of age, gender, height, weight, dominant hand, years of occupation, and practice time (hours) with ultrasound per day. In addition, all obstetricians in the study stated that they use their right hands during USG practice. The height and weight of the participants were converted to body mass index (BMI). The second part of the questionnaire included the presence of numbness and pain.

The ultrasonographic examination was performed by an obstetrician (D.O.) blinded to the participants' specialty and their answers to the questionnaire. The participants were examined with their forearms resting on the bed and their fingers in a semi-flexed position. A Voluson E10 ultrasound machine (Voluson™E10, GE Medical Systems, Zipf, Austria) was equipped with a 9-L 8-MHz linear array probe. The course of the median nerve in the carpal tunnel was evaluated in the sagittal and axial planes without pressing the prob. The sagittal view was used to obtain the first general view of the median nerve, but no measurement was made from this section. While getting the axial (cross-sectional) image, the probe was placed at the level of the wrist crease, and the median nerve visible in front of the flexor tendons was found. The pisiform bone location was obtained as a landmark; the probe was moved laterally to achieve a cross-sectional view of the nerve. At the level of the distal wrist crease, the cross-sectional area of the median nerve was measured. This area was measured three times, and the median value was used for analyses. As calculated in a previous study, the area calculation (measured to the nearest mm²) included a trace running just inside the echogenic surface of the median nerve.[9] An ultrasonographic image of the measurement is given in Figure 1.

Figure 1



Statistical analyses

The sample size was calculated using G Power software (version 3.1; Franz Faul, Universitat Kiel, Kiel, Germany). The effect size of 1.69 was determined

by a p-value of 0.1 and a power of 95% for the sample size. It was planned to include n=13 cases in each group.

Data analyses were performed using IBM SPSS Statistics for Windows (version 22.0, IBM, Armonk, NY, USA). Continuous variables are reported as mean ± standard deviations, and categorical values are reported as counts (percentages). The Kolmogorov-Smirnov test showed that the continuous variables did not conform to a normal distribution. The MNCSA medians and interquartile ranges (IQRs) were calculated and assessed for statistical significance using the Mann-Whitney U test. The proportions were compared using binary variables, the Fisher Exact test of independence. Spearman's correlation test was used to examine the relationships between variables. Percentile calculation was made for the working experience. All tests were considered statistically significant if the p-value was less than 0.05.

Results

This study included 93 obstetricians. Numbness, pain, and the measurement of the MNCSA were evaluated only for the right hand, as all participants stated that they used their right hand in USG practice. Table 1 shows the demographics and symptoms of the obstetricians.

Table1: Demographic and health features of the obstetricians

Age (years)		29.2 ± 4.8
BMI (kg/m²)		23.2 ± 2.8
Gender	Female	68 (73.1%)
	Male	25 (26.9%)
Working experience (years)		4.8 ± 4.1
Daily ultrasonography practice (hours)		1.8 ± 0.9
Right-hand numbness		17 (18.3%)
Right-hand pain		7 (7.5%)
Right MNCSA (mm²)		9.4 ± 1.7

a Values are presented as Mean±Standart Deviation or count (percentage)

There was no significant difference between the MNCSA of female and male obstetricians (Table 2). The data for the years of working experience are arranged from the smallest to the largest. The highest 25% of the working experience data was considered the top quartile. According to our study population, the working experience over ≥8 years was defined as the top quartile (75th percentile) for obstetricians, and the significant difference in MNCSA was reported in Table 3. When the working experience ≥8 years and <8 years were compared, the median age in the ≥8 years group was found to be significantly higher than <8 years (27 vs. 21, p<0.001). The participants' symptoms, according to their work experience, were compared in Table 4.

Table 2: Median nerve cross-sectional area (MNCSA) in the female and male obstetricians

	Female	Male	p-value
	(n: 68)	(n: 25)	
Right MNCSA(mm²)	9 (8;11)	9 (8;10)	.614

a The Mann Whitney U Test (median (IQRs))

Table 3: Differences in median nerve cross-sectional area (MNCSA) according to working experience

	≥8 years	< 8 years	p-value
	(n: 25)	(n: 68)	
Right MNCSA(mm²)	11 (10;13)	8 (8;9)	**<.001***

a The Mann Whitney U Test (median (IQRs))

Table 4: Symptoms of the participitants according to working experience

	≥8 years (n: 25)	<8 years (n: 68)	p value
Right hand numbness	6 (24%)	11 (16.2%)	.381**
Right hand pain	4 (16%)	3 (4.4%)	.081**

** Fisher's Exact Test

Table 5 represents the correlation between right MNCSA with BMI and occupational factors. No significant correlation was found between BMI and right MNCSA measurement. Still, there was a significantly positive moderate correlation between right MNCSA and working experience and daily ultrasonography practice (p<0.001, p<0.001, respectively).

Table 5: Correlation between Right MNCSA with BMI and occupational factors

	BMI (kg/m^2)	Working experience (years)	Daily practice
r value	.083	.557	.561
p value	.427	<0.001	<0.001

a Spearman's Rho Test

Discussion

Work-related risks of CTS have been reported in studies that showed occupations that involve repetitive forceful flexion and extension maneuvers of the hand/wrist.[10,11] Obstetricians often experience physical discomfort due to inappropriate hand/wrist positions and maneuvers to guide the probe during long-term USG examinations. The present study showed that obstetricians who had worked for eight years or more had a significantly higher MNCSA than those who had worked for less than eight years. This suggests the effect of increased exposure to ultrasound maneuvers in daily practice on the increase in the MNCSA. Although MNCSA was higher in those with more than eight years of experience, there was no significant difference in right-hand numbness and pain compared to those with less than eight years of experience. This suggests that changes in MNCSA associated with the years of work experience may occur before symptoms. Considering that there may be an increase in MNCSA before the symptoms of pain and numbness appear, scanning with USG allows obstetricians to be more attentive to symptom awareness.

Our study showed a significant positive correlation between increased MNCSA and the number of years of occupation and daily USG practice hours. This finding was consistent with the study that found that laboratory technicians who had symptoms of CTS had longer working hours than those who did not.[6] It was also supported by the study that found that dentists who had been practicing for many years were more likely to have symptoms.[12] The increase in MNCSA points out an association between working hours and the development of CTS symptoms.

Being overweight and obese has been shown to increase the risk of carpal tunnel syndrome, although there is insufficient evidence for the specific mechanism.[13] Our study could not find a relationship between BMI and MNCSA. This may be because the participants had the lowest BMI of 17.3 and the highest BMI of 27.8. This was consistent with previous studies, which noted a stronger association between BMI > 30 and complaints of CTS symptoms.[5,14]

Gender is frequently mentioned in studies on the etiology of CTS,[15] which have found that gender is an important factor, revealing that women were more likely than men to meet the case definition for CTS. One study showed that women had less palmar bowing and smaller carpal arch than men, so the narrow distal end of the carpal tunnel might lead to a higher incidence of CTS in women.[16] However, one study showed no significant difference in the occurrence of CTS symptoms between male and female dentists.[17] Our study found a similar MNCSA in female obstetricians compared to males. This finding was consistent with the study that showed an equal risk between the genders when occupational exposures were similar.[18] However, a previous study[19] found that the incidence was three times higher, especially in women aged 50-70. In our study, the female obstetricians were younger and fewer in number than the males, and our estimate may be inadequate to represent the prevalence among obstetricians.

