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***MEDICINE***
*Case report*

# ASSOCIATION BETWEEN UNCONTROLLED TYPE 2 DIABETES, AND CUSHING'S DISEASE

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Cushing's syndrome is a condition generated by excess of glucocorticoids. In the etiology of syndrome are involved dependent adrenocorticotropic hormone (ACTH) or independent ACTH conditions including administration of supraphysiologic doses of steroid therapy. The term Cushing's disease is applied to ACTH-secreting pituitary tumors. We describe the clinical case of 65-year-old caucasian postmenopausal women diagnosed with hypertension in 2006, type 2 diabetes (T2DM) in 2007, Cushing's disease generated by pituitary macro adenoma in 2012. We have surveyed the clinical features, the results of therapies performed and the appearance/progression of complications. The surgical cure rate in macroadenoma is low and radiotherapy does not always lead to improvement to hormonal remission. The treatment of complications in Cushing's disease are absolutely necessary in order to reduce the risk of mortality.

*Keywords:* Cushing's disease,diabetes,obesity, osteoporosis.

## INTRODUCTION

Cushing's syndrome is a condition generated by excess of glucocorticoids. In the etiology of syndrome are involved dependent ACTH or independent ACTH conditions including administration of supraphysiologic doses of steroid therapy. The ACTH overproduction can by generated by pituitary adenomas or carcinomas, ectopic tumors, or secondary to an abnormality in the hypothalamus[1–3]. The term Cushing's disease is applied to ACTH-secreting pituitary tumors. Cushing's disease is a rare condition with a peak in adults in the 3rd or 4th decade[4]. Clinical characteristics of hypercortisolic state include: obesity, signs of protein wasting such as bone loss, hypertension and diabetes. Pituitary surgery is the first-line treatment and anticortisolic treatment (agents that inhibit steroidogenesis, modulate ACTH release or block glucocorticoid receptor) is most often proposed in case of failure or recurrence. Pituitary irradiation is recommended in the case of tumors with evidence of loco regional aggressiveness and adrenalectomy when the likelihood of a successful pituitary surgery is low[5, 6].

