The Journal of Neurological and Neurosurgical Nursing
Pielęgniarstwo Neurologiczne i Neurochirurgiczne

Wydawnictwo Państwowej Akademii
Nauk Stosowanych we Włocławku
ul. Mechaników 3, pok. 20
87-800 Włocławek

eISSN 2299-0321 ISSN 2084-8021
https://apcz.umk.pl/PNIN

DOI: 10.15225/PNN.2023.12.3.5 JNNN 2023;12(3):134–139 Case Report

Clinical, Radiological, and Histopathological Characteristics of a Patient with a Pituitary Tumor of the Corticotrophinoma Type — Case Report

Charakterystyka kliniczna, radiologiczna i histopatologiczna pacjentki z guzem przysadki typu corticotropinoma — opis przypadku

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Abstract

Introduction. Cushing disease is a rare but severe endocrine disorder. It is caused by a pituitary tumor producing excessive amounts of adrenocorticotropic hormone (ACTH) which is subsequently responsible for excessive production of cortisol in the adrenal glands. Hypercortisolism manifests with many symptoms and disorders that affect numerous organs.

Aim. To increase knowledge among nursing staff about the symptoms, causes, and treatment of patients with Cushing disease.

Case Report. A 40-year-old patient with a history of infertility treatment was admitted to the Clinical Department of Neurosurgery of St. Raphael Hospital in Krakow due to a pituitary tumor. For 7 years the patient had been experiencing symptoms such as weight gain, excessive tiredness, and menstrual disorders. The MRI examination of the pituitary showed a tumor in the sella turcica with dimensions of 4.5×5.5×4.5 mm. The histopathological examination revealed corticotropic pituitary adenoma (positive for ACTH). The patient underwent surgery after which symptoms of hypercortisolism decreased and menstruation returned. The patient became pregnant and gave birth to a child.

Discussion. A proper diagnosis in this patient's case could protect her from development of many complications related to other organs, such as diabetes mellitus or hypertension.

Conclusions. Cushing disease remains in some cases undiagnosed for many years. The patient is being referred to various specialists (ophthalmologist, gynecologist, rheumatologist) due to symptoms that are in fact complications of hypercortisolism. The case illustrates the importance of early recognition of the main symptoms of hypercortisolism. Such clinical skill would undeniably help to refer the patient to the appropriate specialist, i.e., an endocrinologist much earlier, and thus establish the correct diagnosis and implement appropriate treatment. **(JNNN 2023;12(3):134–139)**

Key Words: Cushing disease, hypercortisolism, pituitary tumor

Streszczenie

Wstęp. Choroba Cushinga należy do rzadkich, ale ciężkich zaburzeń endokrynologicznych. Jej przyczyną może być guz przysadki produkujący w nadmiarze hormon adrenokortykotropowy (ACTH), który następnie odpowiada za nadmierną produkcję kortyzolu w nadnerczach. Hiperkortyzolemia jest przyczyną wielu objawów i zaburzeń ze strony wielu narządów.

Cel. Zwiększenie wiedzy wśród personelu medycznego na temat objawów, przyczyn i leczenia pacjentów z chorobą Cushinga.

Opis przypadku. 40-letnia pacjentka z historią leczenia niepłodności została przyjęta do Oddziału Klinicznego Neurochirurgii Szpitala św. Rafała w Krakowie z powodu guza przysadki. Przez 7 lat pacjentka doświadczała objawów, takich jak przyrost masy ciała, nadmierne zmęczenie i zaburzenia miesiączkowania. Badanie MRI przysadki wykazało

guz w siodle tureckim o wymiarach 4,5×5,5×4,5 mm. Badanie histopatologiczne wykazało gruczolaka przysadki kortykotropowego (dodatniego dla ACTH). Pacjentka przeszła operację, po której objawy hiperkortycyzmu zmniejszyły się, a miesiączka powróciła. Pacjentka zaszła w ciążę i urodziła dziecko.

