

## Autoimmune Syndrome Associated with Autoimmune Diabetes Mellitus

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### Abstract

Autoimmune polyglandular diseases are conditions characterized by the association of two or more specific autoimmune disorders. Diagnosis of polyglandular autoimmune syndrome should be considered in every patient in case of coexistence of two or more autoimmune endocrinopathies. In patients with autoimmune diabetes (diabetes type 1 and LADA) have often, besides immune diabetes markers, also other organ-specific antibodies. Diabetes mellitus with autoimmune support is particularly often accompanied autoimmune thyroid diseases and coeliac disease. In these patients, however, it can reveal a number of other autoimmune polyendocrinopathies. The basis for the diagnosis of autoimmune syndrome is the finding of an increased level of autoantibodies against many organs.

**Keywords:** Autoimmune Polyglandular Syndrome (APS); Autoantibodies, Autoimmune Thyroid Disease; Autoimmune Diabetes Mellitus; Coeliac Disease; Addison's Disease

### Introduction

At patients with the diabetes with the autoimmunologic background one ought to remember the possibility occurrences also other autoimmunologic illnesses. In autoimmunologic syndrome the presence of anti-organ antibodies on long time can outdistance the appearance of clinical symptoms of the illness.

The inclination to the development of autoimmunologic reactions is tied with genetic predispositions, related to the HLA system, with antigens of the class of II histocompatibility complex. In the pathogenesis of autoimmunologic illnesses interleukine-21 (IL-21) plays its role. IL-21 has been proven to play an important role in the immune the system. Long., *et al.* presented the role of IL-21 in the pathogenesis and therapy of autoimmune diseases [1].

Immunological phenomena, similar as in the diabetes with the autoimmunologic background, are observed in the most of autoimmune diseases.

Most often appears the connection of the autoallergy in relation to pancreas  $\beta$ -cells (ICA – islet cell antibodies) with thyroid autoantibodies and with the presence of autoantibodies to the adrenal cortex (ACA – adrenal cortex antibodies). It may also appear StCA – the steroid -producing cell antibodies. To the group of autoimmune diseases that may accompany diabetes mellitus, autoimmune thyroiditis, celiac disease, Addison's disease, autoimmune gastritis, systemic lupus, but also parathyroid dysfunction, vitiligo or autoimmune arthritis may be included [2-8]. It should be remembered that sometimes the appearance of these diseases may precede the emergence of diabetes.

Nederstigt, *et al.* presented a comprehensive analysis of the literature on the comorbidity of autoimmune diseases such as autoimmune thyroid disease, celiac disease, gastric autoimmunization, including pernicious anemia, vitiligo and adrenal insufficiency with type 1 diabetes [5]. This analysis showed that hypothyroidism (in 9.8%) and celiac disease (in 4.5%) are particularly frequent in patients with type 1 diabetes. Similar observations were made by other authors [9].

Autoimmune thyroiditis is particularly often associated with autoimmune diabetes [10]. The order of occurrence of these diseases may vary. However, it may happen that thyroid dysfunction causes glucose metabolism disorders and may underlie the development of type 2 diabetes, which should be kept in mind when determining the type of diabetes [11].

According to Jonsdottir, *et al.* in patients with newly diagnosed Graves' disease (GD), a broader range of autoantibodies testing is indicated [12]. In particular, it is recommended to determine the titre of autoantibodies against Zink transporter 8 (ZnT8A), since the determination of only autoantibodies against glutamic acid decarboxylase (GADA) may be insufficient in the diagnosis of developing diabetes. ZnT8 antibodies are an independent serological marker in the diagnosis of type 1 diabetes, as they occur in 25-30% of patients who do not have GADA or IA2-A antibodies (insulinoma-associated protein-2).

The occurrence of ZnT8A is associated with the likelihood of developing LADA-type diabetes. The use of ZnT8A in the diagnostics of diabetes was also pointed out by other authors [13].

One of the pathologies involved in the autoimmune syndrome may be autoimmune gastritis (autoimmune atrophic gastritis) [14].

Such diagnosis is indicated by the presence of autoantibodies against parietal cells (PCA - parietal cell autoantibody). The disease is particularly often diagnosed in diabetic patients with simultaneous autoimmune thyroid disease as well as other autoimmune diseases [15].

It's worth to remember that diagnostics for autoimmune diseases should also apply to patients with LADA type diabetes.

Each of the units included in the polyglandular autoimmune syndromes is associated with the presence of organ specific antibodies, the determination of which may be important in laboratory diagnostics and in screening tests carried out in people with already diagnosed diabetes. Because in autoimmune diseases, the presence of anti-government antibodies for a long time may precede the occurrence of clinical symptoms of the disease, there have been developed rules of conduct to detect them as early as possible [16].

While these recommendations are implemented in adolescent patients, unfortunately, in adults, they are very often neglected and the diagnosis is delayed. Early detection of autoimmune processes allows the selection of a group of patients with higher risk, requiring particularly careful observation [17,18].

