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Paradoxical association between dyspepsia and autoimmune chronic atrophic gastritis: Insights into Mechanisms, Pathophysiology, and Treatment Options

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Abstract

BACKGROUND

Autoimmune gastritis (AIG) is a progressive, chronic, immune-mediated inflammatory disease characterized by the destruction of gastric parietal cells leading to hypo/anacidity and loss of intrinsic factor. Gastrointestinal symptoms such as dyspepsia and early satiety are very common, being second in terms of frequency only to anemia, which is the most typical feature of AIG.

AIM

This review aims to address both well-established and more innovative information and knowledge about this challenging disorder.

METHODS

An extensive bibliographical search was performed in PubMed to identify guidelines and primary literature (retrospective and prospective studies, systematic reviews, case series) published in the last 10 years.

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RESULTS

A total of 125 records were reviewed and 80 were defined as fulfilling the criteria.

CONCLUSION

AIG can cause a range of clinical manifestations, including dyspepsia. The pathophysiology of dyspepsia in AIG is complex and involves changes in acid secretion, gastric motility, hormone signaling, and gut microbiota, among other factors. Managing dyspeptic symptoms of AIG is challenging and there are no specific therapies targeting dyspepsia in AIG. While proton pump inhibitors (PPIs) are commonly used to treat dyspepsia and GERD, they may not be appropriate for AIG. Prokinetic agents, antidepressant drugs, and non-pharmacological treatments may be of help, even if not adequately evidence-based supported. A multidisciplinary approach for the management of dyspepsia in AIG is recommended, and further research is needed to develop and validate more effective therapies for dyspepsia.

INTRODUCTION

Autoimmune gastritis (AIG) is an immune-mediated disease targeting the H⁺/K⁺ ATPase proton pump in the parietal cells, which are responsible for the secretion of gastric acid and intrinsic factor [1]. The pathogenesis of AIG involves the activation of both T and B lymphocytes, which infiltrate the gastric mucosa and destroy the parietal cells [1-5], leading to hypochloridria and vitamin B12 deficiency.

Symptoms of AIG can be nonspecific, with patients presenting with no or vague symptoms, including postprandial fullness, early satiation, abdominal pain, bloating [6], as well as epigastric pain. Therefore, the diagnosis of AIG can be challenging, as many of these symptoms overlap with other digestive disorders, mainly functional dyspepsia (FD) and gastroesophageal reflux disease (GERD). This overlap in clinical symptoms and characteristics can pose diagnostic challenges between AIG and FD, which share some common characteristics, including clinical symptoms, as well as a higher prevalence among women. Moreover, some patients may present with atypical symptoms, such as fatigue, joint pain, or skin rashes, which can further overlap with functional symptoms. Distinguishing between AIG and GERD can be even more

challenging. While the pathophysiological mechanisms underlying GERD and AIG are different, they can present with similar abdominal symptoms, such as epigastric pain, heartburn, and nausea, which may pose diagnostic challenges, particularly in patients with atypical symptoms.

The pathophysiological mechanisms underlying clinical symptoms in AIG are poorly understood.

Appropriate evaluation, including endoscopy, is therefore required to differentiate these entities; indeed, based on the Rome Global Epidemiology Study, the diagnosis of FD requires the absence of organic, systemic, or metabolic disease upon routine investigation, including endoscopy [7, 8].

It is therefore important to understand the different pathogenesis of symptoms in AIG, GERD, and FD, as the management of these conditions can be very different. This is particularly important when prescribing empirically proton pump inhibitors (PPIs) based therapies, which are often considered to be the first-line therapy for GERD and are often used to manage symptoms of FD. Conversely, in AIG, a condition of hypochlorhydria, PPI therapy could further reduce acid secretion, stimulate gastrin hypersecretion, and further induce enterochromaffin-like (ECL) cell hyperplasia. As a result, the use of PPIs in patients with AIG is generally not indicated.

Therefore, accurate diagnosis and differentiation between these conditions are crucial to avoid inappropriate or potentially harmful management strategies. Understanding the pathophysiology of each condition can also guide the choice of appropriate treatments, including lifestyle modifications, dietary changes, and medication management.

