



Complications of Cushing's disease — prospective evaluation and clinical characteristics. Do they affect the efficacy of surgical treatment?

Powikłania choroby Cushinga — ocena prospektywna i charakterystyka kliniczna
Czy wpływają na wyniki leczenia operacyjnego?

Przemysław Witek¹, Grzegorz Zieliński², Katarzyna Szamotulska³, Joanna Witek⁴, Wojciech Zgliczyński⁵

¹Department of Endocrinology and Radioisotope Therapy, Military Institute of Medicine, Warsaw

²Department of Neurosurgery, Military Institute of Medicine, Warsaw

³Department of Epidemiology, National Research Institute of Mother and Child, Warsaw

⁴Diabetes Outpatient Clinic, National Research Institute of Mother and Child, Warsaw

⁵Department of Endocrinology, Medical Centre of Postgraduate Education, Warsaw

Abstract

Introduction: Hypercortisolaemia is the cornerstone of Cushing's disease (CD). It leads to the occurrence of typical somatic symptoms as well as cardiovascular and metabolic complications, which significantly increase morbidity and mortality and decrease quality of life in CD.

Material and methods: A prospective study included 36 patients with CD who were assessed in terms of duration of their disease symptoms as well as the incidence of: arterial hypertension, glucose intolerance and diabetes, overweight, obesity and decreased bone mineral density (BMD). The relation was assessed between these particular complications and their impact on the efficacy of surgical treatment for CD.

Results: The prevalence in the study group of arterial hypertension was 79%, and diabetes was 16.7%, whereas the proportion of pre-diabetic states was 33%. 36.1% of patients fulfilled the criteria of obesity and an additional 44% were overweight. Decreased BMD was reported in 72.2% of patients. There was a confirmed relationship between the duration of CD symptoms and the occurrence of overt diabetes ($p < 0.01$) and any type of glucose homeostasis alterations ($p = 0.04$). In this studied group with CD, there was also an association demonstrated between the occurrence of arterial hypertension and overweight or obesity ($p = 0.03$). Simultaneously, there was no relationship between the duration of symptoms or the presence of particular organ complications and the efficacy of surgical treatment for CD.

Conclusions: Longer duration of CD is associated with a higher risk of glucose intolerance and/or diabetes. The overweight/obesity presented in the majority of patients increases the risk of secondary hypertension in CD. However, the efficacy of transsphenoidal surgery does not depend directly on either disease duration or type of occurring complications. (*Endokrynol Pol* 2012; 63 (4): 277–285)

Key words: cortisol, Cushing's disease, diabetes, hypercortisolaemia, secondary hypertension, transsphenoidal surgery

Streszczenie

Wstęp: Hiperkortyzolemia w przebiegu choroby Cushinga prowadzi do typowych objawów klinicznych i powikłań, zwłaszcza metabolicznych i sercowo-naczyniowych, które istotnie zwiększają chorobowość i śmiertelność oraz obniżają jakość życia.

Materiał i metody: Przeprowadzono prospektywne badanie, obejmujące 36 pacjentów z chorobą Cushinga, u których oceniono czas trwania hiperkortyzolemii oraz częstość występowania: nadciśnienia tętniczego, zaburzeń gospodarki węglowodanowej, nadwagi lub otyłości oraz zmniejszenia gęstości mineralnej kości. Zbadano także zależności między poszczególnymi powikłaniami oraz ich wpływ na skuteczność leczenia operacyjnego choroby Cushinga.

Wyniki: Częstość nadciśnienia tętniczego w badanej grupie wynosiła 79%, cukrzycy — 16,7%, a stanu przedcukrzycowego — 33%. Otyłość stwierdzono u 36,1% chorych, a nadwagę u dalszych 44%. Zmniejszenie gęstości mineralnej kości występowało u 72,2% pacjentów. Wykazano istnienie związku między czasem trwania choroby Cushinga a wystąpieniem cukrzycy wtórnej ($p < 0,01$) oraz jakichkolwiek zaburzeń gospodarki węglowodanowej ($p = 0,04$). Potwierdzono również zależność między występowaniem nadciśnienia a nadwagą lub otyłością w badanej grupie pacjentów z chorobą Cushinga ($p = 0,03$). Jednocześnie nie stwierdzono związku między czasem trwania choroby i obecnością poszczególnych powikłań hiperkortyzolemii a skutecznością leczenia operacyjnego choroby Cushinga.

