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MAJOR APPROACHES IN AUTO-IMMUNE GASTRITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Autoimmune gastritis (AIG) is a subtype of chronic gastritis that is characterized by autoimmunity to parietal cells, leading to inflammation and atrophy restricted to the oxyntic mucosa, resulting in hypergastrinemia, which can lead to vitamin B12 deficiency and, consequently, pernicious anemia. Standardization of AIG histology reports and classifications in diagnostic practice is a prerequisite. Thus, in the light of endoscopy, the AIG assessment includes a degree of atrophy, remaining oxyntic mucosa, the property of mucus, and tiny whitish scattered protrusions. **Objective:** To analyze through systematic review the main endoscopic approaches and micronutrient deficiencies of autoimmune gastritis, in order to know and present the main medical guidelines to the scientific medical community. Methods: The model followed for the systematic review was PRISMA. A total of 54 clinical studies were compared and submitted to the eligibility analysis and, after that, 17 studies were selected to compose the study. The PubMed, Embase, Ovid and Cochrane Library, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile databases were used. **Main findings:** The present study demonstrated some prominent clinical features and endoscopic findings from AIG. The diagnosis of chronic autoimmune atrophic gastritis (CAAG) can be challenging and usually requires the combination of endoscopic, clinical, serological, and histopathological data. Iron deficiency in AIG is more common than celiac disease. Serological suspicion of AIG helps pre-select patients for endoscopic work. Still, another study showed that there is a significant reduction in the levels of 25 (OH) D in patients with CAAG and a possible impairment of vitamin D absorption can be postulated. **Conclusion:** The standardization of autoimmune gastritis in diagnostic practice is a prerequisite for the implementation of definitive secondary prevention strategies based on multidisciplinary diagnostic approaches that integrate endoscopy, serology, histology, and molecular profile. Upper gastrointestinal endoscopy with pH-measurement of gastric juice and histology can be performed to confirm positive serological results.

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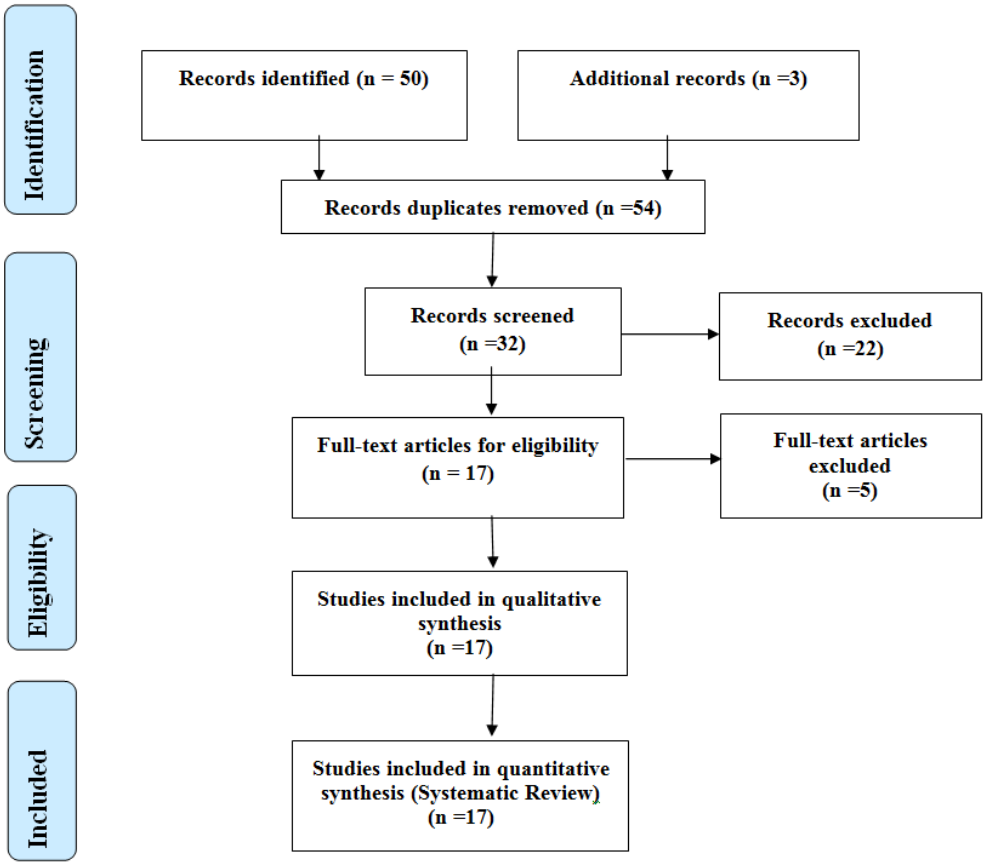
INTRODUCTION

