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Autoimmune gastritis among T1D individuals – important association?

Autoimmunologiczne zapalenie żołądka u pacjentów z cukrzycą typu1 – istotny związek?

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Abstract

The incidence of type 1 diabetes (T1D) is increasing. T1D and other autoimmune diseases have a similar, cell-specified pathogenesis. Due to an increased risk of autoimmune reactions, T1D subjects are statistically more often affected by other autoimmune diseases. During the course of the disease, patients with diabetes may develop, among others, anemia. When the classic and most common causes are excluded, a possibility of a concomitant autoimmune disorder has to be considered. In such cases, the differential diagnosis should include autoimmune atrophic gastritis (AAG). The symptoms of AAG are: iron deficiency microcytic anemia and, thereafter, macrocytic anemia resultant from B12 vitamin deficiency, although nonspecific neurologic disorders may precede the diagnosis. Because autoimmune gastritis (AG) and its severe stage – pernicious anemia (PA) develop unperceptively over many years, often without any symptoms and frequently remain undiagnosed, physicians should closely screen T1D patients. Anti-parietal cell antibodies (APCA), targeting the gastric proton pump – the H+/K+ ATP-ase, are an advantageous tool for AAG screening, and are significantly more frequent among T1D subjects in comparison to the healthy population. That indicates an increased risk of AG. Some authors suggest that patients with T1D need to undergo a regular screening which includes: APCA, complete blood count, vitamin B12, iron and gastrin serum concentrations. Nevertheless, presently none of the official international or national guidelines for T1D treatment mention regular screening for AG.

Key words

diabetes type 1, autoimmune gastritis, pernicious anemia, autoimmunity

Streszczenie

Częstość zachorowań na cukrzycę typu 1 (T1D) wciąż wzrasta. Pacjenci z T1D należą do grupy zwiększonego ryzyka rozwoju innych chorób autoimmunologicznych ze względu na podobne patogenetyczne podłoże zaburzeń. Wraz z czasem trwania choroby pacjenci narażeni są na występowanie powikłań. Jednym z nierzadko występujących objawów jest anemia. Kiedy wykluczy się podstawowe przyczyny występowania anemii, w diagnostyce różnicowej należy wziąć pod uwagę prawdopodobieństwo obecności towarzyszącej choroby z autoagresji – autoimmunologicznego zanikowego zapalenia żołądka. Do jej objawów zalicza się nie tylko anemia makrocytarna, spowodowana niedoborem witaminy B12, ale także mikrocytarna – z niedoboru żelaza, a także niespecyficzne objawy neurologiczne. Zwykle autoimmunologiczne zanikowe zapalenie żołądka oraz jego ciężka postać – anemia złośliwa rozwijają się bezobjawowo przez wiele lat, często pozostają niezdiagnozowane. Z tego powodu pacjenci z DMT1 powinni podlegać okresowej kontroli w celu wczesnego wykrycia nieprawidłowości. Przeciwciała przeciwko komórkom okładzinowym żołądka, skierowane przeciwko H+/K+ ATP-azie, są dobrym markerem służącym do skriningu. U chorych z DMT1 występują ze zwiększoną częstością, co sprawia, że zaliczają się oni do grupy wysokiego ryzyka rozwoju choroby. Istnieją sugestie konieczności wykonywania regularnych oznaczeń: APCA, morfologii, żelaza, witaminy B12 oraz poziomu gastryny, jednak nie są one ujęte w oficjalnych wytycznych polskich i zagranicznych.

Słowa kluczowe

cukrzyca typu 1, autoimmunologiczne zapalenie żołądka, anemia złośliwa, autoimmunizacja

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Introduction

The prevalence of autoimmune diseases is increasing. At present, approximately 9% of the general population is estimated to be affected by them [1, 2]. They tend to occur significantly more often in females [2,3].

The incidence of type 1 diabetes (T1D) in Europe is likewise increasing [4, 5]. T1D is a chronic autoimmune disorder, the base of which is a cell-mediated autoimmune reaction responsible for the loss of insulin-producing beta cells of pancreatic islets [6].

