



# Cushing's disease — assessing the efficacy of transsphenoidal surgery

Choroba Cushinga — jak ocenić skuteczność operacji przezklinowej

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## Abstract

Cushing's disease (CD) is caused by a pituitary adenoma secreting corticotrophin (ACTH) that leads to cortisol excess. Despite a characteristic clinical picture, it is often difficult to make a proper diagnosis, as it requires complex and long-lasting diagnostic procedures. Selective transsphenoidal surgery (TSS) remains the treatment of choice for CD. Untreated or improperly treated Cushing's disease leads to the development of serious complications, which lower patients' quality of life. Mortality in this group is high, reaching 50% within a 5-year follow-up period.

In this study, we present our own experience and discuss the importance of preoperative hormone measurements, magnetic resonance imaging (MRI) of the pituitary, results of histopathological examination (immunohistochemical and ultrastructural in electron microscopy) and post-operative early and late hormonal assessment in the aspect of TSS efficacy. The performed analysis is based on the current criteria for remission of Cushing's disease. Our study emphasises the need for long-term postoperative endocrinological follow-up, which facilitates early detection of recurrent hypercortisolemia. (*Endokrynol Pol* 2012; 63 (5): 398–403)

**Key words:** Cushing's disease, desmopressin, pituitary adenoma, cortisol, transsphenoidal surgery, magnetic resonance, dexamethasone suppression test

## Streszczenie

Przyczyną choroby Cushinga jest gruczolak przysadki wydzielający kortykotropinę (ACTH) i prowadzący do nadczynności kory nadnerczy. Mimo charakterystycznego obrazu klinicznego trudne jest prawidłowe rozpoznanie, wymaga złożonej i długotrwałej diagnostyki endokrynologicznej. Leczeniem z wyboru pozostaje selektywna, przezklinowa operacja guza przysadki. Nieleczona lub źle leczona choroba Cushinga prowadzi do rozwoju poważnych powikłań, które przyczyniają się do obniżenia jakości życia pacjentów. Śmiertelność w tej grupie dotyczy 50% chorych w czasie 5-letniej obserwacji.

Autorzy opracowania prezentują doświadczenia własne i omawiają znaczenie przedoperacyjnych oznaczeń hormonalnych, obrazowania przysadki mózgowej metodą rezonansu magnetycznego, wyników badania histopatologicznego (oceny immunohistochemicznej i ultrastrukturalnej w mikroskopie elektronowym) oraz pooperacyjnej wczesnej i odległej oceny hormonalnej w aspekcie skuteczności leczenia neurochirurgicznego. Dokonana analiza opiera się na obowiązujących kryteriach remisji choroby Cushinga. W opracowaniu podkreślono konieczność długoletniego, pooperacyjnego nadzoru endokrynologicznego, który umożliwia wczesne wykrycie nawrotu hiperkortyzolemii. (*Endokrynol Pol* 2012; 63 (5): 398–403)

**Słowa kluczowe:** choroba Cushinga, desmopresyna, gruczolak przysadki, kortyzol, operacja przezklinowa, rezonans magnetyczny, test hamowania deksametazonem

## Introduction

Cushing's disease (CD) is the commonest cause of endogenous hypercortisolemia. The disease incidence is estimated at 1–3 cases per 1 million people per year with its peak observed in the 3<sup>rd</sup>–5<sup>th</sup> decades of life. The disease affects women 4–8 times more often than men. In the under-10 year-old age group, Cushing's disease is diagnosed sporadically and is the least common cause of hypercortisolemia. After puberty, an increase in the incidence rate is observed [1–4]. During pregnancy, Cushing's disease constitutes about 30% of all causes of endogenous hypercortisolemia [2–5]. Diagnosis of the disease and its

treatment remain one of the major challenges in modern endocrinology [2, 3, 6]. In about 95% of cases, CD is caused by ACTH—secreting pituitary adenoma. In other, rare, cases it results from diffuse corticotroph hyperplasia. Most commonly, a corticotroph tumour is less than 1 cm in diameter (microadenoma). Only in about 15% of cases does at least one tumour diameter exceed 1 cm (macroadenoma) [2–4].

In patients with Cushing's disease, pituitary corticotroph adenoma exhibits autonomous ACTH secretion. This means that adenoma cells are not under inhibitory control of negative feedback mechanism. ACTH synthesis and secretion in the pituitary and cortisol secretion from the adrenals become independent from the needs of the organism. This affects the



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circadian rhythm, which results in high ACTH and cortisol concentrations being maintained even during late evening hours and at night. Hypercortisolemia inhibits secretory function of normal pituitary corticotrophic cells, exerting no effect on neoplastic cells [2–4]. There also occur changes within the receptor profile of pituitary corticotroph cells, especially in terms of increased expression of corticotrophin-releasing hormone (CRH) receptors as well as V3 vasopressin receptors [7–11].