Wnioski: Dłuższy czas trwania choroby Cushinga wiąże się z większym ryzykiem wystąpienia zaburzeń gospodarki węglowodanowej i cukrzycy. Nadwaga lub otyłość, obecne u większości chorych, zwiększają ryzyko wtórnego nadciśnienia w chorobie Cushinga. Skuteczność operacji przezklinowej nie zależy jednak bezpośrednio ani od czasu trwania choroby, ani od typu powikłań. (*Endokrynol Pol* 2012; 63 (4): 277–285)

Słowa kluczowe: kortyzol, choroba Cushinga, cukrzyca, hiperkortyzolemia, nadciśnienie wtórne, operacja przezklinowa



Introduction

Cushing's disease is the commonest cause of endogenous hypercortisolaemia. In the majority of cases, it is caused by a pituitary, corticotroph adenoma autonomously producing ACTH [1–4]. Corticotrophin affects the adrenal cortex leading to cortisol excess. Excessive cortisol secretion, inadequate to the needs, leads to the development of serious complications such as: arterial hypertension, impaired glucose tolerance, diabetes, osteoporosis, increased incidence of infections and depression [2, 4–6]. This results in increased mortality mainly due to cardiovascular reasons (myocardial infarction, arrhythmias, stroke) and impaired quality of life [2, 7, 8]. Currently, the treatment of choice in CD is transsphenoidal, selective adenomectomy performed by an experienced neurosurgeon. The efficacy of surgical treatment, depending on the centre and the adopted criteria of cure, ranges between 60% and 90% [4, 9–11]. Successful treatment leads to improved blood pressure control, decreased blood glucose level and increased bone mineral density [2]. However, it is not always possible to withdraw hypoglycaemic agents and anti-hypertensive treatment.

The advances made in recent decades in terms of hormonal and imaging diagnostics can shorten the duration of undiagnosed Cushing's disease and usually lead to a more prompt decision on initiating neurosurgical treatment. Shortening exposure of tissues to the effects of hypercortisolaemia probably reduces the prevalence of disease complications and — possibly — changes its clinical picture. It seems that currently surgical treatment is more commonly administered to patients with moderate somatic features of hypercortisolaemia, whereas the number of patients with multi-year, full-blown course of the disease is lower.

Therefore, this study aims at prospective evaluation and clinical characteristics of the complications associated with Cushing's disease (in the material of one endocrinological site). Additionally, we prospectively assessed the relationship between particular complications occurring in the preoperative period and the efficacy of transsphenoidal surgery for CD.

Material and methods

Patient population

The study population comprised 36 consecutive patients with Cushing's disease (30 women and six men; F:M ratio: 5:1) hospitalised in the Department of Endocrinology CMKP between 2005 and 2009. The mean age was 36.3 ± 12.9 years (range 17–57 years). After confirmed diagnosis of Cushing's disease, the patients were referred to the Department of Neurosurgery at the

Military Institute of Medicine in Warsaw. They were all operated on by the same neurosurgeon using the same surgical protocol.

All patients were informed about the aims and methods of the study and they signed an informed consent. The study protocol was approved by the Bioethics Committee at the Medical Centre of Postgraduate Education in Warsaw.

Clinical course of the disease

All patients underwent a standard clinical evaluation. The data obtained from past medical history and medical records served as the basis for determining the duration of CD symptoms and previously administered treatment. Particular attention was paid to the symptoms of Cushing's syndrome, the previous surgical treatment of Cushing's disease, and complications of chronic hypercortisolaemia, such as: overweight or obesity, arterial hypertension, glucose homeostasis alterations and decreased bone mineral density (osteopenia or osteoporosis).

Arterial hypertension was diagnosed when blood pressure values exceeded 140/90 mm Hg or if the patient had previously received anti-hypertensive treatment. Diabetes secondary to Cushing's disease (classified as "other specific types of diabetes") was diagnosed according to the recommendations issued by the Polish Diabetes Association on the basis of venous plasma glucose level measured 8–14 hours after the last meal (glucose ≥ 126 mg/dL) or oral glucose tolerance test (OGTT; glucose level in 120' ≥ 200 mg/dL). Prediabetes (impaired fasting glycaemia or impaired glucose tolerance) was diagnosed when venous fasting plasma glucose level exceeded 100 mg/dl or the glucose level following OGTT was ≥ 140 mg/dL, respectively [12]. Decreased bone mineral density was identified when the T-score either of the femoral neck or the lumbar segment of the vertebral column (L2–L4) was lower than or equal to -1.0 (T-score ≤ -1.0) for osteopenia and ≤ 2.5 for osteoporosis. Densitometry was performed using the GE Healthcare Lunar Prodigy Advance (USA). Body mass index (BMI) was calculated on the basis of the standard formula ($\text{BMI [kg/m}^2\text{]} = \text{body mass [kg]} / \text{height [m]}^2$). It was calculated using anthropometric data at the time of CD diagnosis.

