Autoimmune Atrophic Gastritis

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Autoimmune atrophic gastritis is an organ-specific immune-mediated condition characterized by atrophy of the oxyntic mucosa. Autoimmune atrophic gastritis (AIG) is characterized by a progressive loss of acid-secreting parietal cells leading to hypo-achlorhydria. Due to this peculiar intra-gastric environment, gastric microbiota composition in individuals with autoimmune atrophic gastritis was first supposed and then recently reported to be different from subjects with a normal acidic healthy stomach. Recent data confirm the prominent role of Helicobacter pylori as the main bacterium responsible for gastric disease and long-term complications. However, other bacteria than Helicobacter pylori, for example, Streptococci, were found in subjects who developed gastric cancer and in subjects at risk of this fearful complication, as well as those with autoimmune gastritis. Gastric microbiota composition is challenging to study due to the acidic gastric environment, the difficulty of obtaining representative samples of the entire gastric microbiota, and the possible contamination by oral or throat microorganisms, which can potentially lead to the distortion of the original gastric microbial composition, but innovative molecular approaches based on the analysis of the hyper-variable region of the 16S rRNA gene have been developed, permitting us to obtain an overall microbial composition view of the RNA gene that is present only in prokaryotic cells.

Keywords: Autoimmune Atrophic Gastritis ; Gastric Microbiota ; organ-specific immune-mediated condition

1. Introduction

Autoimmune atrophic gastritis (AIG) is a relatively frequent and often undiagnosed disorder with important and potentially life-threatening consequences from a clinical point of view, ranging from micronutrient deficiencies and severe anemia to such neoplastic complications as gastric cancer and gastric type 1 neuroendocrine tumors. Due to its peculiar intra-gastric environment, characterized by severely impaired gastric acid secretion as a result of gastric oxyntic mucosa atrophy, the gastric microbiota composition in individuals with AIG was first supposed and then recently reported to be different from subjects with a normal acidic stomach, possibly assuming a key role in the development of neoplastic complications. This evidence adds new pieces to a constantly developing puzzle on the knowledge of autoimmune atrophic gastritis, a condition far from being completely investigated, and opens the door to new and intriguing perspectives on the management and possible treatment options of this important condition, which reduces the quality of life of millions of persons all over the world. This review addresses different aspects of AIG, focusing particularly on epidemiology, the clinical picture and management, the relationship between hypochlorhydria and long-term complications, and the interplay between the gastric microbiota, autoimmune gastritis and its clinical consequences, as well as the complicated and still debated role of Helicobacter pylori infection, providing an updated summary of recent scientific evidence on this intriguing topic.

2. Epidemiology and Clinical Manifestations of Autoimmune Gastritis

AIG is an organ-specific immune-mediated condition that affects the corpus and fundus of the stomach; AIG is characterized by atrophy of the oxyntic mucosa with subsequent hypochlorhydria, hypergastrinemia, and deficiency of intrinsic factors, leading, in late stages, to pernicious anemia [1]. AIG's classical histopathological alterations consist of corporal-limited Helicobacter pylori (Hp)-negative atrophic gastritis with a spared antrum; sometimes, active Hp infection and/or involved antral mucosa may be observed in AIG, showing overlapping features with the multifocal atrophic gastritis mainly linked to Hp [2]. AIG is a condition that may involve any age group, but more frequently affects the elderly and females; most cases are reported in subjects of Northern European descent [3]. The absence of proactive case-finding strategies for AIG diagnosis, the lack of epidemiological studies, and the frequent indolent disease course, possibly leading to an underestimation of the disease, may contribute to the lack of knowledge of the true prevalence of AIG [4]. Moreover, in most papers published in the recent past, AIG was diagnosed only based on serological biomarkers such as anti-parietal cell or anti-intrinsic factor antibodies (PCA/IFA), pepsinogen, and/or gastrin-17 levels [5][6] without any histological confirmatory diagnosis. Finally, for several years, the diagnosis of AIG was frequently underestimated and

mistakenly considered only in cases of pernicious anemia (PA), with macrocytic anemia due to vitamin B_{12} malabsorption usually manifesting itself in the late stage of the disease [7][8]. Based on this scenario, AIG prevalence has been estimated to be ~0.5–4.5% globally, varying widely owing to different diagnostic criteria, ethnical and demographical settings [4].

