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## HIV INFECTION AND CUSHING'S DISEASE

**ABSTRACT: Introduction:** People with AIDS can have a dysfunction of the hypothalamic - pituitary- adrenal axis. With regard to HIV infection, most often mentioned is iatrogenic Cushing's syndrome or Pseudo-Cushing's Syndrome. So far there are described only two cases of Cushing disease in HIV -infected persons.

**Case report:** A 48-year-old patient, after eleven years of HIV infection and a year since the introduction of HAART, was diagnosed with Cushing's disease based on cushingoid habitus, lack of suppression of cortisol in screening, elevated ACTH and pituitary tumor. She had transfenoidal surgery and histopathologic findings corresponded to basophilic adenoma. After the operation, short time on hydrocortisone substitution, she generally felt well with regular ART. Four years later, again easily bruising, facial redness, oily skin with acne, weight gain, uneven distribution of stomach adipose tissue, sweating, oligomenorrhea and high blood pressure. There was no rest/relapse of tumor on control pituitary MRI. Initially, elevated ACTH, valid cortisol in daily profiles, later the absence of the suppression of cortisol after 4 mg (LDST) and 8 mg (HDST) of dexamethasone along with maintenance of higher ACTH, indicate recurrence of clinical and laboratory relapse wherefore ketoconazole was introduced. Despite increasing doses of ketoconazole, she held slightly higher morning cortisol, ACTH and with persisting Cushing's syndrome.

**Conclusion:** The coexistence of the two entities could lead to overlapping metabolic and phenotypic characteristics and the interaction between and/or synergism.

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## **INTRODUCTION**

At the end of 2011 34 million people worldwide were infected with HIV, registered approximately 2.7 million new infections and 2 million died of AIDS in 2007. It is estimated that 0.8% of adults, between 15 and 49 years, around the world live with HIV infection, despite the epidemiological differences among countries and regions. Individuals with Acquired immunodeficiency syndrome (AIDS) caused by infection with Human immunodeficiency virus type 1 (HIV1) have a distinct immunosuppression, in particular natural and T helper cell-mediated immunity. At the same time, may have a dysfunction of many organs and organ systems, including the hypothalamic-pituitary-adrenal axis (HPA). Over the last 20 years, many papers have presented evidence on the impact of HIV infection on the HPA axis and its target tissues. In HIV-infected persons may occur adrenalitis, adrenal insufficiency, glucocorticoid resistance dependent on the affinity of GR, modulation of the glucocorticoids metabolism, AIDS related insulin resistance and lipodystrophy syndrome.

The term "Cushing's syndrome" related to HIV infection commonly referred to as iatrogenic Cushing's syndrome or Pseudo-Cushing's syndrome. In HIV-infected patients often develop malignancy, lymphoma and Kaposi's sarcoma. Glucocorticoids have the central role in the treatment of these malignancies. They are also used for the treatment of tuberculosis and nephropathy associated with AIDS and in addition to antiretroviral therapy (ART). Some drugs that affect the metabolism of glucocorticoids participate in the etiology of iatrogenic Cushing's syndrome.

Combination of three different types of anti-retroviral drugs, nucleoside (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), and non-peptide inhibitors of the viral protease, referred to as highly active antiretroviral therapy (HAART). In addition to improving the clinical course and extending the life of the patient long-term use has led to the development of new co-morbidities and complications. Among the most important is the syndrome of insulin resistance and lipodystrophy associated with AIDS (ARIRLS). This acquired lipodystrophy most reminiscent of Cushing's syndrome.

Loss of circadian rhythm, normal negative coupling of HPA axis and chronic hypercortisolemia indicate endogenous Cushing's syndrome. The most common cause in 60 to 80% of all cases is the Cushing's disease, ACTH-dependent Cushing's syndrome, a form usually caused by a monoclonal corticotroph adenoma. According to the U.S. Food and Drug Administration Agency (FDA) about the frequency of ACTH-dependent Cushing's syndrome among HIV patients, in 2013 from 37390 persons 2 (0.01%) had Cushing's disease. Although the full form of the classical clinical picture of this syndrome is rarely seen today, some characteristics are obvious. However, the coexistence of the two entities could lead to overlapping metabolic and phenotypic characteristics and the interaction between and / or synergism.

