Endokrynologia Polska
DOI: 10.5603/EP.2015.0062
Tom/Volume 66; Numer/Number 6/2015
ISSN 0423–104X

Outcomes in pituitary surgery in Nelson's syndrome — therapeutic pitfalls

Wyniki leczenia neurochirurgicznego gruczolaków kortykotropowych przysadki w zespole Nelsona — pułapki terapeutyczne

Grzegorz Zieliński[1], Przemysław Witek[2], Maria Maksymowicz[3]

[1]*Department of Neurosurgery, Military Institute of Medicine, Warsaw, Poland*
[2]*Department of Endocrinology and Isotope Therapy, Military Institute of Medicine, Warsaw, Poland*
[3]*Department of Pathology, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland*

Abstract

Introduction: Nelson's syndrome (NS) is a rare clinical syndrome caused by an enlarging, aggressive corticotroph pituitary adenoma that can occur following bilateral adrenalectomy performed in the treatment of refractory Cushing's disease (CD). Such tumours respond poorly to currently available therapeutic options, which include surgery, radiotherapy, pharmacotherapy, and chemotherapy. They are a challenging problem in neurosurgical practice. The aim of this work was to evaluate the early and long-term results of microsurgery in a single surgeon's series of patients with NS.

Material and methods: During the period from January 2000 to December 2005, 10 patients with NS underwent surgery. The authors analysed surgical outcomes in the NS group of seven women and three men with the mean age of 47.99 years (range 39–66, SD ± 8.47 years). NS was diagnosed based on clinical signs and symptoms, especially hyperpigmentation of the skin, elevated serum ACTH levels, and pituitary tumour growth. Parasellar extension of the adenomas was assessed in both groups according to Knosp's and Hardy-Wilson classifications. Pituitary function and radiographs were evaluated in the early postoperative period, 30 days after the operation, and during follow-up. Histological examination was based on the WHO (2004) criteria.

Results: According to the criteria for Nelson's syndrome remission, five patients (50%) were cured. No perioperative mortality was reported. Three patients developed pituitary insufficiency and two patients developed diabetes insipidus. There was one case of postoperative cerebrospinal fluid leakage. One patient was diagnosed with pituitary carcinoma.

Conclusions: Transsphenoidal microsurgical removal of pituitary adenomas is a safe and effective treatment of Nelson' syndrome. **(Endokrynol Pol 2015; 66 (6): 504–513)**

Key words: *pituitary adenoma; ACTH; transsphenoidal surgery; Nelson's syndrome*

Streszczenie

Wstęp: Zespół Nelsona (NS) to rzadko występująca jednostka chorobowa spowodowana agresywnym, inwazyjnym rozrostem gruczolaka kortykotropowego przysadki u pacjentów podanych obustronnej ratunkowej adrenalektomii w następstwie przetrwałej choroby Cushinga. Skuteczność dostępnym metod terapeutycznych: leczenia chirurgicznego, radioterapii, leczenia farmakologicznego i chemioterapii jest w tych przypadkach ograniczona. Leczenie chorych z NS pozostaje wyzwaniem w praktyce neurochirurgicznej.
Celem pracy była ocena wczesnych i odległych wyników leczenia mikrochirurgicznego gruczolaków kortykotropowych przebiegających z objawami NS.

Materiał i metody: Analizie poddano wyniki 10 chorych (7 kobiet i 3 mężczyzn, średnia wieku 47,99 lat (w zakresie 39–66, SD ± 8.47 lat) operowanych w okresie od stycznia 2000 do grudnia 2005 roku przez jednego chirurga. Zespół Nelsona rozpoznano na podstawie objawów klinicznych (hiperpigmentacji skóry i błon śluzowych), wyników badań biochemicznych (wysokie wartości ACTH w surowicy) oraz wzrostu gruczolaka przysadki. Okołosiodłowy rozrost guza przysadki oceniano na podstawie skali Knospa i Hardyego-Wilsona. Czynność hormonalną przysadki analizowano we wczesnym okresie pooperacyjnym, 30 dni po operacji oraz w okresie obserwacji odległej. Ocenę histopatologiczną przeprowadzono według wytycznych klasyfikacji WHO (2004).

Wyniki: Remisję zespołu Nelsona uzyskano u 5 chorych. W analizowanej grupie nie było powikłań śmiertelnych w okresie okołooperacyjnym. Po operacji w 3 przypadkach wystąpiła niedoczynność przysadki, a moczówka prosta u 2 chorych. W jednym przypadku po operacji wystąpił płynotok pooperacyjny. U jednej chorej w okresie obserwacji stwierdzono ewolucję guza w rak przysadki.

Wnioski: Leczenie mikrochirurgiczne gruczolaków przysadki w NS jest metodą skuteczną i bezpieczną. **(Endokrynol Pol 2015; 66 (6): 504–513)**

Słowa kluczowe: *gruczolak przysadki; ACTH; chirurgia przezklinowa; zespół Nelsona*

Introduction

In 1958, Nelson et al. described the case of a female patient with ACTH-producing pituitary tumour growth following adrenalectomy for Cushing`s disease (CD) [1]. Since that time, so-called "Nelson's syndrome" is defined as the signs and symptoms associated with pituitary corticotroph tumour growth that develops

Grzegorz Zieliński M.D., Department of Neurosurgery, Military Institute of Medicine, Warsaw, Poland, e-mail: gzielinski@wim.mil.pl

after bilateral adrenalectomy in CD patients. The syndrome is characterised by hyperpigmentation of the skin and mucous membranes associated with excess ACTH secretion and neurological symptoms resulting from mass effect [2].

