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Case Report

AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE II – CASE REPORT

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SUMMARY – Presentation is made of a 41-year-old man with Addison's disease and coexistent Hashimoto's thyroiditis and hypothyroidism. The two diseases are presumed to be of autoimmune etiology and to manifest as part of the autoimmune polyglandular syndrome type II, as also suggested by tissue typing for HLA B8 locus. Inadequate TSH suppression with standard levothyroxine substitution therapy for a one-year period or with higher substitution doses of 200 mg during TRH stimulation, with FT4 which showed no major increase but remained within lower normal limits, indicated partial hypophyseal resistance to thyroxin and/or possible development of autoantibodies to peripheral thyroid hormones.

Key words: *Polyendocrinopathies, autoimmune, diagnosis; Addison's disease, etiology; Thyroiditis, autoimmune, diagnosis; Case report*

Introduction

Lymphocytic infiltration of the adrenal cortex and thyroid gland was for the first time detected in 1926 by Schmidt's excisional biopsy in a patient who died from adrenal insufficiency. The condition was named Schmidt's syndrome. Later on, involvement of other endocrine glands was also observed, and the syndrome was termed autoimmune polyglandular syndrome type I and type II. Type I includes hypoparathyroidism, mucocutaneous candidiasis, adrenal insufficiency, chronic active hepatitis, malabsorption, primary hypogonadism,vitiligo, pernicious anemia, alopecia, and primary hypothyroidism. Type I is characterized by no HLA system and chromosome 6 compatibility, onset in childhood or adolescence, high prevalence of mucocutaneous candidiasis, and autosomal recessive inheritance. Type II is characterized by vertical transmission through many generations, HLA B8 and DR3 compatibility, chromosome 6 inheritance, onset between age 20 and 60, absence of mucocutaneous candidiasis, and autosomal dominant inheritance. Rodriguez Quiroz *et al.*[1] have recently reported on a patient with autoimmune polyglandular syndrome type III, and defined the state as coexistence of insulin dependent diabetes mellitus, hyper- or hypothyroidism and no other endocrine disease, with or without rheumatic disease. Less common manifestations of the syndrome include pernicious anemia, vitiligo and alopecia. Cellular and humoral immunity disorders are present in most autoimmune diseases. The immune system recognizes its own antigens and does not react to them. The principle is established during fetal life and continues after birth. There are various theories on the occurrence of autoimmune reaction, e.g., abnormal antigen expression, primary hormonogenesis defect, clone theory, and abnormal immune homeostasis as the most important theory.

Thyroid hormone antibodies are known since 1956, when Robbins *et al.*[3] described specific gamma globulin thyroxine carriers in a case of papillary carcinoma of the thyroid. In 1967, Premancharda and Blumenthal[4] demonstrated thyroid gland antibodies in six of 15 patients

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with Hashimoto's thyroiditis. T3 and T4 antibodies have been found in many thyroid diseases, manifesting as a changed level of thyroid hormones. However, these antibodies have no effect on the peripheral level of thyroid hormones if thyroid reserve on TRH stimulation is normal.

There may be a thyroid hormone blocking mechanism on the receptors that suppress endogenous TSH secretion. There may also be antibodies that bind circulating thyroid hormones and inhibit the effect on hypophysis and/or render it unavailable for analysis. TSH hypersecretion is the most common physiological sequel of decreased levels of free thyroid hormones. It can rarely be consequential to hypophyseal cell TSH secreting adenoma or hypothalamic cell TRH secreting adenoma. It may also occur in the form of pituitary generalized or partial resistance, along with thyroid tissue resistance, its most severe manifestation being struma with cretinism or juvenile hypothyroidism. Another form is selective resistance (partial hypophyseal resistance to hypophyseal peripheral hormones without tissue resistance), which is manifested by the clinical picture of hypermetabolism. It is believed that T3 and T4 hormones have multiple cellular effects with nuclear hormone receptors (TR alpha, TR beta). Thyroid hormone resistance is caused by TR beta gene mutation[8].

Case Report

B. M., a 41-year-old man, underwent appendectomy. A week later, he became adynamic, prostrate, hypotensive, with hyperkalemia and hyponatremia. Addison's disease was suspected for dominant skin hyperpigmentation, and verified by hormone testing. The patient was administered corticosteroid and mineralosteroid adjuvant therapy, whereafter he felt well and had satisfactory hormonal and other laboratory test results.

Ten years later, weakness, exhaustion, and physical effort intolerance developed despite appropriate substitution therapy. Hormonal tests showed low peripheral thyroid hormone levels and significantly elevated TSH level, suggesting primary hypothyroidism as part of chronic lymphocytic thyroidism, which was confirmed by biopsy pathohistology. The level of testosterone was lower than expected for the patient's age, and no other abnormalities were found. Upon adjuvant substitution levothyroxine therapy, suppression of TSH secretion proved refractory to long-term standard dose or short-term hormone dose increase.