## **CASE REPORT**

To a 47 year-old patient from Belgrade diagnosis of HIV infection was set in 1993, and since May 2003 HAART is introduced, indinavir (PI), stavudine (NRTI) and didanosine (NRTIs). After three months, it was concluded that the specified treatment shall not expressed a by-effects. In November 2004 due to bruising sent to an endocrinologist who found cushingoid aspect of the patient. Based on the lack of suppression of cortisol in the overnight dexamethasone test hypercortisolemia with elevated ACTH, pituitary tumor with incipient suprasellar and intrasphenoid propagation of the MR examination, the diagnosis of Cushing's disease was made. In January 2005 transsphenoidal tumor resection was done, histopathologic findings correspond basophilic adenoma of the pituitary gland in the back of the tiny fraction of the pituitary. One month of hydrocortisone substitution. In July 2005 good response of cortisol to ACTH test, the establishment of menstrual cycle after 5 years, control MRI - no signs of recurrence of tumors, sellar region only in part fulfilled actually pituitary tissue. Good felt with regular ART by 2009 when again notes easily bruising, with redness of the face, oily skin with acne, weight gain, unequal distribution of adipose tissue of the stomach, sweating, oligomenorrhea and high blood pressure. In laboratory examinations, elevated ACTH (156ng /L) with a neat cortisol profile (569.3, 153.6 nmol/L), erythrocytosis, leukocytosis, increased total cholesterol, LDL cholesterol and triglycerides without increasing blood glucose levels. In September 2010 no recurrence of tumor on MRI of the pituitary gland, slightly higher ACTH without an increase in cortisol. In February 2011 loss of menses and elevated cortisol profile (1117.9, 674 nmol /L) with a neat ACTH (17.5, 31.4 ng /L), lower FSH (3.3 IU/L), LH (2.1 IU/L) and HR (1.8 mIU/L) and slightly increase LTH (955.1, 678.1, 649.6 mIU/L). The lack of suppression of cortisol after 1 mg dexamethasone (744nmol/L) and after 4mg (LDST) and 8 mg (HDST) of dexamethasone along with the maintenance of higher ACTH indicated a clinical and laboratory relapse but no recurrence of tumors in the pituitary gland on MRI which is why ketoconazole introduced. Over the next control, with increasing doses of ketoconazole, held slightly higher morning cortisol (778, 781; 1058nmol /L) and ACTH (22.1, 21.5, 20.3 pmol /L). At the last MRI in February of 2012 pituitary gland finding essentially unchanged compared to the previous one, the most appropriate to postoperative sequelae. Treatment at the time of admission, abacavir / lamivudine (NRTI), efavirenz (NNRTI) and virumin, CD4 + lymphocytes of about 400, PCR negative. Smoker.

The patient is a tall, well-shaped, centripetal obesity, 29.1kg/m<sup>2</sup> BMI and waist 97cm, thinned upper arms, flattened gluteal, rounded, fat face, without bloating the area of the cheeks, plethoric, buffalo hump, purple, thin skin with livid stretch marks on the abdomen, thighs and axillas, neatly hydrated, velus heir of cheeks, hairy chin and chest, slight exophthalmos, large suspended breasts, peripheral arrangement of striae, lipodystrophy of hypochondrium. Reduced subcutaneous adipose tissue, asymmetrical

layout. Finding the lungs clean. Rhythmic heart rate, frequency of 60/min, sounds clear, no noise, TA 150/100mmHg without orthostatic hypotension. Peripheral pulsations symmetrical. Thickening and redness of the skin over the metacarpophalangeal joints without swelling. In laboratory studies: erythrocythemia with negative inflammatory syndrome, hyperinsulinemia without disturbance of fasting blood glucose and in OGTT, increased total, LDL cholesterol and triglycerides, slightly increased alkaline phosphatase, disrupted daily profile of cortisol and elevated ACTH, proper thyroid function and gonadal disturbances. The lack of suppression of cortisol after 8mg dexamethasone (614.7 nmol/L) with interruption of ketoconazole for several days. The EKG right bundle branch block, negative T wave of the V4-V6. On the X-ray of the heart and lungs large, hilar vascular, cardiac silhouette, enlarged, elongated and calcified aorta. At the ultrasound of the abdomen beside slightly enlarged liver, aortic aneurysm in the infrarenal segment of the transverse diameter of 42mm, with wall thrombus, circulating wide lumen of 22 mm, a length of 53mm, with propagation in the left iliac communis, other findings were unchanged.