Despite constant progress in neurosurgical operative techniques and pituitary-targeted medical therapy of corticotroph tumours, bilateral adrenalectomy is still the definitive, lifesaving treatment in difficult cases of CD. Its main advantage is immediate elimination of hypercortisolaemia and a rapid improvement in its clinical symptoms. However, the procedure results in permanent adrenal insufficiency, which requires lifelong hydrocortisone replacement therapy [3, 4]. As mentioned before, it may be also complicated by the development of NS due to corticotroph tumour progression.

The treatment of choice in NS consists of attempting to surgically remove the tumour via the transsphenoidal approach [5]. Frequently, however, the surgery is not radical, which is due to the same anatomical conditions that prevented complete curative surgery for pre-existing CD [3, 4].

The aim of this study was to evaluate the early and long-term results of the microsurgical treatment of patients with NS in a single neurosurgical centre.

Material and methods

Study population

Out of 133 patients operated on for Cushing's disease in the Department of Neurosurgery between 2000 and 2005 we retrospectively selected 10 patients (seven women and three men; F:M ratio: 2.3:1) with confirmed NS (mean age 47.9 ± 8.5 years; range 39–66 years). All of them were operated on by the same neurosurgeon using the same surgical protocol. The follow-up was 45.3 ± 17.8 months (range 10–71 months).

All patients had been informed about the aims and methods of the study and they had signed the informed consent. The study protocol was approved by the Ethics Committee at the Military Institute of Medicine.

Clinical course of the disease

All patients underwent a standard clinical evaluation. Particular attention was devoted to the clinical course of the disease and its complications: the age at the onset of hypercortisolaemia, symptom duration, previous treatment for CD, the age at which bilateral adrenalectomy was performed, and time of NS development after adrenalectomy. The function of the anterior pituitary was assessed according to standard hormonal criteria. The diagnosis of diabetes insipidus was based on the presence of polyuria and positive water depravation test.

The diagnosis of Nelson's syndrome was based on plasma ACTH levels higher than or equal to 200 pg/mL measured 24 hours after withdrawal of glucocorticoid replacement therapy and MRI evidence of pituitary tumour re-growth.

Surgical procedure

The microsurgical transseptal transsphenoidal approach without fluoroscopy was routinely used for resection of corticotroph pituitary adenomas. The sella was exposed and an 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. The pituitary gland was carefully explored, irrespective of preoperative MRI findings. In patients with invasive macroadenomas with intracranial expansion the transcranial (unilateral transfrontal or frontotemporal) approach was used. The side on which the operation was performed was chosen on the basis of the lateral extension of the tumour. In all cases selective adenomectomy with preservation of the normal pituitary tissue was attempted.

Preoperative MRI

All patients underwent high-resolution MRI scans of the pituitary-hypothalamic region (Signa, GE Medical System; 1.5 T). MRI scans were performed before and after intravenous administration of Gd-DTPA. Microadenoma was defined as a pituitary tumour of less than 10 mm in any dimension, whereas macroadenoma was defined as a pituitary tumour with at least one diameter greater than or equal to 10 mm. The perisellar extension of the tumour was evaluated in each case. All tumours were classified according to the Knosp's scale as well as the modified Hardy-Wilson radiographic classification

Immunohistochemical and ultrastructural assessment

In all cases the surgical tissue samples were collected for pathological examination and routinely stained with haematoxylin and eosin (H&E). Immunohistochemical staining was performed on paraffin-embedded specimens with the EnVision Flex Visualisation System (Dako, K8000) with DAB as the chromogen and antibodies against all anterior pituitary hormones (LabVision), and the glycoprotein α-subunit (Novocastra).

For ultrastructural examination, small blocks of tissue were fixed in 2.5% glutaraldehyde and post-fixed in 1% osmium tetroxide, dehydrated in graded alcohols, and embedded in Epon 812. Ultrathin sections were counterstained with uranyl acetate and lead citrate. In all cases a CM120 BioTween Philips electron microscope was used for ultrastructural examination.

The pathological assessment was performed based on the 2004 World Health Organisation (WHO) diagnostic criteria.

Criteria of cure

Following the surgical procedure, all patients were subjected to further postoperative evaluation, which included plasma ACTH and serum cortisol measurements. MRI scans of the pituitary were also obtained in all cases. After the operation, the patients were regarded as cured if they met the following criteria for remission: morning plasma ACTH concentration below 200 pg/mL determined 24 hours after discontinuation of hydrocortisone replacement therapy, with no MRI evidence of a tumour in the pituitary gland.

Hormone assay

Plasma ACTH levels were measured using a specific two-step radioimmunometric assay (IRMA; coated tube technique; Brahms, Germany). Method sensitivity was 1.2 pg/mL and the reference range was 10–60 pg/mL. Chemiluminescent immunometric assays (IMMULITE 2000; Siemens, Great Britain) were used to measure serum cortisol. Method sensitivity was 0.2 μg/dL (5.5 nmol/L). The normal range for cortisol levels was 5–25 μg/dL (138–690 nmol/L).

Visual assessment

All patients underwent routine eye examinations pre- and postoperatively. Visual acuity was assessed using a Snellen's chart, and visual fields were measured using manual and computerised perimetry. Fundoscopy was performed in all patients.

