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Treatment of type 1 diabetes mellitus in female patient with Graves' orbitopathy, receiving intravenous systemic corticotherapy

Leczenie cukrzycy typu 1 u pacjentki z orbitopatią tarczycową, otrzymującej systemową dożylną kortykoterapię

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S u m m a r y

In this article we presented a patient woman with type 2 autoimmune polyglandular syndrome (APS2) – type 1 diabetes mellitus, vitiligo and Graves disease. In the curse of Graves disease she had hyperthyroidism and severe active phase of Graves orbitopathy. Because of orbitopathy she needed high dose of methylprednisolone applicated as intravenous weekly therapy. In the course of corticosteroids therapy her usually doses of insulin was three times higher in the first day, two times higher in the second day and one and a half higher in the third day after treatment in comparison with her usually doses. In discussion we showed problems connected with APS, treatment of orbitopathy and high insulin requirement in the course of corticosteroids therapy.

Key words: type 2 autoimmune polyglandular syndrome, type 1 diabetes mellitus, Graves' disease, Graves' orbitopathy, corticosteroids therapy

S t r e s z c z e n i e

W poniższym artykule przedstawiamy pacjentkę z wielogruczołowym zespołem autoimmunologicznym typu 2 (APS2), na który składały się cukrzyca typu 1, choroba Graves-Basedowa i bielactwo. W przebiegu choroby Graves-Basedowa pacjentka rozwinęła nadczynność tarczycy i ciężką, aktywną fazę orbitopatii, która wymagała masywnej systemowej dożylnej kortykoterapii stosowanej jako cotygodniowe pulsy metylprednisolonu. Leczenie to powodowało znamienne zwiększenie zapotrzebowania na insulinę. Dawki insuliny w pierwszej dobie po wlewie SoluMedrolu osiągały trzykrotną, w drugiej dobie dwukrotną, a w trzeciej półtora razy większą wartość w porównaniu ze zwykłym zapotrzebowaniem. W dyskusji omówiono problemy związane z APS, leczeniem wytrzeszczu oraz zwiększonym zapotrzebowaniem na insulinę w czasie leczenia systemową kortykoterapią dożylną.

Słowa kluczowe: wielogruczołowy zespół autoimmunologiczny typu 2, cukrzyca typu 1, choroba Graves-Basedowa, orbitopatia, systemowa dożylna kortykoterapia

35-year-old female with albinism since 10 years of age and type 1 diabetes mellitus since 12 years of age, recently treated with insulin pump, smoking about 10 cigarettes a day, reported due to clinical and laboratory signs of Graves' disease. Laboratory evaluation at admission revealed reduced concentration of TSH and elevated levels of fT3 and fT4. In addition, abnormal levels of antibodies against thyroid peroxidase (anti-TPO) and against TSH receptor (TRAb) were established – hormone levels before and after treatment are presented in the table 1. Physical examination revealed significantly enlarged thyroid gland, smooth, with audible vascular murmur, and bilateral exophthalmos. In addition, the medical interview indicated that the patient had difficulties in controlling diabetes mellitus over the last 3 months. Thiamazole was administered in the initial dose of 40 mg/day, which was gradually reduced. Despite treatment with thiamazole and gradual improvement in thyroid parameters, exophthalmos gradually increased and double vision additionally occurred. Based on the clinical picture and imaging evaluations (MRI of the head, ultrasound evaluation of the orbital cavities, VEP), an active phase of thyroid orbitopathy with involved external eye muscles and

double vision (class IV according to ATA) was diagnosed, and it was decided that it was necessary to use intravenous systemic corticotherapy (SoluMedrol 6 x 500 mg and 6 x 250 mg every week over 12 weeks). This method of therapy is currently recognized as the most effective in treatment of Graves' orbitopathy (1). Due to poor prognosis in terms of obtaining permanent remission after treatment with thyrostatic drug, large goiter, and maintaining a high level of TRAb antibodies during treatment with corticoids, it was decided that treatment with radioiodine was necessary. Therapeutic dose of ^{131}I 15 mCi was administered. After treatment with radioiodine, administration of maintenance doses of thiamazole was continued. After one year following administration of radioiodine, hypothyroidism occurred and it was necessary to administer thyroxine in initial dose of 25 μg/day.