In this review, we will discuss the putative pathogenic mechanisms underlying symptom generation in AIG, their clinical implications, and the current management strategies for this complex and multifaceted disease.

MATERIALS AND METHODS

An extensive bibliographical search was performed in PubMed to identify guidelines and primary literature (retrospective and prospective studies, systematic reviews, case

series) published in the last 10 years, using both medical subject heading (MeSH) terms and free-language keywords: dyspepsia; dyspeptic symptoms; gastro-intestinal symptoms; chronic autoimmune atrophic gastritis; diagnosis; treatment. The reference lists from the studies returned by the electronic search were manually searched to identify further relevant reports. The reference lists from all available review articles, primary studies, and proceedings of major meetings were also considered. Articles published as abstracts were included, whereas non-English language papers were excluded.

2 **RESULTS**

A total of 125 records were reviewed and 80 were defined as fulfilling the criteria for final consideration. **Figure 1** presents the flow chart showing the process of study selection.

DISCUSSION

Dyspepsia in autoimmune gastritis: clinical manifestations and pathophysiological mechanisms

The spectrum of clinical manifestations in AIG is wide but often nonspecific [9, 10]. Classical manifestations of AIG include pernicious anemia due to vitamin B12 deficiency, which can cause fatigue, weakness, and shortness of breath. Other hematological anomalies comprise micro/normocytic anemia due to the coexistence of iron deficiency anemia [9, 11]. Neurological symptoms such as tingling, numbness, or weakness in the limbs, are due to vitamin B12 deficiency and are characterized by neuronal damage with peripheral neuropathy, myelopathy, and autonomic dysfunction [12, 13]. Furthermore, psychiatric alterations have been reported such as depression, cognitive impairment, and psychosis [14, 15]. As AIG is often associated with other autoimmune conditions, patients may also present with symptoms related to those conditions, such as joint pain, skin rashes, or thyroid dysfunction [16]. Also, the impaired absorption of other vitamins, such as 25-OH-vitamin D, or micronutrients, such as calcium, due to gastric hypo- or achlorhydria, has been hypothesized to be a

predisposing factor also for the development of osteoporosis which can be a possible further extra gastrointestinal (GI) manifestation in AIG patients [17-19].

However, these manifestations usually characterize severe or long-standing disease.

In the early stages of AIG, patients may not present with these specific symptoms, and the patients may begin to experience non-specific GI symptoms such as upper abdominal discomfort, bloating, and nausea [11]. Focusing on GI symptoms, even if AIG is generally regarded as a silent disease, some recent studies highlight a not negligible percentage of patients who report upper GI discomfort mainly characterized by dyspeptic and/or GERD symptoms [20] and as in FD, dyspeptic symptoms may manifest as ¹¹ postprandial distress syndrome (PDS) with early satiation and/or postprandial fullness or as epigastric pain syndrome (EPS).

Indeed, according to both data from literature and real-life clinical practice, dyspepsia is frequently reported by AIG patients, which represents a challenge for their proper management.

In the cross-sectional study by Carabotti et al. [21], more than half of the patients affected by AIG (56.7%, 215 out of 397) reported GI symptoms with a prevalence of upper GI symptoms (69.8%) including dyspepsia (71.2 %), described as postprandial fullness, early satiety and/or epigastric pain, GERD related symptoms (7.2%) such as heartburn and/or regurgitation, overlap dyspepsia-GERD symptoms (17.2%) and nausea and vomiting (3.8%). Moreover, 15.8% of the patients enrolled in this study also reported lower irritable bowel syndrome (IBS) -like GI symptoms with overlapping of upper and lower GI symptoms in 14.4% of the patients (**Figure 2**).

Dyspepsia, meant either as EPS or PDS, together with GERD symptoms such as acid regurgitation and heartburn, are reported as the most frequent symptoms also in the paper by Miceli et al. [22] with a prevalence of 52.4% and 36.3%, respectively in the study population of 99 AIG patients. Contextually, weight loss and nausea are referred to approximately a quarter of patients (28.3% and 22.2%, respectively), while vomiting and dysphagia are in a lower percentage (9.1% and 3%, respectively).