Statistical analysis

Methods of descriptive statistics (mean, median, standard deviation, proportion) were employed in the statistical analysis. Tested hypotheses concerning the relationship between two categorical variables were expressed as frequencies and compared using the exact chi-square test (Fisher's exact test). The significance of differences between the two groups in terms of mean values of continuous variables was analysed by means of Student`s t-test for a normal distribution and the Mann-Whitney U test for small samples when its distribution was not normal. Verification of hypotheses concerning comparisons of the analysed parameters in two time points was conducted using the Wilcoxon test for small samples (for non-normal distributions).

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

Detailed results of clinical and epidemiological assessments of the study population, including demographic characteristics, pre-operative hormone levels, and MRI scans of the pituitary, are presented in Tables I, II.

Table I. *Demographic data and preoperative clinical characteristics of the study group of 10 patients with NS*
Tabela I. *Dane demograficzne i przedoperacyjne wyniki badań w analizowanej grupie chorych z zespołem Nelsona*

Patient	Age	Sex	Age of the onset of hipercortisolemia (years)	Duration of the symptoms of hipercortisolemia before confirmation of CD (months)	Age of the biletaral adrenalectomy (years)	Time of the occurrence of NS symptoms after adrenalectomy (months)	Visual disturbances	Preoperative pituitary function		Number of pituitary adenoma operations	Time of the follow-up
								Secondary hypothyroidism	Hypogonadotropic hypogonadism		
1	40	M	13	18	16	36	–	–	–	1xTS	71
2	45	K	30	10	32	12	–	–	–	1xTS	57
3	42	M	30	9	31	9	+	–	+	1xTS, 1xTK	47
4	66	K	32	24	33	9	–	–	–	1xTS	50
5	50	M	20	36	21	108	–	–	–	1xTS	50
6	53	K	33	60	34	6	–	–	–	1xTS	48
7	46	K	24	18	25	24	+	+	–	2xTS, 1xTK	36
8	56	K	26	6	27	6	–	–	–	1xTS	10
9	42	K	17	6	17	18	+	+	–	1xTK	24
10	39	K	39	18	41	12	–	–	–	1xTS	60

Table II. *Preoperative and postoperative hormonal assessment and type of pituitary adenoma in the study group of 10 patients with NS (nT — thyrotroph pituitary insufficiency, nG — gonadotroph pituitary insufficiency; 1 — yes, 2 — no)*

Tabela II. *Przedoperacyjne i pooperacyjne wyniki badań hormonalnych, typ histologiczny gruczolaka przysadki w analizowanej grupie chorych z zespołem Nelsona (nT — niedoczynność tyreotropowa przysadki; nG — niedoczynność gonadotropowa przysadki; 1 — nie stwierdzono, 2 — obecna)*

Patient	Age	Sex	Preoperative hormonal assesment						Early postoperative hormonal assesment					Late postoperative hormonal assesment					Pathological examination	
			ACTH [pg/mL]	Cortisol [ug/dL]	TSH [mU/L]	fT4 [pmol/L]	FSH [U/L]	LH [U/L]	PRL [ng/mL]	ACTH [pg/mL]	Cortisol [ug/dL]	nT	nG	DI	PRL [ng/mL]	ACTH [pg/mL]	Cortisol [ug/dL]	nT	nG	DI	PRL [ng/mL]	Type of pituitary adenoma	MIB-1
1	40	M	2430	< 1,0	1,06	14,9	14,3	7,1	4,6	137	< 1,0	2	2	2	1,0	43,4	< 1,0	2	2	2	1,0	ACTH-oma	nb
2	45	F	894	< 1,0	0,7	11,8	46	11	12	372	< 1,0	2	2	2	1,0	death		2	2	2	1,0		nb
3	42	M	22000	< 1,0	0,1	7,4	0,3	0,2	3,0	7900	< 1,0	2	2	2	4,0	37000 death	< 1,0	2	2	1	5,0	ACTH-oma	nb
4	66	F	1860	< 1,0	0,4	14,3	32,8	13,7	1,6	286	< 1,0	1	1	2	1,0	528	< 1,0	1	1	1	1,0	ACTH-oma	< 1%
5	50	M	1630	< 1,0	1,22	13,8	3,9	1,8	21,1	412	< 1,0	1	1	1	20	138	< 1,0	1	1	1	21		nb
6	53	F	2540	< 1,0	1,2	14,2	58	18,5	14,2	25	< 1,0	1	1	1	12,8	23	< 1,0	1	1	1	14,8	ACTH-oma	< 1%
7	46	F	87500	< 1,0	0,6	12,6	5,2	0,9	6,0	67500	< 1,0	1	1	1	5,0	68700	< 1,0	1	1	1	8,0	DG-ACTH	> 3%
8	56	F	1100	< 1,0	1,2	17,2	68	32	21	92	< 1,0	1	1	1	12	88	< 1,0	1	1	1	17	DG-ACTH	nb
9	42	F	27800	< 1,0	0,2	8,9	12,4	3,2	43,1	17500	< 1,0	2	1	1	32	17800 death	< 1,0	2	1	1	33	DG-ACTH, SG-ACTH, Pituitary carcinoma	< 1%
10	39	F	8000	< 1,0	0,41	11,6	1,65	0,79	3,0	6,8	< 1,0	1	1	1	3,0	109	< 1,0	1	1	1	6,0	DG-ACTH	< 3%

Clinical and epidemiological assessment

The mean age at onset of symptoms in the studied group of patients was 26.4 ± 7.99 years (range: 13–39 years). The mean period of time from diagnosis of Cushing's disease to bilateral adrenalectomy was 16.2 ± 8.97 months (range 6–36 months), whereas the mean age of patients undergoing this procedure was 27.7 ± 8.02 years (range 16–41 years) (Table I).