Preoperative endocrine evaluation

The diagnosis of ACTH dependent on Cushing's syndrome was made based on the clinical signs and standard hormonal criteria: increased urinary excretion of UFC (urinary free cortisol) or 17-OHCS (17-hydroxysteroids, increased serum cortisol level at 8.00 am, the loss of cortisol circadian rhythm, increased or detectable level of plasma ACTH at 8.00 am and the failure of

serum cortisol to suppress to less than or equal to $1.8 \mu\text{g/dL}$ during the low dose dexamethasone suppression test (LDDST; 0.5 mg q.i.d. for 48 hours). The pituitary aetiology of Cushing's syndrome was confirmed based on a serum cortisol and UFC or 17-OHCS suppression greater than 50% on high dose dexamethasone suppression test (HDDST; 2 mg q.i.d. for 48 h) and positive MRI. In cases of equivocal results of hormonal assessment or pituitary imaging, the diagnosis of CD was confirmed by a positive result of an intravenous CRH (corticoliberin) stimulation test ($100 \mu\text{g}$).

Preoperative MR imaging

Prior to neurosurgical treatment, all patients underwent high resolution magnetic resonance imaging of the pituitary-hypothalamic region (SIEMENS Symphony 2004; 1.5 Tesla). The MRI scans were performed before and after intravenous injection of gadolinium (Gd-DTPA). The radiologist, neurosurgeon and endocrinologist recorded the presence, size and position of any focal lesion. It was determined that the presence of the hypodense lesion after contrast indicates the pituitary adenoma. Microadenoma was defined as a pituitary tumour with a diameter of less than 1 cm on any dimension, whereas macroadenoma was defined as a pituitary tumour with at least one diameter of more than 1 cm. The MRI was qualified as equivocal if the pituitary tumour was not precisely visualised or if only indirect traits of the tumour were present, such as deviation of the pituitary stalk or a convex upper surface of the pituitary gland.

Surgical procedure

In all cases, a microsurgical transseptal transsphenoidal approach was used for resection of an ACTH-secreting pituitary adenoma. The sella was exposed and the H-shaped incision of the dura was made. The dura mater was opened and separated from the pituitary capsule to expose the entire anterior surface of the pituitary gland. Then the pituitary gland was carefully explored. Selective adenectomy was performed in all cases of visualised pituitary adenoma on MR imaging. When the MR was equivocal or no tumour was evident, a series of vertical and horizontal incisions of the pituitary gland was carried out, and all tissue deemed to be abnormal was removed and submitted for pathological examination. If no abnormal tissue could be identified intraoperatively, hemihypophysectomy, subtotal hypophysectomy, or total hypophysectomy was performed.

Histopathological and immunohistochemical assessment

The specimen was collected for histopathological analysis and routinely stained with haematoxylin and eosin (H&E). Immunohistochemical staining was performed

on paraffin-embedded specimens according to the labelled EnVision Flex Visualisation System (Dako, K8000) with DAB as chromogen using antibodies against all anterior pituitary hormones (GH, PRL, ACTH, -TSH, -FSH, -LH; all antibodies from LabVision) and the glycoprotein α -subunit (Novocastra).

The result of the histopathological assessment was considered 'positive' if the presence of adenoma in the histological specimens as well as the immunopositivity for ACTH was confirmed. The result was treated as 'negative' if ACTH-staining was negative.

Postoperative hormonal evaluation and criteria of cure

Blood samples for serum cortisol measurements were collected from all patients at 6.00 am on the first postoperative day. Glucocorticoids were not administered in the perioperative or in the early postoperative period. Hydrocortisone replacement therapy was started either after biochemical confirmation of hypocortisolaemia or the development of clinical symptoms of adrenal insufficiency. During two postoperative days, hydrocortisone was given intravenously in a dose of 50 mg t.i.d. Afterwards, the standard dose of hydrocortisone (20 mg in the morning and 10 mg at 3.00 pm) was started and continued until the next hormonal evaluation.