According to another study [23], including a cohort of 54 patients with AIG, 70% were symptomatic for one or more upper GI symptoms, particularly a quarter of patients referred at least one typical GERD symptom such as regurgitation (18.5%) or heartburn (9%), while a major percentage complained of atypical GERD symptoms including cough (29.6%), non-cardiac chest pain (22.2%) and dysphagia (14.8%).

As far as GERD symptom is concerned, in the prospective observational study published by Tenca et al. [24], the prevalence of GERD has been investigated in a cohort of 41 AIG patients, 28 of whom with upper GI symptoms (53% GERD-related, 47% dyspepsia-like). The authors found that 24% of patients had GERD at multichannel intraluminal impedance-pH (MII-pH) monitoring mostly defined as non-acidic reflux, hypothesizing that non-acidic reflux could play a key role in the pathogenesis of the upper GI clinical manifestations. Consistent with the data above, those from the observational prospective study by Pilotto et al. [25] confirm that among the group of AIG patients complaining of reflux symptoms (38/172, 22%) only 2 patients had documented GERD while 9 patients (24.7%) had reflux hypersensitivity (RH) predominantly related to non-acid-reflux (6/9 patients). The remaining 27 patients didn't have alterations at MII-pH but six of them had a major motility disorder. Therefore, the presence of upper GI symptoms appears to be paradoxical as AIG is typically characterized by gastric mucosal atrophy with resulting hypochlorhydria and alkaline gastric pH.

The pathophysiological mechanisms underlying GI symptoms in AIG are poorly understood. Several mechanisms have been hypothesized. The hypochlorhydria resulting from gastric oxyntic atrophy may contribute to dyspeptic symptoms [5], even if other mechanisms may be responsible, such as delayed gastric emptying [26, 27], visceral hypersensitivity, and hormonal effects. Delayed gastric emptying may occur due to reduced acid secretion, which can lead to incomplete homogenization of gastric contents with macroscopic residues of undigested food and altered peristalsis, giving feelings of fullness, bloating, and discomfort after eating.

However, in patients with AIG, delayed gastric emptying has been described with elevated circulating gastrin levels and increase in parallel with the degree of the atrophy of the gastric mucosa, affecting gastric emptying T $\frac{1}{2}$ time [27]. Visceral hypersensitivity is an important candidate pathogenic mechanism for several disorders characterized by dyspepsia, even if only a few studies are available for AIG patients [26]. Moreover, some gut hormones such as motilin and ghrelin levels were significantly decreased in AIG subjects with delayed gastric emptying and deranged autonomic function[26], suggesting their potential role in the delayed gastric emptying observed in these subjects. Additionally, the loss of intrinsic factor may result in impaired absorption of nutrients such as iron and vitamin B12, which can contribute to fatigue and other symptoms. Also, low-grade chronic inflammation associated with AIG could contribute to the development of dyspepsia, in parallel to what is described for low-grade bowel inflammation with increased numbers of submucosal mast cells and lymphocytes reported in IBS [28]. Finally, chronic inflammation associated with AIG together with impaired gastric acid secretion may cause changes in the gut microbiota, and this may contribute to the development of dyspeptic symptoms; however, further research is needed to better understand the pathophysiological mechanisms underlying dyspeptic symptoms in AIG and to develop more effective treatments for this condition. **It is also important to remember that abnormal thyroid function, which is quite commonly associated with AIG, has been blamed for gastric dysmotility and dyspeptic symptoms [29], which is another possible cause of dyspepsia in AIG patients. However, it is difficult to understand whether the dyspepsia observed in AIG patients is the direct result of abnormal thyroid function or is caused by AIG itself or by a combination of these two autoimmune diseases.**

Table 1 summarizes the most frequent upper GI symptoms reported by AIG patients together with the underlying pathophysiological mechanisms.