Dyskusja. Postawienie właściwej diagnozy w przypadku tej pacjentki mogłoby uchronić ją przed rozwojem wielu powikłań ze strony innych narządów, jak na przykład cukrzyca czy nadciśnienie tętnicze.

Wnioski. Choroba Cushinga może pozostawać przez wiele lat nierozpoznana. Pacjent bywa kierowany do różnych specjalistów (okulista, ginekolog, reumatolog) z uwagi na objawy będące w rzeczywistości powikłaniami hiperkortyzolemii. Przypadek ilustruje znaczenie wczesnego rozpoznania głównych objawów nadmiaru kortyzolu we krwi. Znajomość głównych objawów hiperkortyzolemii pomogłaby szybciej skierować pacjentkę do właściwego specjalisty czyli endokrynologa, a tym samym postawić właściwe rozpoznanie i wdrożyć odpowiednie leczenie. **(PNN 2023;12(3):134–139)**

Słowa kluczowe: choroba Cushinga, hiperkortyzolemia, guz przysadki

Introduction

The cause of Cushing's disease is the excessive secretion of adrenocorticotropic hormone (ACTH) by a pituitary tumor. Cushing syndrome results from prolonged and inappropriately high exposure of tissues to glucocorticoids [1]. Cushing syndrome is the occurrence of clinical abnormalities associated with glucocorticoid excess as a result of exaggerated adrenal cortisol production. Cushing disease is caused by pituitary adrenocorticotropic hormone (ACTH) excess. Cortisol in a healthy person has its circadian rhythm, that is, during the day cortisol values decrease. In Cushing disease, there is no circadian cortisol rhythm.

Diagnosis of Cushing syndrome is often delayed for years, partly because of a lack of awareness of the insidious, progressive disease process and testing complexity [2]. The symptoms of Cushing disease are the result of excessive glucocorticoids and adrenal androgens. Characteristic features on physical examination: central obesity, round facies (moon face), menstrual disorders, hypertension, bruising, thin skin, dorsocervical fat accumulation (buffalo hump), hirsutism, acne. Excess cortisol causes muscle wasting, thin extremities, poor wound healing, osteoporosis, and striae (caused by a loss of connective tissue). Skin thinning arising from atrophy of the epidermis and underlying connective tissue renders the skin susceptible to injury with even minor trauma. In Cushing disease, there is fragility of the vessels which causes easy bruising and wide red striae on the skin of the abdomen, arms and other areas. Reproductive function is commonly impaired. Affected women present with menstrual dysfunction and their infertility results from the direct antigonadal effect of both cortisol and androgen excess. Patients with Cushing disease suffer from impaired immunity. Patients are prone to fungal infections and their respiratory infections can have a severe course. The patients suffer from mental disorders, ranging from depressed mood to depression, mania, and psychosis. Persistence of several features associated with prior hypercortisolism, including affective disorders, cognitive dysfunction, and negative illness perception can have a sustained effect on patients' well-being [3].

Patients with Cushing disease show an adverse cardiovascular disease risk profile that may persist even after successful treatment [4]. Type 2 diabetes is present in up to 30% of patients and dyslipidemia, and low HDL, high LDL, and high triglycerides were reported in 16–64% of cases at diagnosis. In many cases, but not all, type 2 diabetes resolves after remission [5].

Cushing disease can also increase the risk of infection [6]. The high frequency of opportunistic infections in Cushing disease is linked to increased mortality.

Dysfunction of one or more pituitary axes such as central hypothyroidism, gonadal function impairment, infertility, and other complications can be seen among patients with Cushings disease [7].

Another complication is hypercoagulability. Hypercoagulability in Cushing syndrome results in a heightened risk of thromboembolic events which is coupled with an increased bleeding tendency due to skin atrophy and capillary fragility [8].