## ***DISCUSSION***

HIV 1 directly and/or indirectly, through the circulating cytokines and inflammatory mediators, influences the HPA axis. According to various surveys in most HIV patients is present normal or easily elevated serum cortisol and plasma ACTH and preserved circadian rhythm. The increase in serum cortisol levels can be found in the early stages and in severely ill patients. Excretion of free cortisol in 24 hours urine was increased and depends on the severity of AIDS. Adrenocortical reserve based on a standard test ACTH is preserved in the majority of patients, with the exception of advanced cases. Weak response ACTH to stimulation with CRH is present in the terminal stage and is the result of an uneven production of cytokines. The patient in this review, after eleven years of HIV infection and a year since the introduction of HAART, the lack of suppression of cortisol in screening for autonomous hypersecretion aroused the suspicion of endogenous Cushing's syndrome. Elevated ACTH and pituitary tumor on MRI have focused on Cushing's disease, and histopathologic findings basophilic adenoma was also a definite confirmation. The ACTH hypersecretion in Cushing's disease is episodic and random and therefore causes hypersecretion of cortisol, the absence of normal circadian rhythm. Negative feedback inhibition of ACTH physiological levels of cortisol is absent. Episodic secretion of ACTH and cortisol results in different plasma levels, which can sometimes be within normal limits. Due to the absence of diurnal rhythm plasma ACTH and cortisol remained increased throughout the day and night.

Cushingoid aspect of the patient at that time was more the result of chronic hypercortisolemia, but there is an ART impact on extensiveness of phenotypic change

in the coming years. The outbreak of bruises, either spontaneously or after minimal trauma, a patient first noticed, one of the characteristics that indicates Cushing's syndrome most often. Hypercortisolemia causes thinning of the skin with separation and vulnerability of vascular structures in the subcutaneous tissue. The skin of our patients as a whole had a bluish discoloration and almost transparency. This explains the plethora and the reduction of subcutaneous adipose tissues of the face. The skin may be oily, shiny, distinctive look "facies lunata," with acne and fine, uncolored, velus hair on the cheeks and forehead. Livid marks, present in our patient, are almost pathognomonic of Cushing's syndrome. Hirsutism was present in the form of terminal pigmented hair chin and chest. Even a slight exophthalmos described in these patients. In our patient, the apparent centripetal obesity, thinning of the upper arms and gluteus flatness and lipodystrophy hypochondrium, with uneven and irregular appearance of the abdomen.

The patient from the case was treated PI nine years. The first case of redistribution of body fat in the treatment of antiretroviral drugs, including PI, the medical literature has described 1997. After that, there were more reports. Different names are used to describe this syndrome, pseudo-Cushing syndrome, redistribution or maldistribution of fat, PI or HIV associated lipodystrophy syndrome. Today, it is common to use the name ARIRLS AIDS - related insulin resistance and lipodystrophy syndrome - ARIRLS. There is a characteristic redistribution of body fat, loss of subcutaneous adipose tissues of the face (cheeks, twisted), the peripheral parts of the body, especially the legs and glutes - lipohypotrophia and at the same time accumulation of adipose tissue of the neck (double chin), dorsocervical (buffalo hump), in the upper part of the chest and visceral - lipohypertrophia. Loss of peripheral adipose tissue is more subtle in women compared to men, and a major problem is truncal obesity. A similar arrangement of adipose tissue with stretch marks, for subcutaneous defects, even more apparent in the embodiments of the present iatrogenic Cushing's syndrome. Namely, glucocorticoids are used for the treatment of malignancy and opportunistic infection in HIV patients in which metabolism some ART drugs act. Protease inhibitors, which inhibit the activity of virus - encoded proteases, and the inhibitory effect on one of the (CYP) cytochrome P450 enzyme, CYP3A4, which is required for the inactivation of glucocorticoids. Ritonavir is the strongest suppressor CYP3A4 - mediated  $6\beta$  hydroxylation of steroids, indinavir and nelfinavir are moderate suppressors, and least saquinavir. Cases are described fully manifested Cushing's syndrome in patients who use inhaled fluticasone and synthetic ritonavir, because of the extreme decrease in metabolic clearance. There have also been cases of iatrogenic Cushing's syndrome in the application megestrol acetate, a derivative of progesterone, glucocorticoid activity which is used for stimulation of appetite and weight gain in patients with possible kahectic adrenal insufficiency as a consequence of the reversal. Patients with ARIRLS may look muscular with strong superficial veins. And our patient was well shaped. There are breast enlargement in men and