Carpal tunnel syndrome is diagnosed based on clinical history and signs. The features of CTS are pain, numbness, tingling, and burning in the dispersion of the median nerve, which encloses the palmar side of the thumb, index and middle fingers, and the radial half of the ring finger.[20] Excessive chronic flexion and hyperextension of the wrist can increase pressure in the carpal tunnel. Median nerve compression causes inflammation, edema, thickening of the perineurium and endothelium, and median nerve swelling. Thus, these events can lead to median nerve dysfunction, resulting in CTS symptoms.[21] In our study, numbness and pain were higher in senior obstetricians than in residents, but there was no statistically significant difference. Previous studies have shown that there may be a dose-response relationship suggesting that hand positions involving prolonged and repetitive flexion or wrist extension increase the risk of CTS.[22] The results of our study may be because senior obstetricians have been in this occupation longer than residents. Although CTS is more common in dominant hands, the symptoms can occur in both hands. In our study, there were more right-handed participants than left-handed participants. This finding may be due to our study's higher number of right-handed obstetricians. In ad-

dition, left-handed obstetricians prefer to use their right hand during USG practice, which may explain the higher incidence of right-handed complaints in obstetricians. This is similar to the finding in a previous study that repetitive daily hand activities play an essential role in the etiology of CTS.[23] At the beginning of obstetrics training, residents should be informed about avoiding forceful wrist movements and using correct maneuvers when using the USG probe. A recent meta-analysis concluded that an increased cross-sectional area by ultrasonography has a sensitivity of 77.6% and a specificity of 86.8% for diagnosing carpal tunnel syndrome.[24] Similarly, ultrasound provides information in assessing CTS, as it can demonstrate the median nerve extension in the distal wrist crease in symptomatic individuals.[10] A previous study.[25] showed that after five minutes of appropriate teaching, the measurement of MNCSA by inexperienced ultrasound operators was consistent with that of an experienced operator. As ultrasound is a painless and quick method, it may be possible for obstetricians to scan CTS in symptomatic patients in their daily practice. Primary interventions can reduce discomfort and thus improve the quality of life of obstetricians suffering from this condition. Beyond that, the appropriate patient selection is ensured for referral to confirmatory diagnostic tests.

The strengths of our study are its novelty and prospective design. One limitation is that the study was conducted in a single center with relatively few participants. Another limitation was that the median age was higher in the group with a working experience of ≥8 years. In addition, electromyography and other tests did not confirm the diagnosis of CTS, and the participants' long-term results are unknown.

To the best of our knowledge, this is the first study to demonstrate the prevalence of CTS symptoms and measurement of MNCSA by ultrasound in a group of obstetricians. The present study showed that increased MNCSA was associated with obstetricians' working experience and daily practice hours.

In conclusion, considering the prevalence of CTS in specific occupational groups, MNCSA measurement by ultrasound may contribute to early diagnosis and convenient selection for further diagnostic tests. Due to its ease of use and low cost, ultrasound evaluation of MNCSA can be used in the daily practice of obstetricians.

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Declaration of Conflict Interests

The authors declare that they have no conflict of interest.

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Consent

Written informed consent was obtained from all participants. The study was approved by the Ministry of Health of the Republic of Turkey and the Medical Research Ethics Department of the hospital and adhered to the Declaration of Helsinki (E2-21-247).

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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RESEARCH ARTICLE

An early prognostic marker for determining disease severity in acute cholangitis: CRP/albumin ratio

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Abstract

Introduction: This study was undertaken to investigate the importance of the CRP/albumin ratio (CAR) as an early prognostic marker for determining disease severity in acute cholangitis.

Methods: A total of 366 patients aged >18 years diagnosed with acute cholangitis were included in the study. Acute cholangitis severity was determined according to the 2018 Tokyo criteria.

Results: The study population consisted of 49.2% patients with mild, 24.6% moderate, and 26.2% severe acute cholangitis. The cut-off CAR value for predicting moderate risk compared to the mild risk group was found to be >1 with 73.3% sensitivity and 76.7% specificity (AUC±SE: 0.785±0.03; +PV: 61.1%, -PV: 85.2%; p<0.001). The CAR cut-off value for predicting severe risk compared to the moderate risk group was found to be >2.9 with 71.9% sensitivity and 71.1% specificity (AUC±SE: 0.788±0.03; +PV: 72.6%, -PV: 70.3%; p<0.001). The CAR cut-off value for predicting admission to the intensive care unit (ICU) was >2.5 with 77.4% sensitivity and 74.6% specificity (AUC±SE: 0.803±0.03; +PV: 43.1%, -PV: 90.1%; p<0.001). The CAR cut-off value for predicting mortality was >2.8 with 100% sensitivity and 74.9% specificity (AUC±SE: 0.890±0.03; +PV: 19.5%, -PV: 100%; p<0.001). Compared to its components, the CAR was found to exhibit superior diagnostic performance in predicting moderate or severe risk, ICU admission, and mortality.

Conclusion: We found that the CAR is a good prognostic marker in determining the severity of acute cholangitis in the early period.

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Introduction

Acute cholangitis is an emergency clinical condition with obstruction and infection in the biliary tract resulting in mortality if not treated early.[1] It is necessary to evaluate the clinical condition of the patient, to perform imaging, and to determine the severity of the disease as soon as possible in cases of emergency admission.[2] Early determination of severity allows for immediate biliary system decompression and close clinical follow-up.[3]

The Tokyo 2018 criteria are used to determine severity in cases of acute cholangitis.[4] The Tokyo criteria are applied as part of a multisystemic evaluation with a detailed physical examination and imaging and laboratory findings.[4] For this reason, acute cholangitis cannot be classified as soon as the patient presents and emergency treatment cannot be immediately started. For this reason, early prognostic markers are needed to determine the severity in cases of acute cholangitis.

The C-reactive protein (CRP)/albumin ratio (CAR) is an inflammatory index used to determine the severity of infection and it has recently been frequently used to determine the prognosis of gastrointestinal diseases. In studies of patients with acute pancreatitis and hepatocellular carcinoma, the CAR was found to be an appropriate prognostic marker for clinical outcome.[5-8] Likewise, it was determined that the CAR is successful in predicting disease activity in cases of Crohn's disease.[9] Since acute cholangitis is an inflammatory process occurring in the biliary tract, we hypothesized that the CAR may be a good prognostic marker for this disease as well.

Therefore, this study was planned to investigate whether the CAR can serve as a prognostic marker to determine the severity of cases of acute cholangitis.

Material and Methods

This study was planned retrospectively in Ankara City Hospital's Internal Medicine Clinic, and it was approved by Ankara City Hospital's Ethics Committee (Approval Number E2-22-2195). The study was designed in accordance with good clinical practice guidelines and the 1975 Declaration of Helsinki as updated in 2013. Informed consent was obtained from all participants included in the study.

Patients aged >18 years who applied to the emergency department with symptoms such as abdominal pain, fever, jaundice, or confusion and were diagnosed with acute cholangitis upon further examination were included in the study. Such patients admitted between February 2019 and May 2022 were included in the study in order, regardless of gender. Endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography was performed in our hospital for all cases included in the study.

Patients with known rheumatic diseases, active infections in any other systems, inflammatory bowel disease, acute pancreatitis, nephrotic syndrome, antibiotic use, metabolic disease, or nutritional disorders were excluded from the study. The clinical demographic findings of the patients, laboratory findings at the time of admission, and imaging findings were accessed via the hospital's electronic information system. The discharge summary files of all patients were examined in detail. Acute cholangitis severity was determined according to the Tokyo Guidelines 2018: Diagnostic Criteria and Severity Grading of Acute Cholecystitis4. CAR values were obtained by dividing the CRP level by direct albumin.

Statistical analysis

Statistical analysis was performed using SPSS 20 for Windows (IBM Corp., Armonk, NY, USA). The normal distribution of data was evaluated by the Shapiro-Wilk test. Numeric variables with and without normal distribution were plotted as mean±standard deviation and median (25th and 75th interquartile range (IQR)), respectively. Categorical variables were given as numeric and percentile values. Chi-square, Yates correction, and Fisher exact tests were used for the comparison of categorical data. The Student t-test or Mann-Whitney U test was used for comparisons of numeric variables between two groups according to the distribution of normality. ANOVA (post hoc: Bonferroni test) or the Kruskal-Wallis H test (post hoc: Dunn test) were used for the comparison of numeric variables between Tokyo severity groups according to the distribution of normality. The relationship between CAR values and numeric variables was determined by Spearman correlation analysis. Logistic regression analysis was used to identify independent predictors of ICU admission. Cox regression analysis was used to identify independent predictors of in-hospital mortality. Evaluation of the diagnostic performance of the CAR was done by receiver operating characteristic curve analysis and cut-off values were determined according to the Youden index method. Values of $p<0.05$ (*) were considered significant in statistical analysis.