Excessive cortisol secretion leads to the development of somatic symptoms of Cushing's syndrome. These include: facial *plethora*, purple striae, muscular atrophy, and the redistribution of adipose tissue with its accumulation in the face, nape and abdomen. Gradually, hypercortisolemia complications develop, such as arterial hypertension, glucose homeostasis alterations, decreased bone mineral density, venous thromboembolic disease, and increased frequency of infections. There are also observed cognitive function impairment, circadian rhythm disturbances and sleeping disorders. CD sometimes causes psychotic symptoms resulting from vasogenic and metabolic damage to the brain structures and cerebral atrophy associated with the disease. These complications result in both a decreased quality of life and shortened survival time. As many as half of untreated patients will die within five years [2, 4, 12–14].

### Surgical treatment for cushing's disease

Transsphenoidal selective adenomectomy is the treatment of choice in Cushing's disease [2, 15]. The small size of most ACTH-secreting adenomas, the proximity of critical structures such as the optic chiasm and internal carotid arteries, and the possibility of inflicting irreversible damage to the pituitary require transsphenoidal surgery to be performed only by experienced neurosurgeons in reference centres [2]. Surgical procedures performed by experienced neurosurgeons have high efficacy. This, depending on the site, ranges from 60% to over 90%. However, the recurrence rate that follows even an initially effective surgical treatment is high, and reaches 20–25% within five years [15]. Each successive surgical treatment is technically more difficult and yields a poorer outcome than the first one, with a higher probability of developing postoperative complications such as anterior pituitary insufficiency and/or *diabetes insipidus*. Therefore all patients who have undergone surgical treatment for corticotrophic pituitary adenomas require prolonged endocrinological follow-up [2, 3, 15].

### Preoperative hormone measurements

Hormone measurements are of vital importance for the diagnosis of Cushing's disease. In each case it is necessary to measure plasma ACTH, serum cortisol

and urinary free cortisol (UFC) under basic conditions. Assessment of morning serum cortisol following a 1 mg dexamethasone suppression test is of significant diagnostic importance [2, 4]. The commonly performed tests also include the so-called "high-dose" dexamethasone suppression test (HDDST; 2 mg q.i.d. during two consecutive days) with assessment of UFC or 17-hydroxysteroids excretion in daily urine. The CRH stimulation test (100  $\mu$ g *i.v.*) is the most commonly performed dynamic test [4]. Desmopressin stimulation test (DDAVP; 10  $\mu$ g *i.v.*) is not a part of routine diagnostic procedures [4, 16], yet according to recommendations it may be performed within scientific studies and the obtained results could constitute a basis for a re-assessment of its usefulness after gathering more data [16].

Inasmuch as preoperative tests are of key importance for the diagnosis of ACTH-dependent Cushing's syndrome as well as for its clinical picture and number of complications, they do not directly influence the efficacy of TSS. This is applicable both to basic measurements of plasma ACTH, serum and urinary cortisol and excretion of cortisol metabolites in daily urine, as well as results of the hormone measurements following HDDST. It is confirmed both by data from literature and our own observations [17, 18].

### Magnetic resonance imaging

In addition to hormone measurements, MRI of the pituitary is also of significant importance in preoperative diagnostics. The procedure is performed according to a special protocol based on adequately 'dense' cross-sections, as the majority of corticotroph adenomas are microadenomas, with half of them being less than 5 mm in diameter. The MRI scans should be performed before and after intravenous injection of the contrast agent (gadolinium; Gd-DTPA) [4]. The typical MRI of a corticotroph adenoma is presented in Figure 1.

There have been disagreements in the literature as to the importance of preoperative visualisation of corticotroph adenomas and its impact on the effectiveness of surgical treatment. A multicentre retrospective analysis performed by Bochicchio, Losa et al. demonstrated that accurate preoperative localisation of a focal lesion in MR imaging of the pituitary gland is associated with greater effectiveness of surgical treatment, whereas the lack of such a localisation is associated with a poorer prognosis [19]. However, the study, which was based on observations from 25 European endocrinological centres, did not separately assess the effectiveness of treatment in a sub-group of corticotroph pituitary micro- and macroadenomas [19].



