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Effectiveness of chronic treatment with ketoconazole in a patient with diabetic Cushing's disease resistant to surgery

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Abstract

Without treatment, Cushing's disease has significant morbidity and mortality. Where a surgical approach may not be feasible, or is refused by the patient, medical therapy becomes the only option. In this case report, we discuss the effects of two years of ketoconazole treatment on diabetes regulation and insulin resistance in a patient reluctant to agree to surgery. A 62 year-old female patient with uncontrolled type 2 diabetes mellitus was investigated. Cushing's disease was confirmed by the results of high urine free cortisol level and dexamethasone suppression tests.

We discuss the effects of two years of 600 mg/day ketoconazole treatment on diabetes regulation and insulin resistance in a patient with Cushing's disease reluctant to agree to surgery. This case report illustrates the beneficial long-term effects of 24 months of ketoconazole treatment on the clinical and laboratory findings and also on steroid and glucose metabolism. **(Pol J Endocrinol 2011; 62 (3): 271–274)**

Key words: *Cushing's disease, ketoconazole, insulin resistance, HOMA*

Introduction

Cushing's disease has great morbidity and mortality if not treated properly. Usually, cardiovascular complications which occur as a result of metabolic disorders are responsible for this high morbidity and mortality [1]. Insulin resistance due to hypercortisolemia decreases utilisation of glucose at peripheral tissues, and disturbed glucose tolerance (30–60%) and overt diabetes mellitus (25–50%) consequently occur [2, 3]. Insulin resistance may reflect impaired insulin-dependent down-regulation of hepatic glucose release and/or impaired insulin-mediated increase in peripheral glucose uptake. Cortisol can activate either glucocorticoid (type 2 corticosteroid) or mineralocorticoid (type 1 corticosteroid) receptors, although it has a greater affinity for the latter [4–6].

Cushing's disease creates insulin resistance by affecting at postreceptor level. Surgical intervention is the treatment of choice when the etiology is found. If a surgical approach is not applicable, or is refused by the patient, medical therapy becomes the only option. Steroidogenesis inhibitors such as ketoconazole, metyrapone, mitotane and aminoglutethimide are among the choices for medical therapy. But currently no medical agent can be accepted as the optimal choice of therapy [7].

We discuss here the positive effects of two years of ketoconazole treatment on steroid and glucose metabolism and homeostatic model assessment (HOMA) in a 62 year-old female patient being followed up with a diagnosis of Cushing's disease and unregulated diabetes mellitus.

Case report

A 62 year-old female patient with type 2 diabetes mellitus who was followed up in another clinic, attended our clinic with unregulated glycaemic control. She had been treated for hypertension and hyperlipidemia for 15 years and eight years respectively. She had previously undergone coronary artery bypass surgery. Her daily treatment consisted of 10 mg amlodipine, 5 mg ramipril, 90 mg diltiazem, 50 mg aldactazide, 20 mg atorvastatin, 100 mg aspirin, 30 units of regular insulin and 10 units of NPH insulin. There was no cigaratte or alcohol consumption. Her body mass index was 31 kg/m^2 and she had truncal obesity. Blood pressure was 150/100 mmHg and heart rate was 62 min/rhythmic. Lower extremity oedema was found bilaterally. Proximal muscle weakness (3/5) was revealed. Other than a 2/6 systolic murmur at the 5th mid-clavicular intercostal space, she had normal physiological findings. Haemogram tests were normal. Normal

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ejection fraction and moderate mitral insufficiency were found in echocardiographic investigation. The biochemical examination of blood was as follows: glucose 320 mg/dl, BUN 83 mg/dL, creatinine 1.7 mg/dl, sodium 138 mmol/l, potassium 4 mmol/l, total cholesterol 122 mg/dl, LDL-cholesterol 75 mg/dl (under statin therapy), HDL-cholesterol 30 mg/dl, triglyceride 125 mg/dl, C-peptide 1.2 ng/ml. Thyroid function tests and thyroid autoantibody levels were normal. HbA1c was 11.9%. Proteinuria of 120 μ/day and 40 ml/min clearance of creatinine were detected. Preproliferative retinopathy was found. Following hospitalisation, blood glucose levels were measured five times a day. Instead of oral anti-diabetic therapy, intensive insulin treatment was given because of chronic renal insufficiency. The average insulin dose was 220 units per day. Despite adequate insulin treatment (2 units per kg), blood glucose could not be regulated. To prevent glucotoxicity, insulin treatment was conducted as 48 hours of infusion. We planned an appropriate dietary programme.

