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The role of combined low-dose dexamethasone suppression test and desmopressin stimulation test in the diagnosis of persistent Cushing's disease. Case report

Rola połączonego testu hamowania 1 mg deksametazonu i testu stymulacyjnego z desmopresyną w rozpoznaniu przetrwałej choroby Cushinga. Opis przypadku

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Abstract

Cushing's disease is related to a significant increase in mortality due to chronic hypercortisolaemia complications. It is known that 50% of non-treated subjects die within 5 years. Transsphenoidal selective adenomectomy is the treatment of choice. The incidence of relapses, even following a successful surgical procedure, is high and reaches 20–25% during the 5-year follow-up period.

The authors discuss the case of a patient, currently aged 60, after repeat pituitary surgery, with progressive cardiovascular complications, in whom persistent Cushing's disease was diagnosed. The diagnosis was determined despite normal plasma ACTH, serum cortisol levels, and 17-OHCS concentrations in daily urine. There was also a lack of obvious pituitary adenoma features in the magnetic resonance imaging (MRI). Persistent Cushing's disease was diagnosed based on the combined dexamethasone desmopressin test.

The presented case points to the role of provocative testing, including the desmopressin test following 1 mg of dexamethasone, for diagnostically difficult cases of Cushing's disease. **(Pol J Endocrinol 2010; 61 (3): 312–317)**

Key words: *Cushing's disease, desmopressin test, hypercortisolaemia*

Streszczenie

Choroba Cushinga wiąże się z istotnym zwiększeniem śmiertelności wskutek powikłań przewlekłej hiperkortyzolemii. Wiadomo, że 50% nieleczonych chorych umiera w ciągu 5 lat. Leczeniem z wyboru jest przezklinowa, selektywna adenomektomia. Częstość nawrotów — nawet po skutecznym leczeniu operacyjnym — jest jednak duża i wynosi od 20–25% w okresie 5-letniej obserwacji.

Autorzy przedstawiają przypadek 60-letniej kobiety po 2-krotnej operacji przysadki, z postępującymi powikłaniami w zakresie układu sercowo-naczyniowego, u której stwierdzono przetrwałą chorobę Cushinga. Rozpoznanie ustalono pomimo prawidłowych wartości oznaczeń ACTH i kortyzolu w surowicy oraz 17-OHKS w moczu dobowym, wykonanych w warunkach podstawowych oraz braku ewidentnych cech gruczolaka przysadki w obrazowaniu za pomocą rezonansu magnetycznego. Chorobę Cushinga rozpoznano na podstawie łącznego testu hamowania 1 mg deksametazonu i testu stymulacyjnego z zastosowaniem desmopresyny.

Opisywany przypadek wskazuje na istotną rolę testów dynamicznych — w tym testu z desmopresyną po 1 mg deksametazonu — w trudnych diagnostycznie przypadkach choroby Cushinga.
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Słowa kluczowe: *choroba Cushinga, test z desmopresyną, hiperkortyzolemia*

Introduction

Adrenocorticotropic hormone (ACTH) — secreting pituitary adenoma consisting of corticotropic cells is the most frequent cause of endogenous hypercortisolaemia. Its presence can lead to complications, such as hypertension, impaired glucose tolerance, diabetes, osteoporosis, increased incidence of infections, or depression. The consequence of this is higher mortality, mainly due to cardiovascular reasons (myocardial infarction, arrhythmias, and cerebral stroke). Transsphenoidal selective adenomectomy is the treatment of choice [1, 2]. When performed by an experienced neurosurgeon the efficacy of such a procedure is high, resulting in long term remission rates from 60 to more than 90% depending on the site. The highest efficacy is reported for microadenomas distinctly recognised in the pre-operative magnetic resonanse imaging (MRI), lower for macroadenomas, and lowest when the focal lesion cannot be precisely located during the pre-operative MRI [2–4].

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The incidence of relapses, even following successful initial surgery, is high (20–25% in 5 years) [5]. The efficacy of the second or further transsphenoidal surgeries is lower than the first, with the higher probability of postoperative complications (secondary hypothyroidism, hypogonadism, and somatotroph insufficiency as well as diabetes insipidus) [3–5]. Therefore, all patients after the surgical treatment of corticotropic pituitary adenomas require appropriate and long-term endocrinological follow-up. The case we present here illustrates the diagnostic difficulties in a patient with persistent Cushing's syndrome of pituitary origin and the relevance of provocative tests in the diagnostics.