The patients may be in the subclinical phase of the disease. Early diagnosis and appropriate treatment improves metabolic control of diabetes. It reduces the risk of complications and has a positive effect on the quality of life.

Co-occurrence of endocrine gland insufficiency is the basis for the diagnosis of autoimmune polyglandular insufficiency syndrome. Clinical observations on the frequent comorbidity of various autoimmune diseases in families of the ill persons suggests a possible common genetic background [19].

The basis for the diagnosis of autoimmune syndrome is the finding of an increased level of anti-organ-autoantibodies. Epidemiological observations on the coexistence of autoimmune diseases have allowed the identification of several syndromes of polyendocrinopathic nature:

- **APS 1:** (Autoimmune polyendocrinopathy syndrome type 1) is characterized by the presence of chronic candidiasis of the mucous membranes, spontaneous hypoparathyroidism and Addison's disease; some authors believe that other types of antibodies may also be present in this type and autoimmune diabetes may also be present (most often it is a "classic" type 1 diabetes). Most often this type occurs in children.
- **APS 2:** (Autoimmune polyendocrinopathy syndrome type 2) is characterized by the presence of Addison's disease, autoimmune thyroiditis of the Graves or Hashimoto type and/or diabetes mellitus with autoimmune background, i.e. classic type 1 or LADA diabetes.
- **APS 3:** (Autoimmune polyendocrinopathy syndrome type 3) is characterized by autoimmune conditions such as celiac disease, alopecia areata, autoimmune hepatitis or myasthenia gravis and other autoimmune diseases (excluding Addison's disease and hypoparathyroidism), including type 1 diabetes.
- **APS 4:** (Autoimmune polyendocrinopathy syndrome type 4) includes other, not previously included syndromes, which may also be accompanied by diabetes.

### Case Studies

#### Case 1

A 29-year-old female patient; thyroid dysfunction, impaired glucose tolerance and kidney stones have been reported since childhood. Initially, she was not diagnosed or treated.

It was not until the age of 15 that the conducted examinations showed autoimmune thyroiditis, treatment was included. After several years, symptoms of hypoparathyroidism were found. Parathyroid hormone level 7.45 pg/ml at normal calcium level. In the interview, calcium level fluctuations. C peptide 2.12 ng/ml. In the age of 25, glucose homeostasis disturbances occurred. Self-control shows elevated fasting blood glucose levels with normal levels throughout the day. Titer of autoantibody GAD was low - 2.1 IE/ml. In this situation, considering the disturbances of glucose homeostasis at normal C-peptide level and low autoantibodies titer, diagnosis of MODY-type diabetes was considered in the diagnosis.

The tests carried out in the reference center ruled out such a diagnosis.

After one year, the level of C-peptide decreased to 0.55 ng/ml. An increased titre of autoantibodies GAD - 150 IE/ml - was found. Autoimmune diabetes was diagnosed.

The patient suffers from recurrent candidiasis of mucous membranes from childhood, very difficult to treat and constantly recurrent to the present. An autoimmune polyendocrine syndrome was diagnosed.

#### Case 2

13-year-old girl was admitted to the clinic because of severe weakness, increased thirst, polyuria and weight loss. From the age of 10 she was under the care of an endocrine outpatient clinic due to confirmed hypoparathyroidism. Recurrent thrush of the oral mucosa, vulva and vagina has been present since early childhood and skin discoloration has been observed for several months. Upon admission

to the clinic, the child's condition was medium, physical features of dehydration and emaciation (38.5 kg with a height of 167 cm) were observed as well as generalized chestnut skin coloration. Laboratory tests have found significantly elevated glucose levels (24.2 mmol/L), increased HbA1c (7.7%), with reduced C-peptide (0.84 ng/ml) and increased anti-GAD antibody titer - 225.7 IU/ml, abnormalities were found in cortisol secretion profile - no morning peak, serum ACTH levels were significantly increased (1250 pg/ml). Performed diagnostic tests confirmed the diagnosis of hypoadrenocorticism. Increases in thyroid antibody titers: aTPO and aATG have been found. The ultrasound image of the thyroid gland showed chronic inflammation. Based on diagnostic tests in a patient who has previously suffered from hypoparathyroidism and recurrent mucosal candidiasis diagnosed: type 1 diabetes, hypoadrenocorticism and lymphocytic thyroiditis.

### Case 3

A 44-year-old patient who was diagnosed with type 2 diabetes three years earlier.

Initially treated with insulin and then with metformin and a sulphonyl urea. After one year, the drugs were discontinued. C peptide level was 1.24 ng/ml. After a few months, health condition deteriorated. Control tests revealed: oral glucose tolerance test (OGTT): 0' 111; 60' 226; 120' 167 mg/dl (0' 6.2; 60' 12.6; 120' 9.3 mmol/L); C-peptide - 1.08 ng/ml; antibodies GAD > 2000 IE/ml; anti-insulin antibodies (AIA) < 0.1 U/ml.