No further pathology was found except pangastritis in endoscopic evaluation. Abdominal ultrasonography showed grade 2 hepatosteatosis and a left adrenal adenoma of 2 × 3 cm, which was also confirmed by magnetic resonance imaging (MRI). The mass was found hypointense on T1-weighted sequences and hyperintense in T2 sequences, which is significant for adenoma by MRI (Figure 1). To determine the function of the mass, several hormone tests were conducted, the results of which were as follows: serum aldosterone (ng/dl)/plasma activity of renin (ng/ml/h) ratio 1.5, vanil mandelic acid 2.3 mg/day (n: 1–11 mg/day), noradrenaline 32 μg/day (n: 23–105 μg/day), adrenaline 5.7 μg/day (n: 4–20 μg/day), dopamine 146 mg/day (n: 190–450 mg/day), normetanephrine 278 μg/day (n: 105–354 μg/day), metanephrine 291 μg/day (n: 74–297 μg/day). These results were found from the 24 hour urine examination.

ACTH-dependent Cushing's disease was confirmed by the result of high urine free cortisol level and serum cortisol levels unsuppressed by low dose (> 1.8 μg/dl) and suppressed by high dose dexamethasone tests (Table I). Both changes of urinary free cortisol and serum cortisol after low dose and high dose dexamethasone suppression tests before and after ketoconazole therapy are shown in Table I. An 8 × 7 mm diameter microadenoma showing heterogenous enhancement with contrast was detected posteriorly on the pituitary MRI examination (Figure 2).

Surgical mass extraction was proposed, which was refused by the patient. So, ketoconazole treatment 600 mg/day was given to prevent steroid synthesis. Body mass index did not change, however total insulin requirements decreased to 55% and the needs of insulin per kg decreased from 2.0 units/kg to 1.2 units/kg during the ketoconazole 600 mg/day treatment which was continued for two years. Afterwards, the HbA1c value was 8.2%. Since the patient had been using insulin, HOMA-IR was calculated by C-peptide levels. HOMA-IR

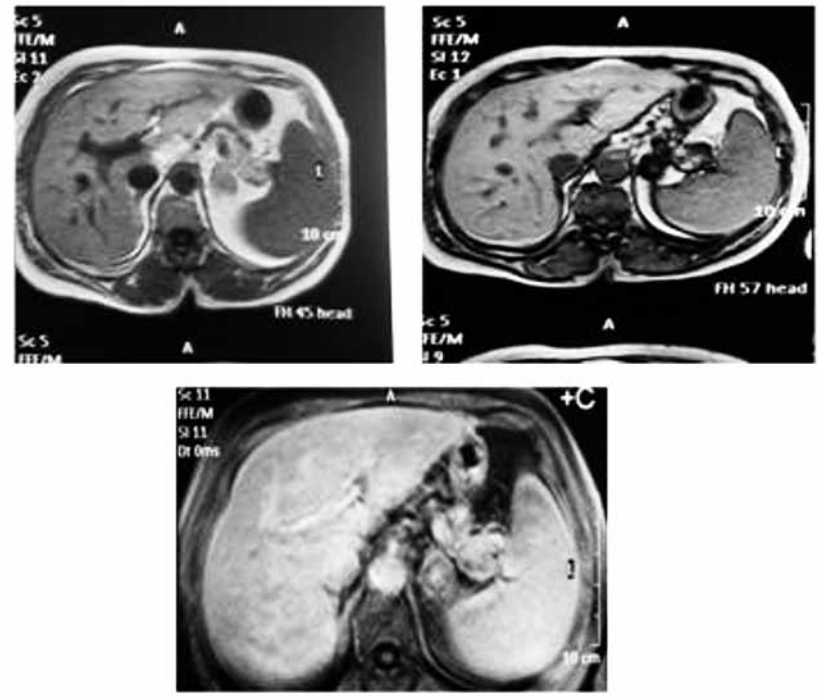

Figure 1. *Magnetic resonance imagine. The mass was found hypointense on T1-weighted sequences and hyperintens in T2 sequences*

Table 1. *Tests for Cushing's syndrome*

	Basal cortisol [μg/dl]	Urinaryfree cortisol [μg/dl]	Over night DST	Low dose DST	High dose DST	ACTH [pg/ml] (n: < 50)	17-αOH progesterone [ng/ml] (n: 0.23–1.36)	DHEAS [μg/dl] (n: 38–313)	Testosterone [ng/ml] (n: 1.8–7.8)
Initial results at diagnosis	15.6	190	4.72	10.25	2.97	25	0.8	35	0.5
Results after second year of treatment	14	50	1.78						

