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Review Article

Anti-parietal cell antibodies-diagnostic significance

Ewa Rusak [a,*], Agata Chobot [b], Agnieszka Krzywicka [b], Janet Wenzlau [c]

[a] Department of Pediatrics, Pediatric Endocrinology and Diabetology, The Upper Silesian Center for Child's Health, Katowice, Poland
[b] Department of Pediatric Gastroenterology and Hepatology, Clinical Hospital No. 1, Zabrze, Poland
[c] Barbara Davis Center for Childhood Diabetes, University of Colorado Denver Aurora, United States

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

* Corresponding author at: Department of Pediatrics, Pediatric Endocrinology and Diabetology, The Upper Silesian Center for Child's Health, Medyków 16, 40-752 Katowice, Poland. Tel.: +48 32 207 18 00; fax: +48 32 207 15 46.
E-mail address: rusakewa@gmail.com (E. Rusak).

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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

Q2 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].

In addition to the majority of PA patients being APCA positive, they often (40–60%) display antibodies against IF [3,14,15]. Type 1 IF antibodies, comprising 70% of cases, block the binding between IF and vitamin B12 whereas type 2 IF antibodies, found in 30% of cases, prevent the IF/vitamin B12 complex from binding to its

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cognate receptor in the small intestine and hence absorption [39]. Both types of antibodies targeting IF are class IgG [40].

It should be noted, that not all APCA positive individuals fulfill the diagnostic criteria for AAG or PA.

A recently published study reports five cases of AAG in children with refractory iron deficiency anemia [41]. All of the observed patients were APCA positive, negative for IF autoantibodies and all revealed corpus atrophic gastritis with lymphocytic infiltration.

Remarkably, APCA are present also in 2.5–9% of healthy people[42]. Their prevalence in the general population rises with age. Lately published studies report APCA frequency of 7.8% in individuals from Canary Islands and 19.5% in 50–74 year-olds from Germany [7,43].

It is noteworthy that the anemia develops longitudinally over many years. The antibodies must be persistent and at a sufficient concentration to elicit – together with autoreactive gastric CD4+ T cells – a local reaction and promote atrophy of the gastric mucosa and parietal cells [36]. Until now the dynamics of APCA concentration relative to time and disease pathology have not been clearly determined. However in patients with severe AAG the disappearance of the antigen source due to advanced mucosa atrophy results in lowering of the APCA titer [14].

2.4. APCA in other autoimmune diseases

APCA are not exclusively found in the serum of patients with AAG or PA. They are also detected in people suffering from autoimmune thyroid diseases as Hashimoto or Graves-Basedow diseases at frequencies up to 20–30% [33,44,45]. Furthermore individuals with higher anti-thyroid antibody concentrations likewise have higher APCA levels [44]. The presence of APCA places these patients at greater risk for development of AAG [33]. The prevalence of APCA positivity in patients with autoimmune thyroid diseases is similar in both sexes and is not age-dependent. Moreover in Hashimoto's disease the presence of APCA does not appear to impact thyroid function. It has been observed, however, that APCA-positive patients require higher doses of levothyroxine [45]. There are also reports of APCA in women with postpartum thyroiditis. In a group of 54 puerperal women, 18 were APCA-positive before child birth. In 10 of the mothers the concentration of the antibodies rose 2–9-fold in the puerperium. When the patients were examined after 5 years, 4 were diagnosed with hypergastrinemia together with low serum pepsinogen and 2 displayed low vitamin B12 concentrations. Gastroscopy performed on 9 patients indicated 6 had chronic mucosal infiltrations while 3 showed signs of gastric mucosa atrophy [46].

APCA are also more prevalent in the serum of patients with T1D [47] and are more common in adults (13–20%) than in children (5%) [47,48]. It is worth noting, that a study using the RIA showed APCA presence in 30% of the T1D children examined [32]. This finding may be related to the higher sensitivity of this method used to measure APCAs. In this study antibodies against the 4A subunit of the gastric proton pump were observed three times more often in females, but no correlation to age, age at diabetes diagnosis, diabetes duration or glycated hemoglobin A1c (HbA1c) was determined [32]. Alternatively, data from another study employing the RIA revealed increasing frequency of APCA positivity with age of T1D onset [11]. Moreover, it was demonstrated that APCA-positivity precedes PA development by many years in T1D patients who present with hypergastrinemia and lower pepsinogen concentrations [49].

In addition to the afore mentioned autoimmune diseases, APCA are more frequent among individuals with vitiligo (15%) and celiac disease (3–10 times more often) [50]. These antibodies are also more common in first and second degree relatives of people with celiac disease [51].

The above data suggest, that people with autoimmune diseases should be closely screened for AAG/PA in order to provide timely adequate treatment to prevent severe long-term complications [52].

2.5. APCA and Helicobacter pylori infection

Long-term *H. pylori* infection is one of the factors that can cause progressing atrophy of gastric mucosa [4]. An interesting and perpetual question to pose is whether APCA presence is related to *H. pylori* infection. The long-lasting discussion concerning this problem is still open. Although the majority of people infected with this bacteria are APCA negative [7,39], these antibodies are found in up to 20.7% of these patients [7]. The etiology of the APCAs remains to be determined in this group of patients. At the time of infection, antibodies against epitopes of the H+/K+-ATP-ase develop. It is possible that the production of these antibodies results from antigen mimicry between *H. pylori* lipopolysaccharides and blood group antigens Lewis Y and X that are present on the beta subunit of the proton pump of the parietal cells [19,20]. It has been hypothesized, that the antigen responsible for the cross-reactivity is one of the surface proteins of *H. pylori* that has strong immunogenic features and are significantly similar to the human heat shock protein [39,53]. Thus *H. pylori* is implicated as one of the candidates causing AAG.

One study shows no relationship between APCA concentration determined by ELISA and *H. pylori* infection, eradication of the pathogen or therapy with proton pump inhibitors. At the same time it confirmed higher APCA levels in patients with severe atrophic lesions of the gastric mucosa in comparison with those with mild atrophy [54]. Another investigation revealed, that patients infected with *H. pylori* were in 9.9% cases APCA-positive and in 18.5% – IF antibody-positive. In the same study, patients without *H. pylori* infection no antibodies were found [55].

3. Summary

APCA can be detected in the general healthy adult population. It Q3 is unknown why a fraction of these sero-positive people, who present no signs or symptoms, will never develop AAG or PA.

APCA are a good biomarker used to identify people at risk for development of PA, since their prevalence is ~90% among patients with PA. These antibodies are also present in individuals with other autoimmune diseases, therefore these individuals need special consideration in order not to overlook ensuing PA or AAG. The frequency of APCAs among individuals with other autoimmune diseases suggests that their role in AAG development in these patients should be further investigated.

Additionally, antibodies against the parietal cells are present in approximately 20% of patients with *H. pylori* infection, but the pathogenesis of this immunologic response is unclear. The presence of these antibodies precedes the atrophic lesions in the stomach by many years.

Screening tests for APCA have been historically based on indirect immunofluorescence, a semi-quantitative and qualitative method. Improvements in antibody detection have been accomplished with the ELISA. Recently a novel test using a RIA format was developed. It is prudent to assess APCA utility as a biomarker for early detection of individuals at risk for progression to AAG or their relationship to other biomarkers.

Conflict of interests

The authors declare no conflict of interests.

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