Following the surgical procedure, all patients were subjected to further postoperative evaluation lasting at least 18 months (median 30 months; range 18–36 months). The first biochemical evaluation of corticotroph function took place on the 7th postoperative day. Subsequent reassessments were performed at six weeks and at three, six, 12, 18, 24 and 36 months after surgery.

The patients were regarded as cured postoperatively if they fulfilled the following criteria for sustained remission: subnormal ($\leq 2.5 \mu\text{g/dL}$) serum cortisol on the 1st postoperative day and at the end of follow-up: clinical and biochemical evidence of eucortisolaemia (morning serum cortisol between $5\text{--}25 \mu\text{g/dL}$); the correct circadian rhythm (late night serum cortisol level $\leq 7.5 \mu\text{g/dL}$); and the ability of serum cortisol to suppress to less than or equal to $1.8 \mu\text{g/dL}$ after the overnight 1 mg dexamethasone suppression test.

Hormone assay

Chemiluminescent immunometric assays (IMMULITE 2000; Siemens, UK) were used to measure serum cortisol and UFC. Method sensitivity was $0.2 \mu\text{g/dL}$ (5.5 nmol/L) for serum and urinary cortisol. The normal range for cortisol is $5\text{--}25 \mu\text{g/dL}$ ($138\text{--}690 \text{ nmol/L}$), for UFC: $20\text{--}90 \mu\text{g/24 h}$. Plasma ACTH was measured using radioimmunoassay (IRMA; coated tube technique; Brahms, Germany). Method sensitivity was 1.2 pg/mL and the referral range: $10\text{--}60 \text{ pg/mL}$. The daily urinary excretion

of 17-hydroxysteroids (17-OHCS) was determined by the method based on Silber-Porter reaction. The referral range was (2.2–7 mg/24 h).

Statistical analysis

Methods of descriptive statistics (mean, median, standard deviations, proportion) were employed in the statistical analysis. Verification of hypotheses concerning the relationship between two categorical variables were expressed as frequencies and compared using the exact chi-square test (Fisher's exact test). Significance of differences between average values of continuous variable in two groups was analysed by means of Student's *t* test for normal distribution and the Mann-Whitney test for small samples when its distribution was not normal. In cases of more than two groups, the Kruskal-Wallis test was employed. Verification of hypotheses concerning comparisons of the analysed parameters in two time points was conducted using the Wilcoxon test for small samples (for not normal distribution).

The level of significance was set at $p < 0.05$. The calculations were made using the commercially available statistical software package SPSS v.18.0.

Results

Results of preoperative clinical and epidemiological assessment

Demographic data and baseline preoperative characteristics of the study group are presented in Table I. Detailed results of clinical assessment including age, gender, body mass index, duration of Cushing's disease syndromes and complications of hypercortisolaemia present at the time of Cushing's disease diagnosis are presented in Table II.

The mean body mass index value in the analysed group was $29.7 \text{ kg/m}^2 \pm 6.04$; (median value: 28.5; range: 20.7–47 kg/m^2). Patients with normal BMI ($< 25 \text{ kg/m}^2$) represented 19.4% of the study group, overweight patients (BMI 25–30 kg/m^2) represented 44.4%, and obese patients (BMI $> 30 \text{ kg/m}^2$) represented 36.1% of the study group. In 28 patients (77.8%), arterial hypertension was confirmed, whereas six patients (16.7%) fulfilled the criteria of diabetes. Other types of glucose homeostasis alterations (such as: impaired fasting glucose or impaired glucose tolerance) were diagnosed in an additional 12 patients (33.3%). Decreased BMD was found in 26 patients (72.2%).

In the study group, we verified whether there were any gender-dependent differences with regards to BMI and systemic complications of hypercortisolaemia. The mean BMI in female patients was $29.55 \pm 5.22 \text{ kg/m}^2$ (median: 28.5 kg/m^2 ; range: 21.5–45.7 kg/m^2) and in male patients it was $30.17 \pm 9.85 \text{ kg/m}^2$ (median: 27.8 kg/m^2 ;