Autoimmune gastritis (AIG) is a subtype of chronic gastritis [1]. The authors Strickland and Mackay [2] were the first to describe AIG, which is characterized by autoimmunity to parietal cells, leading to inflammation and atrophy restricted to the oxyntic mucosa, resulting in hypergastrinemia. AIG and its clinical manifestation, pernicious anemia, have already been reported as dominant in elderly women of northern European ethnicity.

However, studies have indicated that there is no racial specificity, but considerable age diversity in the clinical presentation of the disease. In addition, recent research has shown that gastric dysbiosis associated with improved modern sanitation could cause a relatively increased risk of AIG [3]. In this sense, AIG, because is a chronic inflammatory disease with the destruction of the body's parietal cells and the bottom of the stomach, can lead to vitamin B12 deficiency and, consequently, pernicious anemia. Thus, iron deficiency is commonly found in patients with AIG.

Flow chart



This usually precedes vitamin B12 deficiency and is found mainly in young women. Patients with chronic iron deficiency, especially those refractory to oral iron therapy, should therefore be assessed for the presence of autoimmune gastritis [4]. In this context, AIG can occur due to the autoimmune aggression that attacks parietal cells through a complex interaction of autoantibodies against the proton pump of parietal cells. Given the specific target of this aggression, AIG is restricted to the mucosa of the gastric body (CG). In advanced cases, oxyntic epithelia are replaced by atrophic and metaplastic mucosa, creating the phenotypic picture in which both gastric neuroendocrine tumors and adenocarcinomas can develop [4]. However, there are still no biomarkers available to identify patients at greatest risk of developing gastric cancer. The standardization of AIG histology reports and classifications in diagnostic practice is a prerequisite for the implementation of definitive secondary prevention strategies based on multidisciplinary diagnostic approaches that integrate endoscopy, serology, histology, and molecular profile [5]. Thus, under the light of endoscopy, the AIG evaluation includes a degree of atrophy, remaining oxyntic mucosa, mucus property, and tiny whitish scattered protrusions (SWP). The extent of normal mucosal patterns and local findings in the antrum should also be assessed [1]. Therefore, the present study analyzed, by means of a systematic review, the main endoscopic approaches and micronutrient deficiencies of autoimmune gastritis, in order to know and present the main medical guidelines to the scientific medical community.

METHODS

Study Design: After literary search criteria using the MeSH Terms that were cited in the item below on “Search strategies”, a total of 54 clinical studies were compared that were submitted to the eligibility analysis and, after that, 17 studies were selected, following the systematic review rules – PRISMA (Transparent reporting of systematic reviews and meta-analyzes-HTTP: //www.prisma-statement.org/).

Search Strategy and Information Sources: The search strategy was carried out in the databases PubMed, Embase, Ovid and Cochrane Library, Web Of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: - search by MeSH Terms: Autoimmune gastritis. Chronic autoimmune atrophic gastritis. Micronutrient deficiency, and the use of Booleans "and" between MeSH Terms and "or" among historical findings.

Risk of Bias: Considering the Cochrane tool for the risk of bias, the global assessment resulted in 3 studies with a high risk of bias and 2 studies with uncertain risk. In addition, there was an absence of the source of funding in 3 studies and two studies did not disclose information about the conflict of interest statement.