Table 1. Laboratory parameters before and during treatment of hyperthyroidism.

Parameter	Result before treatment	Result during treatment
TSH mU/L	< 0.004	1.14
fT3 pg/mL	4.94	2.8
fT4pmol/L	15.7	8.96
anti-TPO antibodies IU/L	824	–
anti-TG antibodies IU/L	0	–
TRAb IU/L	9.47	5.5
HbA1C	7.4%	6.6%

As early as during the first intravenous infusion of SoluMedrol in the dose of 500 mg, a significant increase in glycemia occurred, which exceeded 350 mg/dL, and abnormal concentration of glucose maintained over the next 3 days, despite attempts undertaken by the patient in order to regain control. It was necessary to establish a course of action in order to avoid the risk of occurrence of hyperglycemia and potential ketoacidosis in this patient during the next courses of treatment. During the next courses of treatment, a gradual change in insulin dosing was established. Increased demand for insulin took place shortly after starting infusion of SoluMedrol. After approximately 2-3 hours following start of the infusion, a 2-fold increase in basal insulin was necessary (programmed by the patient as the base "steroids"), and 3-fold after completion of administration of SoluMedrol. Another increase of the base was executed by the patient by using rectangular bolus extended over about 12 hours. Simultaneously, on the day of administration of corticoid, a 3-fold increase in doses of pre-meal boluses was necessary. On the second day of treatment, demand for basal insulin decreased to the level of two times higher than normal basal infusion, and demand for pre-meal boluses was similarly higher. On the third day following administration of SoluMedrol, doses of the basal infusion and pre-meal boluses were 1.5 times higher than usual. On the fourth day, it was possible to use regular dosing. During the next courses of treatment with SoluMedrol in the dose of 500 mg, demand for insulin increased to the same level and it did not undergo any further changes. During infusions of SoluMedrol in the dose of 250 mg, demand for insulin was insignificantly lower.

COMMENTS

The case presented above shows problems related, firstly, to autoimmune polyglandular syndrome (APS), and secondly, to increased demand for insulin during steroid therapy, which occurs not only in persons with diabetes mellitus.

Usually, it is assumed that symptoms of type 2 APS, most frequently occur in adults. It is also known that the time between occurrences of the respective components of the syndrome may be long. In the presented female patient, the first disease that occurred was albinism (at the age of about 10 years), then, within short period, type 1 diabetes mellitus (at the age of 12 years), and the next autoimmune disease – Graves' disease – as late as after another 23 years.

In the group of 360 patients with APS observed over 15 years in the Endocrinology Center at the University in Gutenberg (2), it was established that endocrine diseases, which were the most frequently occurring within a course of APS2, included autoimmune diseases of the thyroid gland, which occurred in 99 persons in total, i.e. in 65.6% (including Graves' disease in 50 subjects, i.e. 33.1%, and Hashimoto's disease in 49, i.e. 32.5%). Type 1 diabetes mellitus occurred in 92 persons (60.9%). Addison's disease in 28 patients (18.5%) and hypogonadism in 8 cases (5.3%). The most frequently occurring non-endocrine disease was albinism, which occurred in 30 persons (19.9%), but circumscribed alopecia (6%) and vitamin B12 deficiency anemia (5.3%) occurred more rarely.

Epidemiological data also indicated a significant difference in the age, when the first endocrine disease occurred within a course of APS2. The earliest manifestation is revealed by type 1 diabetes mellitus, which occurred, on average, at the age of 27.5 years. Other components of the syndrome usually occurred between 36.5 and 40.5 year of age, on average. The most common joint occurrence of diseases included diabetes mellitus and thyroid diseases, thyroid diseases and Addison's disease, diabetes mellitus and albinism, thyroid diseases and albinism, and joint occurrence of diabetes mellitus, thyroid diseases and deficit of vitamin B12. Occurrence of one autoimmune disease should encourage performing regular control check-ups for other diseases of auto-aggression. Control check-ups should be conducted every 3 years, but in case of simultaneous occurrence of 2 diseases, once a year. It is also indicated to perform evaluation of thyroid function in the first-degree relatives. In the US, it is recommended to perform routine control of thyroid function in patients with type 1 diabetes mellitus and in their first-degree relatives.