A small dose of insulin glargine was included as a treatment. After half a year, the patient was re-consulted due to hyperglycemia. There was a decrease in the level of C peptide to 0.62 ng/ml, the titres of autoantibodies GAD were still very high. LADA diabetes was diagnosed and intensive insulin therapy was implemented. After 6 months, very high titres of GAD autoantibodies and an increase in the titres of autoantibodies to ICA were found.

An increase in the titre of autoantibodies against thyroid peroxidase (aTPO) - 205.1 IU/ml - was also observed, with normal hormone levels. The patient was under endocrinologist care. After two years, there was an increase in the titre of autoantibody against the parietal cells of the stomach (APCA). An autoimmune polyendocrine syndrome was diagnosed.

### Case 4

A 35-year-old woman was admitted with symptoms of decompensated diabetes. The interview showed that for 4 years she was treated with insulin mix and diagnosed with type 2 diabetes. She was also treated hormonally because of the diagnosis of hypothyroidism.

The immunological tests carried out during the diabetic consultation showed a very high titre of autoantibodies GAD > 2000 IE/ml, which allowed the diagnosis of autoimmune diabetes (LADA type). There was also a high titre of aTPO (autoantibodies against thyroid peroxidase) 120 IU/ml, which in turn allowed the diagnosis of autoimmune thyroid inflammation. The immunoassays performed in connection with stomach complaints showed an increase in the titre of autoantibody against parietal cells (PCA: parietal cell autoantibody). The patient was also diagnosed with developing rheumatoid arthritis. This allows the case to be qualified as the autoimmune polyglandular syndrome

## Discussion

Because in autoimmune diseases the presence of anti-organ antibodies may be ahead of the clinical symptoms of the disease for a long time, rules of conduct have been developed to detect these diseases as early as possible. Early detection of autoimmunity processes allows the selection of a group of patients at increased risk who require particularly careful observation. These patients may already be in the subclinical stage of the disease.

The presented cases illustrate two autoimmune polyendocrine syndromes.

In the first case, considering that the first symptoms occurred during childhood, classification as APS-1 can be discussed [20-24].

Analysis of the diseases occurring in the second case suggests the diagnosis of APS-2. In the second and third and fourth cases, polyglandular polyendocrine syndrome (APS) can be diagnosed. Determining the type requires further observation.

Autoimmune polyglandular syndromes are characterized by the presence of two or more diseases with autoimmune background. The order of occurrence of these diseases may vary, hence determining the type of APS based on the currently proposed division may be difficult [25,26].

### Treatment of autoimmune polyglandular syndrome

Therapy of autoimmune polyglandular syndromes consists of hormonal substitution and specific treatment of other diseases that may occur in their course. The order of turning on individual hormones requires a lot of attention. In the presence of hypoadrenocorticism and hypothyroidism, substitution should be started with hydrocortisone, followed by thyroid hormones. Failure to follow this order may lead to a worsening of hypothyroidism adrenal cortex. Diabetes associated with other autoimmune diseases, as a rule characterized by unsteady course and difficulties in obtaining good metabolic control.

Glucocorticosteroids used to treat Addison's disease cause an increase in insulin requirements in patients with underlying diabetes. Initially, they reduce the affinity of insulin for its membrane receptor and impair utilization glucose in peripheral tissues. They increase later hepatic gluconeogenesis. Autoimmune thyroid conditions worsen the course of diabetes mellitus. Thyroid hormones are diabetogenic and hyperthyroidism induces tissue insulin resistance.

### Conclusion

In patients with autoimmune diabetes, the possibility of other autoimmune diseases should also be considered. The inclination to the development of autoimmune reactions is associated with genetic predispositions associated with the HLA system, with class II antigens of the main histocompatibility complex.

The history of research on endocrine autoimmune disorders is long, dating back to the 20<sup>th</sup> century. In these syndromes, the presence of anti-organ antibodies may be ahead of the clinical onset for a long time. It should be remembered that in patients with any autoimmune disease, the possibility of another disease with the same background should be revealed, so careful observation of such patients and screening is necessary.

Among autoimmune diseases that may accompany diabetes mellitus there are autoimmune thyroiditis, celiac disease, Addison's disease, autoimmune gastritis, systemic lupus and also parathyroid dysfunction, vitiligo or autoimmune arthritis.

Autoimmune thyroiditis is the most common autoimmune endocrinopathy associated with diabetes, More and more attention is being paid to the need to monitor autoimmune gastritis. This disease is particularly common in diabetics with concomitant autoimmune thyroid disorders.

Co-occurrence of endocrine gland insufficiency is the basis for the diagnosis of autoimmune polyglandular syndrome.

Diagnostics for autoimmune diseases should also apply to patients with LADA type diabetes.

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