Major Findings and Development: The evaluation of the gastric body (GB) includes a degree of atrophy, remaining oxyntic mucosa, the property of mucus, and tiny scattered whitish protrusions (SWP). The extent of normal mucosal patterns and local findings in the antrum also need to be assessed. The remaining oxyntic mucosa is defined as normally colored and smooth surface patterns of oxyntic mucous areas contrasted by the surrounding discolored atrophic mucosa [1]. The dense mucus should show a creamy yellowish-white color that is denser and adhered firmly to the mucosa. Furthermore, SWP was defined as tiny hemispheric whitish protrusions spread over the GB mucosa, covered by

epithelial capillaries. The extended narrowband imaging (BEA) method should be applied to patients when endoscopists feel the need for close observation [1]. Thus, for a better understanding of the diagnosis, eleven institutions in Japan formed a research committee to standardize the diagnostic endoscopic appearances to minimize the variability of observations. Therefore, they defined three factors as an endoscopic body predominantly with severe atrophic gastritis, the presence of anti-cellular parietal antibody (PCAb) or anti-intrinsic factor antibody (IFAb) or pernicious anemia and Hypergastrinemia (> 350 pg/mL) [1]. The endoscopic body with predominantly severe atrophic gastritis was defined when the discolored mucosa with marked vascular visibility was observed not only in curvatures but in the entire area of the great curvature of the body, along with the disappearance of folds without an atrophic border, which is called Op (or O-4) atrophy, accompanied by atrophic patterns in the antrum [1]. Pernicious anemia was defined as vitamin B12 (VB12) <233 pg / mL, mean corpuscular volume (CMV)> 80 fl and hemoglobin (Hb) <13.0 g/dL (male) or 11.4 g/dL (feminine). Therefore, the diagnosis of AIG is established when all three criteria are met [1].

Based on the diagnostic description reported in the previous item, the multicenter study with 11 institutions in Japan involving 245 patients with AIG aimed to clarify the characteristics of autoimmune gastritis, especially its endoscopic appearances. The average age was 67.2 ± 11.4 years and 63.7% of the participants were women. The most common approach to diagnosing AIG was an endoscopic examination. The repeated incorrect treatments for H. pylori (Hp) infection and two false-positive results in the 13C-urea breath test ranked third among the bases for the diagnosis of AIG. Thus, the associated gastric lesions were type 1 neuroendocrine tumor (11.4%), adenocarcinoma (9.8%), and hyperplastic polyps (21.1%). Pan-atrophy of the body was the most common appearance (90.1%); however, the remaining oxyntic mucosa was found in 31.5% of the patients (flat, localized type, 48.6%). Dense sticky mucus and SWP were also observed in approximately 30% of patients. Although the antral mucous membranes remain normal, 42.3% of the patients had various extensions of atrophy, and irregular redness and circular patterns similar to wrinkles wereobserved in approximately 20% of the patients. Therefore, this study demonstrated some prominent clinical features and endoscopic findings of AIG [1]. In this context, similar to the results in Western and other Asian countries [4] the results of this study showed that AIG is dominant in women and the elderly [5]. The prevalence of pernicious anemia (39.1%, 52/133) was consistent with that of previous reports [6,7], and the lower prevalence of iron deficiency anemia (6.5%, 13/199) in the elderly cohort (67.5 years) was also in agreement with this study [7]. The association between Hp infection and AIG was previously discussed [8-10], however, the prevalence of the coexistence of the two has not been clarified. The result that 7.8% (17/218) of the patients were positive for the Abgl IgG anti-Hp test is low, considering the high prevalence of Hp infection in the elderly in Japan.

