Advances in Medical Sciences 61 (2016) 175–179

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Review Article

Anti-parietal cell antibodies – diagnostic significance

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ARTICLE INFO

Article history:
Received 28 August 2015
Accepted 31 December 2015
Available online 13 January 2016

Keywords:
Anti-parietal cell antibodies
Autoimmune atrophic gastritis
Autoimmunity
Pernicious anemia

ABSTRACT

Anti-parietal cell antibodies (APCA) are an advantageous tool for screening for autoimmune atrophic gastritis (AAG) and pernicious anemia (PA). The target for APCA is the H+/K+ ATP-ase. It has been demonstrated, that APCA target both, the alpha, and beta subunits of the proton pump, although the major antigen is the alpha subunit. Circulating serum APCA can be detected by means of immunofluorescence, enzyme-linked immunosorbent assay – currently the most commonly used method, and radioimmunoprecipitation assay (RIA) – the 4A subunit has been optimized as a molecular-specific antigen probe. RIA is the most accurate method of antibody assessment, characterized by highest sensitivity. APCA can be found in 85–90% of patients with PA. Their presence is not sufficient for diagnosis, because they are not specific for PA as they are also found in the circulation of individuals with other diseases. APCA are more prevalent in the serum of patients with T1D, autoimmune thyroid diseases, vitiligo, celiac disease. People with autoimmune diseases should be closely screened for AAG/PA. The anemia develops longitudinally over many years in APCA-positive patients, symptomless, slowly promotes atrophy of the gastric mucosa and parietal cells. APCA are present in 7.8–19.5% of the general healthy adult population. A fraction of these sero-positive people, will never develop AAG or PA. An interesting and not fully explained question is whether APCA presence is related to *Helicobacter pylori* infection. APCA are found in up to 20.7% of these patients. *H. pylori* is implicated as one of the candidates causing AAG.

Contents

1. Introduction

It is estimated that autoimmune diseases currently affect up to 9% of the population, although their prevalence is progressively increasing [1,2]. In general autoimmune diseases occur significantly more often in females [2,3]. As one of the causes of disability

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http://dx.doi.org/10.1016/j.advms.2015.12.004
1896-1126/

among people of reproductive age, autoimmune diseases have become a serious medical and socio-economic problem.

Autoimmune atrophic gastritis (AAG) is a chronic, organ-specific, inflammatory disease of the gastric mucosa, that may progress to its final, severe stage – pernicious anemia (PA). Both develop unperceptively over many years, often without any symptoms [4]. As such, PA and AAG often remain undiagnosed yet they affect people on all continents [4–6]. The persistent inflammatory infiltration of the gastric mucosa in AAG/PA results from a complex interaction between sensitized T cells and anti-parietal cell antibodies (APCA) [7–9].

The overall incidence of AAG is estimated to approximate 2%, although AAG and PA seem to be underdiagnosed [7]. AAG/PA incidence increases with age [7,10]. Therefore early diagnosis and treatment of this conditions are imperative to prevent the development of chronic symptoms and irreversible complications [3,11]. Often only severe complications, as in PA or collateral neurological disorders first suggest the diagnosis [12,13]. AAG is especially pervasive in individuals with other autoimmune diseases, such as type 1 diabetes (T1D) or thyroid diseases whereby the AAG prevalence is comparatively three- to fivefold higher [10].

APCA are a serum biomarker of autoimmune gastritis, are present in most patients with AAG and 85–90% individuals with PA [9,14,15]. Therefore APCA are an advantageous tool for screening for disease. However alone their presence is not sufficient for diagnosis, because they are not specific for AAG or PA as they are also found in the circulation of individuals with other autoimmune diseases [3,14,15]. PA diagnostic tests that monitor autoantibodies targeting intrinsic factor (IF) (a product of the parietal cell) are less sensitive (present only in 60% of patients), but more specific (98.6%) [3,14,16].

Circulating serum APCA can be detected using various laboratory methods: immunofluorescence, enzyme-linked immunosorbent assay (EISA), which is currently the most commonly used method, and radioimmunoprecipitation assay (RIA), where the 4A subunit has been optimized as a molecular-specific antigen probe [3,9,11,17,18].