Table I. Characteristics of the study population — baseline data

Tabela I. Charakterystyka badanej grupy — dane podstawowe

Number of patients		36	
Age (years)	Mean	36.3	
	± SD	12.9	
	Median	33.3	
	Range	16.8–57.6	
Sex	Females	N (%)	30 (83%)
	Males	N (%)	6 (16.7%)
Duration of symptoms (months)	Mean	43.9	
	± SD	37.9	
	Median	36	
	Range	6–192	
Surgical treatment	First	N (%)	28 (77.8%)
	Subsequent operation	N (%)	8 (22.2%)
Follow-up period (months)	Mean	28.5	
	± SD	7.9	
	Median	30	
	Range	18–36	
Imaging studies (MRI)	Microadenoma	22 (61.1%)	
	Macroadenoma	6 (16.7%)	
	Equivocal MRI	8 (22.2%)	
Preoperative plasma ACTH [pg/mL]	Mean	100.35	
	± SD	56.25	
	Median	86	
	Range	19–265	
Preoperative serum cortisol [μg/dL]	Mean	25.9	
	± SD	7.35	
	Median	26.05	
	Range	14.4–41.3	
Preoperative 17-OHCS in daily urine	Mean	17.05	
	± SD	8.61	
	Median	15.25	
	Range	8.5–47.5	

range: 20.7–47 kg/m^2). Thus, we found no difference between groups depending on gender ($p = 0.79$). Next, we compared the prevalence of overweight or obesity, arterial hypertension, glucose homeostasis alterations and decreased bone mineral density between males and females in the study group. Overweight or obesity was confirmed in 25 females (83.3%) and four males (66.7%). Glucose homeostasis alterations (diabetes or prediabetes) were found in 15 females (50%) and three males (50%). Arterial hypertension was diagnosed in

Table II. Demographic data, BMI values and complications of Cushing's disease in the material of 36 patients

Tabela II. Dane demograficzne, wartości BMI i powikłania choroby Cushinga w badanym materiale 36 chorych

No	Age	Sex	BMI	Duration of symptoms (months)	Complications			Remission
					Hypertension	Diabetes	↓ BMD	
1	52.6	F	32.4	60	YES	PD	NO	YES
2	24.8	F	37.4	9	NO	NO	YES	YES
3	26.3	F	45.7	72	YES	NO	YES	YES
4	19.9	M	20.7	48	NO	NO	YES	YES
5	52.4	F	30.5	120	YES	YES	YES	YES
6	26.2	F	27.2	48	YES	NO	YES	YES
7	57.2	F	33.7	36	YES	PD	YES	YES
8	43.7	F	30.8	48	YES	PD	NO	YES
9	28.0	F	28.4	36	YES	PD	YES	YES
10	29.9	F	24.4	36	YES	NO	YES	YES
11	34.4	F	27.8	36	NO	NO	NO	YES
12	51.0	F	34	18	YES	NO	YES	YES
13	41.0	F	28	30	NO	NO	NO	YES
14	29.1	F	21.5	36	NO	NO	YES	YES
15	29.7	F	25.9	36	YES	NO	YES	YES
16	20.9	M	22	18	YES	PD	YES	YES
17	18.4	F	21.8	12	NO	NO	NO	YES
18	40.8	F	39.7	12	YES	PD	NO	YES
19	24.3	F	33	24	YES	YES	NO	YES
20	26.3	F	28.4	24	YES	NO	NO	YES
21	25.1	F	26.1	36	NO	NO	YES	YES
22	56.3	F	28.6	120	YES	YES	YES	YES
23	52.1	F	33.7	24	YES	PD	YES	YES
24	57.6	F	27	96	YES	NO	YES	NO
25	34.1	F	23.7	24	NO	PD	NO	NO
26	28.4	F	29.2	24	YES	PD	NO	NO
27	34.8	F	29	6	YES	NO	YES	NO
28	49.3	M	47	24	YES	PD	YES	NO
29	55.8	F	31.6	24	YES	NO	YES	NO
30	16.8	M	26.5	18	NO	NO	YES	NO
31	32.1	F	26.9	60	YES	YES	YES	NO
32	32.4	F	27.9	48	YES	YES	YES	NO
33	39.8	M	29.1	18	YES	PD	YES	NO
34	18.8	M	35.7	24	YES	NO	YES	NO
35	53.8	F	29.3	84	YES	YES	YES	NO
36	42.5	F	23	192	YES	PD	YES	NO

F — female; M — male; PD — prediabetes (impaired fasting glucose or impaired glucose tolerance); ↓ BMD — decreased bone mineral density (T-score ≤ -1.0 for L₂-L₄ or neck)