Case report

The patient (JS, woman), born in 1949, was admitted for the first time to the Department of Endocrinology of the Postgraduate Centre for Medical Education in May 1997. She presented typical somatic symptoms of hypercortisolaemia. Based on the overall clinical picture and hormonal tests performed, ACTH-dependent Cushing's syndrome of pituitary origin was diagnosed. A focal lesion corresponding to pituitary microadenoma was found in the MRI. The patient was referred for surgical treatment to the Neurosurgery Department of the Central Teaching Hospital of the Ministry of Internal Affairs and Administration in Warsaw. The pituitary microadenoma was removed through the sphenoid sinus in April 1998. Clinical improvement was seen with cortisol levels returning to normal, without the need for hydrocortisone replacement treatment. The detailed clinical course and results of hormonal assays are shown in Table I.

The first clinical symptoms of the relapse of hypercortisolaemia occurred eight years later in March 2006. The lack of ACTH and cortisol circadian rhythm and increased urinary excretion of glycocorticoid metabolites (17-OHCS, 17-hydroxycorticosteroid excretion) were found at that time. There were no signs of pituitary adenoma in the MRI. On the basis of plasma ACTH and serum cortisol levels in the upper normal limit and the suppression of 17-OHCS excretion in daily urine, following a high dose dexamethasone suppression test (HDDST), ectopic ACTH-dependent Cushing's syndrome could be ruled out. The decision to perform a re-operation was undertaken and conducted in January 2007 in the Neurosurgery Department of the Military Institute of Health Services in Warsaw. A fragment of the pituitary gland, suspected of neoplastic growth, was removed during the surgery. However, histopathological and histochemical examinations did not confirm the occurrence of the corticotropic cell adenoma, but only the presence of a normal pituitary pattern.

The serum cortisol on the first postoperative day (at 8 a.m.) was 4.08 μg/dL. Due to malaise, headache, and orthostatic hypotension, replacement hydrocortisone doses were administered (20 mg in the morning and 10 mg at about 4 p.m.). On the 7th postoperative day (after hydrocortisone withdrawal) the plasma ACTH and serum cortisol levels were in the lower limit of referral range (Table I) with the normal thyrotroph function (TSH: 0.731 mU/L; fT_4: 17.1 pmol/L). It was decided to retain low hydrocortisone replacement doses, prescribing 10 mg in the morning and 5 mg in the afternoon and increased doses in case of stress situations, if needed. Due to hypertension and paroxysmal atrial fibrillation, bisoprolol treatment in the dose of 5 mg/24 h, ramipril (10 mg/24 h), and indapamide SR (1.5 mg/24 h) were retained.

During the following two and half year follow-up, basic measurements of plasma ACTH, serum cortisol, and 17-OHCS in daily urine as well as 1 mg dexamethasone suppression tests were performed repeatedly. Although plasma ACTH and serum cortisol were within the referral range, the cortisol concentration following low-dose dexamethasone suppression test (LDDST) never reached optimal values (lower than 1.8 μg/dL). The results are shown in Table I. Due to the fact that normal cortisol levels were achieved as early as six weeks after the surgery, hydrocortisone replacement was discontinued. Gradually, however, increasing difficulties in the management of hypertension, deteriorating symptoms of cardiac insufficiency, and frequent atrial fibrillation episodes were observed as well as two episodes of transient ischaemic attacks (TIA).

No suspicious lesions in the sella turcica were found in the subsequent magnetic resonance imaging. However, the presence of numerous hypertensive lesions, apparently of vascular origin, was confirmed in the surrounding white matter (Fig. 1).

Due to the lack of cortisol suppression after the 2nd day of the classic dexamethasone test (Table I), it was decided to perform the combined low-dose dexamethasone suppression test and desmopressin stimulation test.