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## Case report

A 65-year old caucasian postmenopausal women had a 13-year history of T2DM and 14-year history of hypertension (controlled with an angiotensin-converting enzyme inhibitor and a calcium channel blocker). At the time of taking into account at the "Prof. N.C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases Bucharest (2007) the patient present: height 158 cm, weight 67 kg, body mass index (BMI)-26.8kg/m². The patient was begin treated with metformin 2000 mg/day which the values of glycosylated hemoglobin (HbA1c) oscillated in 2007 between 7% and 7.7%. In 2008 due to increased levels of HbA1c-8.9%, has been associated glimepiridum with the initial therapy. Since 2010 insulin therapy has been initiated. In February 2012 patient was hospitalized in the "Prof. N.C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases Bucharest for elevated glycemic values, progressive weight gain, narrowing of the field of vision. At admission patient present height 158 cm, weight 82 kg, BMI 33kg/m², a central distribution of fat with moon facies and cervical fat pat, blood pressure 140/100 mmHg, heart rate 80 beats per minute, HbA1c–8.97%. During the hospital admission, the insulin regimen was re-evaluated, opting for a basal bolus regimen. The patient was directed to perform ophthalmological and endocrinological evaluation. Ophthalmological evaluation confirmed the visual field deficiency and a pituitary magnetic resonance imaging (MRI) with gadolinumwas performed. The investigation highlighted: the replacement formation of pituitary and suprasal space with extension in the sphenoidal sinus, with dimensions of 28 mm/23 mm/30 mm (pituitary macroadenoma).The laboratory testing: basal ACTH: 25.77 pg/mL (normal range: 3–66 pg/mL), basal cortisol AM 30.67 µg/dL (normal range 6.2–19.4 µg/dL), and after long dose dexamethasone suppression test (2 and 8 mg): 18.42 pg/mL respectively 11.63 pg/mL and 11.25 µg/dL respectively 8.23 µg/dL. The suppression profile suggests a Cushing's syndrome ACTH-dependent. Abdominal tomography computer (TC) examination highlights: right and left adrenal space replacement process with a maximum diameter of 1.34 cm/2.94 cm/2.63 cm, respectively 1.42 cm/ 2.09 cm/2.58 cm, the rest of the glands with hyperplastic appearance. In the same year (2012) surgical tumor cure was practiced by transphenoidal approach with the persistence of an important tumor rest. Histopathological examination revealed mixed micro invasive acidophil pituitary adenoma at the capsular level and immuno-histochemical examination revealed: growth hormone, luteinizing hormone and ACTH weakly positive zonal and prolactin, thyroid-stimulating hormone, follicle-stimulating hormone negative. The patient was re-evaluated periodically and in 2013 pituitary MRI revealed an intra and suprasal tissue formation with maximum dimensions of 23 mm/20 mm/14 mm, the laboratory testing basal ACTH: 29.04 pg/mL, basal cortisol AM 36.54 µg/dL and after long dose dexamethasone suppression test (2 and 8 mg): 18.73 pg/mL respectively 14.24 pg/mL and 18.84 µg/dL respectively 7.05 µg/dL. In March 2013 was practiced left supranalectomy by laparoscopic approach. Hormone evaluation post-surgery highlighted: basal ACTH: 51.36 pg/mL, basal cortisol AM 30.68 µg/dL and after long dose dexamethasone suppression test (2 and 8 mg): 31.06 pg/mL respectively 22.49 pg/mL and 8.90 µg/dL respectively 8.24 µg/dL. Loss of suppression in the 2×2 mg dexamethasone test indicates autonomic hypersecretion of cortisol and good suppression at 2×8 mg dexamethasone test orients towards the pituitary origin of ACTH secretion. Treatment with aminoglutethimide (blocker of adrenal steroidogenesis) was associated to which the patient presented a severe skin allergic reaction. In November 2013 was practiced right supranalectomy by laparoscopic approach. The patient was recommended continuous replacement therapy with glucocorticoids (hydrocortisone 25 mg/day) and mineralocorticoids (fludrocortisonum 0.1 mg/day) and evaluation of pituitary MRI imaging and visual field examination to assess the need for pituitary radiotherapy for the prevention of Nelson syndrome. The patient presented the morphological progression of pituitary tumor formation and severe evolution ofoptochiasmatic syndrome that required emergency neurosurgical re-intervention with gamma knife radiotherapy in 2014. From a metabolic point of view the patient showed progressive weight gain (67 kg–2007, BMI: 26.8 kg/m², 100 kg – 2013, BMI: 41 kg/m², 117 kg – 2016, BMI: 47.25 kg/m², 120 kg – 2018, BMI: 49.33 kg/m²) and an average value of the HbA1c that varied between 6.9%–2014 and 9.1% – 2016. In 2016 the patient was admitted once again to "Prof. N.C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases Bucharest. The patient had metabolic imbalance on the basal bolus regimen with an insulin requirement of 1.36 U/kg/body. Opt to discontinue the administration of rapid insulin and initiate analogue glucagon-like peptide analogue 1 therapy. Due to the unfavorable evolution of metabolic control (HbA1c–9.9%) in 2017 resumes basal bolus therapy. Endocrine and neurosurgical re-evaluation carried out in 2018 have shown: ACTH: 110.60 pg/ml, basal cortisol: 0.93 µg/dL and after administration of 10 mg hydrocortisone: 13.99 µg/dL indicating adequate glucocorticoid replacement. Pituitary MRI imaging highlights the morphological progression of the rest of the tumor with severe non-evolutive optochiasmatic syndrome for which it is recommended to repeat gamma knife radiotherapy.

Patient associates osteoporosis and polynodular goiter with euthyroidism. Osteoporosis has been diagnosed in 2013 when dual-energy X-ray absorptiometry (DXA) highlights bone mineral density (BMD) lumbar spine level: 0.869 g/cm$^2$, score T: -2.8 standard deviations (DS), score Z: –2.8 DS and at the level of the hip, BMD: 0.877 g/cm$^2$, score T: –1.2 DS and score Z: -0.7 DS for which treatment with bisphosphonates (ibandronicum acid) has been recommended. In 2014 DXA highlights lumbar spine level BMD: 0.831 g/cm$^2$, score T: –2.9 standard deviations (DS), score Z:

–2.9 DS and at the level of the hip, BMD: 0.812 g/cm$^2$, score T: –1.6 DS and score Z: –1.1 DS with a reduction in bone mass by 4% in the lumbar spine and by 7% in the hip. Treatment with denosumab has been initiated. Revaluation over one year revealed a decrease in BMD in the lumbar spine by 4.33% and a 14% increase in the hip. From 2016 the patient receiving teriparatidum treatment with stationary BMD in 2018. Note that in 2010 the DXA exam highlights: BMD lumbar spine 0.953 g/cm$^2$, score T: –1.9 DS and score Z: –1.4 DS.