Results

The demographic and clinical characteristics of the study population and the distribution of patients according to Tokyo severity are shown in Table 1 in detail. The study population consisted of 366 patients, including 271 cases of choledocholithiasis (74%), 35 cases of benign biliary stenosis (9.6%), 48 cases of malignancy (13.1%), and 12 other causes of cholangitis (3.3%). According to Tokyo severity, 49.2% of the patients had mild, 24.6% had moderate, and 26.2% had severe acute cholangitis. It was determined that the incidence of malignant etiology increased as the Tokyo severity increased. In the severe risk group, the length of stay in the service was longer, the frequency of hospitalization in the ICU was higher, and the duration of hospitalization was longer. It was determined that the mean albumin level decreased as the Tokyo severity increased, while the median CRP and median CAR values increased.

Table 1. Demographic and clinical findings of patients with acute cholangitis

Variables	All population n=366	TOKYO Severity Mild n=180	Moderate n=90	Severe n=96	p
Age, years	65.7±17.2	**57.0±16.2**	74.0±15.4	74.2±12.1	<0.001*
Gender, n(%)					
Female	176(48.1)	87(48.3)	45(50.0)	44(45.8)	0.847
Male	190(51.9)	93(51.7)	45(50.0)	52(54.2)	
Etiology, n(%)					
Benign	318(86.9)	164(91.1)	77(85.6)	77(80.2)	0.035*
Malign	48(13.1)	16(8.9)	13(14.4)	19(19.8)	
Hospitalization, n(%)					
Service	342(93.4)	180(100.0)	84(93.3)	78(81.3)	<0.001*
Length of stay, day	9(6-12)	8(6-10.5)	8.5(6-12)	**10(7-16)**	0.029*
ICU	84(23.0)	3(1.7)	22(24.4)	59(61.5)	<0.001*
Length of stay, day	6(4-10.5)	**8(3-26)**	5(3-9)	6(4-12)	0.235
Composite outcome, n(%)	50(13.7)	5(2.8)	10(11.1)	35(36.5)	<0.001*
Mortality, n(%)	25(6.8)	5(2.8)	4(4.4)	16(16.7)	<0.001*
Duration of hospitalization, day	9(6-14)	8(6-10.5)	9(6-14)	**13(8-17.5)**	<0.001*
White blood count (10^3/μL)	10.1(7.5-12.9)	**9(7-10.8)**	12.6(9.7-15.8)	11.6(8.2-15.2)	<0.001*
Platelet (10^3/μL)	239(189-308)	**276(216.5-330.5)**	**234(193-287)**	**162.5(106-234.5)**	<0.001*
Hemoglobin (g/dL)	13.3±2.0	**13.7±1.9**	**13.1±1.8**	**12.5±2.2**	<0.001*
Hematocrit (%)	40.2±5.8	**41.5±5.3**	39.2±5.3	38.6±6.5	<0.001*
UREA (mg/dl)	38(25-53)	**28.5(21-38)**	**40(29-51)**	**64.5(47-88)**	<0.001*
Sodium (mEq/L)	137.7±3.6	138.5±3.1	137.8±3.8	**136.3±4.2**	<0.001*
Potassium (mEq/L)	4.1±0.5	4.1±0.4	4.1±0.5	4.0±0.6	0.606
Calcium (mEq/L)	8.9±0.7	**9.2±0.5**	**8.8±0.7**	**8.4±0.7**	<0.001*
ALT (U/L)	207.5(107-348)	248(133.5-398.5)	184(115-337)	**133(70.5-242.5)**	<0.001*
AST (U/L)	182.5(98-314)	189(103-329.5)	205(112-330)	141.5(82-259.5)	0.061
ALP (U/L)	256.5(185-423)	243.5(175-396.5)	291.5(199-447)	273(195.5-371.5)	0.136
GGT (U/L)	435.5(248-674)	497(264.5-736)	477(295-740)	**333(180-530.5)**	<0.001*
Total bilirubin (mg/dl)	4.7(2.9-7.6)	**3.6(2.3-6.1)**	5.9(3.8-8.7)	5.6(4-9.5)	<0.001*
Direct bilirubin (mg/dl)	3.2(1.9-5.3)	**2.3(1.3-4.2)**	4.1(2.5-5.8)	4.1(2.8-6.8)	<0.001*
Albumin (g/dl)	39.4±5.7	**42.3±4.2**	**38.7±5.2**	**34.7±5.2**	<0.001*
CRP (mg/L)	45(20-95)	**24(13-41.5)**	**63(40-99)**	**117(62.5-180.5)**	<0.001*
Procalcitonin (μg/L)	0.5(0.2-5.9)	**0.2(0.1-0.5)**	**1.1(0.3-7.4)**	**5.5(1.1-36)**	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Bold characters show the difference between groups. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CAR, CRP to albumin ratio; CRP, C reactive protein; GGT, gamma glutamyl transferase; ICU, intensive care unit; INR, international normalized ratio

The mean age, malignancy etiology, severe risk ratio, and mortality rate were higher among patients admitted to the ICU compared to non-admitted patients. Median CAR values were found to be higher among patients admitted to the ICU compared to those who were not admitted (3.4 vs. 1.3; p<0.001) (Table2). The in-hospital mortality rate was 6.8% (n:25).

Table 2. Factors associated with hospitalization of the intensive care unit in patients with acute cholangitis

Variables	ICU admission No n=282	Yes n=84	p
Age, years	62.5±17.5	76.3±10.8	<0.001*
Gender, n(%)			
Female	136(48.2)	40(47.6)	0.922
Male	146(51.8)	44(52.4)	
Etiology, n(%)			
Benign	254(90.1)	64(76.2)	0.001*
Malign	28(9.9)	20(23.8)	
TOKYO severity, n(%)			
Mild	177(62.8)	3(3.6)	
Moderate	68(24.1)	22(26.2)	<0.001*
Severe	37(13.1)	59(70.2)	
Hospitalization of service, n(%)	282(100.0)	60(71.4)	<0.001*
Length of stay, day	8(6-11)	11(6.5-16.5)	0.075
Composite outcome, n(%)	4(1.4)	46(54.8)	<0.001*
Mortality, n(%)	4(1.4)	21(25.0)	<0.001*
Duration of hospitalization, day	8(6-11)	14(9-19.5)	<0.001*
White blood count (10^3/μL)	9.7(7.2-12.3)	12(9-15.4)	<0.001*
Platelet (10^3/μL)	249(199-312)	206.5(135-291.5)	0.001*
Hemoglobin (g/dL)	13.4±2.0	12.8±1.9	0.029*
Hematocrit (%)	40.4±5.8	39.2±5.8	0.077
UREA (mg/dL)	32(23-47)	55.5(41.5-81)	<0.001*
Sodium (mEq/L)	137.9±3.5	137.1±4.1	0.076
Potassium (mEq/L)	4.1±0.5	4.1±0.6	0.520
Calcium (mEq/L)	9.0±0.7	8.5±0.7	<0.001*
ALT (U/L)	224(115-371)	162.5(82-262)	0.005*
AST (U/L)	184.5(103-317)	176.5(92.5-308)	0.619
ALP (U/L)	247(179-403)	311.5(200-441)	0.093
GGT (U/L)	445(251-708)	375(237-565.5)	0.097
Total bilirubin (mg/dl)	4.3(2.7-7.1)	6(4.3-9.4)	<0.001*
Direct bilirubin (mg/dl)	2.9(1.7-4.8)	4.5(3-6.8)	<0.001*
Albumin (g/dl)	40.6±5.3	35.6±5.3	<0.001*
CRP (mg/L)	37(17-71)	105.5(52-179)	<0.001*
Procalcitonin (μg/L)	0.3(0.1-3.9)	3.1(0.6-19.7)	<0.001*
INR	1.2±0.4	1.4±0.4	<0.001*
CAR	0.9(0.4-1.8)	3.2(1.5-5.0)	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CAR, CRP to albumin ratio; CRP, C reactive protein; GGT, gamma glutamyl transferase; ICU, intensive care unit; INR, international normalized ratio

No significant correlation was found between Tokyo severity and mortality, but ICU hospitalization was associated with an increased risk of mortality (HR: 7.14; p<0.001). Decreases in hemoglobin, hematocrit, sodium, calcium, and albumin levels were found to be associated with an increased risk of mortality. Increases in urea, CRP, and CAR values were associated with an increased risk of mortality (Table 3).