The mean period of time between bilateral adrenalectomy and the onset of NS symptoms was 24 ± 30.95 months (range 6–108 months). The obtained values did not differ between the subgroups of female and male patients.

Preoperative hormone evaluation

The mean preoperative plasma ACTH level in the study group was 15574.4 ± 27021.9 pg/mL (range: 894–87500 pg/mL). The mean ACTH concentration in the subgroup of female patients was 2.1 times higher than that in male patients, although the difference was not significant (18 527.7 ± 31 890.6 pg/mL in females *vs.* 8686.7 ± 11 536.6 pg/mL in males; P = 0.9). In all patients the morning serum cortisol level was lower than 1.0 μg/dL. Detailed results of hormone evaluation are presented in Table II. We confirmed a positive (r = 0.58, P < 0.05) correlation between the preoperative ACTH concentration and adenoma volume.

Of note, in terms of anterior pituitary function, is that in two patients we observed signs of secondary hypothyroidism that required replacement therapy with L-thyroxin. Gonadotrophic function of the pituitary was impaired only in one patient with a giant pituitary tumour. The remaining nine patients had normal pituitary gonadotropic function. Three of the seven women with NS (43%) had regular menses.

None of the studied patients showed symptoms of diabetes insipidus before surgical treatment for NS.

Preoperative MRI scans

Pituitary tumour was precisely visualised in all patients based on MRI. Macroadenomas were found in nine cases and microadenoma in one case (Table III).

The mean maximum diameter of the pituitary tumour was 21.4 ± 15.4 mm (median: 16.2 mm range: 7.7–52.7 mm). The mean adenoma volume was 13 170 ± 24 527.3 mm^3 (median: 2125.8 mm^3; range 234.6–72 812.6 mm^3). We did not confirm a statistically significant difference between the mean tumour volume in the subgroup of female and male patients (8106.7 ± 15 184.5 mm^3 *vs.* 24 984.8 ± 41 428.9 mm^3, respectively; P = 0.1). However, it should be noted that in male patients it was 3.1 times higher than in female patients. The tumours displayed perisellar growth accompanied by cavernous sinus invasion. Invasive macroadenomas were found in nine of the ten patients (90%) (Fig. 1).

Table III. *Demographic data and neuroradiological assessment of the pituitary adenomas of the study group of 10 patients with NS*
Tabela III. *Dane demograficzne i charakterystyka radiologiczna wzrostu gruczolaków kortykotropowych w analizowanej grupie chorych z zespołem Nelsona*

Patient	Age	Sex	Size of the tumor	Diaameters of the tumor [mm]	Mean diameter of the pituitary adenoma [mm]	Volume of the pituitary adenoma [mm^3]	Perisellar growth/invasion		
							Knosp's scale	Hardy-Wilson's classification	
								Grade	Stage
1	40	M	M	20 × 14 × 13	15,67	1905,9	IIº	III	A
2	45	K	M	14 × 16 × 20	16,67	2345,7	IVº	III	E
3	42	M	M	66 × 49 × 43	52,67	72812,6	IVº	IV	E
4	66	K	M	17 × 18 × 22	19	3524,9	IVº	IV	E
5	50	M	m	7 × 8 × 8	7,67	234,6	IIº	III	0
6	53	K	M	15 × 10 × 7	10,67	549,8	IIIº	II	A
7	46	K	M	64 × 34 × 37	45	42155,9	IVº	IV	E
8	56	K	M	10 × 12 × 12	11,33	753,9	IIº	II	0
9	42	K	M	35 × 25 × 15	25	6872,2	IVº	IV	E
10	39	K	M	13 × 10 × 8	10,33	544,5	IIº	III	E

Ophthalmological assessment

Preoperatively, three patients (No. 3, 7, and 9) were diagnosed with visual disturbances in the form of deterioration of visual acuity and visual field deficits due to suprasellar growth of pituitary tumours (Table I, Fig. 2).

Histopathological and immunohistochemical evaluation

The histopathological and immunohistochemical examination of the surgically removed specimens revealed the presence of corticotroph adenoma in all 10 cases.

In four cases an ultrastructural examination with electron microscopy was performed and revealed densely granulated ACTH adenomas (DG-ACTH).

In five cases the presence of the Ki-67 antigen was assessed using MIB-1 antibodies. In four patients, the MIB-1 index was lower than 3%. In one patient (case No. 7) the MIB-1 index was higher than 3% and was accompanied by high p53 nuclear protein expression. This patient was diagnosed with atypical corticotroph adenoma.

The results of pathological examination are presented in detail in Table II and Figures 3, 4.

Evaluation of postoperative complications

There were no fatal complications in the perioperative period, i.e. within the first 30 days after performed surgery. In total, three deaths occurred throughout the follow-up period (Table I, II). Patient No. 2 died 57 months after surgery due to cardiovascular and metabolic complications of poorly controlled diabetes. Patient No. 3 died after 47 months of follow-up as a result of invasive adenoma infiltrating the skull base. The third patient (No. 9) died 37 months after pituitary surgery in a different centre. The cause of death was not known.

