CASE REPORT

# Fatal course of cyclic Cushing's disease – lessons from a case

**Daria Baszko-Błaszyk [1], Katarzyna Ziemnicka [1], Ryszard Waśko [1], Leszek Pietz [1], Joanna Waligórska-Stachura [1], Paweł Gut [1], Maciej Biczysko [2], Jerzy Sowiński [1]**

1 Department of Endocrinology, Metabolism and Internal Medicine, Karol Marcinkowski University of Medical Sciences, Poznań, Poland
2 Department of General, Gastroenterological and Endocrine Surgery, Karol Marcinkowski University of Medical Sciences, Poznań, Poland

*Correspondence to:* Daria Baszko-Błaszyk MD., PhD.
Department of Endocrinology, Metabolism and Internal Medicine,
Karol Marcinkowski University of Medical Sciences,
49 Przybyszewski Str., 60-355, Poznań, Poland.
tel: +48 61 869 1330; fax: +48 61 869 16 82; e-mail: dbblaszyk@ump.edu.pl

*Submitted: 2011-04-14 Accepted: 2011-05-16 Published online: 2011-06-29*

*Key words:* **cyclic Cushing's disease; hypokalemia**

Neuroendocrinol Lett 2011; **32**(3):238–241 **PMID:** 21712786 NEL320311C01 

**Abstract**

We present a 56-year-old patient with cyclic Cushing's disease (CCD) observed for 28 months, who presented clinically and biochemically with alternating episodes of hyper-, normo- and hypocortisolemia. The course of the disease was fatal, the patient died due to severe hypokalemia.

## INTRODUCTION

Cyclic Cushing's disease or syndrome (CCD/S) is a rare disorder. Patients may present with permanent or transient manifestations, only one or more less specific symptoms of Cushing's syndrome may be present. To date, the minimal clinical and biochemical thresholds to diagnose CCD/S have not yet been established. According to different authors, at least two or three episodes of hypercortisolemia followed by periods of clinical and biochemical remission should be documented (Alexandraki *et al.* 2009) (Meinardi *et al.* 2007). The cause of the disease in 54% of cases is a pituitary corticotroph adenoma, in 26% an ectopic tumor producing ACTH, in 11% an adrenal tumor and in the remainder the origin is unknown. Bilateral macronodular adrenal hyperplasia with expression of aberrant LH or GIP receptors may also result in Cushing's syndrome, which is rather due to pregnancy or "food dependent" and not truly cyclic (Meinardi *et al.* 2007).

Cushing's syndrome is associated with an increased mortality rate (Lindholm *et al.* 2001). It is still unknown however, whether CCD/S affects prognosis.

We present a 56-year-old patient with cyclic Cushing's disease who died as a result of severe hypokalemia during a phase of acute and severe hypercortisolemia.

## CASE REPORT

A 56-year-old woman was admitted to hospital on February 2004 with suspected Cushing's syndrome. She had suffered from arterial hypertension, which had been treated successfully, for many years. The only manifestations of Cushing's syndrome were: a "moon" face with plethora and a protuberant abdomen with slim upper and lower extremities but stable body mass. She also suffered from bilateral coxarthrosis. Biochemical results confirmed the diagnosis of ACTH-dependent Cushing's syndrome (Table I). The MRI of the pituitary gland and CT of the adrenals were normal. No treatment was undertaken at this point, but two months later

the patient was admitted for re-evaluation. The manifestations had not changed and the biochemical results were normal, except for the absent diurnal cortisol rhythm. Sixteen months later the patient was admitted for the third time due to nausea, loss of appetite and skin hyperpigmentation. Her blood pressure was 110/70 which necessitated a reduction in the dosage of antihypertensive drugs. Repeated testing showed partial secondary adrenal gland insufficiency (see Table 1). Treatment commenced with small doses of hydrocortisone (10 mg in the morning), however there was a rapid progression of cushingoid manifestations and the drug was stopped after 2 months. The patient was then admitted to hospital for a fourth time. Moderate hypercortisolemia was confirmed for the second time and treatment with ketokonazole was started. At a dose of 400 mg daily a remission of symptoms was noted. Six months later, whilst under treatment with ketokonazole, the patient developed asymptomatic secondary partial adrenal gland insufficiency and the drug was stopped. Four weeks after treatment with the drug was discontinued, serum morning cortisol levels were still within the low normal range (289.2 nmol/l). The results of repeated testing with pituitary MRI, HRCT of the chest and abdomen and octreoscan were normal. Two months later, in August 2006, the patient was admitted to another hospital because of diarrhea and weakness which had been present for two preceding days. Severe hypokalemia was discovered ($K^+$ 1.5 mmol/l) and very slow improvement during treatment was observed. At the same time, an evening cortisol concentration was increased to > 1655 nmol/l, TSH was in suppression and FT4 – low normal. Hypernatremia was also observed (146–153 mmol/l). After the hypokalemia was corrected the patient deteriorated, she suffered from severe lumbar pain and, one week later, right-sided paresis occurred. A CT of the brain showed only generalized atrophy of the cortex without focal lesions. A lumbar spine CT showed osteoporosis, osteoarthritis and osteolytic lesions within L3 and L4 were suspected. The patient died two days later. An autopsy was not performed.