Hirsutism, due to a slight excess of adrenocortical androgens, is extremely frequent among women. Excess adrenal androgens and cortisol both suppress the gonadotroph function which results in an array of gonadal dysfunctions: most female patients have oligomenorrhoea and amenorrhea. Infertility is frequent [9].

Laboratory tests: The initial test is the overnight low-dose dexamethasone (1 mg) suppression test (LDST). In healthy patients, a dexamethasone inhibits ACTH secretion, thereby decreasing cortisol concentrations. A serum cortisol concentration of less than 1,8 µg/dL (50 nmol/L) at 08.00 h in the morning after 1 mg dexamethasone given at 11 p.m is considered to be a normal response [10].

The low-dose (2 mg) Dexamethasone suppression test is useful if the results are ambiguous.

The high-dose (8 mg) Dexamethasone test is useful to determine the etiology of Cushing syndrome. ACTH undetectable or decreased and lack of suppression indicates the adrenal cause of Cushing syndrome. ACTH normal or increased and lack of suppression indicates ectopic ACTH production. ACTH normal or increased and partial suppression suggests pituitary excess (Cushing disease).

The diurnal rhythm of cortisol is maintained in healthy people. In Cushing disease is not diurnal rhythm of cortisol.

Table 1. Differential diagnosis of Cushing disease (ACTH, Adrenocorticotropin; N, normal)

Cause	Plasma ACTH	Plasma Cortisol (pm)
Pituitary-dependent	N — slightly ↑	↑
Adrenal-dependent	↓ — undetectable	↑
Pseudo-Cushing	N — slightly ↑	N — ↑
Ectopic Cushing	↑↑↑	↑↑

Laboratory Tests: In laboratory studies of patients with Cushing disease, it can be stated: hypokalemia, hypochloremia, metabolic alkalosis, hyperglycemia, and hypercholesterolemia. Imaging Studies: A CT scan or MRI of adrenal glands is performed in the case of suspected adrenal Cushing syndrome. MRI of the pituitary gland with gadolinium is the preferred procedure for localizing a pituitary tumor in the case of suspected pituitary Cushing syndrome. The definitive treatment of Cushing syndrome is the surgical removal of the tumor causing excessive production of cortisol. Transsphenoidal surgery is recommended as first-line therapy for patients with Cushing disease [11].

The aim of the study is to increase the knowledge of nursing staff about the symptoms, causes, and treatment of patients with Cushing disease. Knowledge of the basic clinical symptoms of Cushing disease will allow for faster detection of the disease and referral of the patient to the appropriate specialist.

Case Report

A 40-year-old woman suspected of having Cushing disease was admitted to the Internal Medicine Department. The physical examination revealed abdominal obesity, fatty hump, easy formation of petechiae on the skin, deterioration of visual acuity in the last 6 months, recurrent chalazion requiring ophthalmic procedures, excessive sweating, and insulin resistance. Moreover, the patient suffered from excessive bruising with a minor injury, redness of the face on the forehead and cheeks, and an increase in abdominal circumference. The patient was suspected of having irritable bowel syndrome. She was given mesalazine to no avail. Medical history was relevant for menstrual disorders, long-term problems with getting pregnant, and lack of pregnancy despite treatment. Eventually, menstruation disappeared. The gynecologist suspected premature menopause.

The patient also reported an accumulation of body fat on both sides of her neck that she had not had before. Over time, excessive hair began to develop on the back, face, and buttocks. The patient noticed weight gain around her neck and abdomen, muscle atrophy on the lower and upper limbs, and muscle weakness. She also observed brittle blood vessels and lesions on the skin. The patient went to a dermatologist, but the medications included did not help. There was chalazion which, despite ophthalmic treatment, did not subside. The patient had problems with concentration and memory which made her work difficult. Over time, depression appeared. Over the years, the patient was consulted and evaluated by numerous specialists (ophthalmologist, dermatologist, rheumatologist, gynecologist) and took many drugs that did not help.