Table 3. Factors associated with in-hospital mortality in patients with acute cholangitis

Variables	Survival		Univariable Regression			
	Alive n=341	Exitus n=25	HR	95% CI lower	95% CI upper	p
Age, years	65.0±17.3	74.8±13.8	1.02	0.99	1.05	0.216
Gender, n(%)						
Female	168(49.3)	8(32.0)	ref			
Male	173(50.7)	17(68.0)	1.14	0.47	2.78	0.773
Etiology, n(%)						
Benign	254(90.1)	64(76.2)	ref			
Malign	28(9.9)	20(23.8)	6.68	2.76	16.15	<0.001*
TOKYO severity, n(%)						
Mild	175(51.3)	5(20.0)	ref			
Moderate	86(25.2)	4(16.0)	1.01	0.27	3.81	0.993
Severe	80(23.5)	16(64.0)	2.28	0.79	6.62	0.129
Hospitalization, n(%)						
Service	326(95.6)	16(64.0)	0.05	0.02	0.13	<0.001*
Length of stay, day	8(6-12)	16(10.5-23)	0.88	0.81	0.96	0.003
ICU	63(18.5)	21(84.0)	7.14	2.32	21.96	<0.001*
Length of stay, day	6(4-10)	6(3-14)	0.97	0.92	1.02	0.215
Composite outcome, n(%)	25(7.3)	25(100.0)	29.30	2.09	169.20	0.006*
Duration of hospitalization, day	9(6-13)	14(7-29)			-	
White blood count (10^3/μL)	10(7.5-12.8)	11.8(8.7-15.3)	1.02	0.97	1.08	0.468
Platelet (10^3/μL)	240(193-307)	217(158-355)	1.00	1.00	1.01	0.115
Hemoglobin (g/dL)	13.4±2.0	11.5±2.0	0.72	0.60	0.87	<0.001*
Hematocrit (%)	40.5±5.6	35.3±6.0	0.90	0.84	0.96	<0.001*
UREA (mg/dl)	36(25-51)	58(40-87)	1.02	1.01	1.03	<0.001*
Sodium (mEq/L)	138.0±3.5	134.6±3.9	0.81	0.73	0.90	<0.001*
Potassium (mEq/L)	4.1±0.5	4.2±0.8	1.30	0.63	2.65	0.479
Calcium (mEq/L)	8.9±0.7	8.2±0.7	0.40	0.23	0.71	0.002*
ALT (U/L)	224(121-358)	76(38-121)	0.99	0.99	1.00	0.004*
AST (U/L)	188(103-319)	98(66-218)	1.00	0.99	1.00	0.161
ALP (U/L)	250(184-389)	423(304-631)	1.00	1.00	1.00	0.816
GGT (U/L)	439(251-691)	327(169-574)	1.00	1.00	1.00	0.441
Total bilirubin (mg/dl)	4.6(2.9-7.3)	9.1(4.5-11.7)	1.02	0.97	1.07	0.492
Direct bilirubin (mg/dl)	3.2(1.9-5.1)	6.8(3.6-9.2)	1.03	0.96	1.10	0.389
Albumin (g/dl)	40.1±5.1	30.8±5.7	0.83	0.77	0.88	<0.001*
CRP (mg/L)	42(19-83)	112(79-161)	1.01	1.00	1.01	0.021*
Procalcitonin (μg/L)	0.5(0.1-5.5)	1.4(0.7-13)	1.00	0.98	1.01	0.747
INR	1.2±0.4	1.5±0.5	0.97	0.51	1.85	0.937
CAR	1.1(0.5-2.2)	3.8(2.8-5.2)	1.35	1.14	1.59	<0.001*

*p<0.05 indicates statistical significance. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CAR, CRP to albumin ratio; CRP, C reactive protein; GGT, gamma glutamyl transferase; ICU, intensive care unit; INR, international normalized ratio

Positive correlations were observed between CAR values and age (r=0.466; p<0.001), length of hospital stay (r=0.238; p<0.001), white blood cell (WBC) count (r=0.326; p<0.001), and procalcitonin (r=0.657; p<0.001). The relationships between CAR values and laboratory findings are shown in Table 4.

Table 4. Factors associated with CAR levels in patients with acute cholangitis

Variables	CAR	
	r	p
Age	0.466	<0.001*
Length of stay in service	0.127	0.019*
Length of stay in ICU	0.088	0.427
Duration of hospitalization	0.238	<0.001*
White blood count	0.326	<0.001*
Platelet	-0.377	<0.001*
Hemoglobin	-0.237	<0.001*
Hematocrit	-0.244	<0.001*
UREA	0.551	<0.001*
Sodium	-0.314	<0.001*
Potassium	-0.051	0.329
Calcium	-0.468	<0.001*
ALT	-0.295	<0.001*
AST	-0.207	<0.001*
ALP	0.096	0.066
GGT	-0.099	0.057
Total bilirubin	0.239	<0.001*
Direct bilirubin	0.267	<0.001*
Procalcitonin	0.657	<0.001*
INR	0.553	<0.001*

*p<0.05 indicates statistical significance. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CAR, CRP to albumin ratio; CRP, C reactive protein; GGT, gamma glutamyl transferase; ICU, intensive care unit; INR, international normalized ratio

In the multivariate regression model, in which the variables associated with Tokyo severity were included, the independent predictors of moderate risk compared to mild risk were found to be older age, higher WBC count, and higher total bilirubin and CAR values. Independent predictors of severe risk compared to moderate risk were increased procalcitonin, urea, and CAR values. According to this model, compared to the group with mild risk, a 1-unit increase in the CAR increased the likelihood of moderate risk by 1.75 times (OR: 1.75; p=0.003), while compared to moderate risk, it increased the likelihood of severe risk by 1.63 times (OR: 1.63; p<0.001) (Table 5).