During the course of the disease patients with diabetes may develop, among others, anemia. The causes of anemia in T1D are multifactorial and frequently not completely clear and obvious. When the classic and most common causes are excluded, a possibility of a concomitant autoimmune disorder has to be considered. The differential diagnosis should, in such cases, include autoimmune atrophic gastritis (AAG) – a chronic, inflammatory disease of the gastric mucosa [7]. The permanent inflammatory infiltration is a result of a complex interaction between sensitized T cells and anti-parietal cell antibodies (APCA) [8–10]. AAG may progress to its final, severe stage – pernicious anemia (PA). AAG as well as PA develop unperceptively over many years and often without any symptoms [11]. Therefore, both diseases often remain undiagnosed, although they occur in people all over the globe [11–13].

In general, the incidence of AAG is estimated at ~2%, although AAG as well as PA seem to be under-diagnosed [8]. The incidence of both these diseases increases with age [8, 14]. AAG is more common in individuals with other autoimmune diseases, such as T1D, or thyroid diseases (in such patients its prevalence is comparatively three- to fivefold higher) [14]. In order to prevent the development of chronic symptoms and irreversible complications, early diagnosis and treatment of these conditions are imperative [3, 15]. This is particularly important inT1D patients, who are exposed to complications associated with the underlying disease. Often only severe complications, as in PA or resultant neurological disorders first suggest the diagnosis [16, 17].

APCA are a serum biomarker of autoimmune gastritis. They are present in most patients with AAG and 85–90% of individuals with PA [10, 18, 19]. This fact makes APCA an advantageous tool for screening. Nevertheless, the presence of these antibodies only is not sufficient for the diagnosis. It is because they are not specific for AAG or PA. They can also be found in the circulation of individuals with other autoimmune diseases [3, 18, 19]. The diagnostic tests for PA 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, 18, 20].

APCA circulating in the blood can be detected by means of various laboratory methods: immunofluorescence, enzyme-linked immunosorbent assay (EISA), and radioimmunoprecipitation assay (RIA). ELISA is currently the most commonly used method, while in RIA the 4A subunit has been optimized as a molecular-specific antigen probe [3, 10, 15, 21, 22].

The aim of this article is to present the current knowledge on the risk of autoimmune gastritis in patients with type 1 diabetes, diagnostic guidelines and therapeutic methods.

Genetic background

T1D affects individuals with genetic susceptibility. These patients are exposed to the development of other autoimmune diseases (like autoimmune thyroid disorders, Addison – Biermer disease, celiac disease, vitiligo) [4]. Likewise, PA seems to be genetically determined, although the inheritance model is poorly understood. The occurrence between family members and coexistence with other autoimmune diseases (T1D, autoimmune thyroid diseases, vitiligo, and others) support the most likely theory of a genetic background of the disease. PA correlates with the *B8DR3* haplotype. The identification of other genes responsible for the susceptibility is currently under investigation [23].

A study recognized an association between the presence of different autoantibodies (to GAD, IA-2, zinc transporter 8, autoantibodies against thyroid peroxidase (TPO), transglutaminase, 21-hydroxylase, APCA) and the susceptibility loci in individuals with T1D. The SNPs were identified in susceptibility loci: *IFIH1*, *PTPN22*, *SH2B3*, *BACH2*, and *CTLA* and a significant association with more than one autoantibody was noted. Furthermore, 11 loci were significantly associated with a single autoantibody. These results prove shared genetic background for T1D and other autoimmune diseases [24].

Wenzlau et al. identified a correlation between autoantibodies against ATP4a subunit of gastric parietal cells and variants in HLA class II, *PTPN22*, and *CTLA4* genes. Moreover, among APCA positive individuals an increased frequency of *DRB1*0404*, *DPB1*0201*, and *PTPN22 R620W (rs2476601-T)* and a decreased frequency of *DRB1*0101*, *DPB1*0301*, and *CTLA4 CT60* (*rs3087243-T*) were determined [25].

T1D and APCA presence

APCA are a biomarker of autoimmune gastritis (AG) targeting the gastric proton pump – the H+/K+ ATP-ase. As evaluated by a meta-analysis APCA are significantly more frequent among T1D subjects in comparison to the healthy population [26, 27]. That indicates an increased risk of AG. The prevalence of AG and its severe stage – PA – among T1D individuals is 5-10%, and 2.6-4% respectively (relative to respectively 2% and 0.15-1% in the general population) [4, 28].