The cortisol level concentration was 10.9 μg/dL; subsequently, 1 mg of dexamethasone was administered orally. At 8 a.m. the following day, 10 mg of desmopressin was given intravenously (Minirin 4 mg/mL; *Ferring Pharmaceuticals*). The blood samples were taken at the following time points: 0′; 15′; 30′; 60′; 90′; 120′; 180′ in order to determine stimulated plasma ACTH and serum cortisol levels. The peak ACTH value was observed at 30 and 60 minutes into the test (18 pg/ml rise in relation to the baseline value; $\Delta\% = 200$). The peak cortisol value occurred at 60 minutes (19.8 μg/dL; $\Delta\% = 192$). The presented values (Table II) clearly suggest an improper, positive result of the coupled dexametha-

Table I. *Clinical course along with hormonal measurements: ACTH (range: 10–60 pg/ml), cortisol (range: 5–25 μg/dL), 17-OHCS (range: 2.2–7.0 mg/24 h) and "free" corticoids (range: 40-280 μg/24 h) and results of dexamethasone suppression tests in the presented case of patient JS, born 1949, with ACTH-dependent Cushing's syndrome. 17-OHCS — 17-hydroxycorticosteroid excretion; LDDST — low-dose dexamethasone suppression test; LVEF — left ventricular ejection fraction; BP - blood pressure; NYHA — New York Heart Association; MRI — magnetic resonance imaging; TIA — temporary ischaemic attacks*

Tabela I. *Obraz kliniczny w zestawieniu ze szczegółowymi wynikami oznaczeń ACTH (norma: 10-60 pg/ml), kortyzolu (norma: 5–25 μg/dl), 17-OHCS (norma: 2,2–7,0 mg/24 h) i „wolnych" kortykoidów (norma: 40–280 μg/24 h) oraz w testach hamowania deksametazonem pacjentki JS ur. 1949 roku z ACTH-zależnym zespołem Cushinga. 17-OHCS — dobowe wydalanie 17-hydroksysteroidów; LDDST — test hamowania małą dawką deksametazonu (1 mg); LVEF — frakcja wyrzutowa lewej komory; BP — ciśnienie tętnicze; NYHA — Nowojorskie Towarzystwo Chorób Serca; MRI — badanie rezonansu magnetycznego; TIA — przemijający napad niedokrwienny*