**Figure 1.** Magnetic resonance imaging of the different types of ACTH-secreting pituitary adenomas — authors' own material. **A.** Coincidence of an empty sella and a minute ACTH-secreting pituitary adenoma located close to the left cavernous sinus; **B.** Pituitary microadenoma; **C.** Intra- and suprasellar pituitary macroadenoma; **D.** pituitary macroadenoma with right cavernous sinus invasion and destruction of the sella turcica floor

**Rycina 1.** Obrazy MRI gruczolaków kortykotropowych przysadki u chorych z chorobą Cushinga — materiał własny autorów. **A.** Współistnienie pustego siodła i gruczolaka kortykotropowego przysadki zlokalizowanego po lewej stronie siodła tureckiego; **B.** Mikrogruczolak przysadki; **C.** Śród- i nadsiodłowy makrogruczolak przysadki; **D.** Makrogruczolak przysadki mózgowej naciekający prawą zatokę jamistą i niszczący dno siodła tureckiego

A study conducted by British authors, based on retrospective assessment of 16 cases of patients with pituitary macroadenomas, demonstrated that treatment effectiveness in this group of patients is low [20]. Only two of 16 patients were surgically cured (12.5%) and in five patients (31.3%) it was possible to achieve remission after supplementary radiotherapy. In as yet unpublished material of ours, we found the effectiveness of surgical treatment of patients with pituitary macroadenoma to be greater than or equal to as much as 50%.

A separate issue, seemingly affecting about 10–15% of patients with biochemically confirmed Cushing's disease, is lack of an accurately localised focal lesion within the pituitary gland. In this difficult clinical situation, one can consider the performance of the so-called diagnostic sellar exploration, which in some cases leads to removal of a lesion of the type characteristic of CT and a visually undetectable by MR pituitary microadenoma (e.g. less than 3 mm in diameter) and remission of Cushing's disease [21].

### Immunohistochemical and ultrastructural assessment

Histological assessment supplemented by immunohistochemical staining is an essential element of Cushing's disease diagnostics. A positive test result is the ultimate and explicit confirmation that the pathological lesion within the pituitary caused the development of ACTH-dependent hypercortisolemia. This is why a neurosurgeon while performing a surgical procedure should meticulously collect the tissue specimens removed in the course of the TSS and send it to a pathology laboratory experienced in examining and assessing pituitary tumours. In the light of previous retrospective studies [19, 22] and our own observations [23] it should be stated that a positive result of an immunohistochemical and/or ultrastructural examination is more commonly associated with remission of Cushing's disease. The histology, immunochemistry and ultrastructure of typical corticotroph adenoma is presented in Figure 2.

Furthermore, it seems that positive pathological examination results are of particular significance in patients with equivocal results of MR imaging of the pituitary. In such cases, confirmation of neoplastic tissue in immunohistochemical and ultrastructural examination may make total removal of a small corticotroph pituitary tumour more worthwhile. In patients with corticotroph macroadenomas (particularly those with features of infiltration of adjacent structures) one should expect absence of cure, despite positive result of a pathological examination. This results from the fact that removal of