APS2 is genetically based polymorphism including many genes. They include polymorphisms of genes of class I (MICA) and II of HLA system, PTPN22 and CTLA4 genes (2). However, the diseases usually occur under influence of environmental factors, including infections (the most frequently viral infections), stress or smoking. Smoking is also one of risk factors for occurrence of thyroid orbitopathy within a course of Graves' disease (1).

Establishing active orbitopathy is currently a indication for systemic treatment with pulses of corticoids. Intravenous corticotherapy significantly reduces levels of antibodies against TSH receptor (TRAb) (4). Pulses of high doses of steroids result in decreasing level of antibodies against eye muscles (5). Number of CD4 + CD45RA + and CD11+CD82+ cells significantly increases in peripheral blood. Also, the previously increased number of CD11-CD8+ cells returns to normal. In addition, glucocorticoids reveal an inhibiting effect on circulating dendritic cells. Pulses with high doses of corticoids result in their disappearance from circulation, however, after eight days, their number returns to an initial level. For this reason, it is necessary to repeat these pulses (7).

Corticoids reveal many adverse effects. One of them includes action opposite to insulin in reference to carbohydrate metabolism. Glucocorticoids directly act in the liver by inducing synthesis of enzymes of gluconeogenesis, including: pyruvate carboxylase, phosphoenolpyruvate kinase, fructose-6-phosphatase and glucose-6-phosphatase. Induction of synthesis of gluconeogenesis enzymes, stimulation of glucagon secretion and increased supply of substrates for gluconeogenesis (amino acids and glycerol) result in increased hepatic gluconeogenesis and excessive release of glucose from the liver. Furthermore, hypercortisolemia affects fatty tissue, which initially intensifies lipolysis, leading to an increase in serum levels of free fatty acids and glycerol. Excess of free fatty acids intensifies insulin resistance, and glycerol is a substrate for gluconeogenesis (8). It results in an additional increase in demand for insulin. Within the study with an insulin clamp, Serbian investigators established that there were no changes in insulin resistance during the first 30 minutes of corticoid infusion, and there was a statistically significant reduction in insulin sensitivity within 4 hours in patients without diabetes mellitus treated with intravenous glucocorticoids. Reduction was maintained during the next infusions (9). Corticoids also increase secretion of glucagon, which also intensifies gluconeogenesis. Increased concentration of insulin, not only basal, but also after stimulation, has been established in patients without diabetes mellitus, who were treated with high doses of corticoids. In some persons, it compensates increased demand for insulin, but not in all of them. For this reason, it is believed that the presence of disturbances in carbohydrate metabolism accompanied by excess of glucocorticoids (endogenous as well as exogenous) depends on beta cell secretory reserve (8).

However, treatment of a person with type 1 diabetes mellitus shows how significantly a demand for insulin may increase during treatment with high doses of corticoids. In the observed female patient, it was three times higher than it was under normal conditions, and it went up within short period after starting intravenous administration of corticoids. Return to initial values took place after the 3rd day following administration of corticoids. A similar increase of demand for insulin is only observed in some females with type 1 diabetes mellitus in the third trimester of pregnancy. Using an insulin pump by our patient significantly simplified treatment of diabetes mellitus and it facilitated smooth adjustment of demand for insulin during corticotherapy. The physician forced to adjust insulin doses administered by injectors (injection pens) would face a significantly greater challenge. In such case, controlling glycemia would be much more difficult, because safe administration of a sufficient dose of basal insulin would actually be impossible, and controlling glycemia would be mainly based on the administration of corrective doses of rapid acting insulin. It should be also believed that in case of each patient with diabetes mellitus, demand for insulin would be slightly different and it would be necessary to adjust this demand individually in each case. Also in patients with type 2 diabetes mellitus, demand for insulin will be different compared to patients with type 1 diabetes mellitus, and different in the respective patients, due to a different degree of overweight or obesity and insulin resistance.

Due to the fact that various autoimmune diseases may coexist with each other, and in some diseases, it may be necessary to provide systemic intravenous corticotherapy, it seems that our experience in management of this female patient with type 1 diabetes mellitus may be useful for other physicians.

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