## DISCUSSION

Endogenous Cushing's syndrome is a rather uncommon disease, with an incidence of two to three cases per 1 million inhabitants per year (Etxabe *et al.* 1994, Lindholm *et al.* 2001). CCD/S is very rare (Nieman *et al.* 2008) and there were only several dozen cases reported in literature till 2007 (Asano *et al.* 2007) (Meinardi *et al.* 2007). However, in a big 60-year retrospective study the prevalence of CCD/S in the population of all patients with Cushing's syndrome was estimated at 15% (Alexandraki *et al.* 2009). Such discrepancies in reported incidence may result from a lack of commonly accepted criteria for the definition of CCD/S. Some authors recommend that two peaks of hypercortisolemia suffice to make a diagnosis (Alexandraki *et al.* 2009), while others require documentation of at least three peaks (Meinardi *et al.* 2007).

Manifestations of the disease are not specific, edema, proxymal myopathy and hypokalemia may predominate over the typical cushingoid appearance (Yasuda *et al.* 1994).

Generally, a diagnosis of Cushing's syndrome is frequently challenging, therefore various tests are used: urinary free cortisol (UFC), late-night salivary cortisol, 1-mg overnight dexamethasone suppression test (DST), longer low-dose DST (2 mg/d over 48 hrs), dexamethasone-CRH test or the midnight serum cortisol test and, in doubtful cases tests are repeated over some time (Nieman *et al.* 2008). In CCD/S measurements of UFC or midnight salivary cortisol are recommended (Nieman *et al.* 2008). Having confirmed the presence of endogenous hypercortisolemia, the measurement of plasma ACTH concentration helps to differentiate ACTH-dependent from ACTH-independent cases. Establishing a pituitary or ectopic source of ACTH excess may also be very difficult in some cases, as tumors producing ACTH or CRH may be small, well below MR resolution. The results have to be correlated with the overall clinical picture.

Over the three years, up to the patient's death, we observed three episodes of symptomatic hypercortisolemia, followed by normocortisolemia and then hypocortisolemia as a result of secondary partial adrenal insufficiency. Variable responses to 8 mg dexamethasone suppression test during phases of hypercortisolemia were observed.

During the follow-up the main problem which we observed was the lack of trust the endocrinologists caring for the patient had for the medical staff who collected blood and urine samples and were responsible for the dynamic testing, and towards the laboratory. Usually the first comment on such results focused on possible sources of errors. It was difficult to put together divergent results in one patient. The reason of death was severe hypokalemia and its sequel, which was most probably the result of acute severe cortisol hypersecretion. In literature there is one report of a 78-year-old woman with CCD/S who also died due to severe hypokalemia of 1.2 mEq/l and multiple organ failure during an active phase of the disease (Asano *et al.* 2007).

Another surprising finding in the patient was the transient suppression of TSH both during episodes of hypo- and hypercortisolemia and later on, of LH and FSH during the episode of hypercortisolemia. The suppressive effects of high doses of exogenous glucocorticoids on the hypothalamus and pituitary is a well-known fact. There is a report on a significant adverse correlation between serum cortisol and TSH concentrations (r=0.86) (Yamaguchi *et al.* 2003), but there are no reports of episodes of suppressed TSH in association with hypocortisolemia. There may be other pituitary abnormalities accompanying peaks and nadirs of cortisol secretion.

