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Original Article

Polyautoimmunity in autoimmune gastritis

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ABSTRACT

Objectives: Autoimmune gastritis may be associated with other organ-specific autoimmune disorders, but the prevalence of this association is not entirely quantified. The aims of this study were to investigate the prevalence of autoimmune disorders and evaluate the factors that might affect this association in patients with autoimmune gastritis.
Methods: A total of 320 patients with autoimmune gastritis were retrospectively studied and data on concomitant autoimmune diseases, serum gastrin and chromogranin A levels, anti-Hp IgG, antiparietal cell antibodies, presence of enterochromaffin-like cell hyperplasia and gastric atrophy were gathered for each patient and associations between autoimmune gastritis and studied parameters were explored through descriptive statistics and logistic regression analysis.
Results: Of the 320 atrophic body autoimmune gastritis patients, 171 (53.4%) had an associated autoimmune disorder. Autoimmune thyroiditis was the most common concurrent disease, diagnosed in 116 patients (36.2%). Multivariate analysis showed that, presence of enterochromaffin cell hyperplasia (odds ratio [OR] 9.445, 95% confidence [CI]: 4.42–20.22), serum gastrin (OR 3.1, 95% CI: 1.46–6.60) and serum chromogranin A (OR 4.14, 95% CI: 2.01–8.52) levels remained significantly associated with the coexistence of an autoimmune disease.
Conclusions: Concurrent autoimmune diseases are common in patients with autoimmune gastritis. Autoimmune thyroiditis is the most encountered disease. These data suggest that patients with autoimmune gastritis should be investigated for the presence of an autoimmune disease, in particular patients with enterochromaffin cell hyperplasia and those with serum gastrin and chromogranin A levels above cut-off values.

1. Introduction

Autoimmune gastritis (AIG) is an autoimmune and inflammatory disorder of the oxyntic mucosa characterized by autoantibodies directed against structures containing H^+/K^+-ATPase and intrinsic factor, with subsequent loss of parietal cells. In this disease, the destruction of gastric oxyntic glands leads to atrophy of the gastric body, which causes hypo- or achlorhydria, secondary hypergastrinemia, antral G-cell hyperplasia and low serum pepsinogen I concentrations [1]. The loss of gastric parietal cells results in the replacement of the parietal cell mass by atrophic and metaplastic mucosa; however, this change in the mucosa impairs the metabolism of vitamin B_{12} and sometimes iron deficiency anemia occurs [2]. Autoimmune gastritis is usually clinically 'quiescent' in the early stages of the disease and the lack of specific symptoms related to this disease often causes a delay in the diagnosis, thus diagnosis merely depends on clinical suspicion. Autoimmune gastritis (AIG) is a common and frequently underdiagnosed disease, with a prevalence of nearly 2% in the general population [3,4] However, its prevalence increased 3- to 5-fold in patients with other autoimmune disorders such as type 1 diabetes, thyroid disease, and primary biliary cirrhosis [5]. The risk of developing pernicious anemia, gastric carcinoid tumors and gastric cancer is increased in patients with AIG [6–8]. Moreover, more than half of patients with atrophic body gastritis were found to have various thyroid and autoimmune thyroid diseases and patients with AIG should be investigated for an autoimmune thyroid disease [9]. Thus, the aim of the present study was to investigate the prevalence of and factors associated with autoimmune diseases in order to find out which parameter(s) predict the presence of an autoimmune disease in a wide group of patients with AIG.

2. Materials and methods

Medical records of patients ($n = 320$) with primary diagnosis of AIG who were referred to our center during the last 5 years were analyzed by means of the presence of an associated autoimmune disease (AD). The diagnosis of AIG was mainly based on the histopathological findings in gastric biopsy tissue. Moreover, serum gastrin level and presence of antiparietal cell antibody (APCA) were also used in the diagnosis in each patient as described by Vargas et al. [10]. Histologically, AIG is

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characterized by a chronic inflammatory infiltrate accompanied by loss of oxyntic glands, parietal and zymogenic cells affecting the fundus and corpus of the stomach [4]. Besides, upper GI endoscopic/histopathologic findings according to updated Sydney classification [8], routine biochemistry, and anti-Hp IgG were also investigated and serum chromogranin A level was measured by using commercially available kits (CGA-ELISA CT; CIS bio international, Gifsur-Yvette Cedex, France). Results of histological examination of biopsy specimens by means of enterochromograffin-like cell (ECL) status were retrieved from hospital electronic database system and were classified according to the classification described by Solcia et al. [11]. Based on this histological evaluation, endocrine hyperplasic changes have been graded as follows; 0: absent, 1: diffuse hyperplasia, 2: linear hyperplasia, and 3, micronodular hyperplasia.

2.1. Definitions

2.1.1. Autoimmune gastritis

The diagnosis of AIG was mainly based on the histopathological findings in gastric biopsy tissue. Moreover, serum gastrin level and presence of APCA were also used in the diagnosis in each patient as described by Vargas et al. [10]. Histologically, AIG is characterized by a chronic inflammatory infiltrate accompanied by loss of oxyntic glands, parietal and zymogenic cells affecting the fundus and corpus of the stomach [4].

2.1.2. Autoimmune thyroid disease

The diagnosis of autoimmune thyroiditis was based on the presence of antiperoxidase antibodies (antibody titers >200 IU/ml) and characteristic ultrasound features (i.e., nonhomogeneous pattern with diffuse reduction of echogenicity), according to Rago et al. [12], in the presence, but even in the absence of mild or overt hypothyroidism [13].

