

Dyspepsia-Like Symptoms in *Helicobacter pylori*-Negative Chronic Gastritis are Associated with ASCA-, ANCA-, and Celiac Seropositivity but Not with Other Autoimmune Parameters: A Single-Centre, Retrospective Cross-Sectional Study

Noémi Zádori^{1,2}, Dávid Németh¹, Levente Frim¹, Nóra Vörhendi^{1,2}, Lajos Szakó^{1,2}, Szilárd Vánca¹⁻³, Péter Hegyi¹⁻³, József Czimmer^{1,4}

¹Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary; ²János Szentágotthai Research Centre, University of Pécs, Pécs, Hungary; ³Centre for Translational Medicine, Semmelweis University, Budapest, Hungary; ⁴Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary

Correspondence: József Czimmer, First Department of Medicine, University of Pécs Medical School, Ifjúság street 13, Pécs, H-7624, Hungary, Email czimmer.jozsef@pte.hu

Introduction: Dyspeptic symptoms are frequent in the general population, with a high socioeconomic burden. *Helicobacter pylori* (*H. pylori*) might be a possible etiological factor; however, it is also common in *H. pylori* negative gastritis. Clarification of the underlying aetiology might be beneficial to set up the optimal treatment strategy for dyspepsia and chronic gastritis (CG) itself. We aimed to assess the prevalence of dyspeptic symptoms in patients with *H. pylori* negative CG and explore autoimmunity's possible role.

Methods: This retrospective study included data from patients with *H. pylori* negative CG. Exclusion criteria were (1) acute gastritis; (2) reactive gastropathy; (3) subjects without any serology testing results; (4) *H. pylori* positivity; (5) presence of atrophy, intestinal metaplasia (IM), gastroesophageal reflux disease (GERD), ulcer, or cancer. The following endpoints were assessed (1) the rate of dyspepsia-like symptoms; (2) association between dyspepsia and autoimmune disease-related seromarker positivity (AISP); (3) frequency of other symptoms in CG and its association with AISP; (4) location of the inflammation and its association with AISP.

Results: From a total of 285 patients, 175 were included in this study. Among these patients, 95 experienced dyspeptic symptoms (54.29%) and were associated more with AISP ($p = 0.012$), especially with celiac seropositivity ($p = 0.045$), anti-neutrophil cytoplasmic antibody (ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) positivity ($p = 0.043$). A significant association was not found with other tested autoimmune (AI)-related antibody positivity.

Conclusion: Positivity of seromarkers of autoimmune diseases in chronic gastritis may predispose to have dyspeptic symptoms and may be the causative factor behind some cases of uninvestigated dyspepsia. These data suggest that further prospective studies are needed to clarify whether screening for autoantibodies in patients with dyspepsia is cost-effective and helps the earlier diagnosis of autoimmune diseases.

Keywords: chronic gastritis, autoimmunity, auto-antibody, dyspepsia

Introduction

Dyspepsia is a complex condition, refers to a group of symptoms, which originate from the upper gastrointestinal region. The Rome IV criteria define dyspepsia as any combination of the four following symptoms: postprandial fullness, early satiety, epigastric pain, and epigastric burning sensation.¹ Regarding the aetiology, organic and functional dyspepsia can

be distinguished. When dyspeptic symptoms are not manifestations of organic pathologies, such as gastroesophageal reflux disease (GERD), peptic ulcer disease, or gastric tumour, it is classified as functional dyspepsia (FD).

Dyspeptic symptoms are frequent in the general population, with a prevalence of 20–40%,^{2–4} and it is the most common indication for upper gastrointestinal (GI) endoscopy.⁵ The diagnostic value of gastroscopy in diagnosing dyspepsia is controversial. Although it is a possible method to differentiate patients with organic dyspepsia from those with functional, referring the patients to endoscopy should be considered due to its invasiveness and low cost-effectivity. Furthermore, a large number of uninvestigated dyspepsia cases are functional.^{6,7}

The exact pathogenesis of FD is unknown; however, visceral hypersensitivity, such as gastric hypersensitivity to distension and acids and abnormal gastric motility, might play a role in developing dyspeptic symptoms.^{8,9} According to the definition, functional disorders are characterised by the absence of any organic pathology explaining the symptoms. A notable exception can be the *Helicobacter pylori* (*H. pylori*) infection, which is included in the definition of FD according to the Rome III criteria.¹⁰ Moreover, extensive population-based studies indicate that *H. pylori* might be a possible etiological factor in the pathogenesis of FD.^{11,12}