From a pathological point of view, AIG is thought to be the result of a complex interaction between environmental factors and host-related factors such as genetic susceptibility, but data are scant. An Italian study showed a significantly higher prevalence of HLA-DRB1*03 and HLA-DRB1*04 alleles in patients with AIG than in a healthy control group [9]. By contrast, a Finnish study found an association between AIG and HLA-DRB1*04/HLA-DQB1*03, but not with HLA-DRB1*03 [10]. These HLA haplotypes are also frequently associated with other autoimmune diseases, in particular autoimmune thyroid disease, thereby underlining a common HLA-dependent autoimmune pathway [4].

Despite the advancements in knowledge that have been made in the field of AIG, the trigger precipitating the autoimmune response has not been clarified. The resulting immunological dysregulations involve sensitized CD4+T lymphocytes and PCA/IFA, while gastric corpus/fundus tissue damage results from an antibody-mediated destruction of the parietal cells due to selective targeting of the H+/K+ ATPase proton pump [11]. PCA are of immunoglobulin G type, they are directed against the parietal cell H+/K+ ATPase, and they are mainly considered serological markers of autoimmune gastritis. PCA/IFA positivity is considered a helpful tool for AIG diagnosis. However, detection of those antibodies is not sufficient for AIG diagnosis, because they are not specific and are also found in healthy individuals for in escaped negative thymic selection or in patients with other autoimmune diseases such as type 1 diabetes or thyroid diseases, whereby the AIG prevalence is comparatively three- to fivefold higher [12].

Furthermore, serology against H. pylori (IgG AbHp) may be positive in AIG patients with previous contact with the bacterium or in those previously treated for the infection. When a positive serological titer of AbHp is found in a patient with AIG together with a polymorphonucleate inflammatory infiltrate in the gastric mucosa, an active H. pylori infection should be suspected [13].

From a clinical point of view, AIG has been traditionally considered a silent condition, often suspected due to its hematologic findings, and rarely by the presence of gastrointestinal symptoms. Despite the fact that most patients are pauci- or asymptomatic, several studies have shown that dyspeptic symptoms such as postprandial fullness, early satiety, and nausea are among the most common symptoms complained about by AIG patients [14][15][16]. Most commonly, AIG may be suspected in the presence of an iron deficiency and, in particular, anemia due to iron malabsorption consequent to reduced gastric acid secretion (25–50% of patients with AIG) or, rarely, in the presence of pernicious anemia, which is found in up to 15–25% of AIG patients [17][18][19][20]. Less frequently, AIG patients may complain of neurological symptoms such as paresthesia, abnormal proprioception, numbness, ataxia, cognitive impairment, mood disorders, and psychosis. Neurological symptoms are consequences of vitamin B_{12} deficiency, due to an impairment of sensory and peripheral nerve function linked to a reduced production of succinyl coenzyme A, which is essential for myelin sheath structure [21] [22]. Finally, concomitant autoimmune diseases, especially Hashimoto thyroiditis or a positive family history for AIG may contribute to increasing the suspicion of an AIG diagnosis.

3. Conclusions Remarks and Research Agenda

As in other body districts, in the stomach, growing knowledge of the possible role of the microbiota in health and disease is emerging from recent studies. Recent data confirm the prominent role of Hp as the main bacterium responsible for gastric disease and long-term complications. However, other bacteria, and possibly other poorly or not yet investigated viral or fungal microbiota components, are emerging and likely play a role in conditions with an altered intragastric environment such as AIG, which is notably characterized by a non-acidic stomach favoring the overgrowth of microorganisms that are otherwise not viable in the acidic stomach. Some of these bacteria, for example, Streptococci, are found in subjects who have developed gastric cancer and in subjects at risk of this fearful complication, such as those with AIG. These first pieces of evidence certainly cannot be interpreted as a point of arrival, but should rather be viewed as a starting point for future research in this very complex and intriguing field in which much work is yet to be done. In the last few years, many pieces have been added to the knowledge puzzle, and future research is needed. As detailed in Table 1, several aspects are still awaiting clarification, to ultimately pave the way for possible innovative treatment strategies to eventually prevent the progression of AIG or neoplastic complications by therapeutic gastric microbiota modulation.

Table 1. Proposal of research agenda on gastric microbiota.

1 To standardize techniques and gastric samples used to assess the viable microbiota in the stomach by giving priority to innovative methods based on RNA for sequencing

2 To perform studies considering possible confounding factors on the gastric microbiota such as drugs and dietary, smoking, and alcohol habits
3 To perform longitudinal, multicentre studies to increase the knowledge on the role of gastric microbiota in gastric carcinogenesis
4 To launch studies on the gastric microbiota in Caucasian populations as the available data on Asian populations may not be necessarily comparable and valid in non-Asian subjects

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