Thus, the diagnosis of AIG generally depends on biopsy sampling that complements other laboratory data or clinical manifestations [11]. However, according to the consensus advocated in Japan, endoscopic appearances were first considered as a basis for diagnosis before any other diagnostic features. Some of the patients who underwent treatments were incorrectly classified as positive for Hp. A previous report suggested that the proliferation of urease-positive bacteria, in addition to Hp, under non-acidic circumstances, possibly resulted in positive results in the 13C-urea test [12]. In this sense, and as an extension of the clinical description of AIG, chronic autoimmune atrophic gastritis (CAAG) is the endpoint of chronic processes, with the loss of glandular cells and their replacement by the intestinal epithelium, pyloric glands, and fibrous tissue [14]. As a consequence, hydrochloric acid, pepsin and the intrinsic factor are impaired, resulting in pernicious anemia [15]. The exact causal agent is not yet known, but genetic and environmental factors appear to play a decisive role. Also, clinical onset may have different characteristics. Recent evidence reported the onset of CAAG at a younger age may be related to iron deficiency anemia or upper gastrointestinal symptoms. The diagnosis of CAAG can be challenging and usually requires a combination of clinical, serological, and histopathological data. Also, patients with CAAG are often misdiagnosed as refractory to Hp eradication therapy, probably because gastric achlorhydria can allow urease-positive bacteria, in addition to Hp, to colonize the stomach, causing positive results on the 13C- urea. Furthermore, CAAG represents a pre-neoplastic condition, since patients with CAAG are very likely to develop type 1 gastric neuroendocrine tumors and gastric adenocarcinomas, as well as several other neoplastic diseases [13].

Also, iron deficiency is a common challenge for gastrointestinal endoscopy. In pre-menopausal women, current guidelines recommend a serological evaluation of celiac disease only. A retrospective study of 373 patients with iron deficiency was included, about half of whom were anemic systematically analyzed serological screening for AIG in a large cohort of patients with iron deficiency. Patients with ferritin <50 µg/L or transferrin saturation <15% were included. Laboratory work included endomysium antibodies and parietal cell antibodies (PCA). Upper gastrointestinal endoscopy with pH-measurement of gastric juice and histology was performed to confirm positive serological results. The patients were predominantly female with a median age of 40 years. Positive endomysial antibodies were found in 4 (1%) patients, elevated levels of PCA (> 20 U/mL) were found in 69 (18.5%) patients, PCA> 100 U/mL in 23 (6.2%) . Twenty-six were followed up by gastroscopy; in 12 of 26 patients, the diagnosis of AIG was confirmed by histology with 2 additional patients diagnosed as early and/or questionable AIG. In 20 patients, gastric pH was measured. Achlorhydria was found in 7 patients all diagnosed with AIG. Therefore, in this iron deficiency cohort, AIG is more common than celiac disease. PCA above 100 U/mL is a sensitive and specific cut for investigating patients with iron deficiency before endoscopy. Serological suspicion of AIG helps pre-select patients for endoscopic work [16]. Still, CAAG may play a role in the pathogenesis of nutritional deficiencies, and there has been a possible association between CAAG and 25-OH-Vitamin D deficiency [25 (OH) D]. Thus, a study of 87 patients (71 women; mean age 63.5 ± 12.8 years) assessed the prevalence of 25 (OH) D deficiency in patients with CAAG. Then, 25 (OH) D, vitamin B12, parathyroid hormone, and calcium were measured in all patients. The results were compared with a control group of 1232 healthy individuals. In the CAAG group, the mean levels of 25 (OH) D were significantly lower than in the control group (18.8 vs. 27.0 ng/mL, p <0.0001). Levels of 25 (OH) D <20 ng/mL were observed in 57 patients, while levels <12.5 ng / mL in 27

patients. There was a significant correlation between vitamin B12 values at diagnosis and levels of 25 (OH) D (rs = 0.25, p = 0.01). Also, 25 (OH) D levels were significantly lower in CAAG patients with gastric carcinoids when compared to gastric carcinoids only (11.8 versus 19.8 ng/mL; p = 0.0041). Therefore, the results of this study showed a significant reduction in 25 (OH) D levels in CAAG patients and a possible impairment of vitamin D absorption can be postulated [17].

Conclusion

The standardization of autoimmune gastritis in diagnostic practice is a prerequisite for the implementation of definitive secondary prevention strategies based on multidisciplinary diagnostic approaches that integrate endoscopy, serology, histology, and molecular profile. Upper gastrointestinal endoscopy with pH-measurement of gastric juice and histology can be performed to confirm positive serological results.

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