women, as well as in patients from this view. It is not known whether it is caused by enlargement of the gland or accumulation of body fat, or both. In principle, the good general conditions, with rare opportunistic infections, in contrast to highly disordered and the quality of life for the more frequent infections despite endogenous Cushings. May have a disorder of menstrual cycles, while acanthosis lipodystrophy and other features are not described. However, amenorrhea of our patient at the beginning was a result of hypogonadotrophic hypogonadism in endogenous Cushing's syndrome, which is reversible, since after the operation of pituitary adenomas and reduction in cortisol menstrual cycles start again. But the subsequent loss of menstrual periods may be thought of as a combination of the impact of ART therapy and persistence of cortisol. A very striking feature of Cushing's syndrome, hypertension, occurs in up to 75 % of cases. Hypertension, together with contributing to the metabolic effects of the cardiovascular events are most frequent cause of mortality of untreated patients. Long-standing hypertension in our patient can be considered as the main cause of cardiomyopathy and aneurysms and thus represents an additional risk if not monitored. Glucocorticoid-induced osteoporosis, fractures can cause considerable disruption to the bone quality of life. However, our patient did not have a decrease in bone density or significant myopathy.

Since the metabolic effects of our patients had a high degree of insulin resistance without glucose tolerance disorders, and an increase in the total and "bad" cholesterol to low HDL cholesterol and an increase in triglycerides. Hypercholesterolemia is an appropriate level for the treatment with statins given the high risk of cardiovascular events. Insulin resistance / dyslipidemia is the third main feature of ARIRLS besides lipohypotrophia and lipohypertrophia. Dyslipidemia is characterized by hypertriglyceridaemia, hypercholesterolemia, and low HDL cholesterol values. Between 50 and 70% of patients treated with PI had dyslipidemia, and ritonavir increases the risk of triglyceride from 8 to 20 times than the cholesterol. Prior to the introduction of the treatment of dyslipidemia PI is characterized by reducing the total, HDL, and LDL cholesterol and an increase in triglycerides. The prevalence of hyperglycemia ranges from 0 to 20% on treatment with PI. Impaired glucose tolerance was present in 62% of cases, and observed an increase in levels of blood glucose after initiation of PI therapy. In one paper states that 11 of the 14 patients with this syndrome have diabetes as compared to 4 out of 20 persons who were treated with HAART PI within 14% of the patients and the treatment of the hyperglycemia of the NRTI. Described is a increase in basal and postprandial insulin and C peptide on therapy with or without PI. There is a higher prevalence of IR on PI therapy in comparison to an NRTI. Glucose intolerance, hyperinsulinemia, and IR may be an early manifestation of syndromes treated with PI. In contrast to all, in Cushing's syndrome, endogenous insulin resistance and hyperinsulinemia with impaired glucose tolerance are at 20 to 30% of cases, and even in the manifest DM 30 to 40% of cases. There is an increase in cholesterol and triglyceride levels, and different impact on HDL cholesterol. Transsphenoidal partial

hypophysectomy with the aim of removing adenomas and preserving intact the remaining pituitary function is the treatment of choice for the Cushing's disease. The rate of cure was 80 to 90% to 50%, for microadenomas and makroadenomas, in the best centers. Recurrence of Cushing's disease occurs in about 25% of the transsphenoidal operated cases. Repeatability neurosurgical intervention is imposed as an initial option. Clinical improvement after surgery of pituitary adenomas and proper function of HPA axis to test a few months later off the persistent hypercortisolemia and the existence of possible residual tumor of our patient. In the coming years there is a re-occurrence of symptoms and signs of Cushing's syndrome with normal / elevated serum ACTH and neat at first, then disrupted cortisol profile with no recurrence of the tumor on MRI of the pituitary gland followed by the same neurosurgeon. When suppression tests proved the presence hypercortisolemia was supposed to make a decision about further treatment. Since there was no evidence of tumor recurrence on MRI of the pituitary gland possibility of reoperation and radiation therapy are discussed. Ketoconazole, an inhibitor of steroidogenesis, is also available, well tolerated and was a reasonable choice in a situation not so high cortisol. Other medical therapy, somatostatin analogs, dopaminergic agonists and mitotane use in pathological conditions that are considered to have a crucial advantage. Perhaps the fact that the value of ACTH used to be normal, sometimes slightly more, and cortisol neat ago could explain the influence of HIV infection on the HPA axis and ART. Repeated recording pituitary MRI pointed to a lack of recurrence of the tumor. In such a case it is less likely to be able to think of a cyclic Cushing's syndrome. Not seeking treatment for depression and denied alcohol abuse alcohol to be considered the possibility of pseudo-Cushing's syndrome. Persistence of clinical symptomatology, which is also under the influence of ART, maintenance hypercortisolemia, though not extreme, and loss of circadian rhythm on ketoconazole therapy imposes the search for further arrangements. Come into consideration radical hypophysectomy or bilateral adrenalectomy if comorbidities (hypertensive cardiomyopathy, aortic aneurysm) allowed. In the case of bilateral adrenalectomy have the highest risk of developing Nelson's syndrome, which is not negligible. Most likely neurosurgery reintervention is radiosurgery, more modern method, such as the use of gamma knife (GammaKnife).