Laboratory tests performed during the patient's hospital stay yielded the following results: cortisol at 8 a.m. 74.5 nmol/L and at 4 p.m. 27.6 nmol/L; ACTH 160 pmol/L; 24-h urine 17-CS 1 mg; 24-h urine 17-OHCS 0.6 mg; 8-h stimulation with 25 U ACTH showed no suppression; serum aldosterone <191.3 pmol/L; 24-h urine <11.82 mmol/L; serum renin >8.00 pg/ml; T3 0.9 nmol/L; T4 33.6 nmol/L; TSH >80 mIU/L. Highly positive microsomal autoantibodies and thyroid biopsy cytology indicated chronic Hashimoto's thyroidism. TRH test basal: TSH 0 min 47.6; 30 min 53.6; FT4 11.6 pmol/L; levothyroxine 100 mg: TSH 0 min 24.5; 30 min 48.2; FT 4 12.9; levothyroxine 150 mg: TSH 0 min 13.9; 30 min 46.8; FT 4 12.9; parathormone <20 pg/ml; Ca and P homeostasis normal. Chest and abdominal x-ray and CT scan of the hypophysis were normal. Immunologic status: LE cell, Walter Rose and Latex, and total complement tests were negative; C3 0.63 g/L; C4 0.21 g/L; ANF negative; circulating immunocomplex 3.8 mg/mill; lymphocyte markers (% of total lymphocyte count) CD4/T4/helper 59.7; CD8/T8/suppressor 13.0; CD20/B1 10.1; T4/T8 4.59, elevated as the result of low T8/CD8 level. HLA system antigens: locus HLA-A 1 26; locus HLA-B 8 12; total protein 75 g/L; protein immunoelectrophoresis normal; IgG 11.9; IgA 2.21; IgM 0.64.

Discussion

In our patient, the diagnosis of Addison's disease was verified by laboratory (hormone) testing, which showed high serum ACTH, low serum cortisol, and low 24-h urine cortisol levels. Serum and urinary aldosterone showed decreased values, while renin was elevated, indicating mineralocorticoid insufficiency of primary hypocorticism. Pathohistology revealed significantly positive microsomal antibodies, pointing to Hashimoto's thyroiditis. Low thyroid peripheral hormones and significantly elevated TSH levels confirmed the diagnosis of primary hypothyroidism. The patient received one-year substitution therapy with 100 mg levothyroxine without TSH suppression for partial hypohyseal resistance to peripheral thyroid hormones. The patient was admitted to the hospital, underwent TRH stimulation test, and was prescribed progressively rising levothyroxine dosage up to 200 mg/L for coexistent Addison's disease refractory to the high dose of the drug. However, increased TSH levels persisted, along with positive stimulation test, while free FT4 remained within the lower normal limits. It was presumed, therefore, that

in spite of partial thyroxine thyrotropic resistance, autoantibodies to thyroid hormones may have existed, as suggested by unchanged FT4 levels in spite of the high levothyroxine dosage. CT scan excluded TSH adenoma and tuberculotic etiology of Addison's disease. The two diseases could be considered as part of the autoimmune polyglandular syndrome type II, as also indicated by the HLA B8 locus.

The pathogenesis of autoimmune polyglandular syndrome remains obscure. The medications used for immunosuppression still have serious side effects. The concept of the locus HLA B8 and HLA DR3 related syndrome appears to be quite intriguing. Early detection of the disease allows for significant morbidity and mortality reduction in patients with autoimmune polyglandular syndrome. Family members and kindred should be screened annually. Many syndrome diseases can be treated with respective substitution therapy. However, most authors consider that in the future, immunologic therapy should be focused on immunomodulation rather than immunosuppression.

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Sažetak

AUTOIMUNI POLIGLANDULARNI SINDROM TIP II. – PRIKAZ SLUČAJA

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Prikazan je 41-godišnji bolesnik s Addisonovom bolešću i pridruženim Hashimotovim tireoiditisom i hipotireozom. Za pretpostaviti je da su ove dvije bolesti autoimune etiologije i da se javljaju u okviru autoimunog poliglandularnog sindroma tipa II., na što upućuje i tipizacija tkiva u smislu HLA B8 lokusa. Nedovoljna supresija TSH standardnom nadomjestnom terapijom levotiroksinom kroz dulje vremensko razdoblje od godinu dana, kao i većim nadomjestnim dozama od 200 mg tijekom stimulacije TRH, uz FT4 koji se nije značajnije povisio, nego je ostao u nižem normalnom rasponu, ukazivala je na djelomičnu rezistenciju hipofize na tiroksin i/ili mogućnost razvoja autoantitijela na periferne hormone štitnjače.

Ključne riječi: *Poliendokrinopatije, autoimune, dijagnostika; Addisonova bolest, etilogija; Tiroiditis, automuni, dijagnostika; Prikaz slučaja*