Diagnostic work-up of dyspepsia in AIG

According to recent guidelines on the management of dyspepsia [30-32], upper GI endoscopy (esophagogastroduodenoscopy, EGDs) is a key test to identify any organic disease of the upper digestive tract (i.e., peptic ulcer, neoplasm), which may explain dyspeptic symptoms. Since EGDs is an invasive and expensive test and most patients with dyspepsia have FD [32], the American and British guidelines suggest limiting the use of EGDs to patients with suspected organic disease. Both the American and the British guidelines [30, 32] as well as a recent evidence-based revision of the existing guidelines [31] suggest screening patients for past medical history and family history, medications, previous examinations, presence of *H. pylori* infection, age, alarm symptoms and signs (i.e. anemia or bleeding, weight loss, age > 55 years, recurrent vomiting, dysphagia or odynophagia, fever). When one of the aforementioned alarm symptoms or signs is present, EGDs is mandatory to exclude or confirm an organic disease. If EGDs is negative for esophago-gastric diseases, an abdominal computed tomography (CT)-scan is suggested in order to exclude pancreatic, liver, or biliary tract cancers [32]. Distinguishing between AIG and FD in patients with dyspeptic symptoms may result difficult, as the two conditions can produce similar symptoms [20, 21]. However, certain factors such as a medical history of autoimmune disease, anemia (including microcytic and macrocytic), vitamin B12 deficiency, and positivity for anti-parietal cells antibodies (APCA) should raise clinical suspicion of AIG. In such cases, it is important to perform an EGDs to confirm the diagnosis, stage the disease, and evaluate for possible pre-cancerous lesions [33]. According to international guidelines [33], gastric biopsies should be picked up according to Sidney protocol. The protocol requires 5 gastric biopsies, which should be placed in separately labeled jars: 2 from the antrum along the lesser and greater curvature, within 2-3 cm of the pylorus; 2 from the gastric corpus (including 1 from the lesser curvature at 4 cm proximal to the incisura angularis and the other from the middle portion of the greater curvature of the gastric body at 8 cm from the cardia), and 1 from the incisura angularis [34]. Severity and topographic distribution of atrophic lesions should be reported according to Operative Link for Gastritis Assessment (OLGA) [35] and Operative Link for Gastric Intestinal

Metaplasia Assessment (OLGIM) [36]. By following this protocol, it is less likely to miss the diagnosis of AIG. Moreover, OLGA e OLGIM scores are then used to determine whether endoscopic surveillance is needed and its frequency. Conversely, if there is no suspicion of organic disease, FD could be diagnosed. However, even in these cases, both the American and British guidelines [30, 32] suggest testing dyspeptic patients for *H. pylori* with non-invasive tests (i.e. fecal antigen or carbon-urea breath testing) and treating the infected ones accordingly, as *H. pylori* infection is considered to be an etiologic factor of dyspepsia in 5% of dyspeptic patients [37].

In case of PDS, with dyspeptic symptoms that recall altered gastric emptying, gastric emptying scintigraphy (GES) is a useful tool to explore impaired (rapid or delayed) gastric dysmotility. Briefly, the test consists of a standard meal, which is marked with Technetium (Tc)-99m; after food ingestion, imaging is performed in the anterior and posterior projections at only four-time points (0, 1, 2, and 4 h). Delayed gastric emptying is determined to be >90% at 1 h, >60% at 2 h, and >10% gastric retention at 4 h. Conversely, rapid gastric emptying is determined to be < 30% at 1 h [38]. While GES performs well in diagnosing gastroparesis [39], it is not reliable for the diagnosis of FD, which is supposed to be a lighter spectrum of the same gastric disorders [40], and no specific studies exist for AIG, therefore further studies are needed to clarify this item [39]. However, this technique can be time-consuming, as the test requires imaging at set intervals over several hours, it involves radiation exposure from the radioactive material in the meal and, as for FD, also in the case of AIG, it may not be reliable, as there is only a milder form of a gastric motility disorder. Moreover, it appears to have limited therapeutic implications, as it may suggest treating the patient with prokinetic drugs at most, which can also be done ex adjuvantibus. Recently, the wireless motility capsule (WMC) has been introduced, in order to simultaneously assess both regional and whole gut transit [41, 42]. Ingestion of this non-digestible capsule that simultaneously measures luminal temperature, pH, and pressure facilitates the measurement of the gastric, small bowel, and colonic transit times. Approved by the FDA for the evaluation of gastroparesis and slow colonic transit, WMC should be