In all 10 cases selective adenomectomy was performed. It led to thyrotrophic and gonadotropic pituitary insufficiency in three patients. Two patients (20%) were diagnosed with transient diabetes insipidus, and an additional two patients (20%) with persistent ADH insufficiency.

Intraoperative CSF leakage occurred in four patients (40%). The patients underwent sellar floor reconstruction during the initial operation. In three cases watertight closure of the intracranial space was achieved. In one case, during the early postoperative period (20 days following the surgical procedure), CSF leakage was observed without signs of meningitis. The patient underwent a subsequent surgery resulting in achievement of watertight closure of the intracranial space without additional complications.

Effectiveness of surgical treatment

All of the patients in the study group were treated surgically. In the study group there was not a single case treated by radiotherapy. These ten patients underwent a total of 13 operations. The transsphenoidal approach was the most common technique and was performed 10 times (nine surgeries via the transseptal transsphenoidal approach, and one via the right-sided lateral rhinotomy). Transcranial surgeries were performed in three cases (two fronto-temporal and one unilateral trans-frontal craniotomies).

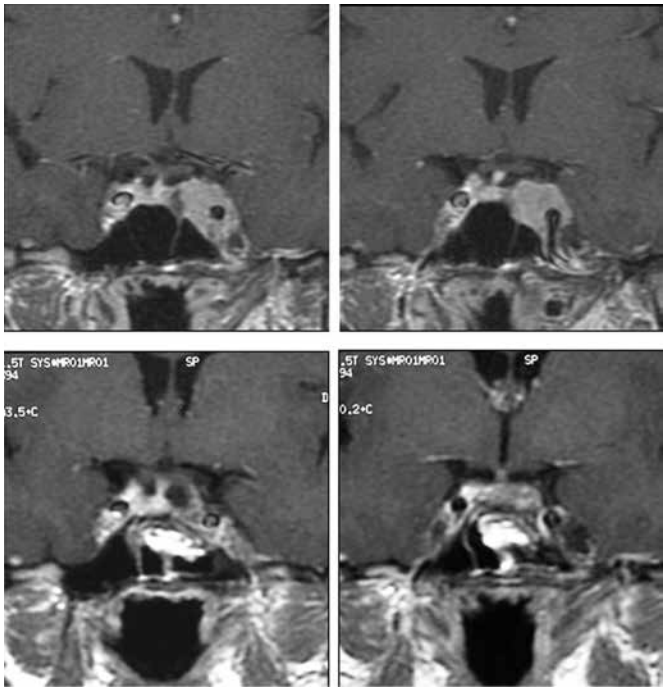

Figure 1. *Coronal T1 weighted after Gd-DTPA magnetic resonance imaging (preoperative and postoperative) of the aggressive ACTH-secreting pituitary tumour invading the left cavernous sinus (Knosp IV[b]) with encasement of the left cavernous carotid artery and erosion of the sellar floor.*

Rycina 1. *Inwazyjny gruczolak kortykotropowy naciekający lewą zatokę jamistą (Knosp IV[b]) i niszczący dno siodła tureckiego (wynik przedoperacyjny i pooperacyjny badania MR po podaniu środka kontrastowego, przekrój czołowy, czas T1-zależny)*

In eight patients the operation was to be inherently radical and was undertaken with curative intent. In the two remaining cases, the performed surgical procedures were palliative in nature and their purpose was to reduce tumour volume, and improve neurological status and quality of life.

Because of the diversity of the surgical approaches used, we decided not to conduct an assessment of early results of surgical treatment. Detailed long-term results of surgical treatment were obtained during follow-up.

Five patients (50%) achieved a sustained reduction in ACTH concentration to values below 200 pg/mL and no remnants of pituitary tumour were visible on postoperative MRI. It was accompanied by a decrease in the intensity of skin hyperpigmentation. This group included one patient with microadenoma and four patients with macroadenomas, with limited perisellar expansion (grade II and III according to Knosp's scale).

In the remaining five patients the neurosurgical treatment was not curative. Instead, its purpose had been to improve the patients` neurological condition. Severe growth and infiltration of cranial base structures, primarily the cavernous sinus, constituted the reason for incomplete removal of the pituitary tumours. Grade IV tumours (Knosp's scale) with infiltration of the cavernous sinus were identified in all cases that failed to be cured.

The extent of perisellar growth, as measured by Knosp's scale, was established to be the main factor influencing the effectiveness of NS surgical treatment.

The surgical treatment resulted in visual field widening and acuity improvement only in case No. 9. In patients No. 3 and 7 no improvement was observed, despite significant decrease in tumour volume.

Six months after surgery, a 46-year-old female (patient No. 7) developed acute deterioration of visual acuity with accompanying limitation of visual field in all quadrants. Subsequent surgery attempts failed to improve her vision. In case No. 3 re-growth of an invasive pituitary tumour caused serious visual deterioration and paresis of both abducens and the left oculomotor nerves.