DST — dexamethasone suppression test

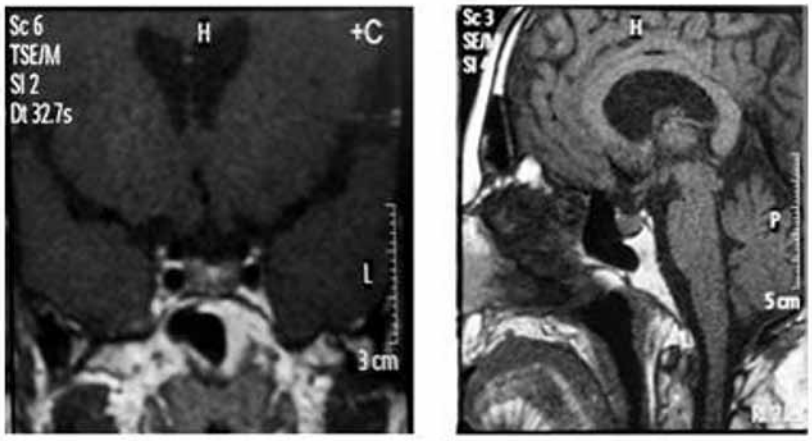

Figure 2. *8 × 7 mm daimeter microadenoma showing heterogenous enhancement with contrast was detected posteriorly on the pituitary MRI examination*

levels had decreased from 3.2 to 1.1 at the end of the two years [8]. The results of plasma cortisol after overnight dexamethasone test and urinary free cortisol value were detected as 1.78 μg/dl and 50 μg/dl respectively at the end of the two year treatment. There was a significant improvement in the constitutional complaints. Muscle strength was improved. No change in the mass size was detected in the MRI. The same treatment is still being conducted today.

Discussion

Ketoconazole is a wide spectrum antifungal agent that inhibits adrenal and testicular steroids reversibly. Several studies havereported that ketoconazole treatment results in 30–90% remission in Cushing's disease, with even higher rates being obtained in Cushing's syndrome of adrenal origin.

But what the duration and dose of therapy should be is yet to be established. Literature reports patients who have been administered ketoconazole for between 15 days and 13 years at various doses [9]. Sanino et al. [10] treated five female patients with Cushing's disease with ketoconazole for one month at 800 mg/day and for two months at 600 mg/day, and they observed significant clinical and laboratory improvements in all patients.

Angeli et al. [11] detected a rapid improvement in five female patients with hypophyseal Cushing's disease during the first two weeks of ketoconazole therapy. This improvement became more prominent in 1–2 months and was highest at the third month of therapy. Kong et al. [12] treated patients with Cushing's syndrome of adrenal origin for one month with 500 mg/day aminoglutethimide and with 600 mg/day ketoconazale during the following six weeks and then followed the patients for nine months with 400 mg/day ketoconazole. They reported that with ketoconazole treatment improvement in laboratory and clinical settings is obtained at a dose of 0.6 mg/day. HOMA is a parameter used in detecting beta cell function and insulin resistance. It is calculated from fasting blood glucose and insulin levels or C-peptide concentration. Since it was first described in 1985, computer models have been used instead of mathematical formulas and these models have been validated in many studies. [13]

In our case, we proposed surgical intervention to the patient. Because the patient refused the surgery, we gave ketoconazole at 600 mg/day. There is no very strong proof regarding this therapy modality in the literature. The clinical and laboratory findings in our case decreased. A significant improvement in the constitutional complaints was revealed, and muscle strength improved.

The results of plasma cortisol after overnight dexamethasone test and urinary free cortisol value were detected as 1.78 μg/dl and 50 μg/dl respectively at the end of the second year. Declines in the insulin (55%) and A1c levels (–3.7%) were found after two years of treatment. The glycaemic regulation was improved by reduction of insulin resistance. Since the patient had been using insulin, HOMA-IR was calculated by C-peptide levels. HOMA-IR levels decreased from 3.2 to 1.1 at the end of the two years, a decline of two thirds. Metformin could not be used because of renal insufficiency. According to this, the cause of the reduction in insulin resistance was thought to be due to the inhibition of steroid synthesis. Despite reports of adverse affects of ketoconazole treatment such as hepatic failure (12%) [14–16] and hypoadrenalism and gastrointestinal complaints, no adverse effect was seen in our patient.

In conclusion, this case report supports the beneficial long-term effects of 24 months of ketoconazole treatment on the clinical and laboratory findings and also on steroid and glucose metabolism.

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