considered in suspected GI motility disorders as it provides a single study capable of simultaneously assessing for regional, multi-regional, or generalized motility disorders [43]. Triadafilopoulos et al. [43] suggested a potential WMC role in AIG diagnosis since it is able to register intragastric pH (usually > 6) and eventually associated dysmotility [43]. However, as for GES, even for WMC at present, considering the limited availability of prokinetic drugs, therapeutic implications are limited. Finally, a recent physiologic tool has been proposed to assess the functionality of the pyloric sphincter. The functional luminal imaging probe known as EndoFlip® is a 240-cm catheter with impedance electrodes at its distal end [44, 45], that is used to assess the functionality of the pyloric sphincter. The device is placed in the pylorus either through the endoscope, under endoscopic visualization [45], or either by fluoroscopy guidance [46]. After positioning the device, the balloon is filled to set volumes of 10, 20, 30, 40, and 50 ml using a stepwise protocol, and the cross-sectional area (CSA), bag pressure, and distensibility index are recorded. The pyloric distensibility index (P-DI) is calculated in the zone with the narrowest CSA with the corresponding intra-bag pressure [46]. A decreased P-DI has been observed in patients with gastroparesis [47], and also in patients with chronic nausea and vomiting without delayed gastric emptying, suggesting that pyloric dysfunction could explain "gastroparesis-like" symptoms in this group of patients [48]. However, normal and pathological values still need to be confirmed.

As mentioned above, GERD symptoms are frequently reported by AIG patients [24, 25]. According to recent guidelines [49] and Lyon consensus [50], GERD is usually a clinical diagnosis, based on patients' symptoms (typical GERD symptoms, pyrosis, and acidic regurgitation) and empiric proton pump inhibitors (PPIs) treatment response (i.e. single dose for 4-8 weeks).

Since AIG patients are supposed to have a higher intragastric pH (registered in one study, being median intragastric pH of 6.2 (4.6-7.0) [24], due to parietal cells atrophy, it may be surprising that AIG patients complain of GERD symptoms. A previous paper by Tenca et al. [24] registered that 15 out of 41 AIG patients had GERD symptoms.

Among them, acidic reflux, recorded by MII-pH monitoring, had a minor role, being present in one patient only. This could be explained by the residual production of acid from partially atrophic mucosa. Non-acidic reflux was instead more frequent, being present in 22% of the AIG population studied. It is common knowledge that non-acidic reflux can give rise to typical or atypical GERD symptoms [51-53].

Moreover, it could be useful to study these patients with MII-pH-monitoring, which is able to identify acidic, weakly acidic, and non-acidic reflux events. The observation of a role of GERD in these patients' symptoms independently of acid is clinically relevant because it can guide their management. These patients may benefit from drugs that lower their visceral sensitivity (i.e., tricyclic antidepressants and selective serotonin reuptake inhibitors) [7, 54]. Furthermore, for those with severe drug-unresponsive symptoms anti-reflux surgery is an option [55, 56]. Another study by Pilotto et al. [25] characterizes AIG patients according to their GERD symptoms and MII-pH-monitoring results. Similarly, Tenca et al. [24] found pathologic esophageal acid exposure in two out of 38 patients reporting GERD symptoms. On the contrary, a great part of them (30 out of 38 patients) had an increased number of non-acidic reflux episodes. Combining symptoms and MII-pH-monitoring results, the Authors classified AIG patients as having GERD (5%), functional heartburn (50%), and reflux hypersensitivity (24%). Interestingly, the Authors studied AIG patients with high-resolution esophageal manometry (HRM) and found that 37% of AIG patients had various motility disorders, including 8 minor disorders (n=7 weak peristalsis and n=1 hypertensive peristalsis), and 6 major disorders (n=6 EGJ outflow obstruction) according to Chicago classification v 3.0 [57]. Whether these manometric findings correlate with AIG is still debated. Similarly, the role of HRM in the diagnostic work-up of these patients remains unclear. MII-pH-monitoring could also have a role in the diagnosis of dyspepsia. It is known from the literature that epigastric pain is often more frequent in patients with pathologic MII-pH-monitoring [58]. In the population studied by Tenca et al. [24], two dyspeptic patients showed a positive correlation between epigastric pain and non-acidic reflux.