Discussion

Diagnosis and treatment of NS remains one of the greatest challenges of contemporary endocrinology [6]. This rare form of CD is caused by ACTH-secreting pituitary adenoma with unpredictable, usually aggressive clinical course that often leads to serious, life-threatening complications [3, 7]. Diagnostic criteria for NS were proposed in 1958 and originally included: abnormally high plasma ACTH, enlargement of the sella turcica shown in X-ray of the skull, vision disturbances re-

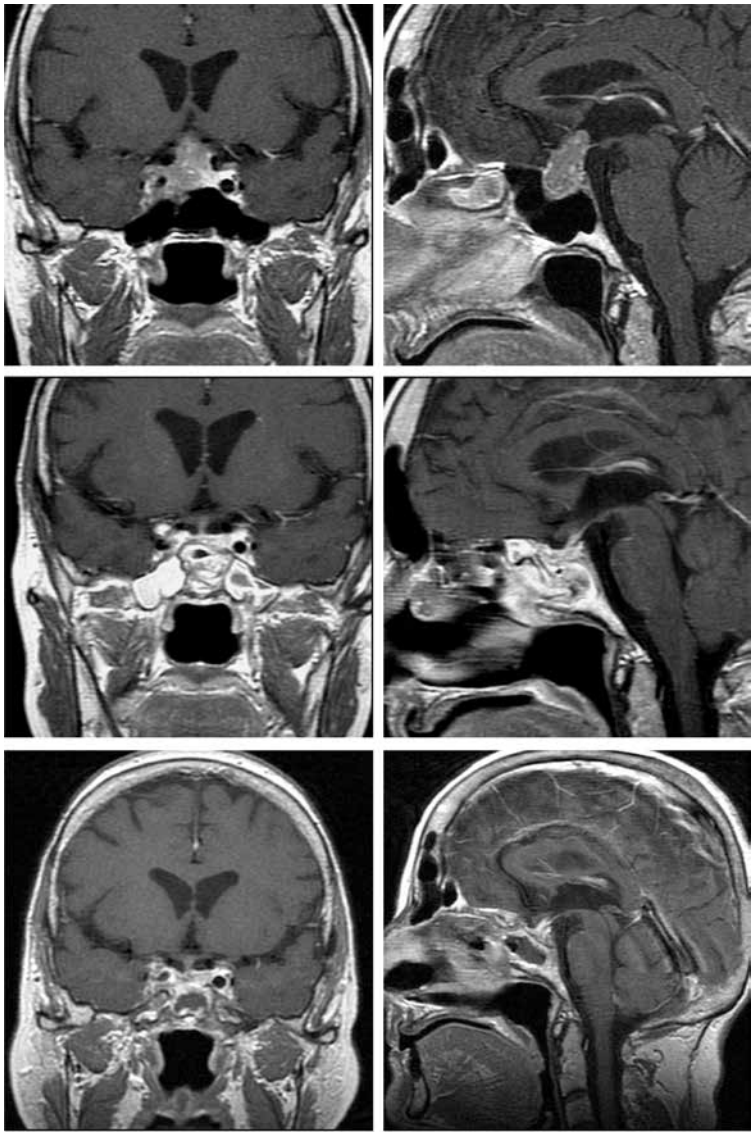

Figure 2. *Preoperative and postoperative MRI of the sellar region (coronal and sagittal T1-weighted before and after Gd-DTPA administration) revealed an invasive tumour mass with parasellar extension and right cavernous sinus invasion (Knosp IV°). Optic chiasm is compressed and displaced*

Rycina 2. *Inwazyjny gruczolak kortykotropowy charakteryzujący się wzrostem okołosiodłowym, naciekający prawą zatoke jamistą (Knosp IV°) i uciskający oraz przemieszczający skrzyżowanie wzrokowe (wynik przedoperacyjny i pooperacyjny badania MR po podaniu środka kontrastowego, przekrój czołowy i strzałkowy, czas T1-zależny)*

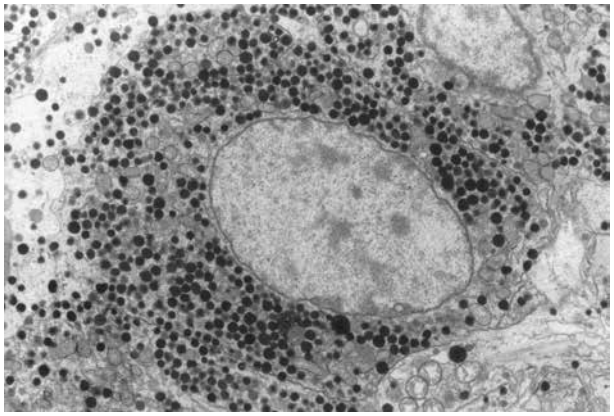

Figure 3. *Electron microphotograph (12500×) of the densely granulated corticotroph adenoma (DG-ACTH) in Nelson's syndrome. The big, ovoid nuclei is seen. The cytoplasm is abundant and possesses RER membranes, a prominent Golgi apparatus, and many secretory granules in the size range of 200 to 500 nm*

Rycina 3. *Bogatoziarnisty gruczolak kortykotropowy w zespole Nelsona. Widoczne duże, owalne jadra komórkowe. Rozbudowana cytoplasma, siateczka cytoplasmatyczna oraz aparat Golgiego z widocznymi licznymi ziarniostościami wewnątrzwydzielniczymi o średnicy 200–500 nm. Badanie mikroskopii elektronowej, powiekszenie 12500×*

sulting from compression of the optic chiasm by the enlarging pituitary tumour, and hyperpigmentation of the skin and mucous membranes [1, 2].