Table III. Relation between duration of disease symptoms and risk of complications of Cushing's disease (CD)**Tabela III.** Zależność między okresem utrzymywania się objawów choroby a ryzykiem powikłań choroby Cushinga (CD)

Complications		Duration of CD symptoms (months)				p
		N	Mean	± SD	Median	
Arterial hypertension	YES	28	48.6	41.4	36	p = 0.199
	NO	8	27.4	13.7	30	
Secondary diabetes	YES	6	76	39.2	72	p = 0.01
	NO	30	37.5	34.9	27	
Glucose homeostasis alterations (diabetes and prediabetes)	YES	18	54	47.5	36	p = 0.243
	NO	18	33.8	22.3	33	
Decreased BMD (osteopenia and osteoporosis)	YES	26	49.5	42.6	36	p = 0.232
	NO	10	29.4	15.1	24	

24 women (80%) and four men (66.7%) whereas decreased BMD was detected in 20 female patients (66.7%) and in all male patients. In the Fisher's exact test, there was no significant difference in the proportion of the described complications depending on gender ($p = 0.573$, $p = 1.0$, $p = 0.596$, $p = 0.157$, respectively).

Then we analysed whether there was any association between duration of symptoms and development of particular complications of Cushing's disease. It was demonstrated that complications of chronic hypercortisolaemia, such as hypertension, diabetes and glucose homeostasis alterations, as well as decreased BMD, were associated with longer duration of symptoms. The difference was significant with reference to diabetes, which was associated with significantly longer duration of hypercortisolaemia ($p = 0.01$). However, with reference to arterial hypertension and decreased bone mineral density, longer duration of symptoms was insufficient to achieve statistical significance ($p = 0.199$ and $p = 0.232$, respectively). Occurrence of glucose homeostasis alterations (diabetes and prediabetes) was also associated with longer duration of the disease, yet the difference was not significant ($p = 0.243$). However, after dividing patients into three subgroups (normal glucose tolerance, prediabetes and diabetes), a significant difference was achieved, which confirmed a relationship between the occurrence of glucose homeostasis alterations and the duration of CD symptoms ($p = 0.043$). Detailed results are presented in Table III.

Next, we verified the relationship between BMI and the risk of developing hypertension and glucose homeostasis alterations in the studied group of patients with CD. Results of Fisher's exact test confirmed the association between overweight and/or obesity ($\text{BMI} \geq 25 \text{ kg/m}^2$) and arterial hypertension ($p = 0.03$). Simultaneously, we did not confirm a significant relation between increased BMI values and the occurrence of carbohy-

drate metabolism disorders ($p = 1.0$). However, it was demonstrated that all subjects with diagnosed diabetes ($n = 6$) could be found in the group of patients with BMI of $\geq 25 \text{ kg/m}^2$ although it was not statistically significant ($p = 0.317$). Detailed results and described relations are presented in Table IV.

We also investigated whether there was a relationship between the occurrence of particular complications in the preoperative period and the effectiveness of transsphenoidal surgery for Cushing's disease. Based on the adopted criteria, 23 patients (63.9%) were considered to be surgically cured, whereas in 13 patients (36.1%), persistent Cushing's disease was confirmed. The prevalence of hypertension in the cured group was 73.9% vs. 84.6% in the non-cured group. The proportion of either overweight or obesity ($\text{BMI} \geq 25 \text{ kg/m}^2$) in the cured group was 78.3% vs. 84.6% in the non-cured group, whereas the frequency of glucose homeostasis alterations was 43.5% vs. 61.5%, respectively. No association between prevalence of the discussed complications and effectiveness of transsphenoidal surgery was confirmed ($p = 0.68$, $p = 1.0$, $p = 0.49$, respectively).

Next, we compared the duration of symptoms in the groups of patients surgically cured and non-cured. Mean symptoms duration was 40.8 ± 29.3 months (median: 36 months, range: 9–120 months) in the cured group vs. 49.4 ± 50.7 months (median: 24 months, range: 6–192 months) in the non-cured group ($p = 0.825$). Simultaneously, it was determined that duration of symptoms in the group of patients operated on for the first time was shorter (mean: $37.6 \text{ months} \pm 28.8$; median: 33 months) than in patients re-operated on (mean: $66 \text{ months} \pm 58.1 \text{ months}$; median: 42 months), although the obtained result was not significant ($p = 0.149$).