A possible diagnostic algorithm is represented in **Figure 3**.

In summary, dyspeptic symptoms and GERD are common in AIG patients; the diagnostic algorithm provides an EGDs study as the first diagnostic test, to exclude organic disease and to confirm AIG diagnosis. If GERD symptoms are present, MII-pH-monitoring is useful to measure the entity of reflux and to classify patients (GERD, functional heartburn, hypersensitive esophagus) and treat them accordingly. Moreover, it could be useful in dyspepsia diagnosis. Esophageal motility tests, as well as gastric emptying tests, could have a role in AIG patients but further studies are needed to clarify these items.

Treatment

Dyspepsia is a common symptom in AIG and its management can be challenging, as the pathophysiology underlying dyspeptic symptoms in AIG is multifactorial. However, this issue is still understudied, and more research is needed to better understand the mechanisms of dyspepsia in AIG and to develop effective treatments tailored to the individual patient's symptoms and underlying pathophysiology. Indeed, although the primary goal of AIG treatment is to address vitamin deficiencies and prevent and monitor for gastric neoplasms, effectively managing common and difficult-to-treat symptoms like dyspepsia is crucial for improving patients' quality of life.

As a matter of fact, according to available guidelines [10], ⁵ there is poor evidence regarding the best treatment options for dyspeptic symptoms in patients with AIG, also considering that PPIs are not indicated in this subset of patients who are typically hypochlorhydric. Despite this, several AIG patients referring dyspeptic symptoms are often prescribed PPIs by General Practitioners or gastroenterologists with no or low knowledge of this disease. The use of PPIs in this subgroup of patients should be discouraged for two main reasons. Firstly, AIG is characterized by a suppressed gastric acid secretion and consequent hypochlorhydria, thus treatment with antisecretory drugs is generally ineffective as already reported [24, 59] taking into account that these patients refer reflux-like symptoms whose nature is non-acid. Secondly, and far more

important, the long-term use of PPIs has been reported to be associated with the development or progression of gastric pre-malignant lesions. Of note, as already reported [60], the long-term treatment with PPIs which is responsible for increased levels of serum gastrin seems to be linked to a higher risk of progression of ECL-cell hyperplasia which precedes the development of gastric type 1 neuroendocrine neoplasm [61]; however, no clear-cut evidence was found between PPI therapy and increased progression of AIG or intestinal metaplasia [60].

Initial management of dyspepsia in AIG may involve dietary modifications, such as avoiding trigger foods or eating smaller, more frequent meals. Patients may also benefit from lifestyle modifications, such as weight loss or stress reduction techniques, even if these procedures are not evidence-supported.

It is important to highlight that patients with AIG often have evidence of current or prior *H. pylori* infection [62]. Therefore, it is important to test these patients for *H. pylori* and, if positive, to eradicate it according to guidelines that suggested the “Test and treat” strategy [63]. Of note, *H. pylori* eradication appears to reduce the risk of gastric cancer [64]. In the specific setting of AIG, according to a randomized double-blinded placebo-controlled trial [65], that compared triple eradication therapy for *H. pylori* with placebo in histologically diagnosed AIG patients, at 3-years follow-up dyspeptic symptoms scores improved significantly in the patients in whom *H. pylori* had been eradicated. Similar findings were reported by another recent study [66], which showed that the beneficial effect of *H. pylori* eradication treatment on dyspeptic symptoms lasted until one year after treatment, being associated with a higher pretreatment symptom score and age inferior to 70 years old. Obviously, the benefit of *H. pylori* eradication in AIG patients is further increased by the fact that *H. pylori* more than autoimmunity per se, is linked to the risk of evolution towards dysplasia and gastric cancer in AIG, as recently described [1].

