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AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 2 – A CASE REPORT

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Abstract

Autoimmune polyglandular syndromes are characterized by the association of two or more autoimmune diseases. They are classified into two major subtypes, each having its own characteristics. The autoimmune polyglandular syndrome type 2 is defined by the presence of at least two of the following diseases: Addison's disease, type 1 diabetes mellitus and thyroid autoimmune disease. Other autoimmune diseases belonging to the autoimmune polyglandular syndrome type 2 are: primary hypogonadism, myasthenia gravis, celiac disease, pernicious anemia, alopecia, vitiligo. We are going to present the case of a patient, aged 40, with diabetes mellitus (probably latent autoimmune diabetes of the adult), chronic autoimmune thyroiditis and celiac disease.

key words: *autoimmune polyglandular syndrome, autoimmune diabetes, chronic autoimmune thyroiditis, celiac disease*

Background and Aims

Autoimmune polyglandular syndromes bring together endocrine, neurologic, dermatologic, gastrointestinal and other disorders, which share the autoimmune pathogenesis [1].

The two major subtypes are autoimmune polyglandular syndrome type 1 (APS type 1) and autoimmune polyglandular syndrome type 2 (APS type 2). There are differences between them regarding the time of onset, gender distribution, presence of various autoimmune diseases and modality of transmission. APS type 1 is a disease with monogenic autosomal recessive transmission, the first symptoms usually appear during childhood, but the full picture is shaping up to the age of 20 [1,2]. It is defined by the presence of at least two of the three major manifestations: primary hypoparathyroidism, primary adrenocortical insufficiency (Addison's disease) and mucocutaneous candidiasis [2,3].

APS type 2 is the most common form of autoimmune polyendocrinopathy. The modality of transmission is complex and polygenic [1]. The diagnosis is usually established in patients aged between 20 and 60 years. APS type 2 is defined by the presence of at least two of the following diseases: Addison's disease, type 1

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diabetes mellitus (DM) and autoimmune thyroid disease. Other autoimmune diseases characteristic for the APS type 2 are: primary hypogonadism, myasthenia gravis, celiac disease, pernicious anemia, alopecia and vitiligo [1,2]. The most common associations are between type 1 DM (50%) and chronic autoimmune thyroiditis (70%) [3]. About 3 to 16% of the patients with type 1 DM may develop celiac disease [4].

Case report

We are presenting the case of a female patient, aged 40, living in an urban area. She was diagnosed in 2008 with chronic autoimmune thyroiditis with hypothyroidia, after some lab tests performed in an outpatient setting: TSH = 8.1 μU/L (normal range: 0,35-4,94 μU/L), thyroperoxidase antibodies (TPO Ab) = 78.9 U/mL (normal range: <5,6 U/mL), thyroglobulin antibodies (Tg Ab) = 11.3 U/mL (normal range: <4,1 U/mL). Consequently a replacement therapy with levothyroxine 25 μg/day was initiated and the dose was gradually increased. At the same time a high glycemic value (211 mg/dL) was detected, and she was referred to a diabetes specialist.

The patient presented specific clinical symptoms of DM (polyuria, polydipsia, xerostomia, weight loss) and an elevated fasting blood glucose, (211 mg/dL), confirmed by an increased, HbA_{1c} (7%). The measurement of the C-peptide, which had a normal value (2.3 ng/mL), led to the diagnosis of type 2 DM and oral antihyperglycemic medication was recommended (initially metformin 2 g/day, afterwards associated with sitagliptin 100 mg/day). After an initial period of obtaining target glycemic values, which lasted for about 9 months, the glycemic control worsened and HbA_{1c} increased gradually to 8.4%, 9.4% and finally, to 12.4%. A new measurement of C-peptide was performed, that showed a decrease to 1.7 ng/mL. In order to rule out the possibility of iatrogenic hyperthyroidism as the cause for this unsatisfactory glycemic control, TSH, FT_3 and FT_4 were determined, but they were in the normal range (during levothyroxine replacement therapy). Given the age of 40 years, the initial satisfactory glycemic control obtained by life style changes and combination of two oral drugs, and the decreasing C-peptide, the suspicion of latent autoimmune diabetes in adults (LADA) was raised. The physical examination showed markers of insulin resistance: acanthosis nigricans in the elbow and the neck, abdominal obesity (a waist circumference of 108 cm and a BMI of 32 kg/m^2), an elevated triglyceride level (184 mg/dL) and a decreased level of HDLc (45 mg/dL). Unfortunately, the pancreatic antibodies, namely glutamic acid decarboxylase (GAD) antibodies, could not be determined. Under these circumstances, in 2009, insulin therapy in a basal-bolus regimen was started.

In March 2012, the patient was hospitalized because of gastrointestinal symptoms (diffuse abdominal pain, diarrhea, flatulence). Biologically, microcytic hypochromic anemia was found (Hb = 10.8 g/dL, MCH = 21.2 pg, MCV = 71.1 fl, MCHC = 29.8 g/dL, serum iron = 20 μg/dL). Given the association of chronic autoimmune thyroiditis and DM (probably LADA), a celiac disease diagnosis (gluten enteropathy) was suspected. Anti-transglutaminase antibodies were measured, and their level was high (97.1 U/mL, normal range: <10 UI/mL). Upper digestive endoscopy with duodenal mucosa biopsy sampling was performed, and the diagnosis of celiac disease type III A Marsh was established. The patient was recommended a gluten-free diet and the digestive symptoms did improve.

Discussions

LADA is a form of autoimmune DM to be considered within the spectrum of diabetes in adults. The term is disputed by some authors, as diagnostic criteria are not very clear, and confirmation of diagnosis requires quite expensive investigations. For the therapy of LADA, before proceeding to insulin therapy, oral drugs (used in the therapy of type 2 DM, as well) may be recommended, but it is highly important to initiate therapy with insulin at the right time [5,6].

Gluten enteropathy is about ten times more common in diabetic patients than in the general population, routine serologic screening being recommended by some authors in patients with type 1 DM, even in the absence of clinical signs. Untreated, it may lead to several complications as a consequence of the accompanying malabsorbtive syndrome [4,7,8].

In this patient, elements indicating type 2 DM (presence of insulin resistance markers and components of the metabolic syndrome, like increased waist circumference, acanthosis nigricans, hypertriglyceridemia) overlapped with elements suggesting an autoimmune diabetes with latent onset (association with other autoimmune diseases: chronic autoimmune thyroiditis, celiac disease; lack of satisfactory glycemic control with non-insulinic antihyperglycemic therapy, C-peptide levels decreasing in a short period of time). The progressive worsening of glycemic control during non-insulinic therapy, as well as the decrease of C-peptide, in a patient known as having an autoimmune thyroid disease, oriented the diagnosis towards LADA (diagnosis of probability in the situation in which pancreatic antibodies could not be determined).

Conclusions

The patients with APS type 1 and APS type 2 should be monitored for the rest of their lives because they run the risk of developing a new autoimmune disorder. Monitoring involves periodic physical examination and some tests, as well as advising patients (and their relatives) regarding the symptoms and early signs of the major components of the syndrome. The active detection of patients with APS type 1 and APS type 2 allows the establishment of an early diagnosis and appropriate treatment to prevent complications.

Diagnosing the type of DM is not always easy, particularly if the disease is diagnosed in patients aged between 30 and 40 years, whose initial symptoms seem to indicate type 2, but the subsequent evolution involves a progressive decline in the pancreatic function that imposes insulin therapy. The most challenging is the determination of the type of diabetes when elements associated with type 2 – insulin resistance – overlap with elements associated with type 1 – the presence of other autoimmune diseases.

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