Table 5. Independent predictors for endpoints

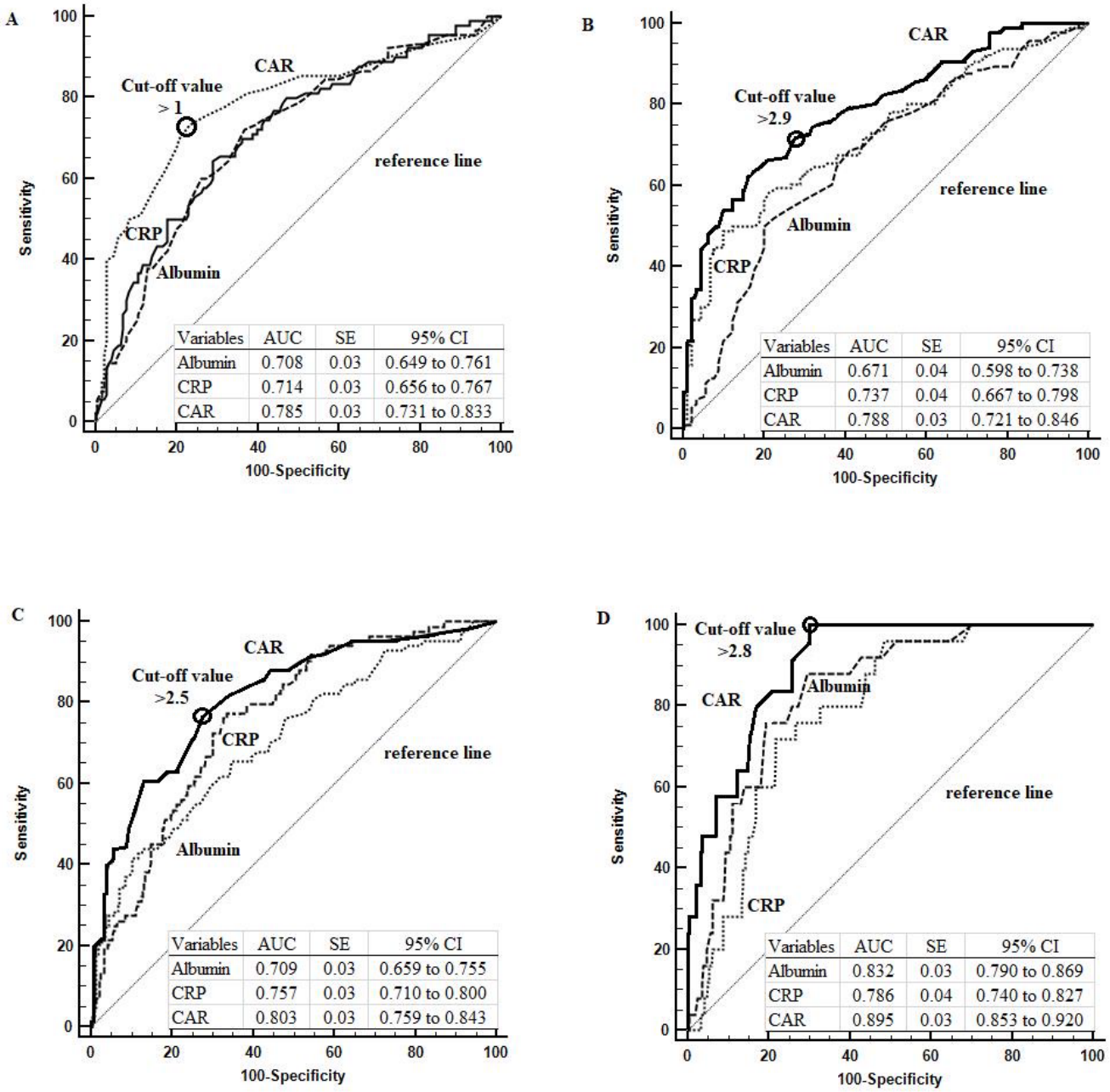
Variables	OR	95% CI Lower	95% CI Upper	p
TOKYO Severity				
Moderate (ref: mild)				
Age	1.06	1.03	1.09	<0.001*
White blood count	1.23	1.12	1.35	<0.001*
Total bilirubin	1.15	1.06	1.24	0.001*
CAR	1.75	1.21	2.53	0.003*
		Nagelkerke R^2= 0.537, p< 0.001		
Severe (ref: moderate)				
Procalcitonin	1.04	1.02	1.08	0.004*
UREA	1.03	1.01	1.04	0.001*
CAR	1.63	1.27	2.08	<0.001*
		Nagelkerke R^2= 0.493, p< 0.001		
ICU admission				
Age	1.04	1.01	1.07	0.006*
Tokyo Severity				
Mild	ref			
Moderate	9.09	2.45	33.78	0.001*
Severe	30.67	8.18	115.02	<0.001*
Procalcitonin	1.02	1.01	10.3	0.035
CAR	1.27	1.06	1.53	0.011*
		Nagelkerke R^2= 0.543, p< 0.001		
Mortality	HR			
ICU admission	3.47	1.08	9.71	0.028*
UREA	1.02	1.01	1.03	0.037
CAR	1.36	1.14	1.63	0.001*
		-2Log Likelihood=168.6. p<0.001		

*p<0.05 indicates statistical significance.
Abbreviations: CI, confidence interval; CAR, CRP to albumin ratio; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio;

Older age, increased Tokyo severity, and increased procalcitonin and CAR values were determined as independent predictors of ICU admission. Accordingly, it was determined that a 1-unit increase in the CAR increased the risk of admission to the intensive care unit by 1.27 times (OR: 1.27; p=0.011). ICU admission, increased urea, and increased CAR were independent predictors of mortality. It was determined that a 1-unit increase in the CAR increased the risk of mortality by 1.36 times (OR: 1.36; p=0.001).

The cut-off value of the CAR in predicting moderate risk compared to mild risk was found to be >1 with 73.3% sensitivity and 76.7% specificity (AUC±SE: 0.785±0.03; +PV: 61.1%, -PV: 85.2%; p<0.001) (Figure 1A). The cut-off value of the CAR in predicting severe risk compared to moderate risk was found to be >2.9 with 71.9% sensitivity and 71.1% specificity (AUC±SE: 0.788±0.03; +PV: 72.6%, -PV: 70.3%; p<0.001) (Figure 1B). The cut-off value of the CAR in predicting admission to the ICU was >2.5 with 77.4% sensitivity and 74.6% specificity (AUC±SE: 0.803±0.03; +PV: 43.1%, -PV: 90.1%; p<0.001) (Figure 1C). The cut-off value of the CAR in predicting mortality was >2.8 with 100% sensitivity and 74.9% specificity (AUC±SE: 0.890±0.03; +PV: 19.5%, -PV: 100%; p<0.001) (Figure 1D). Compared to its components, the CAR was found to exhibit superior diagnostic performance in predicting moderate or severe risk, ICU admission, and mortality (Figure 1).

Figure 1. Diagnostic performance assessment of CAR values in predicting moderate (A) and severe (B) Tokyo severity, ICU admission (C), and in-hospital mortality (D)



Discussion

In the present study, we investigated whether the CAR could predict severity as an early prognostic marker in acute cholangitis. To our knowledge, this study is the first of its kind in this field. We determined that the CAR, which can be calculated shortly after admission to the emergency department, successfully predicts severity among patients with acute cholangitis. It also proved to be a good prognostic marker for the prediction of ICU admission and mortality.

Determining the severity of acute cholangitis is very important in making decisions about the type of patient follow-up, prognosis, treatment strategies, and the timing of biliary decompression.[10] The 2018 Tokyo criteria provide convenience to the clinician in the management of acute cholangitis. According to the guidelines, in the event of failure of any organ (kidneys, lungs, heart, liver, hematological system, etc.), the patient is considered to have severe acute cholangitis, while moderate acute cholangitis is considered in the presence of deterioration in clinical and laboratory parameters. Mild acute cholangitis is diagnosed for patients who are not classified as having moderate or severe cases.[4]

We could not find any previous study examining the prognostic significance of the CAR in acute cholangitis. In a study conducted with acute pancreatitis patients, however, it was determined that the CAR was a prognostic marker associated with mortality.[6] In a study conducted with patients with Crohn's disease, it was determined that CAR values were associated with the Crohn's disease activity index.[9] In a study of ulcerative colitis, it was determined that the CAR was closely related to clinical disease severity.[11] The CAR was also found to be closely related to prognosis in cases of esophagus, stomach, colorectal, and liver malignancies and cholangiocarcinoma.[7,12-15]

In the literature, there are studies on procalcitonin, an inflammatory marker similar to the CAR, and acute cholangitis. In these studies, it was concluded that the level of procalcitonin increases in acute cholangitis and may be an early prognostic marker in determining the severity of acute cholangitis.[16-19] Similarly, in a study conducted on presepsin, an inflammatory marker, it was concluded that presepsin is a good marker for determining the severity of acute cholangitis.[20]

In our study, CAR values were found to differ among mild, moderate, and severe stages of acute cholangitis. Along with those results, relationships were found between many parameters of the 2018 Tokyo, Sepsis-Related Organ Failure Assessment (SOFA), and Systemic Inflammatory Response Syndrome (SIRS) criteria and CAR values. For example, positive correlations were found between CAR values and age, WBC count, urea, total bilirubin, direct bilirubin, indirect bilirubin, procalcitonin, and international normalized ratio values, and negative correlations were found for platelet count, hemoglobin, and hematocrit. These results show that the CAR is a marker that works similarly to the 2018 Tokyo, SOFA, and SIRS criteria.

Many studies have shown that procalcitonin is a good marker in the classification of acute cholangitis.[14-17] In our study, while procalcitonin did not predict moderate acute cholangitis in regression analysis, it predicted severe acute cholangitis with an OR lower than that of the CAR. Since procalcitonin is not a molecule that can be studied directly in all centers, it is a less useful predictor than the CAR.