A recent study has shown that patients with FD had a high prevalence and severity of chronic gastritis (CG) without *H. pylori* infection.¹³ Nevertheless, *H. pylori* infection was thought to be the leading cause of chronic gastritis.¹⁴ The aetiology of CG in *H. pylori*-negative patients was unknown and its implications in the pathogenesis in FD. Data regarding the relationship between *H. pylori* negative chronic gastritis and specific dyspeptic symptoms are lacking. Therefore, clarification of the underlying aetiology might be beneficial to set up the optimal treatment strategy for dyspepsia, and the *H. pylori* negative CG itself.

Studies suggest that immune activation might play a role in the pathogenesis of FD.^{15,16} Innate immune activation in the mucosa in FD has been described,^{17,18} but the prevalence of AI disorders due to immune activation in FD is uncertain.

This study aimed to assess the occurrence and pattern of GI symptoms, the prevalence of dyspeptic symptoms in patients with *H. pylori*-negative CG, and explore the possible role of the established etiological factors behind CG autoimmunity in the expression of dyspeptic symptoms.

Materials and Methods

Patients histologically diagnosed with chronic gastritis who underwent immune-serological testing between January 2016 and January 2020 were enrolled. For diagnosing gastritis, multiple biopsies (minimum of five) were taken from definite sites of the stomach, predefined by the updated Sydney system.¹⁹ Additional biopsies were performed from the areas of every detected focal lesion if any presented. To avoid performance bias, diagnosis and treatment of enrolled patients were carried out by the same single-unit medical team (one pathologist specialised in GI pathology reviewed all the histological findings, and one gastroenterologist performed all the endoscopy). Another, no dyspepsia-related study was previously performed on this population.²⁰

All patients having any of the followings: (1) acute gastritis; (2) reactive gastropathy;²¹ (3) subjects without any serology testing results; (4) *H. pylori* positivity; (5) GERD, ulcer, or cancer were excluded from this study. Diagnosis of *H. pylori* infection was established by endoscopy, serological testing, followed by a urea breath test. The diagnosis of acute gastritis, reactive gastropathy, GERD, ulcer or cancer was confirmed by histological findings. Regarding the well-known association between dyspepsia and *H. pylori* infection, *H. pylori* can be considered as a confounding factor. Therefore, patients with *H. pylori* infection were excluded from the analysis to reduce bias.

Possible eligible patients from all clinical records of the outpatient unit led by a single specialist investigator were identified from an electronic database. Data collection was performed focusing on baseline characteristics of the population, histological results (location of the inflammation); autoantibody positivity (celiac disease-, Sjögren's syndrome-, systemic lupus erythematosus (SLE)-, AI hepatitis-, rheumatoid arthritis (RA)-, SSc (systemic sclerosis)-, polymyositis/dermatomyositis-, AI thyroiditis-, IBD-, vasculitis-, AIG-related antibodies); *H. pylori* infection status (histology, results of the urea breath test and/or serology), symptoms (key symptoms, presence of dyspepsia-like symptoms: postprandial fullness, early satiety, epigastric pain, and epigastric burning). Patients were also categorised

according to their autoantibody positivity: autoantibody seropositive (AISP) and autoantibody seronegative (AISN) groups. Patients were categorised into AISP group in case of at least one antibody positivity.

Autoantibody positivity was assessed using the threshold of our laboratory in accordance with the European Autoimmunity Standardisation Initiative (EASI).^{22,23} According to their occurrence in these conditions, detected autoantibodies were divided into autoimmune disease groups ([Supplementary File 1](#)). Grouping of patients was performed as per our previous autoimmune seromarker positivity and CG-related study.²⁰

The following primary endpoint was investigated: association between AI positivity and dyspepsia-like symptoms (according to the Rome IV criteria¹). In the case of the presence of one or more of the following symptoms: postprandial fullness, early satiety, epigastric pain, and epigastric burning, patients were categorized into the dyspepsia group.

The following secondary endpoints were assessed (1) the frequency of symptoms in CG, assessed in each patient by the same gastroenterologist; (2) the association between AISP and the most frequently occurred symptoms; (3) the location of the inflammation in the stomach assessed in each patient during endoscopy by the same gastroenterologist and confirmed by histopathological results; (4) association between AISP and the affected region of the inflammation.