Table IV. Interrelation between BMI and arterial hypertension and diabetes in the studied material

Tabela IV. Zależność między wskaźnikiem masy ciała a nadciśnieniem tętniczym i cukrzycą w badanym materiale

Complication		BMI $\leq$ 25 kg/m ²	BMI $\geq$ 25 kg/m ²	p
Secondary diabetes	YES	0 (0%)	6 (20.7%)	p = 0.32
	NO	7 (100%)	23 (79.3%)	
Arterial hypertension	YES	3 (42.9%)	25 (86.2%)	p = 0.03
	NO	4 (57.1%)	4 (13.8%)	

We also examined whether there was a relationship between preoperative plasma ACTH and serum cortisol levels and the presence of particular complications of chronic hypercortisolaemia: hypertension, glucose homeostasis alterations, overweight or obesity and decreased BMD. Mean plasma ACTH and serum cortisol levels in subjects with hypertension were 99.2 ± 52.5 (median: 86 pg/mL) and 25.7 ± 7.4 (median: 26.2 μ g/dL), respectively, whereas in non-hypertensive patients it reached 104.3 ± 71.5 (median: 75.8 pg/mL) and 26.5 ± 7.7 (median: 24.9 μ g/dL), respectively ($p_{\text{ACTH}} = 0.89$; $p_{\text{CORT}} = 0.79$). In the group of patients with prediabetes or diabetes, the mean results were 96.2 ± 55.2 (median: 71 pg/mL) and 27 ± 6.8 (median: 26.7 μ g/dL), respectively, whereas in the group of normal glucose tolerance they reached 104.3 ± 58.6 (median 92.5 pg/mL) and 24.8 ± 7.9 (median: 23.7 μ g/dL), respectively ($p_{\text{ACTH}} = 0.76$; $p_{\text{CORT}} = 0.39$). In the subgroup of CD patients with BMI $\geq$ 25 kg/m² mean plasma ACTH and serum cortisol levels were 108.5 ± 59.3 (median: 92.5 pg/mL) and 25.4 ± 7.1 (median: 26.3 μ g/dL), respectively. In subjects with BMI $<$ 25 kg/m² mean plasma ACTH and serum cortisol were 67.7 ± 23.6 (median: 60.2 pg/mL) and 28 ± 8.5 (median: 25.8 μ g/dL), respectively ($p_{\text{ACTH}} = 0.06$; $p_{\text{CORT}} = 0.41$). In subjects with decreased BMD, hormone measurements were 97.3 ± 59.4 (median: 82 pg/mL) and 27 ± 6.7 (median: 27 μ g/dL), whereas among patients with normal BMD they were: 107.9 ± 49.6 (median: 105.5 pg/mL) and 23.2 ± 8.6 (median: 22.3 μ g/dL), respectively ($p_{\text{ACTH}} = 0.4$; $p_{\text{CORT}} = 0.18$). There was no relationship between preoperative hormone measurements and the development of particular complications of hypercortisolaemia in Cushing's disease.

Discussion

In the presented study, the mean age of the studied patients with Cushing's disease at the time of transsphenoidal surgery was 36.3 ± 12.9 years (median: 33.3 years), which is consistent with the data reported by most authors [13–18]. Cushing's disease is definitely

more common in women, which is also reflected in the presented material: 83% of the studied subjects were women, and the ratio of women to men was 5:1. A similar ratio has been reported by other authors [6, 16, 17]. However, in the material of Esposito et al. and Fomekong et al., the ratio of women to men exceeds 12:1 [10, 19]. In the retrospective material gathered by the Dept. of Endocrinology CMKP, the ratio is 3:1 [20] and in the Dept. of Neurosurgery of the Military Institute of Medicine it is similar (3.6:1) [21]. Thus it seems that our studied group which included predominantly young people (in the third and fourth decades of life) is representative of the adult population of patients. This material lacks any data on children, in the case of whom — in the opinion of some authors — Cushing's disease has a different, and often more aggressive, course [22–24]. In the study of Batista et al. on paediatric cases of Cushing's disease, the gender distribution significantly differs from the distribution presented in this study (F:M ratio of 1:1), which confirms the assumption that the incidence of Cushing's disease in the paediatric population depends less on the patient's gender [25]. In this study, we also found that among four of the youngest patients who underwent surgery before reaching the age of 20, there were as many as three male patients (half of all the male patients in the studied group).