Description of the patient in her own words: The face looked more and more swollen, the neck was getting bigger, the belly as if pregnant, hair almost all over the body, cracks on the face skin, red elbows, amenorrhea, diabetes, depression, loss of vision, memory impairment, problems with concentration, pain in internal organs.

Results: In blood tests, the following are noteworthy: diabetes in OGTT, ↑LDL, ↑pH, in morphology: ↑leukocytes, ↓lymphocytes, ↑monocytes, ↓eosinophils. In hormonal tests: lack of circadian rhythm of cortisol, ACTH within normal limits.

BP — 140/100 mmHG, 120/80 mmHg. ECG: Sinus regular rhytm, 80/min.

Pituitary MRI: SE (T1-sag., cor), FSE (T2 ax. cor) and after administration of Gadovist in SE (T1-ax. cor. ag)+dynamic test. Pituitary gland of the correct size with dimensions of 10.5×16×7 mm (AP×RL×CC). In the pituitary transition zone, a visible change with a low signal in T2-dependent and discreetly elevated T2 images in 3×12×6 mm dependent T1 images corresponding to the Rathe's pocket cyst. From the front to the described change, a circular change of 4.5×5.5×4.5 mm with a discreetly reduced signal in T1-dependent images undergoes heterogeneous amplification after contrast in the central part — microadenoma. The typical posterior lobe high signal in T1-dependent images is not found. The structures of the hypothalamus and suprasaddle reservoirs correct. Cavernous sinuses normal.

The patient was admitted to the Department of Neurosurgery in Krakow in January 2022. Transsphenoidal resection of the pituitary tumor was performed. After the procedure, symptoms of diabetes insipidus occurred (polydipsia, polyuria, low specific gravity of urine — 1.005 g/ml). Desmopressin was included in the treatment, after which symptoms were improved.

Examinations after surgery: urine specific gravity test — 1.005 g/ml, Na — 142, K — 4.1 mmol/l.

Table 2. Laboratory tests of the patient

Laboratory tests	Laboratory results
Complete blood count	WBC — 13.19 10^3/mm^3(N<10.0), RBC — 4.74 10^6/mm^3 (N: 4.0–5.2), HGB — 14.6 g/dl (N: 12–16), HCT — 45.9% (N: 36–46%), PLT — 271 10^3/mm^3 (N: 150–400), LYMPH — 18.0% (N: 20–45), MON — 10.9% (N: 2.0–8.0), NEU — 69.7% (N: 50–70), NEU — 9.2 10^3/mm^3 (N: 2.0–7.0), BASO — 0.4% (N: 0.0–1.0), EOS — 0.4% (N: 1.0–5.0),
Electrolytes (mmol/l)	Na — 141.0 mmol/l, K — 4.3 mmol/l, Cl — 103 mmol/l
OGTT (75 g glu) (mmol/l)	Glucose: 0–5.3 mmol/l, 120 min — 11.88 mmol/l
Circadian cortisol rhythm (N: 6.2–19.4 ug/dl)	Time: 6:00 a.m. — 17.8 µg/dl, 10:00 a.m. — 16.6 µg/dl, 12:00 p.m. — 14.8 µg/dl, 6:00 p.m. — 14.4 µg/dl
ACTH (N: <63 pg/ml)	31.4 pg/ml
PRL (N: 127–637 mIU/l)	595.9 mIU/l
FSH (N: 0–12.5 IU/l-follicular phase)	2.26 IU/l
LH (N: 0–12.6 IU/l-follicular phase)	2.55 IU/l
Estradiol (N: follicular phase: 12.5–166, ovulatory phase: 85–498 pg/ml)	516.90 pg/ml
TSH (N: 0.27–4.2 uIU/ml)	1.58 uIU/ml
Thyroid hormones	fT4 — 1.10 ng/dl (N: 0.9–1.7), fT3 — 2.26 pg/ml (N: 2.6–4.4)
Creatinine (N: 44–88 µmol/l)	79.0 µmol/l
GFR (N: ≥90 ml/min/1.73 m²)	82 ml/min/1.73 m²
Lipid profile (mmol/l)	Total cholesterol — 4.9 mmol/l (N<5.2), HDL — 0.97 mmol/l (N: 0.0–1.68), LDL — 3.18 mmol/l (N: 0.0–2.59), TG — 1.47 mmol/l (N: 0.0–2.26)
Liver tests	GPT — 36 U/L (N: 10–35), GOT — 22 U/L (N: 10–35)
Acid — base balance	pH — 7.465 (N: 7.35–7.45), pCO_2 — 29.5 mmHg (N: 32.0–45.0), BE — 1.8 (N: 3–3), HCO_3 — 20.7 mmol/l (N: 22–26), pO_2 — 107 mmHg (N: 83.0–108.0), oxygen saturation — 98.4% (N: 94–98)

