

# CLINICAL CASE

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## A Case of Nelson's Syndrome Diagnosed 22 Years after Bilateral Adrenalectomy for Cushing's Disease

### Przypadek zespołu Nelsona rozpoznany 22 lata po obustronnej adrenalectomii w przebiegu choroby Cushinga

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#### Abstract

The authors report on a rare case of Nelson's syndrome, which was diagnosed in a 54-year-old woman 22 years after bilateral adrenalectomy for Cushing's disease. The aim of the paper is to illustrate what serious consequences for the patient's outcome the performance of bilateral adrenalectomy in case of secondary hypercortisolism may have. The authors also underline other aspects in the pathogenesis of Nelson's syndrome (*Adv Clin Exp Med* 2005, 14, 1, 183–186).

**Key words:** Nelson's syndrome, corticotroph adenoma, bilateral adrenalectomy.

#### Streszczenie

Autorzy opisują rzadki przypadek zespołu Nelsona, który został rozpoznany u 54-letniej kobiety 22 lata po wykonaniu obustronnej resekcji nadnerczy. Celem pracy jest przedstawienie, jakie poważne następstwa dla pacjenta może mieć przeprowadzenie obustronnej adrenalectomii w przypadku wtórnego hiperkortyzolizmu. Autorzy również zwracają uwagę na inne aspekty patogenezy zespołu Nelsona (*Adv Clin Exp Med* 2005, 14, 1, 183–186).

**Słowa kluczowe:** zespół Nelsona, gruczolak kortykotropowy, obustronna adrenalectomia.

Nelson's syndrome is the occurrence of progressive cutaneous melanosis, elevated ACTH-level and an expanding tumour as a late complication following bilateral adrenalectomy for Cushing's disease. Nelson's syndrome is becoming increasingly less common mostly because transsphenoidal hypophysectomy has become the first line treatment for ACTH-secreting tumours. We describe the case of a 54-year-old woman diagnosed of Nelson's syndrome 22 years after bilateral adrenalectomy for Cushing's disease.

## Case Report

### First Presentation

A woman was diagnosed of Cushing's syndrome at the age of 32 years. Clinical symptoms as

well as laboratory tests suggested moderate hypercortisolism<sup>1</sup>. Diagnostic retroperitoneum revealed asymmetric bilateral enlargement of the suprarenal glands. As the high-dose suppression dexamethasone test was positive, computed tomography (CT) of the hypophysis was performed. CT was negative so the possibility of an ACTH-secreting pituitary adenoma was excluded.

The patient underwent a total bilateral adrenalectomy. Histological sections of the adrenal glands displayed hyperplasia of the glandular cortices. Immediately after the operation steroid replacement therapy was introduced. The early postoperative period was complicated by the

<sup>1</sup> Moderate hypercortisolism is characterized by hypertension, diabetes, obesity, muscular loss with absence of respiratory and cardiac insufficiencies.

occurrence of a gluteal abscess. The long term follow-up period revealed regression of both clinical and laboratory evidence of hypercortisolism.

## Second Presentation

The patient presented 22 years later with skin hyperpigmentation, deterioration in her visual fields, headache and hypopituitarism. The onset of the clinical symptoms did not exceed 3 weeks. Visual field assessment revealed bitemporal hemianopsia. Visual acuity was markedly decreased in the left eye. Hormonal tests revealed highly-elevated ACTH-levels (ACTH – 125 000 pg/ml) as well as gave evidence of subclinical hypothyroidism (TSH – 1.840 mIU/l, fT4 – 5.53 pmol/l, fT – 3.98 pmol/l) and hypogonadism (LH – 2.29 mIU/ml, FSH – 9.29 mIU/ml, estradiol – 24.30 pg/ml). Prolactin (PRL) and somatotrophin (GH) level was normal (PRL – 18.4 ng/ml, GH – 0.54 ng/ml). Magnetic resonance investigation (MRI) showed a large intra- and suprasellar tumour (3.7/2.5/2.5 cm) expanding into the right sinus cavernous and compressing the optical chiasm and the third ventricle (Fig. 1).