In our study, it was determined that the CAR, with different cut-off values, classified acute cholangitis in accordance with the 2018 Tokyo guidelines. In regression analysis, the CAR and the 2018 Tokyo criteria were determined as parameters that could predict admission to the ICU. While the CAR performed well in predicting mortality, the Tokyo criteria were not associated with mortality. Based on these results, we can say that the CAR, which is a marker that can be calculated shortly after a patient's entry to the emergency room, can be used to classify acute cholangitis similarly to the 2018 Tokyo criteria and to predict admission to the ICU, but it is superior to the Tokyo criteria in that it can also predict mortality.

The main limitation of our study is its retrospective nature. However, the systematic recording of patients' clinical and demographic data, physical examination findings, laboratory findings, and imaging results minimized that limitation. Another limitation is that it was not known when acute cholangitis began in these cases or how long after the onset of this clinical condition the patients presented. Another limitation is that we do not know how CAR values changed during the course of acute cholangitis, i.e., from hospitalization to the clinical outcome.

Conclusion

In this study, we found that the CAR is a good prognostic marker for the detection of severe acute cholangitis in the early period. We concluded that the CAR is superior to other prognostic mar-

kers in that it predicts early admission to the ICU and mortality in cases of acute cholangitis. Since the CAR can be easily calculated, obtained quickly, and is a cheap and practical method, it provides great convenience for the clinician to determine the severity of acute cholangitis at the time of the patient's first application. We think that it would be valuable to continue studying the diagnostic performance of this marker in prospective studies to support the wider use of the CAR in clinical practice.

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CASE REPORT

Neuromyelitis Optica associated with Myastenia Gravis: A Case Report

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Abstract

Neuromyelitis optica (NMO, Devic syndrome) is an inflammatory, demyelinating central nervous system disorder typically associated with optic neuritis and transverse myelitis involving three or more segments in the spinal cord. Myasthenia Gravis (MG) is an autoimmune disease characterized by weakness in fatiguing muscles due to impaired neuromuscular transmission. NMO can coexist with autoimmune diseases, and its association with myasthenia gravis is common. Studies in existing patients with both NMO and MG support that MG symptoms often appear earlier and tend to be milder. Here, we present a case of a 45-year-old woman with concurrent NMO and MG, aligning with findings from previous studies.

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Introduction

Neuromyelitis optica (NMO, Devic syndrome) is an inflammatory, demyelinating central nervous system disorder typically associated with optic neuritis and transverse myelitis involving three or more segments in the spinal cord. Despite being recurrent, it differs from Multiple Sclerosis in its more severe course, less involvement of the brain, and association with a longitudinally extensive lesion in the spinal cord. Additionally, NMO is linked to the serum autoantibody NMO-IgG, targeting aquaporin-4, and is recurrent in over 90% of patients.[1] Pathophysiology: Aquaporin-4 immunoglobulin-G (IgG) is thought to bind to aquaporin-4 on astrocytes, leading to complement-dependent cytotoxicity, which in turn results in leukocyte infiltration, cytokine release, and disruption of the blood-brain barrier.[2] These initial events contribute to oligodendrocyte death, myelin loss, neuronal death, and consequently, clinical neurological impairment. Especially in regions where aquaporin-4 expression is high, such as the optic nerve and spinal cord, these autoantibodies cause damage and inflammation, leading to blindness, paralysis, and chronic disability.[3] Myasthenia Gravis (MG), on the other hand, is an autoimmune disease characterized by weakness in fatiguing muscles due to impaired neuromuscular transmission.[4] NMO can coexist with autoimmune diseases, and the association with myasthenia gravis is common. Autoimmune myasthenia gravis is 100 times more common in patients with NMO compared to the general population (2% vs. 0.02%).[5] A case is presented where MG symptoms were milder than NMO symptoms in cases of coexistence of MG and NMO.

Case

A 45-year-old female patient presented to the neurology clinic with a complaint of decreased vision in the left eye for the last two days. In her medical history, she reported experiencing weakness throughout the body and drooping of the right eyelid towards the evening while performing daily activities in 2011. Following investigations, she was diagnosed with MG based on a positive Anti-Ach receptor antibody result. The cranial MRI at that time was normal, and repetitive EMG revealed neuromuscular junction involvement consistent with the diagnosis, along with a positive Anti-Ach receptor antibody in blood tests. The patient was started on Pyridostigmine bromide 60 milligrams (mg) tablet, 360 mg/day, and Azathioprine 25 mg tablet, 75 mg/day during that period..Upon further detailing the patient's history, it was found that in 2019, she had a sudden onset of complete vision loss in the right eye and balance disturbance. The family history of the patient was unremarkable. Neurological examination revealed ptosis in the right eye and increased deep tendon reflexes. A relative afferent pupillary defect was diminished on the right side. Examination of the fundus of the eye revealed a pale right optic disc and a slightly swollen left optic disc. The patient's visual acuity was measured at counting fingers from 30 centimeters in the left eye, while it was measured as 20/20 in the right eye. There was concentric narrowing in the arcuate region of the left eye's visual field. The patient was classified as Class 1 in the Myasthenia Gravis Foundation of America (MGFA) classification.For central pathologies, cranial, cervical, and orbital MRIs were performed. Orbital MRI, after intravenous contrast injection, revealed contrast enhancement in both the right and left optic nerves (Figure-1). Cranial and spinal imaging were unremarkable.

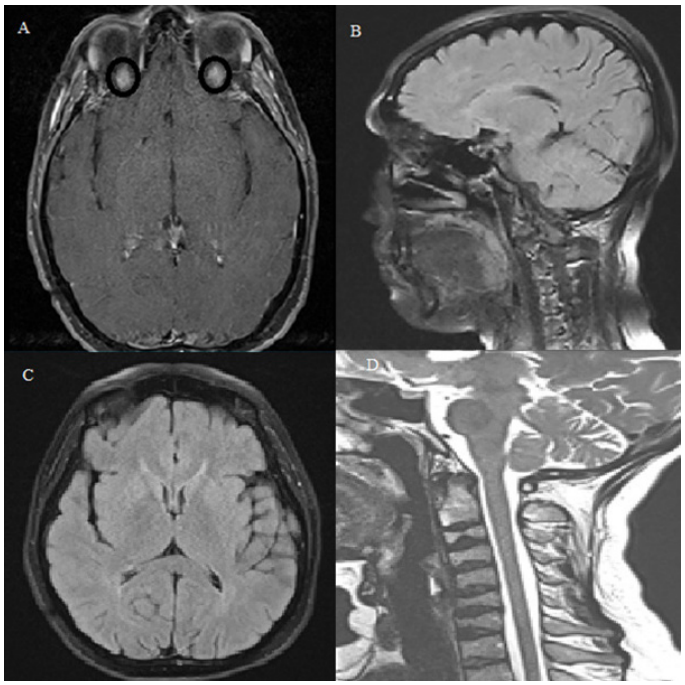

Figure-1: A: The patient's T2 sequence contrast-enhanced orbital MRI imaging shows bilateral contrast uptake in the optic nerve in the transverse section, suggesting the presence of optic neuritis with some degree of uncertainty indicated by the question mark.
B,C,D: The patient's T2 sequence contrast-enhanced brain MRI and cervical MRI images were obtained. No neuropathological findings were detected.

Considering the patient's history of bilateral vision loss at different times, a possible coexistence of demyelinating disease and MG was considered. Vasculitic, infectious, and paraneoplastic markers were found to be negative. Oligoclonal band and NMO-MOG antibodies were requested. The Aquaporin-4 receptor result was reported positive. Our patient met the diagnostic criteria for NMO with the positivity of one of the absolute criteria (optic neuritis) and the presence of aquaporin-4 antibody positivity in the serological examination. Additionally, contrast enhancement was observed in bilateral optic nerves on orbital MRI, serving as supporting evidence. In the current patient, the coexistence of NMO and MG was considered in the context of an acute NMO presentation, and the patient was treated with 1000 mg pulse steroids for 5 days. Oral corticosteroid treatment was continued as maintenance therapy. The patient's vision complaint partially improved. One month after treatment, the patient's visual acuity in the left eye improved to 20/30, while it remained normal in the right eye. During the follow-up period, there was no worsening of symptoms observed, and the symptoms of MG were under control.