2.1.3. Other autoimmune diseases

2.1.3.1. Systemic lupus erythematosus. Diagnosis of SLE was made according to the "Systemic Lupus International Collaborating Clinics classification criteria" [14].

2.1.3.2. Rheumatoid arthritis. The diagnosis of rheumatoid arthritis was based on the diagnostic criteria defined by the American College of Rheumatology/European League Against Rheumatism collaborative initiative [15].

2.1.3.3. Celiac disease. The diagnosis of celiac disease was based on the diagnostic criteria according to the "Oslo definitions" [16].

2.1.3.4. Autoimmune hepatitis. Diagnostic criteria defined by "The American Association for the Study of Liver Diseases" were used for the diagnosis of autoimmune hepatitis [17]. The study protocol was approved by the Ankara University School of Medicine Ethics Committee and was performed in accordance with the Declaration of Helsinki (decision date: December 28, 2015 and No. 20-848-15).

2.2. Statistics

Statistical analysis was performed using SPSS v.16.0 for Windows 10 (SPSS, Inc., Chicago, IL, USA). The Shapiro–Wilk test was used to determine the normality of the distribution of data, and according to the results, parametric or non-parametric tests were preferred. Values are shown as mean ± SD unless otherwise stated and nominal variables are shown as *n* (%). The significance of the difference in mean values between groups was determined using Student's *t*-test, and the significance of the difference in median values was determined via the Mann–Whitney *U* test. Nominal variables were evaluated using Pearson's chi-square test or Fisher's exact test. While investigating the concordance between grouped values of 2 methods, the kappa coefficient and significance were calculated; however, while investigating the concordance between 2 continuous variables, the ICC coefficient and significance were calculated. Receiver operating characteristic (ROC) curves were used to describe and compare the ability of serum chromogranin A and gastrin levels to predict the presence of an autoimmune disease. Optimal cut-off points were calculated using the Youden index and possible maximum values for both sensitivity and specificity. Relationships between 2 continuous variables were evaluated using Pearson's correlation test for normally distributed data, versus Spearman's correlation test for data not normally distributed. The significance of difference of mean values between groups was analyzed by using ANOVA test. The level of statistical significance was set at $p < 0.05$.

Table 1
Prevalence of autoimmune diseases in patients with autoimmune gastritis (one patient may have more than one disease).

Autoimmune disease	*n* (%)	Autoimmune disease	*n* (%)
Hashimoto thyroiditis	116 (36.25%)	Hashimoto thyroiditis/RA	16 (5%)
RA	28 (8.75%)	Hashimoto thyroiditis/SLE	7 (2.2%)
SLE	20 (6.25%)	Hashimoto thyroiditis/CD	3 (0.9%)
CD	11 (3.43%)	Hashimoto thyroiditis/AS	2 (0.6%)
OIH	9 (2.81%)	Hashimoto thyroiditis/SSc	1 (0.3%)
Graves'	8 (2.5%)	Hashimoto thyroiditis/OIH	1 (0.3%)
AS	6 (1.87%)	Graves'/RA	2 (0.6%)
SSc	3 (0.9%)	Graves'/SLE	1 (0.3%)
Sjögren's syndrome	2 (0.6%)	OIH/RA	1 (0.3%)
PBS	2 (0.6%)	Graves'/SSc	1 (0.3%)
Vitiligo	2 (0.6%)	Graves'/OIH	1 (0.3%)

(RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, CD: celiac disease, OIH: autoimmune hepatitis, AS: ankylosing spondylitis, SSc: systemic sclerosis, PBS: primary biliary cirrhosis).

3. Results

Three-hundred twenty patients (mean age: 54.54 ± 13.22 years, 211 women) with AIG were enrolled into the study. In our cohort of 320 patients with AIG, a total of 171 patients (53.4%) were diagnosed with additional autoimmune diseases. Out of 171 patients, while 135 patients had single autoimmune disease (42.2%), 36 patients exhibited more than one AD (11.3%). Autoimmune thyroiditis was the most common concurrent disease, diagnosed in 116 patients (36.2%). Other concurrent autoimmune diseases comprised rheumatoid arthritis (28 patients, 8.75%), SLE (20 patients, 6.25%), celiac disease (11 patients, 3.43%), autoimmune hepatitis (9 patients 2.8%), Graves' disease (8 patients, 2.5%) and ankylosing spondylitis (6 patients, 1.87%) (Table 1).

Besides the incidence of concurrent ADs in patients with AIG, factors that might affect the presence of an AD were also investigated and illustrated in Table 2.

When AIG patients with a coexistent autoimmune disease were compared to patients without an autoimmune disease by means of univariate analysis, an increased risk of occurrence of an AD was associated

Table 2
Factors that might affect the presence of an autoimmune disease in patients with autoimmune gastritis.

Patients	With AD	Without AD	*p*
$n = 320$	171 (53.4%)	149 (46.6%)	
Age	55.17 ± 11.82	53.02 ± 14.40	0.056
Gender (F/M)	123/48	88/61	0.016
Anti-Hp IgG (+/−)	97/74	78/61	0.769
APCA (+/−)	158/13	134/16	0.647
Cg A (ng/ml)	285.45 ± 91.41	122.16 ± 43.15	<0.001
Gastrin (pg/dl)	675.53 ± 103.02	260.18 ± 70.38	<0.001
ECLH (+/−)	155/16	31/118	<0.001

AD: autoimmune disease, F: female, M: male, APCA: antiparietal cell antibody, Cg A: chromogranin A, ECLH: enterochromaffin-like cell hyperplasia.