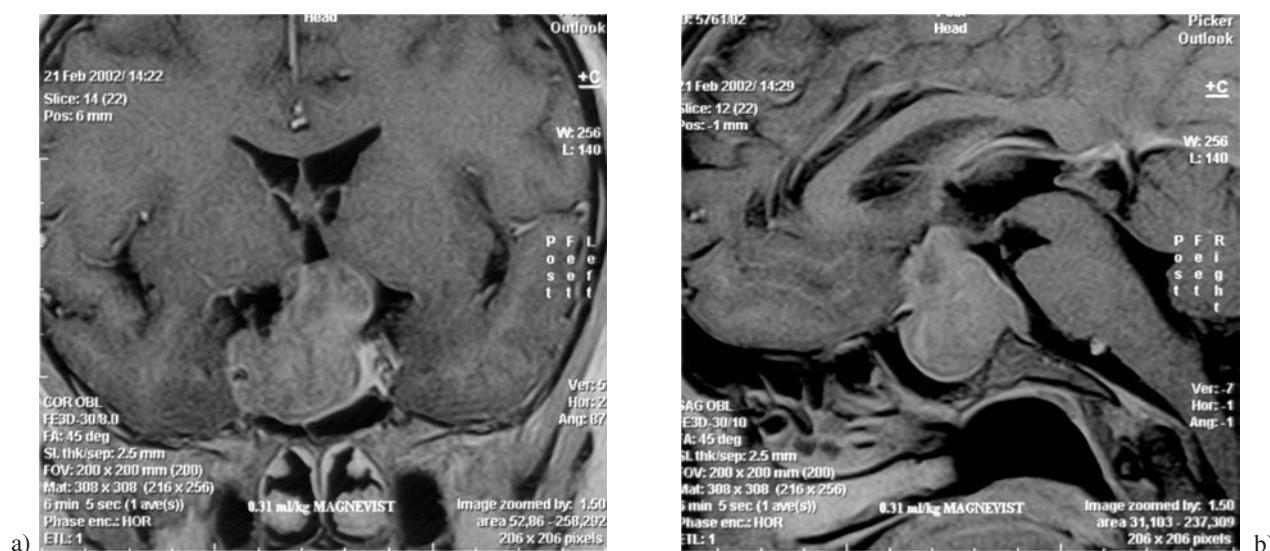
The evidence of a large and aggressive pituitary tumour, secreting very high concentrations of ACTH, skin hyperpigmentation as well as the history of bilateral adrenalectomy permitted the diagnosis of Nelson's syndrome. The patient underwent an intracranial resection of the tumour. Left pterional approach was used to access the hypophysis as the left optic nerve was compressed to a greater extent

than the right one. The tumour was almost totally resected, except a small fragment of neoplastic tissue that was left in the right cavernous sinus. Histological examination revealed an adenoma infiltrating the tumour capsula. Immunohistochemistry was positive only for ACTH.

The postoperative period was uneventful. Hormone replacement therapy including hydrocortisone, fludrocortisone and thyroxine was applied. Two weeks after the operation improvement of the visual field and visual acuity were observed both during the neurological examination as well as diagnostic tests (visual field assessment, visual evoked potentials). As the tumour was subtotally resected, surgery was followed by radiotherapy in which the resection bed received 58 Gy radiation in 24 cycles (cobalt was the radiation source).

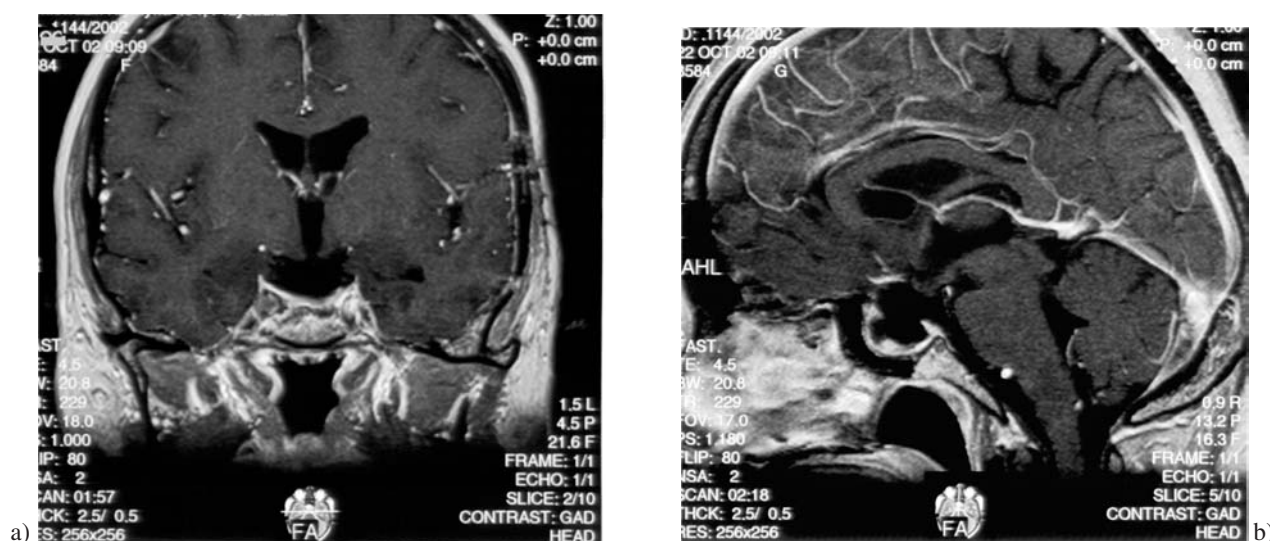
## Third Presentation

Six months following the operation the patient still showed improvement of the visual field and visual acuity. Hyperpigmentation had markedly decreased. No adverse effects attributed to the radiation therapy were observed. Daily levels of ACTH varied from 562 pg/ml to 1250 pg/ml. The levels of the remaining hormones were normal (prolactin – 13.40 ng/ml, TSH – 1.300 mIU/l, fT4 – 7.10 pmol/l, fT3 – 3.42 pmol/l, GH – 0.26 ng/ml). Control MRI investigation conducted 6 months post surgery did not show any evidence of tumour debris (Fig. 2).