The assessment of all variables was done on the level of AI disease and according to AISP and AISN groups.

Approval for this study was retrieved officially from the president of the Clinical Centre and the director of the First Department of Medicine of the University of Pécs (Institutional Review Board; case number: KK/999-1/2020). This study complies with the ethical guidelines of the Declaration of Helsinki updated in 2013 as reflected in a priori approval by the Institutional Review Board.²⁴

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline²⁵ was followed during the data collection and analysis and the current legal environment ([Supplementary File 2](#)). According to the GDPR, all participating patients received a numeric code to protect privacy and personal data. Informed consent was not required in this retrospective set, although the data of those patients who refused data handling for scientific causes were not included.

Statistical Analysis

SPSS 25.0 software was used for the analysis of the data. Descriptive statistics (mean, standard deviation, minimum, maximum), and univariate analyses were performed. A 2-sided Pearson Chi-square test was done to compare dichotomous variables. In case of significant differences, standardised residuals were also observed to reveal the exact results. In the case of continuous variables, an independent sample *t*-test was used. We observed the distribution on Q-Q-plot. A P-value of less than 0.05 was considered statistically significant.

Results

In the final analysis, 175 patients (52 men and 123 women) with *H. pylori*-negative chronic gastritis were included. The mean age of the study population was 61.6 years (± 15.13 years), ranging from 21 to 89. As described in our previous study, fifty-five per cent (97/175) of the analyzed patients had positive immunoserology (AISP group).²⁰

Clinical Symptoms

Most frequently occurred symptoms were the followings: retrosternal burning sensation in 17.14% (30/175 patients); bloating and/or diarrhoea in 9.14% (16/175); diffuse abdominal discomfort/pain not relating to meals in 8.57% (15/175); globus sensation in 4% (7/175); nausea in 4.57% (8/175) and vomitus in 2.29% (4/175). All details about the symptoms can be seen in [Table 1](#).

Diffuse abdominal pain/discomfort in the AISP group was significantly more common than in the AISN group (9 vs 6 patients, respectively, $p = 0.023$). Globus pharyngeus was more common in group AISP than the AISN group ($p < 0.001$): 6 patients experienced globus sensation in the AISP group, while one patient in the AISN group.

We did not find any significant differences with the other symptoms between AISP and AISN groups in our analysis. Retrosternal burning occurred in 12 patients in the AISP group and 18 patients in the AISN group ($p = 0.0713$). Less common symptoms included nausea (4 AISP and 4 AISN patients, $p = 1.000$), vomiting (1 AISP and 3 AISN patients, $p = 0.325$), and bloating and/or diarrhoea (9 AISP and 7 AISN patients, $p = 0.152$) ([Table 1](#)).

Table 1 Distribution of Frequently Occurred Symptoms and Location of the Inflammation Between AI Positive and Negative Groups

	Overall (n=175)	AI+ (n=97)	AI- (n=78)	p-value
Key symptom				
Dyspepsia-like symptoms N ⁰ (%)	95 (54.29)	58 (58.76)	37 (48.72)	0.012
Retrosternal burning N ⁰ (%)	30 (17.14)	12 (12.37)	18 (23.08)	0.0713
Globus pharyngeus N ⁰ (%)	7 (4.00)	6 (6.19)	1 (1.28)	<0.001
Nausea N ⁰ (%)	8 (4.57)	4 (4.12)	4 (5.13)	1.000
Vomiting N ⁰ (%)	4 (2.29)	1 (1.03)	3 (3.85)	0.325
Bloating, diarrhea N ⁰ (%)	16 (9.14)	9 (9.28)	7 (8.97)	0.152
Abdominal discomfort/pain N ⁰ (%)	15 (8.57)	9 (9.28)	6 (7.70)	0.023
Location of the gastritis				
Antrum N ⁰ (%)	56 (32.00)	33 (34.02)	23 (29.49)	0.042
Corpus N ⁰ (%)	15 (8.57)	9 (9.28)	6 (7.70)	0.023
Pangastritis N ⁰ (%)	104 (59.43)	57 (58.76)	47 (60.26)	0.269

Note: P-values marked in bold indicate statistically significant p-values.