APCA are more prevalent in the serum of GADA-positive patients with T1D [29, 30] and are more common in adults (13% – 20%) than in children (5%) [27, 31]. 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 frequently in

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females, but no correlation with 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 [15]. Additionally, a recent study found APCA in 20.9% of T1D patients – their prevalence was increasing with age and they were more common among females (25.3%) than in males (16.5%) [25]. Moreover, it was demonstrated that APCA positivity precedes the PA development by many years in T1D patients who present with hypergastrinemia and lower pepsinogen concentrations. In the same study, the benefit of simultaneously pepsinogen I and APCA determination is emphasized. Associated abnormal outcomes (low pepsinogen I together with APCA positivity) were determined as a prognostic marker of the development of B12 deficiency [33]. Also ghrelin, which is mainly produced in the stomach corpus, was assessed as a AG marker among T1D subjects, but was found not to be associated with the presence of AG [34].

Although advanced mucosa lesions are rare in T1D children, there are reports of histologic early AG symptoms [31], and even anemia with pancytopenia from vitamin B12 deficiency that required intramuscular injections [35]. Therefore, it is desirable that APCA positive T1D children should be closely screened. Although part of the patients becomes APCA-negative during the follow-up, the majority of them will achieve higher APCA levels and are at risk of developing AG [30].

Anti-parietal cell antibodies

The target for APCA is the gastric proton pump – the H+/K+ ATP-ase [36, 37]. It is composed of four subunits: 2 alpha (100 kDa) and 2 beta (60-90 kDa) multipass transmembrane proteins. The proton pump functions to produce hydrochloric acid by exchanging cytoplasmic hydrogen ions for extracellular potassium ions [38]. The exported hydrogen ions combine with chloride ions to produce hydrochloric acid (HCl) [39] 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 [15, 21, 40]. 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 [18].

Circulating serum APCA can be detected by means of indirect immunofluorescence on histological samples. These results are semi-quantitative and qualitative, as they vary according to the experience of the technician [18].

Since the gastric H+/K+ ATP-ase has been proven to be the antigen for APCA, the diagnostic measures aiming to detect these antibodies were improved by the development of ELISA [41,42]. This method afforded concordance among labs and is approximately 30% more sensitive than immunofluorescence [22, 10]. The ELISA is quantitative, which facilitates monitoring of antibody titer [18]. 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 [15, 21]. In comparison to the ELISA, the RIA is a more accurate and precise method for the assessment of autoantibodies [43–46]. It may, therefore, also be a useful tool for early autoimmune gastritis and AAG screening [9, 10, 32, 47]. However RIA requires special laboratory conditions and specialist laboratory devices.

Clinical consequences of APCA presence

The autoimmune reaction, mediated mainly by CD4 T cells reactive to the gastric proton pump and evidenced by the presence of APCA, leads to the destruction of parietal cells in the stomach [9, 10]. APCA detection in the serum indicates an increased risk for the development of AAG [48]. 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 and myelin production. Late stage AAG and progressive atrophy of the mucosa is classified as PA, the most common cause of vitamin B12 deficiency [10].

Nonetheless, profound megaloblastic anemia is not the only symptom of the disease. Neurologic disorders (numbness, paresthesia, weakness and ataxia) may precede anemia by many years [16–18]. Microcytic anemia may present earlier than megaloblastic anemia because an adequate acidity of the gastric environment is necessary for proper iron absorption. The developing achlorhydria leads to iron deficiency and ultimately to sideropenic anemia [49]. 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 [50]. Likewise, among children with iron deficiency anemia of an unclear reason, refractory to oral supplementation, an associated autoimmune disease should be considered. A recently published study reports five cases of AAG in children with refractory iron deficiency anemia [51]. All of the observed patients were APCA positive, negative for IF autoantibodies and all revealed corpus atrophic gastritis with lymphocytic infiltration. That knowledge should alert physicians to implement appropriate diagnostic measures [51]

Patients with AAG/PA are at a 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 carcinoid tumors [47, 52–54]. The

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overall relative risk of gastric cancer in patients with PA is 6.8 (95% CI 2.6-18.1) [53].

However, it should be noted, that not all APCA positive individuals fulfill the diagnostic criteria for AAG or PA. Remarkably, APCA are present also in 2.5–9% of healthy people [55]. Their prevalence in the general population rises with age. Recently published studies report APCA frequency of 7.8% in individuals from the Canary Islands and 19.5% in 50-74 year-olds from Germany [8, 56].

It is also 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 [52]. 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 an advanced mucosa atrophy results in lowering of the APCA titer [18].