**Fig. 1.** MRI of sella turcica. The coronal (a) as well as the sagittal (b) plain shows a large intra- and suprasellar tumour compressing the optical chiasm and the third ventricle. The tumour also expands into the right cavernous sinus (a)

**Ryc. 1.** MRI siodła tureckiego. Wieńcowy (a) i strzałkowy (b) przekrój przedstawiają olbrzymi wewnątrz- i zewnątrz-siodłowy guz uciskający skrzyżowanie wzrokowe oraz trzecią komorę. Guz wrasta również w kierunku prawej zatoki jamistej (a)



**Fig. 2.** MRI of sella turcica performed 6 months post resection of the hypophysial tumour (images obtained following contrast administration): a) coronal plain, b) sagittal plain

**Ryc. 2.** MRI siodła tureckiego wykonane 6 miesięcy po zabiegu resekcji guza przysadki (badanie z kontrastem): a) przekrój wieńcowy, b) przekrój strzałkowy

## Discussion

Bilateral adrenalectomy has proved to be a safe operation resulting in fast regression of the symptoms of hypercortisolism with low recurrence rate ranging from 0% to 4.5% [1]. It is considered as a treatment of choice in cases of ectopic ACTH-release and failure of transsphenoidal surgery or pituitary radiotherapy for ACTH-secreting pituitary tumours [2]. Yet normalisation of the cortisol level following adrenalectomy in patients with an ACTH-secreting microadenoma induces an increase in corticotropin-releasing hormone (CRH) production, which has trophic influence on the tumour, stimulating its growth [3]. This growth results in 7.5 to 29% of the cases in the occurrence of an invasive ACTH-secreting macroadenoma, which is referred to as Nelson's syndrome [4, 5]. The incidence of Nelson's syndrome is particularly high in females at the age before 35 that had not undergone prophylactic pituitary radiotherapy after total adrenalectomy [2, 6].

In our case total bilateral adrenalectomy was performed in a patient who belonged to the group of high risk of developing Nelson's syndrome. The decision to remove the suprarenal glands was based on the finding of their enlargement with the simultaneous absence of any radiological evidence of pituitary tumour (negative CT of the hypophysis and negative plain X-ray of sella turcica). The patient was mistakenly diagnosed and treated for primary suprarenal hyperplasia.

We claim that the diagnostic steps taken when the first symptoms of hypercortisolism occurred in

our patient were incomplete. Firstly, the high-dose dexamethasone suppression test was positive, so it gave evidence of ACTH-dependence. Although CT of the hypophysis was negative this could not exclude the presence of an ACTH-secreting hypophysial microadenoma. It is known that approximately 30% to 50% of pituitary adenomas in patients with Cushing's disease do not appear on CT or even on MRI [7]. Based on the current evidence, if the pituitary MRI or CT is negative but other investigations indicate ACTH-dependence, the ovine CRH-stimulated bilateral inferior petrosal sinus sampling test should be used to determine finally the appearance of a corticotroph adenoma [8]. The inferior petrosal sinus sampling test as well as the cavernous sinus sampling test are the most reliable tests confirming the presence of an ACTH-secreting pituitary tumour with sensitivity varying from 97% to 100% respectively [9]. Besides, both tests can also assist in lateralizing of the tumour allowing the performance of a safe and effective hypophysectomy [8, 9]. Unfortunately, by the time the patient was diagnosed for hypercortisolism, neither MRI nor the discussed sinus sampling tests were available.

The described case of Nelson's syndrome shows clearly how difficult is to diagnose Cushing's disease. Besides it sheds new light on the pathomechanism of occurrence of Nelson's syndrome. The transformation from micro- into macroadenoma secreting ACTH takes usually place from 5 to 10 years following bilateral adrenalectomy. The long asymptomatic period between adrenalectomy and the appearance of

Nelson's syndrome (22 years) may confirm the thesis that at the time of setting of primary diagnosis the patient may have presented symptoms of hypercortisolism as a result of adenomatous hypertrophy of the hypophysis. We believe that the

performance of bilateral adrenalectomy had the same trophic influence on the hypertrophic hypophyseal gland as it normally exerts on an ACTH-secreting microadenoma, resulting in formation of invasive corticotroph adenoma.

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