In addition to *H. pylori* eradication, several treatment options [67] have been investigated for their efficacy in managing dyspeptic symptoms in AIG. These treatments include prokinetic agents, neuromodulators, and herbal agents, as well as

non-pharmacological treatments such as acupuncture, cognitive-behavioral therapy, and hypnotherapy. However, the evidence regarding their effectiveness is conflicting also taken into account the lack of dedicated prospective studies exploring the efficacy of prokinetics and neuromodulators in this specific setting of patients, making the management of AIG patients experiencing dyspeptic symptoms very challenging. Medications such as prokinetic agents including metoclopramide or domperidone may be used to improve gastric motility and reduce symptoms of bloating and nausea in patients with predominantly PDS symptoms. For patients presenting with EPS symptoms, a rational approach could therefore be to guide therapy based on the altered pathophysiological mechanism. As mentioned before, 24-hour MII-pH-monitoring may be a useful tool to classify AIG patients having GERD symptoms. If MII-pH-monitoring found true acidic GERD, PPIs treatment could have a role. Being this an extremely rare condition, there are no clear-cut recommendations on treatment dosage and duration. Conversely, if MII-pH-impedance diagnoses a non-acidic reflux disease, as well as functional heartburn and reflux hypersensitivity, these patients may benefit from drugs that lower their visceral sensitivity (i.e. tricyclic antidepressants and selective serotonin reuptake inhibitors) [7, 54]. Moreover, patients who did not respond to medical treatment as well as patients with a high burden of non-acidic reflux, may benefit from anti-reflux surgery [55, 56].

In cases where dyspepsia is associated with underlying anxiety or depression, treatment with antidepressants or anxiolytics may be warranted [7, 54]. However, future research is needed to identify more effective treatments for dyspepsia in AIG and to better understand the underlying mechanisms that drive dyspeptic symptoms in this condition.

Furthermore, a known consequence of atrophic gastritis-related hypochlorhydria and/or achlorhydria is a change in the gastric microbiome composition. However, there are currently no specific therapies targeting dyspepsia in AIG based on changes in the microbiota, even if an abnormally elevated presence of endoluminal bacteria which produce acetaldehyde from glucose metabolism has been described [68]. Again,

according to some authors [69, 70], L-cysteine, a non-essential amino acid, can modify the microenvironment of the achlorhydric stomach by both inactivating acetaldehyde and promoting recovery of gastric function [71, 72]; furthermore, there is some anecdotal evidence that L-cysteine might improve functional symptoms often associated with atrophic gastritis. Based on these observations, Di Mario et al. [73] recently conducted a study including a total of 330 patients with atrophic gastritis (both autoimmune or *H. pylori*-related), who were divided into two groups, treated with long-term L-cysteine and no specific treatment, respectively, and reported a significant improvement in the symptom scores of patients treated with L-cysteine when compared to the non-treated group. Of note, symptom improvement lasted all the two years of the follow-up. One limitation of this study is the inclusion of different etiologies from atrophic gastritis, which might be responsible for a certain grade of heterogeneity. While research into the gut microbiota and its role in AIG is ongoing [74, 75], some studies suggest that probiotics and prebiotics may have a role in modulating the gut microbiota and reducing symptoms in patients with dyspepsia, including those with AIG [76, 77]. Overall, while the potential for microbiota-based therapies in managing dyspepsia in AIG is promising, further research is needed to develop and validate such approaches.

Finally, further treatment may be available in the near future. Gastric per-oral endoscopic myotomy (G POEM) is a novel endoscopic procedure that has shown promising results in the management of refractory gastroparesis [78]. This technique has received increasing attention and emerged as a promising treatment for refractory gastroparesis, targeting the pylorus [79], as a result of the use of new tools to identify pyloric dysfunction in routine care, including functional luminal impedance planimetry (FLIP). The procedure involves creating a myotomy or an incision in the inner lining of the stomach, thereby allowing for better gastric emptying. Since AIG patients with PDS may have the same functional dysfunction of patients affected by gastroparesis, both from a pathophysiological and clinical point of view, G POEM may represent a feasible treatment for AIG patients with severe dyspeptic symptoms, which did not respond to

medical treatment. Even if it is considered a safe procedure, a potential concern associated with G POEM is the risk of complications, such as bleeding, perforation, and infection [80]. Additionally, the long-term outcomes of G POEM are still unclear, and more studies are needed to assess its durability and impact on patient quality of life. Recently, Mandarino et al. [81] found that a lower Intra-gastric Meal Distribution (IMD) at pre-intervention gastric emptying study, which indicates antral food retention, could be associated with post-procedural functional success, defined as a decrease of more than 30% % 2-hour retention. However, further data are needed to establish long-term efficacy of endoscopic pyloromyotomy, especially in the management of dyspeptic AIG patients.