Population studies and clinical observations indicate that Cushing's disease is associated with a significant (as much as four-fold) increase in mortality compared to the general population [7, 26, 27]. This results from Cushing's disease complications — the increased mortality occurs due to cardiovascular causes such as myocardial infarction or cerebral stroke. Chronic hypercortisolaemia also contributes to an increased frequency of infections and decreased BMD leading to increased fracture frequency. In the course of the active phase of the disease, glucose homeostasis alterations such as impaired glucose tolerance or diabetes are often observed. Along with impaired insulin secretion, insulin resistance and abdominal obesity develop, which intensify hyperglycaemia and additionally increase

the risk of cardiovascular complications by increasing inflammatory conditions and atherosclerosis progression [2, 5, 7, 28].

In the studied material, particular attention was paid to complications associated with Cushing's disease, such as arterial hypertension, which occurred in 77.8% of patients, prediabetes (33.3% of patients), secondary diabetes (16.7%), overweight (44.4%) and obesity (36.1%), as well as decreased bone mineral density (72.2%). These complications, except for the lower prevalence of glucose homeostasis alterations in the studied group, demonstrate frequencies similar to those presented in the Ancona Consensus of 2003 [2]. In the study conducted by Faggiano et al., it was demonstrated that there was a similar rate of overweight/obesity as well as secondary diabetes, although the frequency of prediabetes was two-fold higher (64%) compared to the frequency reported in the presented study [27].

Increased cardiovascular risk observed by some authors even after surgical cure of Cushing's disease is of particular importance in terms of patient prognosis. In the abovementioned study, Faggiano et al. demonstrated persistent thickening of the intima-media complex in ultrasound examination of carotid arteries one year after effective surgical treatment of corticotroph pituitary adenoma [27]. This is consistent with earlier observations made by Colao et al. in which it was demonstrated that there was increased cardiovascular risk even as long as five years after successful surgical treatment [29]. These observations additionally confirm the need for the earliest possible diagnosis of Cushing's disease and strict postoperative monitoring, so that treatment of possible recurrence of hypercortisolaemia can start as quickly as possible. This is of particular importance, as longer disease duration is reflected in increased risk of cardiovascular complications, which — as has been demonstrated by Fallo et al. — are associated with persistent left ventricular hypertrophy [8].

In the presented study, the association between increased prevalence of secondary diabetes or prediabetes and longer duration of symptoms was confirmed. There was also reported longer disease duration in the group of patients with decreased bone mineral density and arterial hypertension, although no significant difference was demonstrated.

Additionally, our original observation consists of demonstrating an interrelation between overweight or obesity and the prevalence of arterial hypertension in the studied group of patients with CD before TSS. In the subgroup with BMI of ≥ 25 kg/m² there were significantly more patients with hypertension than in

the subgroup with BMI of < 25 kg/m². This observation has confirmed that the development of hypertension in Cushing's disease — apart from the obvious influence of excessive cortisol, corticosterone and deoxycorticosterone (DOC) — is also affected, similarly to the general population, by body mass and BMI [1, 30]. Thus it seems reasonable to recommend appropriate diet and lifestyle modifications in patients with hypercortisolaemia, apart from typical anti-hypertensive treatment (thiazide diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers) and if necessary adrenal steroidogenesis inhibitors [2, 4]. No significant association between BMI and the risk of developing prediabetes and diabetes was demonstrated in our study, although it was observed that all cases of secondary diabetes occurred in the group of people with BMI ≥ 25 kg/m².

In the presented study, we demonstrated no relation between the number and type of complications related to chronic hypercortisolaemia and the outcome of surgical treatment for CD. Thus it seems that the number and type of complications are important for long-term prognosis in CD, reflected by increased standardised mortality ratio (SMR) within the period of five years after surgery, rather than by the assessment of TSS efficacy [7, 9]. Regardless of the above, it is obviously necessary to provide optimal and effective anti-hypertensive and glucose-lowering treatment during the pre- and peri-operative period [2, 24].

Conclusions

Patients with CD have a serious risk of cardiovascular and metabolic complications such as hypertension, glucose homeostasis alterations, and overweight or obesity. Overt diabetes and any type of glucose homeostasis alterations are related to duration of CD symptoms, which confirms the need to promptly decide on the appropriate treatment. Overweight and obesity increase the risk of secondary hypertension in CD which additionally impairs quality of life. However, the efficacy of surgical treatment does not depend directly on the duration of symptoms or the type of complications.

Disclosure

The authors report no conflict of interest.

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