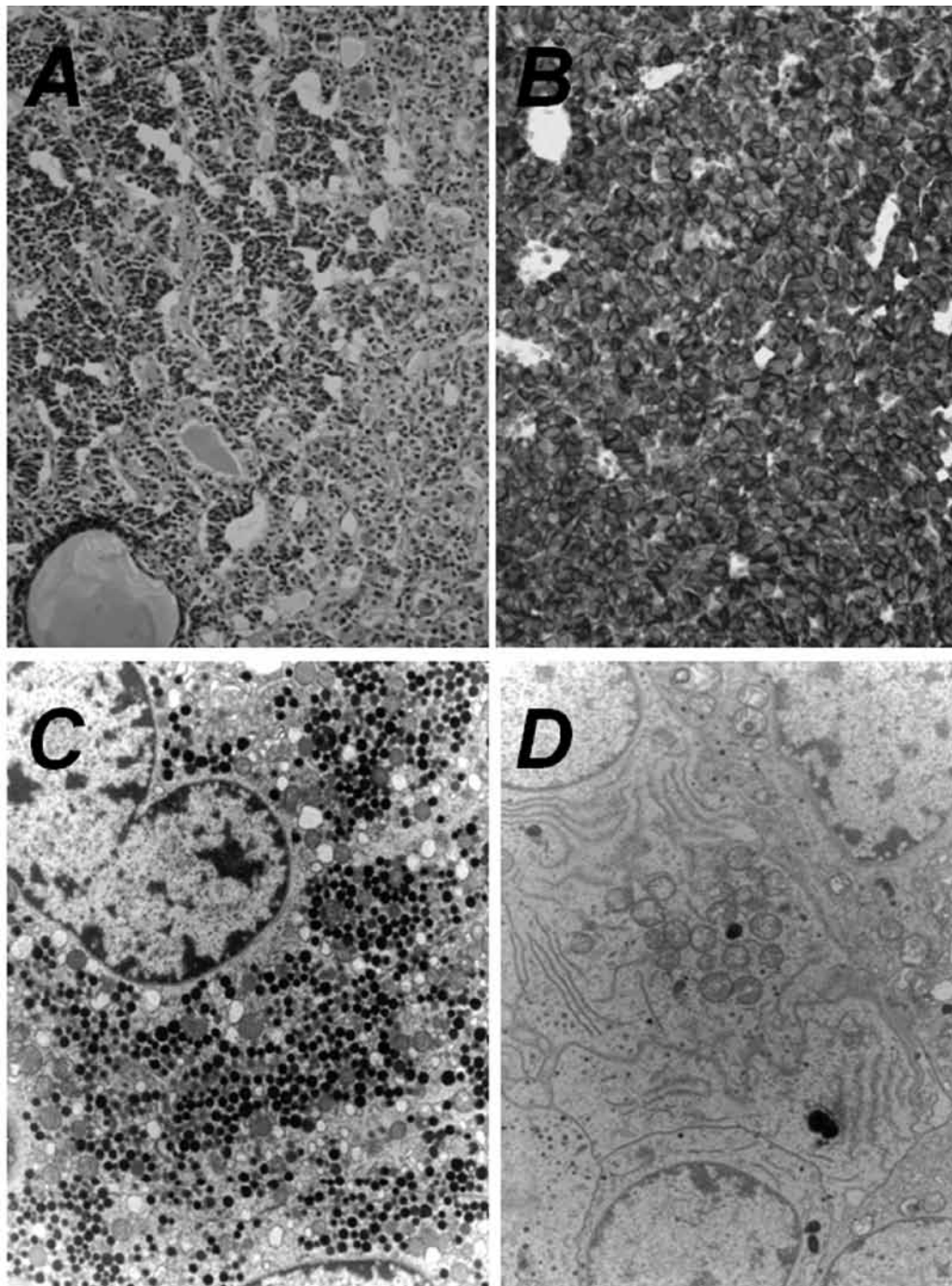
only a small part of a large corticotroph tumour obviously translates to a positive result of histopathological, immunohistochemical and ultrastructural examinations, with simultaneous lack of surgical completeness and persistence of Cushing's disease [23].

### Postoperative hormonal assessment

In recent years, increasing importance has been attached to the so-called early postoperative hormone assessment. This consists of measuring serum cortisol concentration during the first week after transsphenoidal surgery (optimally on the first, second or third day). Clinical observations demonstrate that achievement of the so-called subnormal cortisol levels (i.e.  $< 2.0 \mu\text{g/dL}$ ) is an indicator of surgical treatment efficacy forecasting persistent remission of CD [2, 17, 24, 25]. In a prospective, as yet unpublished, study assessing the effectiveness of surgical treatment of ACTH-secreting pituitary adenomas, we confirmed disease remission in all patients with cortisol concentrations lower than  $2.5 \mu\text{g/dL}$  on the first day after surgical treatment. Furthermore, lack of remission or disease recurrence was observed in all patients with cortisol concentrations more than or equal to  $2.5 \mu\text{g/dL}$ .

A major advantage of early postoperative assessment of serum cortisol is the possibility of immediate detection and selecting those patients in whom the TSS was ineffective. In some of those patients, it is possible to perform repeated transsphenoidal surgery (sellar re-exploration) during the same hospital stay [24, 26]. Assessment based on early measurements of serum cortisol is limited by the possibility of obtaining low (or even subnormal) cortisol levels during the first days after the TSS in patients prepared with high doses of adrenal steroidogenesis inhibitors (i.e. ketokonazol) [2].

A separate and interesting issue is the use of ACTH and cortisol desmopressin stimulation test in assessment of surgical treatment effectiveness [9–11, 27]. Its use is based on the confirmed presence of V3 vasopressin receptors expressed in pituitary corticotroph tumours [7–11]. In the persistent presence of neoplastic tissue, which is characterised by autonomous ACTH secretion, after desmopressin stimulation there occurs a significant ( $\geq 30\%$ ) increase in ACTH and cortisol ( $\geq 20\%$ ) secretion in more than 85% of corticotroph adenoma cases. Its advantage (as opposed to the CRH test) lies in its easy availability and lower costs. However, the main objection raised against this test is the possibility of V3 receptors being present on normal corticotroph cells of the pituitary, although the frequency of this phenomenon has not been explicitly determined. However, in order to eliminate the possibility of normal corticotroph