Date	Results of hormonal measurements and suppression tests	Clinical course
06/1997	ACTH 8 a.m: 52 pg/mL; 10 p.m.: 40 pg/mL Cortisol 8 a.m.: 26 μg/dL; 10 p.m.: 18 μg/dL 17-OHCS: 15 mg/24 h 17-OHCS 2nd day of dexa: (0,5mg q.i.d.): 4.8 mg/24 h 17-OHCS 4th day of dexa: (2 mg q.i.d.): 2.9 mg/24 h "free" corticoids: 444.0 μg/24 h	For about 7 years, body weight increase, easy bruising, plethora, red abdominal and thigh striae. Difficulties with arterial pressure control (BP: 180/100). Paroxysmal atrial fibrillation. Features of mixed hyperlipidaemia and impaired glucose tolerance found in laboratory results. Microadenoma found in the pituitary MRI Height: 157cm; body weight: 69 kg
04/1998	First transsphenoidal surgery. Aminoglutethimide (250mg t.i.d) was administered as the preparation for the surgery	
05/1998	ACTH 8 a.m.: 15 pg/mL; 10 p.m.: 5 pg/mL Cortisol 8 a.m.: 8 μg/dL; 10 p.m.: 5.2 μg/dL 17-OHCS: 3.6 mg/24 h;	Improved clinical condition. BP and glycaemia back to normal. Decreased body weight. Striae turning paler. No necessity of hydrocortisone replacement. Height: 157 cm; body weight: 66 kg BP: 145/95
12/2006	ACTH 8 a.m.: 48 pg/mL; 10 p.m.: 33 pg/mL Cortisol 8.00: 24 μg/dL ; 10 p.m.: 15 μg/dL 17-OHCS: 9.4 mg/24 h; 17-OHCS 2nd day of dexa: (0.5 mg q.i.d.): 4.0 mg/24 h 17-OHCS 4th day of dexa: (2 mg q.i.d.): 1.7 mg/24 h "free" corticoids : 274.0 μg/24 h	Worsening clinical condition. Renewed body weight gain, plethora and abdominal striae. Deteriorated arterial pressure control and recurrent atrial fibrillation episodes. No adenoma found in the pituitary MRI
01/2007	Second transsphenoidal surgery. Ketoconazole (200 mg t.i.d.) was administered as the preparation for the surgery Cortisol 8 a.m.: (2nd postop. day): 4.08 μg/dL	
01/2007	Cortisol 8 a.m.: (7th postop. day): 7,44 μg/dL ACTH 8 a.m.: (7th postop. day): 12 pg/mL	Slightly improved clinical condition. Slightly decreased body weight. Reduction in hypotensive drug doses. Replacement with low doses of hydrocortisone
02/2007	Cortisol 8 a.m.: 10.3 μg/dL ACTH 8 a.m.: 14 pg/mL	Hydrocortisone replacement was discontinued 6 weeks after the surgery. Slightly decreased body weight (2kg). Hypotensive treatment with bisoprolol, amlodipine, and ramipril was retained. Due to paroxysmal atrial fibrillation, acenocumarol was initiated. Height: 154 cm; body weight: 64 kg BP: 150/90
07/2007	Cortisol 8 a.m.: 12.7 μg/dL ACTH 8 a.m.: 12 pg/mL 17-OHCS: 3.2 mg/24 h	Worsened cardiovascular condition. Difficulty in blood pressure control and another atrial fibrillation episode
01/2008	Cortisol 8 a.m.: 19.2 μg/dL ACTH 8 a.m.: 21 pg/mL 17-OHCS: 4.7 mg/24 h Cortisol after LDDST: 4.65 μg/dL	Worsening cardiovascular condition. The next atrial fibrillation episodes. TIA episode. Increase in hypotensive drug doses necessary. Chronic anticoagulation treatment
01/2009	ACTH 8 a.m.: 12 pg/mL; 10 p.m.: 10 pg/mL Cortisol 8 a.m.: 14.1 μg/dL; 10 p.m.: 10.9 μg/dL Cortisol after LDDST: 10.3 μg/dL Cortisol 2nd day of dexa (0.5 mg q.i.d.): 4.17 μg/dL Cortisol 4th day of dexa (2 mg q.i.d.): 1.91 μg/dL 17-OHCS: 4.2 mg/24 h; 17-OHCS 2nd day of dexa (0.5 mg q.i.d.): 0.8 mg/24 h 17-OHCS 4th day of dexa (2 mg q.i.d.): 1.1 mg/24 h "free" corticoids : 175.0 μg/24 h	Still deteriorating cardiovascular condition. Clinical symptoms of congestive heart failure (IIæ/IIIæ NYHA). Difficulty in blood pressure control despite increased hypotensive drug doses. Atrial fibrillation and TIA episodes. No microadenoma features in the MRI examination. Signs of left ventricular and left atrial hypertrophy in the echocardiogram with decreased ejection fraction (LVEF: 39%). Ketoconazole 200 mg t.i.d. was initiated with improved blood pressure control and partial clinical improvement

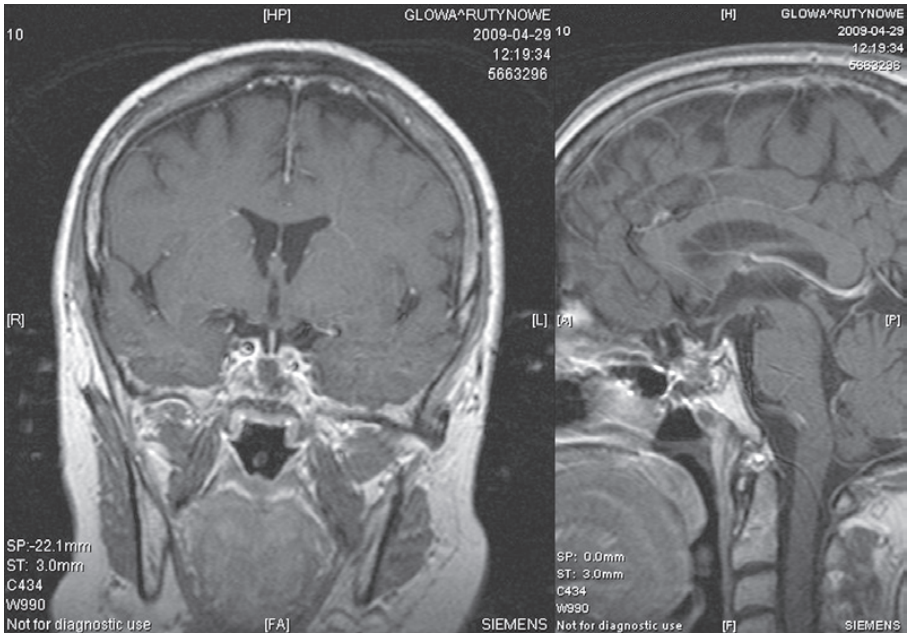

Figure 1. *The MRI of the sellar region performed in 2009 (2 years after the repeat surgery). **A.** Frontal section; **B.** Sagittal section*