OGTT, oral glucose tolerance test; ACTH, Adrenocorticotropin; PRL, Prolactin; TSH, Thyroid-stimulating hormone; LH, Luteinizing hormone; FSH; Follicle-stimulating hormone; GFR, Glomerular filtration rate.

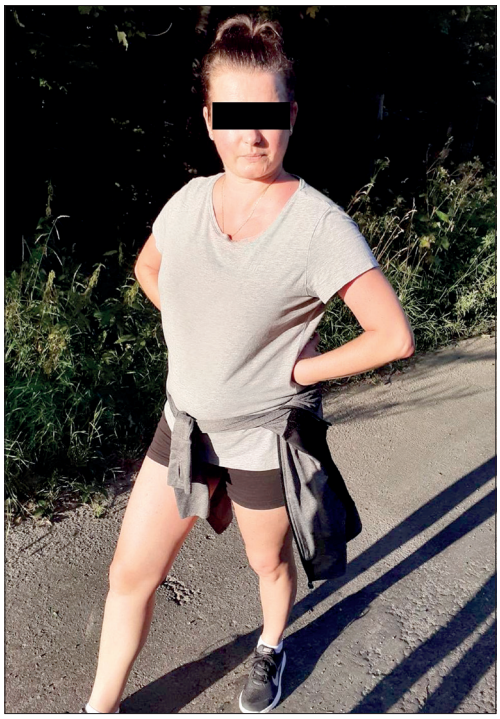
The patient was discharged home with the following medications: Hydrocortisone (HC) 30–20–0 mg/day orally, and Desmopressin 2×1 tbl/day sublingually.

The patient was instructed to increase the dose of Hydrocortisone in conditions of high stress (flu, infections, injuries, tooth extraction). In addition, the patient was instructed that in the event of fainting and a significant drop in blood pressure, the patient should be given HC intravenously and referred to the Department of Internal Medicine.

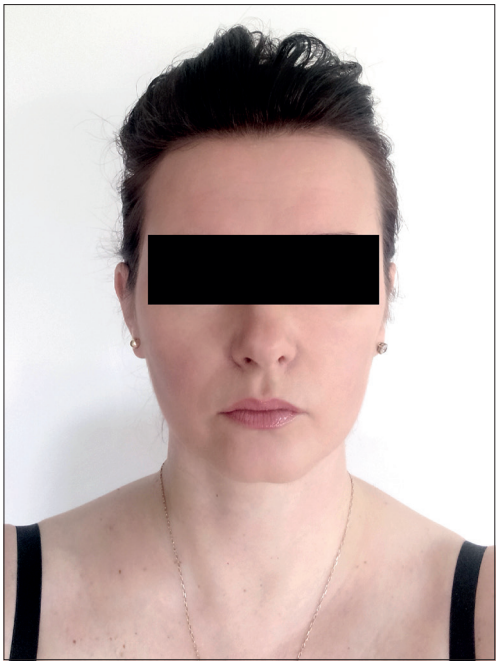
The Result of Histopathological Examination: Corticotroph pituitary adenoma (sparsely granulated) — Pituitary neuroendocrine tumor PitNET: Immunoprofile: GH–, TSH–, ACTH+, PRL, LH–, FSH–, SF1–, Tpit+

(60%), Pit1–, p53–, SSTR2A-2 (scale 0–12), ER-0 (scale 0–12), chromogranin+, Li Ki 67<1% (Transcription factors: Tpit, Pit1, SF1).