CONCLUSION

AIG can cause a range of clinical manifestations, including dyspepsia. Accurate diagnosis and appropriate management of dyspepsia in AIG are important to improve the patient's quality of life, as well as to prevent and monitor for potential complications such as vitamin deficiencies and gastric neoplasms.

The pathophysiology of dyspepsia in AIG is complex and involves changes in acid secretion, gastric motility, hormone signaling, and gut microbiota, among other factors. Specifically, investigating the role of visceral hypersensitivity, impaired gastric accommodation, and impaired gastric motility in AIG-related dyspepsia may help to identify new targets for treatment.

Managing dyspeptic symptoms of AIG is challenging and there are no specific therapies targeting dyspepsia in AIG. While PPIs are commonly used to treat dyspepsia and GERD, they may not be appropriate for AIG, as the condition is already characterized by hypochlorhydria. Instead, prokinetic agents, antidepressant drugs, and non-pharmacological treatments may be of help, even if not adequately evidence-based supported.

Targeting dyspepsia in AIG based on changes in the microbiota is an area of ongoing research and some studies suggest that probiotics and prebiotics may have a role in reducing symptoms.

G POEM may represent a feasible treatment for AIG patients with severe dyspeptic symptoms, even if more research is needed to establish its safety and efficacy in this specific setting of patients.

Figure 4 summarizes the possible therapeutic approaches for dyspeptic or with GERD-like symptoms in patients with AIG.

Overall, a multidisciplinary approach for the management of dyspepsia in AIG is recommended, and further research is needed to develop and validate more effective therapies for dyspepsia in AIG, as well as to better understand the underlying pathophysiology of the disease.

ARTICLE HIGHLIGHTS

Research background

Gastrointestinal symptoms such as dyspepsia and early satiety are very common in autoimmune gastritis (AIG), being second in terms of frequency only to anemia, which is the most typical feature of AIG. Understanding the pathophysiology of each condition can also guide the choice of appropriate treatments, including lifestyle modifications, dietary changes, and medication management.

Research motivation

The management of dyspepsia in patients with autoimmune gastritis (AIG), a chronic, immune-mediated disease, remains a challenge, as it can overlap with functional dyspepsia and gastroesophageal reflux disease. Currently, there are no specific therapies. A tailored treatment approach based on a better understanding of putative pathogenic mechanisms underlying symptoms is needed.

Research objectives

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In this review, we will discuss the putative pathogenic mechanisms underlying symptom generation in AIG, their clinical implications, and the current management strategies for this complex and multifaceted disease.

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Research methods

An extensive bibliographical search was performed in PubMed to identify guidelines and primary literature (retrospective and prospective studies, systematic reviews, case series) published in the last 10 years, using both medical subject heading (MeSH) terms and free-language keywords: dyspepsia; dyspeptic symptoms; gastro-intestinal symptoms; chronic autoimmune atrophic gastritis; diagnosis; treatment.

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Research results

A total of 125 records were reviewed and 80 were defined as fulfilling the criteria.

Research conclusions

AIG can cause a range of clinical manifestations, including dyspepsia. The pathophysiology of dyspepsia in AIG is complex and involves changes in acid secretion, gastric motility, hormone signaling, and gut microbiota, among other factors. Managing dyspeptic symptoms of AIG is challenging and currently, there are no specific therapies. A tailored treatment approach based on a better understanding of putative pathogenic mechanisms underlying symptoms is needed. While proton pump inhibitors (PPIs) are commonly used to treat dyspepsia and GERD, they may not be appropriate for AIG. Prokinetic agents, antidepressant drugs, and non-pharmacological treatments may be of help, even if not adequately evidence-based supported. A multidisciplinary approach for the management of dyspepsia in AIG is recommended, and further research is needed to develop and validate more effective therapies for dyspepsia.

Research perspectives

As a future perspective, targeting dyspepsia in AIG based on changes in the microbiota and advanced endoscopic techniques to treat severe dyspeptic symptoms might be an area of ongoing research.

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