Kemink et al. suggested other clinical characteristics of NS [5]. They defined NS based on plasma ACTH concentration measured 24 hours after discontinuation of hydrocortisone replacement therapy. They adopted the plasma ACTH level of 200 pg/mL as the lower cut-off point in NS. Furthermore, they recognised the detection of pituitary macroadenoma in MRI as a nec-

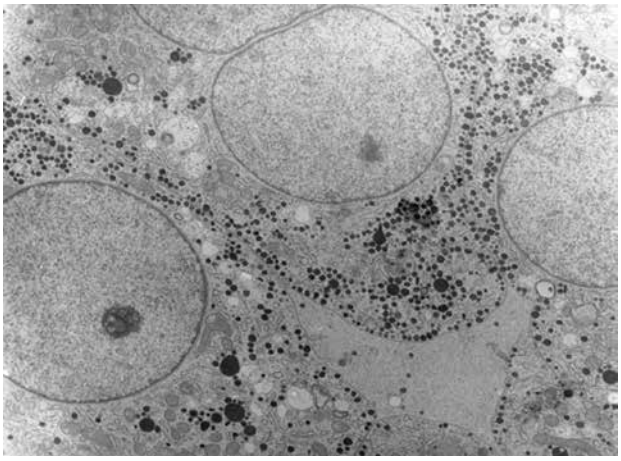

Figure 4. *Electron microphotograph (12500×) of the sparsely granulated corticotroph adenoma (SG-ACTH) in Nelson's syndrome. There are numerous mitochondria and well developer Golgi complex in the adenoma cells. Spherical secretory granules (vary in electron density) line up along the cell membranes. A scattered chromatin and single nucleoli are seen in large ovoid nuclei.*

Figure 4. *Ubogoziarnisty gruczolak kortykotropowy w zespole Nelsona. W komórkach widoczne liczne mitochondria i rozbudowany aparat Golgiego. Wzdłuż błon komórkowych ułożone okrągłe ziarnistości wydzielnicze o zdróżnicowanej gęstości elektronowej. Duże jądra komórkowe z rozproszoną cytoplasmą i pojedynczymi jąderkami. Badanie mikroskopii elektronowej, powiekszenie 12500×*

essary condition for NS diagnosis [5]. However, this last issue remains particularly controversial. While most authors indeed report invasive macroadenomas while presenting cases of patients with NS [8–10], other authors emphasise that in 20–40% of cases the condition is associated with pituitary microadenomas [7, 11, 12]. Notably, the efficacy of surgical treatment of small tumours is much higher when compared to the results achieved in cases of invasive macroadenomas [7, 8].

In our own material, microadenoma was identified only in one of the ten patients with NS. However, remission was achieved only in patients with smaller pituitary tumours and limited, intrasellar expansion. In the case of invasive macroadenoma the results of surgical treatment were definitely worse. We still considered this case to be a partial success due to the achieved vision improvement through optic chiasm decompression.

Tindal et al. achieved similar results [13]. In their study the main predictive factor of radical surgery was tumour size, assessed according to the Hardy-Wilson classification. The authors also reported that the extent of suprasellar expansion did not limit the transsphenoidal approach, but the presence of infiltration of adjacent structures, in particular the cavernous sinus, limited the effectiveness of treatment [13].

In earlier publications, the incidence of NS was estimated at 3–42% in adults [9, 11, 15] and at 25–66% in children [4, 14]. In one of the largest research studies on NS with long-term follow-up, conducted in a group of 37 patients Kasperlik-Zaluska et al. indicated a significantly higher incidence of NS, reaching up to 71% [7]. Kelly et al. identified corticotroph tumour in 24 out of 46 patients (52%) after bilateral adrenalectomy [9]. Similar rates were also reported by other authors [2, 4, 10]. Assie et al. suggested assessing the change in corticotroph tumour size (CTP, Corticotroph Tumour Progression) to monitor patients with Cushing's disease following therapeutic bilateral adrenalectomy [3]. According to these authors, pituitary tumour enlargement typically precedes development of Nelson's syndrome (elevated ACTH levels, skin hyperpigmentation, visual disturbances) and is a definitive sign of corticotroph adenoma growth and transformation into an invasive, aggressive pituitary neoplasm [3]. Therefore, the higher incidence of CTP and NS reported in newer studies probably results from improved pituitary tumour visualisation techniques, particularly MRI, which is commonly used in neuroradiological diagnostics.

In light of the already mentioned reports by Kasperlik-Zaluska et al. and Assie et al. we can conclude that prognostic factors for pituitary tumour growth and NS development include: short history (rapid course of the disease), age at the onset of CD, high (over 1000 pg/mL) ACTH concentration measured two hours after the administration of the morning hydrocortisone replacement dose, and MRI evidence of a pituitary tumour prior to bilateral adrenalectomy [3, 7]. Thus, in patients with visible, inoperable or incompletely removed pituitary tumour the decision to perform bilateral adrenalectomy should be made with particular caution. In such cases one should consider using stereotactic radiotherapy or radiosurgery and/or extended treatment with an adrenal steroidogenesis inhibitor (ketoconazole, metyrapone, or mitotane) [3, 7, 16].