## **CONCLUSION**

HIV infection and Cushing's syndrome are two complex entities "per se". Existence at the same time at one person is an additional challenge for the understanding and clinical biochemical characteristics, because of possible overlapping and/or synergism, and in that sense adequate treatment. These patients require a multidisciplinary approach and the cooperation of different specialty physicians, infectious disease specialists, endocrinologists, radiologists and neurosurgeons. In order to provide

a better quality of life, with the assessment of the benefit and risk ratio, one has to choose among the available therapeutic treatments.

***Abbreviations:***

- 1) HIV – Human Immunodeficiency Virus
- 2) AIDS – Acquired Immunodeficiency Syndrome
- 3) HHA – Hipotálamo-Hipofizo-Adrenal Axis
- 4) GR – Glucocorticoid Receptor
- 5) NRTI – Nucleoside Reverse Transcriptase Inhibitors
- 6) NNRTI – Non-Nucleoside Reverse Transcriptase Inhibitors
- 7) PI – Proteasa Inhibitors
- 8) ARIRLS – AIDS - Related Insulin Resistance and Lipodystrophy Syndrome
- 9) ACTH – Adrenocorticotropic Hormone
- 10) MR – MRI
- 11) FSH – Follicle-Stimulating Hormone
- 12) LH - Luteinizing Hormone
- 13) HR – Growth Hormone
- 14) LTH – Prolactin
- 15) LDST – Low Dose Dexamethasone Test
- 16) HDST – High Dose Dexamethasone Test
- 17) PCR – Polymerase Chain Reaction
- 18) OMG – Osteomuscular shape
- 19) OGTT – Oral Glucose Tolerance Test
- 20) RTG – Rentgenography
- 21) EKG – Electrocardiography
- 22) CRH – Corticotropin-Realising Hormone
- 23) CYP – Cytochrome



**Table 1. Complete Blood Count**

Erythrocytes 5,05x10 <sup>6</sup> /l	Trombocytes 198x10 <sup>3</sup>
Hemoglobin 153g/dl	Leukocytes 7,43x10 <sup>9</sup> /l
Hematocrite 0,472 L/l	SR 12mm/h
MCV 93,4 fl	

**Tabela 2. Biochemistry**

glucose 5mmol/L				
urea 5,2 mmol/L	t. bilirubin 8,1 µmol/L	cholesterol 6,50 mmol/L	sFe 11,9 µmol/L	Na 142 mmol/L
creatinine 61µmol/L	AST 16 U/L	HDL 0,87 mmol/L	UIBC 45 µmol/L	K 4,4 mmol/L
ac. urricum 310 µmol/L	ALT 11 U/L	LDL 4,52 mmol/L	TIBC 56,9 µmol/L	Cl 106 mmol/L
proteins 65 g/L	ALP 132 U/L	triglicerydes 2,45 mmol/L	satur. transferi- na 21	Ca 2,26 mmol/L
albumin 38 g/L	gama GT 52 U/L		ferritin 2,24 pg/L	PO4 1,10 mmol/L

**Tabela 3. Oral glucose tolerance test**

glucose mmol/L	4,0	6,6	8,4	8,6	6,4
insuline mIU/l	20,6	52,2	37,5	58,7	48,8

**Tabela 4. Hormonal status**

ACTH 21,4 pmol/L	FSH 35,4 IU/L	TSH 0,77 mIU/L	LTH 8 <sup>h</sup> 535,7 mIU/L
cortisol 8 <sup>h</sup> 784,2 nmol/L	LH 9,3 IU/L	FT4 12,8 ng/L	LTH 9 <sup>h</sup> 646,3 mIU/L
cortisol 20 <sup>h</sup> 560,5 nmol/L	SHBG 45,6nmol/L	FT3 3,95 ng/L	LTH 10 <sup>h</sup> 433,3 mIU/L
cortisol 24 <sup>h</sup> 441,7 nmol/L	estradiol 172		

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