## DISCUSSIONS

Previous studies have shown a high prevalence of subclinical Cushing's syndrome in obese or uncontrolled diabetic patients[7, 8]. Subclinical or occult Cushing's syndrome is a entity characterised by various degrees of cortisol hypersecretion[7]. Catargi B *et al* assessed the prevalence of subclinical or occult Cushing's syndrome in two hundred consecutive overweight or obese T2DM patients with poor metabolic control. Fifty-two patients had impaired 1 mg dexamethasone supression test. In overweight T2DM patients the study revealed a 2% and 3.5% prevalence of definite or possible occult Cushing's syndrome. Leibowitz G and coworkers evaluated the prevalence of pre-clinical Cushing's syndrome in obese patients with uncontrolled diabetes. The authors concluded that "*The prevalence of pre-clinical Cushing's syndrome in obese patients with poorly controlled diabetes appears to be considerably higher than previously believed*"[8]. The results of a study published in 2007 by Caetano MS *et al* in which they analyzed cortisol abnormalities and subclinical or occult Cushing's syndrome in 103 overweight T2DM patients showed that the prevalence of condition is considerably higher in population at risk than in the general population[9]. In a prospectively study Reimondo G and coworkers evaluated 100 consecutive diabetic patients at diagnosis from 2003 to 2004. The authors concluded that unknown Cushing's syndrome is not rare among T2DM patients and that screening of condition may be feasible at the clinical onset of diabetes with the possibility to improve the prognosis of diabetes[10]. In contrast, results of a prospective study conducted in Italy in which they were enrolled 813 patients with known T2DM, the diagnosis of Cushing's syndrome was confirmed in six patients (0.7%) and authors state that *"the results of the present study do not support the application of a wide-scale screening of Cushing's syndrome in patients with type 2 diabetes, unless more efficient screening procedures will become available. The frequency of Cushing's syndrome in an unselected patient population was low compared with the number of false-positive results to make a routine screening strategy applicable in practice"*[11]. Budyal S *et al.* evaluated the prevalence of subclinical Cushing's syndrome in a cohort of 993 patients with T2DM patients. None patients had subclinical Cushing's syndrome and the authors suggest that screening should be carried on clinical grounds in such low risk unselected T2DM cohort[12].

The most frequent and sensitive sign in Cushing's syndrome is obesity with centripetal fat deposition and the protein wasting which includes bone loss and myopathy is the most specific sign[4]. Morbid obesity (BMI > 40 kg/m²) is not characteristic of the Cushing's syndrome. Janković D and coworkers evaluated the prevalence of endocrine disorders including Cushing's syndrome and hypothyroidism in 433 consecutive morbidly obese patients. The prevalence of Cushing's syndrome was below 0.6% and the authors concluded that Cushing's syndrome appears to be a rare cause of morbid obesity[13]. In a review of twenty-nine surgically proven cases of Cushing's syndrome only three patients met criteria of morbid obesity. The authors concluded that *"the history and physical signs and symptoms of morbid obesity contrast markedly with Cushing's syndrome"*[14]. In our patient progressive weight gain can be partially explained by non-adherence to specific diet and severe insulin resistance. Epidemiological and clinical studies have shown that obesity and T2DM are coupled with altered redox status implicated in the developmentof chronic complications[15–17].

The prevalence of osteoporosis assessed by DXA due to endogenous excess has been reported to be 50–59%[18]. The mechanism of glucocorticoids on bone turnover include: increase bone resorption, reducing bone formation and intestinal calcium absorption, increased urinary calcium excretion and alteration of vitamin D metabolism[19]. Previous studies have shown that bisphosphonates induce improvement in bone mineral density in the osteoporosis of patients with Cushing's syndrome[20–24]. A phase 2 trial published in 2010 by Dore RK *et al.* highlighted that denosumab improved lumbar spine BMD in patients with rheumatoid arthritis treated with glucocorticoids and bisphosphonates[25]. In our patient both therapies resulted in a reduction in

BMD in the lumbar spine. On treatment with teriparatidum the patient not show a reduction in BMD. Teriparatidum treatment has been shown to be effective in improving BMD in patients with glucocorticoids-induced osteoporosis[26–28]. Teriparatidum treatment is limited to 2 years and from 2018 the patient has resumed denosumab therapy. In the case of the patient presented it is necessary to periodical endocrinological evaluation as well as the treatment of complications and the identification of other risk factors[29, 30].

## CONCLUSION

We have surveyed the clinical features of patient with Cushing’s disease generated by pituitary macro adenoma, the results of therapies performed and the appearance/progression of complications. The surgical cure rate in macro adenoma is low and radiotherapy does not always lead to improvement to hormonal remission. The treatment of complications in Cushing’s disease are absolutely necessary in order to reduce the risk of mortality.

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