**Figure 2.** Histopathology, immunohistochemistry and ultrastructure of corticotroph pituitary adenomas. **A.** Histopathology of corticotroph pituitary adenoma. Note the uniformity of the cells and loss of the typical, acinar architecture of the pituitary (light microscopy; H&E; original magnification  $\times 20$ ); **B.** Strong immunostaining for ACTH in corticotroph pituitary adenoma (light microscopy, original magnification  $\times 20$ ); **C.** Ultrastructural features of densely granulated corticotroph pituitary adenoma with typical abundant endoplasmic reticulum and Golgi complex. Notice numerous intra-plasmatic secretory granules (original magnification  $\times 4,800$ ); **D.** Ultrastructural features of sparsely granulated corticotroph pituitary adenoma with typical well-differentiated intracellular organelles (endoplasmic reticulum, Golgi complex, minor mitochondria and small, intra-plasmatic secretory granules; original magnification  $\times 4,800$ )

**Rycina 2.** Obrazy histopatologiczne, immunohistochemia i ultrastruktura gruczolaków kortykotropowych przysadki. **A.** Histopatologia gruczolaka kortykotropowego w mikroskopii świetlnej (H&E; powiększenie oryginalne  $\times 20$ ). Zwraca uwagę jednorodność komórek i utratę typowego, zrazikowego utkania przysadki; **B.** Barwienie immunohistochemiczne skrawków guza kortykotropowego wykazujące silny, dodatni odczyn dla ACTH w mikroskopii świetlnej (powiększenie oryginalne  $\times 20$ ); **C.** Bogatoziarnisty gruczolak kortykotropowy przysadki w badaniu ultrastrukturalnym z rozbudowanym endoplazmatycznym i układem Golgiego. Widoczne liczne śródplazmatyczne ziarnistości wydzielnicze (mikroskop elektronowy, powiększenie oryginalne  $\times 4800$ ); **D.** Ubogozziarnisty gruczolak kortykotropowy przysadki w badaniu ultrastrukturalnym. Widoczne typowe, dobrze zróżnicowane struktury śródplazmatyczne (retikulum endoplazmatyczne, układ Golgiego, drobne mitochondria, małe, nieliczne, okrągłe ziarnistości wydzielnicze; (mikroskop elektronowy, powiększenie oryginalne  $\times 4800$ ))

cells stimulation by desmopressin, some authors have suggested applying a modification of this test consisting in the administration of 1 mg dexamethasone eight hours before the administration of 10  $\mu$ g desmopressin bolus. This combined dexamethasone suppression and desmopressin stimulation test facilitates the inhibition of normal pituitary corticotroph cells and the stimulation of neoplastic cells only [10, 27].

Our own experience and data available in literature concerning the use of desmopressin test (including the one preceded by 1 mg oral dexamethasone) demonstrate its usefulness for a selected group of patients [9–11, 27]. Given the typical course of Cushing's disease recurrence with evident clinical symptoms, a pituitary adenoma visible in MRI and typical results of hormone measurements is not difficult to diagnose. Cases of atypical, moderately intensified ACTH-dependent hypercortisolemia, particularly those with unclear results of imaging examinations (postoperatively altered morphology in the sellar region, lack of adenoma features in MRI) are frequently associated with diagnostic difficulties and limitations.

An obtained positive result of a desmopressin stimulation test makes easier a diagnosis of persistent ACTH-dependent hypercortisolemia and also makes deciding on sellar re-exploration easier. However, the test described must not be interpreted irrespective of other clinical data and — until more experience is acquired — should be regarded as an auxiliary diagnostic tool [16].

## Summary

Cushing's disease remains a challenge both for endocrinologists and neurosurgeons. The high percentage of recurrence, even after initially effective transsphenoidal surgery, requires meticulous and long-term monitoring in the postoperative period. A favourable prognosis is associated with the achievement of subnormal serum cortisol in the early postoperative period, confirmation of corticotroph adenoma presence in a histopathological examination of removed specimens, and persistent postoperative adrenal insufficiency, requiring long-term hydrocortisone replacement therapy. An unfavourable prognosis seems to be associated with: the presence of pituitary macroadenoma, lack of precise localisation of the tumour in MRI of the pituitary, and previous ineffective surgical treatment.

Persistent ACTH and cortisol response in the desmopressin stimulation test seems to be a useful, auxiliary, diagnostic tool in a selected group of patients. Preoperative results of hormone concentration measurements are of no importance in terms of predicting surgical treatment efficacy.

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