Currently, the patient remains in the care of the endocrine clinic. She takes HC orally at a reduced dose and Desmopressin 0.12 mg 2×1 tbl/d. After reducing the HC dose, she experienced severe musculoskeletal pain throughout her body and weakness in the evening and night.



Typical symptoms of Cushing disease in our patient before surgery: centripetal fat depositing with truncal obesity contrasting with the muscular atrophy of the thighs and legs, and redness of the face



Change of facial features in the patient after surgery

3 months after the neurosurgical operation, the patient experienced fainting with loss of consciousness, headaches, neck pain, and vomiting during high effort. The patient was hospitalized in the Department of Internal Medicine. In laboratory tests: blood pressure 90/60 mmHg, K — 3.8 mmol/l, Na — 144 mmol/l, the specific gravity of urine — 1.025.

The patient received HC intravenously. They then returned to Hydrocortisone orally, but at a dose of 60 mg/d in 4 doses, and then reduced to 40 mg/d at longer intervals. The patient required HC administration 3–4/day, also in the evening due to the long period of adaptation to evening and night hypercortisolemia before surgery.

After neurosurgery, the patient was diagnosed with adrenal axis insufficiency and diabetes insipidus. In the treatment of diabetes, metformin was maintained.

A few months after the neurosurgical procedure, the body weight decreased by about 10 kg, the return of regular menstruation was achieved, swelling on the face decreased, red discoloration on the elbows disappeared. Periodically there were problems with sleep, severe pain in the left shoulder, and numbness of the upper limb appearing every night. In November 2022, the patient became pregnant, and gave birth to a healthy baby in July 2023.

The patient remains under the control of a gynecological, endocrine, and diabetic clinic.

Discussion

Cushing disease remains undiagnosed for many years. The patient is referred to various specialists (ophthalmologist, gynecologist, rheumatologist) due to symptoms that are complications of hypercortisolemia. Increasing obesity, redness of the face, bullish neck, easy bruising, atrophy of the muscles of the upper and lower limbs, excessive sweating, tendency to infection, lack of menstruation, and excessive hair are the most characteristic symptoms. In blood studies, attention is drawn to the tendency to hypokalemia, hyperglycemia. In morphology: a decreased number of eosinophils and lymphocytes and an increase in leukocytes and monocytes. The patient develops hypertension and diabetes mellitus. Important it is to know the common symptoms of hypercortisolemia. That would help to refer the patient to the appropriate specialist, i.e., an endocrinologist, and thus make the right diagnosis and implement appropriate treatment.

However, it is crucial to mention that after neurosurgery due to a pituitary tumor, hypopituitarism may develop in the adrenal, thyroid, or gonadal axis and diabetes insipidus [12]. In the case of adrenal insufficiency, you should always remember to increase the dose of Hydrocortisone in case of stress or infection.

Conclusions

The case illustrates the importance of early recognition of the main symptoms of hypercortisolism. Such clinical skill would undeniably help to refer the patient to the appropriate specialist, i.e., an endocrinologist much earlier, and thus establish the correct diagnosis and implement appropriate treatment.

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Conflict of Interest: None
Funding: None
Author Contributions: Anna Krzentowska[A–C, E, F, H], Filip Gołkowski[G, H], Ryszard Czepko[G, J]

A — Concept and design of research, B — Collection and/or compilation of data, C — Analysis and interpretation of data, E — Writing an article, F — Search of the literature, G — Critical article analysis, H — Approval of the final version of the article, J — Providing part of the documentation

Received: 5.09.2023
Accepted: 29.09.2023