Dyspepsia-Like Symptoms in Autoimmune Seropositivity

Dyspepsia-like symptoms were present in 54.29% of the patients (95/175) and were associated more with AISP ($p = 0.012$). Association was found regarding celiac disease-related antibody positivity and dyspepsia ($p = 0.045$), while ANCA and ASCA positivity were also associated with dyspepsia-like symptoms ($p = 0.043$). However, the analysis could not find a significant association between dyspepsia-like symptoms and other AI-related antibody positivity, like Sjögren's syndrome, SLE, AI hepatitis, RA, SSc, polymyositis/dermatomyositis, and AI thyroiditis ($p > 0.05$). No significant association was found considering AIG-related antibody positivity and dyspepsia either ($p = 0.677$). Detailed results regarding the association between autoimmunity and dyspeptic symptoms are given in [Table 2](#).

Table 2 Detailed Results Regarding the Association Between Autoimmunity and Dyspeptic Symptoms

Association with Dyspepsia	
AI Disease Groups/Antibodies	p-value
AIG	0.677
Celiac disease	0.045
Sjögren's syndrome	0.563
SLE	0.585
AI hepatitis	0.617
RA	0.252
Scs	1.000

(Continued)

Table 2 (Continued).

Association with Dyspepsia	
AI Disease Groups/Antibodies	p-value
Polymyositis/dermatomyositis	n/a
IBD	0.043
AI thyroiditis	0.229
Anti-parietal cell antibody	0.677
Anti-gliadin antibody	0.065
Anti-nuclear antibody	0.230
Anti-dsDNA antibody	1.000
Anti-nucleosome antibody	1.000
Anti-rheumatoid factor	0.252
Anti-Saccharomyces cerevisiae antibody	0.043
Anti-neutrophil cytoplasmic antibody	0.043

Note: P-values marked with bold indicate statistically significant p-values.

Location and Extent of the Inflammation

Most of the examined patients had pangastritis (59.43%); the inflammation affects the entire stomach in 57 (58.76%) patients of the AISP group and 47 (60.26%) patients of the AISN group. Lesions of gastritis were found in the antrum in 33 (34%) AISP and 23 AISN patients and were associated with autoimmune positivity ($p = 0.042$). Isolated corpus affection was related to autoimmunity as well ($p = 0.023$); inflammation of the corpus was found in 9 (9.28%) AISP and 6 (7.70%) AISN patients, respectively (Table 2).

Discussion

This retrospective cross-sectional study, including data of 175 patients, aimed to investigate the possible relationship between autoimmunity and dyspeptic symptoms in patients with *H. pylori* negative chronic gastritis. One of our significant findings was that the prevalence of dyspepsia-like symptoms was 54.29%. Regarding the association between the symptoms and autoimmunity, dyspeptic symptoms, diffuse abdominal pain/discomfort, and globus pharyngeus seem to be more common in patients with AISP. A significant association was found between celiac disease-related antibody positivity, ASCA and ANCA positivity and dyspeptic symptoms. However, the analysis could not prove that other AI disease-related antibody positivity was more common in CG patients with FD.

It was previously shown in the literature that *H. pylori* infection might be associated with FD: the prevalence of *H. pylori* infection is more frequent in dyspeptic patients than in healthy controls.^{26,27} A meta-analysis of 12 randomized controlled studies concluded that eradication of *H. pylori* is associated with improvement of dyspeptic symptoms in patients with FD.²⁸ Several studies suggested that *H. pylori* can alter gastric functions: it causes hypergastrinemia, hyperpepsinogenemia, and acid hypersecretion, which might play a role in the pathogenesis of FD.²⁹

A high prevalence of dyspeptic symptoms was also reported in patients with *H. pylori*-negative CG.¹³ Although CG is a prevalent pathology found in upper GI endoscopy, the underlying aetiology often remains unknown;³⁰ therefore, we looked for possible causative factors behind CG that may be associated with dyspeptic symptoms.