Autoimmune polyglandular syndrome (APS)

T1D and other autoimmune diseases have a similar, cell-specified pathogenesis. The humoral and cell-mediated immune response are responsible for a chronic inflammatory injury to tissues, organ-specific humoral reaction, and destruction of cells. Due to an increased risk of autoimmune reactions, T1D subjects are statistically more often affected by other autoimmune diseases [57]. Disorders associated with T1D are: autoimmune thyroid disease, most prevalent coexistence (15–30%), AG (5–10%), PA (2.6–4%), vitiligo (2–10%), Addison's disease (0.5%) celiac disease (4%) [4, 57–59]. APS is defined as an autoimmune activity against more than one endocrine organ, although non-endocrine organs can be affected. Gouveia et al. established an APS diagnosis in 25.2% of T1D patients, higher prevalence of autoimmune thyroiditis was observed in females. In the same study the frequency of markers for AG was assessed at 17.2% [60].

Glandular abnormalities known as APS type III include the following: T1D, autoimmune thyroid disease and AG [59]. This combination also affects young patients [35]. Therefore, it is necessary to regularly screen T1D individuals, particularly those subjects with organ-specific antibodies, for early diagnosis and initiation of treatment when required [61].

Regular assessment of T1D patients

Based on the results of studies, some authors suggest that patients with T1D need to undergo a yearly screening which includes: complete blood count, vitamin B12, iron, and gastrin serum concentrations. They alsopropose that APCA levels should be measured at the moment of diabetes diagnosis and then once yearly during the first 3 years, and at 5-year intervals thereafter. It is also suggested that subjects with an elevated gastrin titer and positive for APCA should be considered for a gastroscopic (with biopsy) evaluation at least once [62]. An examination should be performed urgently in case of any suspicious symptoms. It ought to be noted that within T1D patients, individuals with GADA and/or TPO high levels are at even higher risk of anemia development [28, 58, 62].

Nevertheless, presently none of the official international or national guidelines for T1D treatment (for example International Society for Pediatric and Adolescent Diabetes, American Diabetes Association, Diabetes Poland) mention regular screening for AG (APCA or iron/vitamin B12 concentrations) [63,64,65].

Treatment recommendations

Treatment depends on the stage of disease. As mentioned before, in early stages microcytic anemia from iron deficiency can occur, thereafter macrocytic – from B12 deficiency- develops. Early supplementation of iron and vitamin B12 respectively could protect from full-blown disorders. Iron can be supplemented orally or intravenously. Vitamin B12 is administered in intramuscular injections [28].

APCA and *Helicobacter pylori* infection

Long-term *Helicobacter pylori* infection is one of the factors that can cause progressing atrophy of gastric mucosa [11]. An interesting and perpetual question to pose is whether APCA presence is related to *Helicobacter pylori* infection. The long-lasting discussion concerning this problem is still open. Although the majority of people infected with this bacteria are APCA negative [8, 66], these antibodies are found in up to 20.7% of these patients [8].

Thus *Helicobacter pylori* is implicated as one of the candidates causing AAG. However a study in T1D patients showed that the HLA susceptibility differs between those infected with *Helicobacter pylori* and subjects positive for APCA (*Helicobacter pylori* infection correlated with *HLA-DQA1*0501-B1* 0201*, while APCA positivity with *HLA-DQA1*0501-B1*0301*) [67].

Summary

T1D affects individuals with an increasing frequency. Due to a shared genetic background and similar cell-specified pathogenesis, T1D subjects are statistically more often affected by other autoimmune diseases. The concomitant disorders are: autoimmune thyroid diseases, celiac disease, vitiligo, Addison's disease, autoimmune atrophic gastritis and its severe stage – PA. Coexistence of more than one autoimmune condition known as APS occurs in approximately 25% of T1D patients. Because AG/PA develop unperceptively over many years, often without any symptoms and frequently remain undiagnosed, physicians should closely screen T1D patients.

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APCA are a good biomarker used to identify people at risk for development of AG/PA. APCA are significantly more frequent among T1D subjects, especially those GADA positive, in comparison to the healthy population. Likewise, low pepsinogen I together with APCA positivity are a prognostic marker of B12 deficiency development. Most common symptoms of AG are iron deficiency microcytic anemia and, thereafter, macrocytic anemia resultant from B12 vitamin deficiency, although neurologic disorders (numbness, paresthesia, weakness and ataxia) may precede anemia by many years. The role of early diagnosis is emphasized, as appropriate treatment may prevent irreversible complications occurrence.

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