2. Review

2.1. Antigens for anti-parietal cell antibodies

The target for APCA is the gastric proton pump – the H+/K+ ATP-ase [19,20]. It is composed of four subunits: 2 alpha (100 kDa) and 2 beta (60–90 kDa) multipass transmembrane proteins that reside in the membrane of the intracellular secretory channels of parietal cells, deep invaginations of the cell membrane that increase its surface area. Upon stimulation by gastrin, histamine, acetylcholine, for example, the H+/K+ ATP-ase and potassium channel proteins (Kir 4.1) migrate via exocytosis to the cell surface [19–21]. The proton pump functions to produce hydrochloric acid by exchanging cytoplasmic hydrogen ions for extracellular potassium ions [22]. The exported hydrogen ions combine with chloride ions to produce hydrochloric acid (HCl) [21] whereas the imported potassium ions are immediately transported outside of the cell by means of the Kir 4.1 channel.

It has been demonstrated, that APCA target both, the alpha, and highly glycosylated, beta subunits of the proton pump, although the major antigen for these autoantibodies is the alpha subunit [11,17,23]. The circulating APCA in the serum belong to three immunoglobulin classes: IgG, IgA, IgM in contrast to APCA found in the gastric juice which are classes IgG and IgA [14].

2.2. Laboratory methods

Circulating serum APCA can be detected by means of indirect immunofluorescence on histological samples. A typical antigen source of the gastric H+/K+ ATP-ase is the stomach tissue of rat [3] or monkey [24]. The tissue section is incubated with the serum of an AAG patient to permit the antibodies to bind to the antigen. Subsequently, fluorescein-labeled immunoglobulin is added, which binds to the antibody–antigen complex. Microscopic images are scored for immunofluorescence by comparison to immunohistochemistry conducted with non-disease sera. It is possible to roughly estimate the antibody titer in the circulation by serial dilution of the sera [3]. These results are semi-quantitative and qualitative, as they vary according to the experience of the technician [14].

Since the gastric H+/K+ ATP-ase has been proven to be the antigen for APCA, the diagnostic measures aiming to detect these antibodies was improved by development of ELISA [25,26]. This method afforded concordance among labs and is approximately 30% more sensitive than immunofluorescence [9,18]. The ELISA is quantitative, which facilitates monitoring of antibody titer [14]. Presently most investigators in the field utilize the ELISA to measure APCAs.

Another method used in APCA diagnosis is RIA developed by scientists at the Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, USA. The 4A subunit of the H+/K+ ATP-ase, the main antigen for APCA, has been optimized as a molecular-specific antigen probe for these assays [11,17]. In comparison to the ELISA, the RIA is a more accurate and precise method for the assessment of autoantibodies [27–30]. It may therefore also be a useful tool for early autoimmune gastritis and AAG screening [8,9,31,32]. However, RIA requires special laboratory conditions and specialist laboratory devices.

2.3. Clinical consequences of APCA presence

The autoimmune reaction, mediated mainly by CD4T cells reactive do the gastric proton pump and evidenced by the presence of APCA, leads to the destruction of parietal cells in the stomach [8,9]. APCA detection in the serum indicates an increased risk for development of AAG [33]. The consequence of the immune attack of the sensitized T cells over many years is the eventual atrophy of the stomach mucosa, especially in the body and fundus. Among others, the IF-producing parietal cells are destroyed. Consequently, the production of the HCl and IF is disturbed. IF is a cofactor required for vitamin B12 absorption in the ileum. Vitamin B12 itself is crucial for erythropoiesis an myelin production. Late stage AAG and progressive atrophy of the mucosa is classified as PA, the most common cause of vitamin B12 deficiency [9]. Nonetheless profound megaloblastic anemia is not the only symptom of the disease. Neurologic disorders, as numbness, paresthesia, weakness and ataxia may precede anemia by many years [12–14]. Microcytic anemia may present earlier than megaloblastic anemia because an adequate acidity of the gastric environment (via HCl production) is necessary for proper iron absorption. The developing achlorhydria leads to iron deficiency and ultimately to sideropenic anemia [34]. Therefore, the differential diagnostics in patients with an unknown cause of iron deficiency should include screening for autoimmune gastritis via ELISA or RIA as AAG is diagnosed in 20–27% of the former cases [35]. Patients with AAG/PA have significantly higher risk of developing intestinal-type gastric adenocarcinoma, pyloric gland adenoma, squamous cell carcinomas (SCC), gastric carcinoid type I as well as other gastric carcinoids tumors [31,36–38]. The overall relative risk of gastric cancer in with PA is 6.8 (95% CI 2.6–18.1) [37].