**Tab. 1.** The most important biochemical results of a patient with CCD over 2 years of follow-up.

| | 02.2004 | 04.2004 | 08.2005 | 12.2005 | 06.2006 Ketokonazole[4)] | 08.2006 | Reference range |
|---|---|---|---|---|---|---|---|
| Cortisol, serum; 8 A.M. | 764<br>309.4 | 261.7 | 35.09 | 1405<br>1247 | 180.3 | | 220–690 nmol/l |
| Cortisol, serum;<br>11 P.M. | 380.9 | 235 | 67.36<br>63.93 | 974.6<br>2113 | 11.53 | >1655 | 64–327 nmol/l |
| UFC | – | – | 41 | 598 | 33 | | 100–379 nmol/24h |
| Cortisol in 1mg DXM[1)]<br>suppression test | 484.7 | 47 | 25.69 | 1136 | | | |
| Cortisol in 8 mg DXM[1)]<br>suppression test | 91.45 | | | 856.7 | | | |
| ACTH | 30.6 | | 10.9 | | 19.7<br>22.8 | | 0–60 pg/ml |
| Cortisol in ITT[2)] test<br>time points (min)<br>Cortisol (nmol/l)<br>glycemia (mg/dl) | | | 0′ – 132.2 (81)<br>20′ – 178.7 (49)<br>30′ – 167.1 (59)<br>60′ – 196.0 (85) | | | | |
| DHEAS | 158.8 | 207 | 153.7 | 148.5 | 104.6 | | 20–100 nmol/l |
| TSH | 1.23 | | 0.098<br>0.105 | 1.7 | 0.785 | 0.09 | 0.27–4.2 µIU/ml |
| FT4 | 13.26 | | 17.32 | 17.74 | 10.81 | 9.60 | 11.5–21.0 pmol/l |
| PRL | 547.4 | | 492.3 | 624.2 | 521.2<br>276.7 | | 70–590 nmol/l |
| LH | | | 53.27 | 0.1 | 42.92 | | 7.5–58.5 mIU/ml |
| FSH | | | 127.8 | 3.45 | 127.1 | | 26–135 mIU/ml |
| E2 | | | | | 15.3 | | < 25 pg/ml |
| L1-L4 BMD[3)]<br>T-score | –0.79 | | –0.30 | –0.55 | –0.57 | | |
| Fasting plasma glucose | 63 | | 78 | 62 | 76 | | 70–100 mg/dl |

DXM[1)] – dexamethasone; ITT[2)] – insulin tolerance test; L1-L4 BMD[3)] – lumbar bone density
[4)] on ketokonazole 400 mg/d
Serum and urinary cortisol, TSH, FT4, LH, FSH, PRL and DHEAS were determined using Elecsys electrochemiluminescence immunoassay (Roche Diagnostics) for Cobas.
ACTH was determined using immunoradiometric assays (BRAHMS ACTH RIA) immunoradiometric assay.

Oversecretion of ACTH in our patient was periodic and irregular. MR imaging did not show pituitary abnormalities, but up to 50% of patients with Cushing's disease demonstrate a normal pituitary in MR scans (Hall *et al.* 1994, Tabarin *et al.* 1998). In literature there are some speculations on the possible causes of periodicity in CCD/S. Infarcts (Scott *et al.* 1979), partial necrosis (Schweikert *et al.* 1985), calcification (La Civita *et al.* 1989), episodes of haemorrhages or necrosis, apoptosis, patient stress (Popovic *et al.* 1990) and hypothalamic dysregulation (Yasuda,1996) have been reported in patients with CCD/S.

The treatment approach to patients with CCD/S does not differ from the general rules applied to patients with the non-cyclic form of the disease. Pituitary transphenoidal approach is a first-line treatment. Pituitary radiation is reserved only for the few selected cases which do not respond to other forms of treatment. Medical therapy is commonly used to treat hypercortisolemia and subsequent metabolic disarrangement. But the few, nonspecific symptoms and transient episodes of hypercortisolemia in this case of CCD/S prevented us from radical treatment. Medical therapy, which in fact was delayed, seemed to be a much better option. Accurate follow-up is mandatory to identify hypocortisolism, which may complicate medical treatment or present a spontaneous remission phase in the course of the disease. Medical therapy includes drugs indirectly inhibiting adrenal steroidogenesis, such as ketokonazole or mitotane, or decreasing ACTH production such as cabergoline (Feelders *et al.* 2010, Petrossians *et al.* 2010, Vilar *et al.* 2010). The effectiveness of neuromodulators such as serotonin, GABA or PPARγ agonists has not been proved (Jones *et al.* 1979, Kasperlik-Zaluska

*et al.* 1989, Kreutzer *et al.* 2009, Winczyk *et al.* 2009). SOM230 (pasireotide), a novel long acting somatostatin analogue is promising for patients with Cushing's disease (Pedroncelli 2010).

It can be concluded that establishing a diagnosis of CCD/S can be extremely difficult. Awareness of the existence of CCD/S is most important (Meinardi *et al.* 2007). Treatment is often difficult and suboptimal because of a variable clinical picture and discrepant biochemical results.

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