In our study, more than half of the patients with non-investigated chronic gastritis showed systemic autoantibody positivity, and it was associated with dyspeptic symptoms. Several articles in the literature mention the possible association

between autoimmune diseases and dyspepsia. Dyspeptic symptoms are presented in 50–60% of the patients with AI disorders and may result from gastroparesis and antral distension.^{31,32} However, Koloski et al concluded that autoimmune diseases are risk factors for functional gastrointestinal disorders, such as FD, due to immune dysregulation.³³

In line with our results, Jocelyn A Silvester et al showed that FD occurs in 27% of patients with coeliac disease, which is relieved in most cases following the treatment of a gluten-free diet,³⁴ and A. Maertens et al reported a case about how dyspepsia led a diagnosis of Morbus Crohn.³⁵ Furthermore, our study confirms the investigation of Lebwohl et al about the association between *H. pylori*-negative CG with celiac disease.³⁶ Higher incidence of dyspeptic symptoms has also been observed in patients with Sjögren's syndrome, SLE, RA, and AI thyroiditis,^{31,32,37–42} however, our study could not confirm these associations.

Gastrointestinal manifestation occurs in most patients with systemic autoimmune disorders,^{43–45} and these symptoms might be subclinical, non-specific, with considerable overlap among different conditions. Sometimes it can be the only presented sign of an underlying AI disease. The advent of serologic testing for immune-mediated GI disorders (eg, celiac disease, IBD) allows broader screening, helping differentiate organic disease from functional GI disorders.

To our knowledge, this is the first study, which investigated the possible organic etiological factors behind chronic *H. pylori*-negative gastritis in association with FD. As mentioned above, there were previous descriptions of the possible connection between certain autoimmune disorders and dyspepsia; however, a comprehensive study, excluding confounding factors to answer this question in a targeted manner, has not been performed previously. This work contains the investigation of the widest coverage of systemic AI disorders related antibody positivity and dyspepsia, and the study was conducted following a rigorous, pre-defined methodology. Furthermore, in the chronic gastritis patient population, where there is no identified etiological factor behind chronic inflammation, the cause of dyspepsia-like symptoms has not been investigated before.

However, our research had several limitations, which should be considered for a correct interpretation. The results are based on a single-centre, retrospective analysis, with a relatively low event rate in each antibody positivity, which might be the reason for insignificance in some cases. It is well known that the prevalence of FD is significantly higher in women, smokers, non-steroidal anti-inflammatory drug (NSAID) users,²⁷ and in the ageing stomach,⁴⁶ they should be considered confounding factors in our study. Moreover, chronic atrophic gastritis itself may contribute to the development of dyspeptic symptoms by influencing the level of gastric acid, pepsin, and ghrelin secretion;^{8,47} however, data regarding the relationship between atrophic gastritis and specific dyspeptic symptoms are lacking. The limited information on this topic and our research's limitations could serve as a subject for conducting prospective clinical studies with a larger event rate.

Conclusion

In conclusion, autoimmune positivity in histologically established *H. pylori*-negative CG may predispose to dyspeptic symptoms and may be the causative factor behind uninvestigated FD. In this study, celiac disease-related antibody positivity, ASCA and ANCA positivity were associated with dyspeptic symptoms. However, our analysis could not prove any association between dyspepsia-like symptoms and Sjögren's syndrome, SLE, AI hepatitis, RA, SSc, Polymyositis/dermatomyositis, AI thyroiditis, or even AIG.

Based on our data, screening for celiac disease or ASCA and ANCA-related AI disorders (IBD, vasculitis) in the presence of dyspeptic symptoms might be crucial. Furthermore, screening for these autoantibodies (ANCA-, ASCA-, celiac-disease-related antibodies) in patients with FD can be more cost-effective, considering the earlier diagnosis of these autoimmune diseases. However, our results should be interpreted with caution since the retrospective nature of this study. To establish a higher quality of evidence, further prospective studies are required to prove the association between AI disorders (especially GI-related AI disorders; eg, IBD, celiac disease and vasculitis) and dyspeptic symptoms.

Abbreviations

AI, autoimmune; AISN, autoimmune disease-related seromarker negativity; AISP, autoimmune disease-related seromarker positivity; ANCA, anti-neutrophil cytoplasmic antibody; ASCA, anti-Saccharomyces cerevisiae antibody; CG, chronic gastritis; FD, functional dyspepsia; GERD, gastro-esophageal reflux disease; GI, gastrointestinal; *H. pylori*,

Helicobacter pylori; IBD, inflammatory bowel disorders; IM, intestinal metaplasia; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; Ssc, systemic sclerosis.

Ethics and Dissemination

Ethical approval: University of Pécs, Clinical Centre, Institutional Review Board; case number: KK/999-1/2020.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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