Discussion

Myasthenia Gravis (MG) and neuromyelitis optica (NMO) are autoimmune disorders mediated by humoral immunity targeting acetylcholine receptor (AChR) and aquaporin-4 (AQP4), respectively. MG affects the peripheral neuromuscular junction (NMJ) outside the central nervous system (CNS), while NMO primarily impacts the central nervous system. Due to autoimmune channelopathies in both the peripheral and central nervous systems, MG and NMO share many similarities: they develop based on the relationship between genetic factors and environmental influences, both are mediated by T cell-mediated, B cell-dependent immunopathology, and are influenced by the effects of antibodies and complement. It is now recognized that complement dysfunction is central to the pathogenesis. Human leukocyte antigen (HLA) genes are associated with these two autoimmune diseases in terms of genetic factors. Antigen-presenting cells (APCs) and lymphocytes demonstrate the importance of specific adaptive autoimmune responses in transferring signals from the activated innate immune system, contributing to the establishment of long-lasting autoimmune memory. Epigenetic mechanisms link environmental factors and genetics in the disease, including microRNAs, DNA methylation, and others.[6] When environmental factors are evaluated, many such factors, including diet, vitamin D, and microbiota, contribute as predisposing factors to the onset and severity of autoimmune diseases, or they may exacerbate as triggering factors, such as infections, pollutants, and pharmacological molecules.[7,8] These diseases share some common features, including genetic predispositions, environmental factors, impaired tolerance, collaboration of T cells and B cells, and T helper cell (Th1/Th2/Th17) dysregulations, abnormal cytokine, antibody secretion, complement activation, among others. However, some aspects of the immune mechanisms differ. Both targets (AChR and AQP4) are expressed in the periphery and CNS, but MG mainly affects the NMJ outside the CNS, while NMO affects the central nervous system.[9] Relationships between NMO and other autoimmune diseases exist, with 30% of NMO patients having a concurrent autoimmune disease, and 40% having other autoantibodies without a distinct accompanying disease.[1] Common coexisting diseases with NMO include systemic lupus erythematosus, MG, and antiphospholipid syndrome.[10]

The coexistence of MG and NMO among these mentioned diseases is of particular interest to researchers because it is more frequent than expected in the general population.[8] In a study of 177 NMO patients, 2% had accompanying MG, and 11% had AChR antibodies.[11] In another study involving 164 MG patients, 10-15% had CNS involvement resembling NMO, and half of them had positive AQP4-IgG.[12] The course of MG in the context of this coexistence is generally benign, but central nervous system involvement, especially when accompanied by thymomas, can be potentially more severe.[8,11] In most cases, MG symptoms develop before the onset of NMO, and early-onset AChR-MG is often detected in these patients.[8]

Studies support that AQP4-IgG positive NMO is more associated with MG, and they argue that thymectomy may predispose to the development of NMO.[13] In this association, since MG symptoms typically start first, performing thymectomy in patients with existing thymic pathology may exacerbate NMO symptoms. This situation could pose challenges in treatment. Especially in MG patients presenting with atypical symptoms, the coexistence of NMO should be considered.

Conclusion

Neuromyelitis optica and Myasthenia Gravis are two diseases that can coexist through autoimmune mechanisms. In these patients, MG symptoms typically start earlier and have a better prognosis.

In the presented case, the diagnosis of MG was made in 2011 before the diagnosis of NMO, and the clinical history of the patient shows a more favorable course for MG, consistent with findings in clinical studies. Following the diagnosis of the disease, Azathioprine treatment has been completely discontinued, and the use of Pyridostigmine HCl has been reduced from 360 mg/day to 120 mg/day, allowing the patient to maintain their daily life. However, it should not be forgotten that NMO can have an aggressive course, especially in cases of atypical MG symptoms. Therefore, this association should be kept in mind.

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CASE REPORT

Urothelial cell carcinoma of bladder in the second trimester of pregnancy: A clinical case presentation

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Abstract

Bladder cancer in pregnant women is a rare and challenging condition to manage due to its potential impact on both the mother and the fetus. Bladder cancer may be incidentally detected or manifest with macroscopic hematuria and irritative symptoms. However, the physiological processes occurring during pregnancy, influenced by hormonal changes, can complicate the diagnosis by masking these symptoms. Due to the limited number of cases reported in the literature, there is a lack of guideline recommendations for the follow-up and treatment of bladder tumors in pregnant individuals.

In this case report, we aim to present a patient with transitional cell urothelial cancer who presented with macroscopic hematuria in the second trimester, a detected mass in bladder on ultrasound, and underwent complete resection by bipolar transurethral resection.

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Introduction

Over the cours of pregnancy, cancer is a rare condition. Breast malignancy, cervical malignancy, Hodgkin's disease, malignant melanoma, and leukemias being the most commonly observed at the same time as this period.[1] Bladder cancer (BC), however, is extremely rare. Diagnosing it can be challenging during pregnancy due to the physiological changes, which may overlap with symptoms of hematuria, irritative voiding, or bladder outlet symptoms. Urinary ultrasonography, cystoscopy, and magnetic resonance imaging (MRI) are regarded as reliable diagnostic methods throughout pregnancy.[2] However, careful evaluation is required due to the displacement of the bladder caused by the enlargement of the uterus and physiological hydronephrosis.

Diagnosing and managing malignancy during pregnancy is challenging due to its impact on both the mother and the fetus. Specific treatment guidelines and intervention indications for BC during pregnancy have not been established, given its rarity and the limited number of case reports in the literature.

Case

A 28-year-old pregnant patient at 22 weeks of gestation (Gravida 2, Parity 1, Abortion 0) presented to the urology clinic with painless, macroscopic hematuria with clots for the last month. She had no additional medical history, medication use, or smoking history. Abdominal examination revealed a uterus compatible with a 22-week gestation. Complete blood count revealed Hb: 10.9 g/dl, Htc: 34.3%. Urinalysis was consistent with macroscopic hematuria. Urine culture showed no growth. Urinary ultrasonography detected a lesion in the left lateral wall of the bladder, measuring 28x22x25 mm, showing papillary extension into the bladder, with irregular borders and vascularity. The upper urinary system was normal. At 23 weeks of gestation, cystoscopy was performed under spinal anesthesia, revealing a tumoral lesion consistent with the ultrasonography findings (Figure 1). The tumor was completely resected with bipolar transurethral resection (Figure 2). The histopathological diagnosis was non-invasive, low-grade urothelial carcinoma (pTa, LG). No intraoperative or postoperative complications were observed. Subsequent cystoscopies in the early postpartum period and at 3 months showed no recurrence. The patient was included in the routine BC follow-up program after delivery.

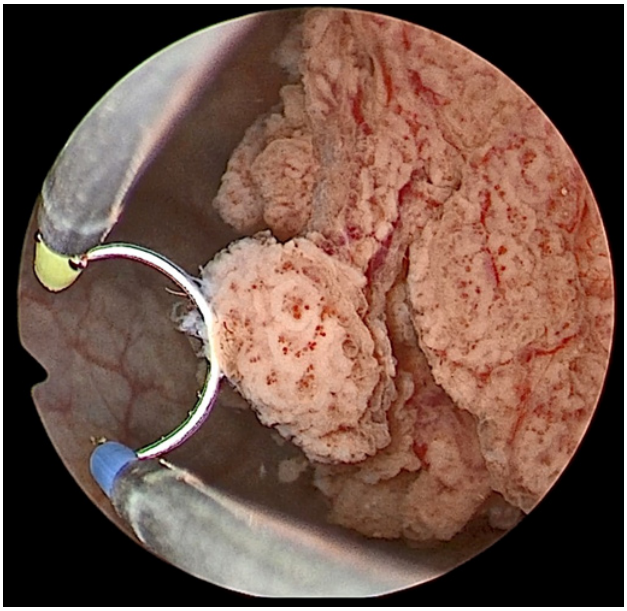

Figure 1: Bladder papillary urothelial carcinoma located on the left lateral wall. Bipolar resectoscope loop width 5 mm.