Rycina 1. *Zdjęcia rezonansu magnetycznego okolicy siodła tureckiego wykonane w 2009 roku (2 lata po powtórnej operacji przezklinowej). **A.** Przekrój czołowy; **B.** Przekrój strzałkowy*

Table II. ***Results of ACTH and cortisol stimulation by 10 μg desmopressin IV after administration of 1 mg dexamethasone***

Tabela II. ***Wyniki stymulacji ACTH i kortyzolu za pomocą 10 μg desmopresyny* i.v. *po uprzednim podaniu 1 mg deksametazonu***

Time	ACTH [pg/ml]	Cortisol [μg/dL]
0′	9	10.3
15′	25	10.5
30′	27	21.2
60′	27	30.1
90′	23	25.1
120′	19	19.4
180′	15	20.5

sone desmopressin test. This confirms the presence of persistent, ACTH-dependent hypercortisolaemia with moderate clinical expression. However, it might be responsible for the progression of cardiovascular complications in the presented case.

Following the positive result of the combined dexamethasone desmopressin test, the decision to pharmacologically inhibit the adrenal steroidogenesis was made. Treatment with ketoconazole (200 mg t.i.d.) was recommended. Some clinical improvement was seen. Neither hypersensitivity symptoms nor signs of liver damage were observed. In a longer perspective, repeat sellar exploration may be considered, and if it fails, bilateral adrenalectomy (as a definitive treatment).

Discussion

The presented case of persistent Cushing's disease is an example of the diagnostic difficulties often found in sites where patients with this rare, severe, and devastating disease are treated [6]. The typical course of Cushing's disease, with evident clinical symptoms and pituitary adenoma recognised in MRI, as well as high plasma ACTH and serum cortisol levels suppressed by high dose of dexamethasone, presents no challenge. Cases of moderate, ACTH-dependent hypercortisolaemia without clear focal lesions in the sella often cause diagnostic problems [3, 7]. The important issue at this point is the variable sensitivity of various tissues to the cortisol action. It depends both on receptor densities in the tissues and on their individual sensitivity to glycocorticosteroids [8]. Due to the debilitating nature of therapeutic procedures such as treatment with adrenal steroidogenesis inhibitors (hypersensitivity reactions and the risk of liver failure in the case of ketoconazole) and possible post-surgical complications (hypopituitarism, diabetes insipidus, severe complications of bilateral adrenalectomy), correct diagnosis is of the utmost importance for further prognosis [1–3].

It is widely accepted that transsphenoidal, selective adenomectomy is the treatment of choice for ACTH-secreting adenomas [1–3]. The patient JS has already

been subjected to two surgical procedures. Each subsequent transsphenoidal surgery has lower efficacy. Another factor which contributes to poorer prognosis with respect to recovery is the lack of histopathological confirmation of corticotropic adenoma after the second surgery [9].

The important issue that requires attention in this case is the lowest serum cortisol level achieved within the first 48 hours after surgical treatment (4.08 μg/dL). Clinical findings from recent years prove that so-called subnormal serum cortisol values (that is, < 2.5 μg/dL) on the 1st or 2nd postoperative day are an early predictor of successful surgical treatment and are a prognostic indicator of long-term remission [1, 4, 10]. In a prospective study to evaluate the efficacy of surgical treatment of ACTH-secreting pituitary adenomas, we confirmed remission in all patients (n = 24) with cortisol values < 2.5 μg/dL on the 1st or 2nd postoperative day. In turn, in all patients (n = 8) with cortisol values > 2.5 μg/dL, no remission occurred or relapse of the disease was reported [10].

The recognised factor of good prognosis is also clinical, postoperative adrenal insufficiency, which requires long-term hydrocortisone replacement. In the presented case, the serum cortisol levels exceed the lower limit of referral range as early as seven days after the surgical treatment, and the replacement therapy was discontinued altogether after six weeks. According to our own data discussed earlier, the majority of patients required hydrocortisone replacement after successful surgery for at least six months [10].