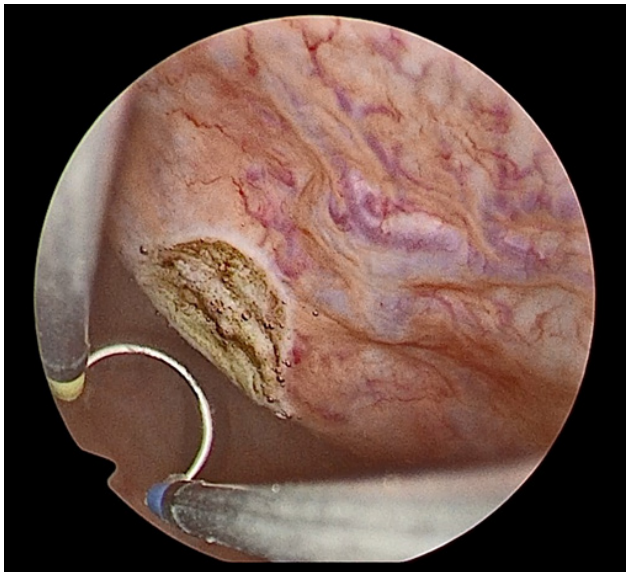

Figure 2: Completely resected urothelial carcinoma tumor base.

Discussion

Bladder cancer is predominantly observed in the elderly, less frequently in young individuals, and extremely rarely in pregnant women. The first documented case of bladder tumor during pregnancy dates back to 1927, and approximately 50 cases have been reported in the literature to date.[3]

While BC during pregnancy may present symptoms such as irritative symptoms, microscopic or macroscopic hematuria, recurrent urinary tract infections, and bladder outlet obstruction, it can also be in-

cidentally detected during routine transvaginal ultrasonography.[4–6] In this case, BC became symptomatic with the classical symptom of macroscopic hematuria.

In cases where malignancy is suspected, ultrasonography is preferred as the safest imaging method for pregnant women. Even if the diagnosis is incidentally made during routine follow-up with transvaginal ultrasonography performed by obstetricians, it should be noted that it is limited to the pelvic area. Therefore, in symptomatic patients, a complete urinary system ultrasonography should be performed. In the differential diagnosis, leiomyomas, schistosomiasis, endometriosis, and particularly placenta percreta invading the bladder, which can cause life-threatening bleeding, should be considered.[7–9] When malignancy is detected on ultrasonography, the safest advanced imaging method that can be applied is MRI, and it is preferably performed after the first trimester. However, the use of gadolinium-enhanced MRI during pregnancy, especially in the first 24 weeks, should be avoided due to the uptake of gadolinium by the embryo, excretion through the urinary tract, and re-entry into the fetal circulation.[10]

During pregnancy, the treatment of BC is not different from non-pregnant patients. If ultrasonography or flexible cystoscopy suggests invasive or advanced disease, staging MRI should be performed, and treatment should be planned accordingly. As in most patients, if ultrasonography or flexible cystoscopy suggests noninvasive disease, transurethral resection of the bladder tumor should be performed. The timing of the intervention depends on various factors such as the stage and aggressiveness of cancer, the stage of pregnancy, and the condition of the mother and fetus. Treatment decisions should also be shaped according to the desires of the pregnant woman. Early intervention can pose a risk to the fetus's life, while delayed treatment can lead to the progression of the disease. Surgical intervention is generally avoided during the first three months when organogenesis occurs, while the second trimester is generally safe for intervention. If cancer is diagnosed in the late second trimester or third trimester, intervention may be better performed at 28 weeks of gestation when fetal lungs are mature. Although congestion due to pregnancy and possible distortion of the bladder may pose technical challenges, transurethral resection of the bladder tumor under spinal or general anesthesia is safe during pregnancy. Serious complications of this procedure have not been reported in pregnant patients.

Transurethral resection using monopolar or bipolar energies has limited experience regarding its effects on the fetus and outcomes of pregnancy, making the effects poorly defined. However, bipolar loop resection with saline irrigation appears to be a safe procedure.[3] In this case, complete resection was performed using bipolar energy, and no complications were encountered. The optimal management of bladder tumors during pregnancy has not been determined due to their rarity and limited reported experiences in the literature. Bipolar transurethral tumor resection in the second trimester is a safe surgical approach. This case illustrates the need for a careful evaluation of all treatment options during pregnancy, including early surgical intervention when appropriate.

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LETTER TO THE EDITOR

Assessing Healthcare Challenges in Somalia: A 2024 Perspective

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Somalia, a country located in the Horn of Africa, has long grappled with significant healthcare challenges exacerbated by decades of conflict, instability, and underdevelopment. In 2024, despite ongoing efforts to rebuild its healthcare system, Somalia continues to face multifaceted healthcare issues that hinder the delivery of essential services to its population. This report aims to provide an in-depth analysis of the current state of healthcare in Somalia, focusing on challenges, recent advancements, and potential solutions. Somalia's healthcare system is characterized by a fragile infrastructure, inadequate resources, and a shortage of skilled healthcare professionals. The country's healthcare services are predominantly provided by non-governmental organizations (NGOs) and international agencies, with limited government capacity to deliver healthcare at the national level. Access to healthcare remains a significant challenge in Somalia, particularly in rural and conflict-affected areas. Factors such as geographic barriers, insecurity, and financial constraints impede individuals' ability to seek and receive healthcare services.[1] Somalia's healthcare infrastructure is severely underdeveloped, with many healthcare facilities lacking essential resources such as medical equipment, medications, and trained personnel. The quality of healthcare services varies widely across regions, with urban areas generally having better-equipped facilities compared to rural areas. Infectious diseases such as malaria, cholera, and measles continue to pose significant public health threats in Somalia. Weak disease surveillance systems, inadequate access to clean water and sanitation facilities, and population displacement contribute to the spread of communicable diseases.[2]

Somalia's maternal and child health indicators are among the poorest globally, with high maternal and child mortality rates attributed to limited healthcare access, and cultural and socio-economic factors. Recent years have seen the emergence of telemedicine and mobile health initiatives in Somalia, leveraging technology to improve access to healthcare services, particularly in remote and underserved areas. Mobile health applications and teleconsultation services enable individuals to receive medical advice and consultations remotely, overcoming barriers to access. International partnerships and humanitarian assistance play a vital role in supporting healthcare delivery in Somalia. Organizations such as the World Health Organization (WHO), UNICEF, and Médecins Sans Frontières (MSF) provide essential

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medical supplies, healthcare training, and support for healthcare facilities in the country. Community-based healthcare initiatives, including community health workers and outreach programs, are instrumental in delivering healthcare services at the grassroots level.[3]

These initiatives focus on health education, disease prevention, and maternal and child health, addressing healthcare needs within local communities. Investments in healthcare infrastructure, training, and capacity building are crucial for improving healthcare delivery in Somalia, including upgrading facilities, providing resources, and expanding coverage to underserved areas. Training programs in Somalia should enhance clinical skills, promote evidence-based practices, and strengthen healthcare management while empowering communities through health education, mobilization, and participatory decision-making processes. Engaging communities in healthcare planning and implementation ensures that interventions are culturally appropriate and responsive to local needs. Enhancing disease surveillance systems and improving outbreak response capacity are crucial for controlling infectious diseases in Somalia. This includes strengthening laboratory capacity, training healthcare workers in disease surveillance and reporting, and enhancing coordination among healthcare stakeholders. The healthcare challenges facing Somalia are complex and multifaceted, requiring coordinated efforts from the government, civil society, and the international community to address them effectively. By prioritizing investments in healthcare infrastructure, strengthening healthcare systems, and empowering communities, Somalia can make significant strides toward improving healthcare access and outcomes for its population.

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