Therefore, during the early stages after re-operation, there are four factors that contribute to poor prognosis with respect to permanent recovery. For this reason we decided to further monitor the patient closely. This is of particular importance as the patient had been exposed to high cortisol concentrations from as early as 1989, which led to permanent damage within the cardiovascular system. Therefore, even if the status of the condition is now moderate, it can cause serious and life-threatening complications. In addition, the case of excessive receptor sensitivity to glycocorticosteroids cannot be excluded [8].

Issues of utmost concern included recurrent tachyarrhythmia episodes, difficulties with arterial pressure control. and progression of cardiac insufficiency (Table I). This indicated that diagnostics had to be extended. In spite of normal cortisol and ACTH values, no complete serum cortisol suppression was found following the 1 mg dexamethasone test performed a year after the last surgery (cortisol after LDDST: 4.65 μg/dL). Normal values of glycocorticosteroid metabolite excretion (17-OHCS) in daily urine were found at that time. Considering the lack of pituitary adenoma features in the MRI, it was decided to adopt a strategy of further monitoring, assuming that there were insufficient grounds to initiate any kind of therapeutic procedure.

Due to the constantly deteriorating cardiovascular condition of the patient, it was decided to perform a high-dose dexamethasone suppression test (HDDST). According to the literature data and our own experience, the diagnostic reliability of this test is approximately 80% [2, 7, 11]. It is furthermore noted that no single test is sufficient for the diagnosis of difficult cases of ACTH-dependent Cushing's syndrome with a non-typical course, such as the present one. Therefore, hormonal assessment in basic conditions (including late-night salivary cortisol), as well as the dexamethasone suppression tests, should be supported by the provocative test. The suppression of cortisol and 17-OHCS following a high dose of dexamethasone along with a positive result of a stimulation test (either with corticoliberin or desmopressin) is typical for Cushing's disease and makes the diagnosis of persistent disease much more likely.

The desmopressin test is an easy and straightforward diagnostic procedure. It is based on the confirmed occurrence of V3 vasopressin receptors on cells of most corticotropic tumours [12]. Therefore, in the presence of tumour cells (persistent after surgery), which are autonomous with respect to ACTH secretion, a distinct increase in ACTH and cortisol excretion is observed following desmopressin bolus injection in approximately 85% of corticotropic adenoma cases. The result of the test may be regarded as positive if the increase in plasma ACTH is more than 35%, and for serum cortisol more than 20%, with respect to the baseline values [12–14]. Its advantage, contrary to the CRH test, is good availability and the lower price of the medication. The results of two large studies published within the last six months indicate high sensitivity and specificity of the desmopressin test both in diagnostics and in the monitoring of the efficacy of surgical procedures [15, 16].

The primary objection to the test, however, is the possibility that V3 receptors on normal corticotropic cells may occur, although the frequency of this phenomenon has not been determined clearly. Therefore, in order to eliminate the possibility of the stimulation of normal corticotropic cells by desmopressin, we performed a modified version of the test with desmopressin administration eight hours after 1 mg of dexamethasone. This ensures that normal corticotropic pituitary cells are inhibited and only autonomous cells are stimulated [16]. A highly positive increase both in ACTH ($\Delta\%$ = 200) and in cortisol ($\Delta\%$ = 192) has been achieved in this case, which confirms the occurrence of autonomous corticotropic cells as well as persistent Cushing's disease.

Owing to the confirmation of persistent Cushing's disease using a combined dexamethasone desmopressin

test, it was possible to start treatment with ketoconazole in order to inhibit the adrenal steroidogenesis. Clinical improvement was seen, which also confirms our diagnosis. In the future we are going to perform further sellar exploration. Should it prove ineffective, it will be considered whether or not to qualify the patient to bilateral adrenalectomy so as to minimize the risk connected with the increased cardiovascular complications resulting from active Cushing's disease.

It is noted in the summary that the described test facilitated correct diagnosis and let us determine the further treatment schedule. Therefore, the use of this test may be helpful in diagnostically difficult cases of Cushing's disease, especially in postoperative follow-up. Within a broader context, it should remind us that provocative tests are a valuable and often necessary supplement to measurements conducted under basic conditions.

Conclusions

The combined low dose dexamethasone desmopressin test may be useful in the diagnosis of Cushing's disease with moderate hypercortisolaemia.

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