These observations were confirmed by Fisher et al., who demonstrated a more aggressive course of the disease and rapid expansion of pituitary adenomas in patients under 20 years of age [17]. Identical conclusions were also reported by other authors, who observed a higher risk of Nelson's syndrome and a more aggressive course of the disease in children [18, 19]. In contrast, Pereira et al. failed to demonstrate a relationship between the younger age of CD patients and the risk of NS occurrence in a group of 30 patients with NS [10].

In our material the mean period from bilateral adrenalectomy to NS diagnosis was 24 months and ranged from 6 to 108 months. There were no confirmed gender differences with regard to NS incidence in the analysed group. The time of NS development after bilateral adrenalectomy is of great importance for the proper planning of post-operative follow-up. However, in

accordance with the opinion of most authors, an accurate prediction of the NS onset is not possible. Moreover, NS can occur at any time, regardless of any possible methods of prevention [3, 9]. Kasperlik-Załuska et al. observed NS development within the period of 1 to 18 years after bilateral adrenalectomy [7]. Lüdecke et al. presented similar data [20]. Kemink et al. reported an extreme case of NS with pituitary tumour enlargement accompanied by skin hyperpigmentation even 29 years after adrenalectomy [21]. However, the greatest risk of Nelson syndrome exists within the first three years after adrenal gland removal, and it definitely decreases after seven years [3, 12].

The results of surgical treatment of NS are vastly inferior to those observed with other types of pituitary tumours [5, 7]. Most authors emphasise the fact that the tumours in this disease are mostly macroadenomas and are characterised by infiltration of adjacent structures, especially the cavernous sinus [22, 23, 24]. Kemink et al. reported infiltration into the cavernous sinus in 9 of 15 observed patients (60%) [5]. Assie et al. and Xing et al. reported a lower incidence of cavernous sinus invasion [3, 12]. Other authors have pointed out that the main factor influencing the effectiveness of surgical treatment, and highly important in terms of prognosis, is the degree of extrasellar expansion [3, 25]. Suprasellar growth together with visual disturbances resulting from optic chiasm compression occurs quite frequently in NS [5, 7]. Lüdecke et al. reported this in 31% of patients [20].

In the presented study, macroadenoma was detected in 9 of the 10 patients. Radiographic evidence of cavernous sinus invasion was detected in all patients from our group. Visual disturbances were identified in 3 of the 10 patients (30%).

Neurosurgical treatment of NS helps achieve remission in just 20–30% of patients [12, 26, 27]. Significant size and advanced perisellar expansion of adenomas are the reasons for low effectiveness of this form of treatment [20, 28].

Encouraging outcomes of surgical treatment were presented by Fukushima, who achieved remission in 7 out of 10 patients; however, all tumours in that study were characterised by intrasellar expansion only [11]. Similar results were also published by Lüdecke et al. [20]. De Tommasi et al. achieved normalisation of ACTH levels only in 16.6% of operated patients with NS [8]. Kemink et al. reported remission of NS in 5 out of 11 patients (45%) [5]. Xing et al. confirmed a complete tumour removal in 56% of patients [12]. All of the authors cited above emphasised the fact that tumours characterised by smaller size and intrasellar expansion have a more favourable prognosis and lower incidence of postoperative complications [5, 7, 9, 12, 20]. In our group – based on adopted criteria – we considered five patients (50%) to be in remission of NS.

Three patients (30%) from our study group were diagnosed with anterior pituitary insufficiency, whereas two patients (20%) were diagnosed with permanent diabetes insipidus. CSF leakage occurred in one patient and required reconstruction of the sellar floor. Lüdecke et al. reported only one case of pituitary insufficiency [20] Xing et al. listed only oculomotor nerve injury among complications related to surgical treatment in 23 patients with NS, but there was no information regarding postoperative pituitary function [12]. Kemink et al. reported one (9%) case of pituitary insufficiency and two (18%) cases of persistent diabetes insipidus [5]. Kelly et al. reported five cases of persistent diabetes insipidus (38.5%) and nine cases of new-onset anterior pituitary insufficiency (69%) [9].

Conclusions

Successful treatment of NS remains a challenge. Our results confirm that microsurgical treatment is a relatively effective and safe procedure, although the outcomes are worse in comparison to those achieved in other types of pituitary tumours. Our data support the view that a more favourable prognosis is attributed to cases of microadenomas and intrasellar macroadenomas. On the contrary, extrasellar growth with cavernous sinus involvement is the main factor negatively influencing the effectiveness of surgical treatment. Additionally, a long-term endocrinological follow-up is necessary for an accurate assessment of postoperative complications in NS, especially in terms of pituitary insufficiency.

References

1. Nelson DH, Meakin JW, Dealy JB et al. ACTH-producing pituitary tumor of the pituitary gland. NEJM 1958; 259: 161–164.
2. Nelson DH, Meakin JW, Thorn GW. ACTH-producing tumors following adrenalectomy for Cushing's disease. Ann Int Med 1960; 52: 560–569.
3. Assié G, Bahurel H, Coste J et al. Corticotroph tumor progression after adrenalectomy in Cushing's disease. A reappraisal of Nelson's syndrome. JCEM 2007; 92: 172–179.
4. Barber TM, Adams E, Wass JA. Nelson syndrome: definition and management. Handbook of Clinical Neurology 2014; 124: 327–337.
5. Kemink L, Grotenhuis JA, De Vries J et al. Management of Nelson's syndrome: observations in fifteen patients. Clin Endocrinol 2001; 54: 45–52.
6. Lindholm J. Cushing's syndrome: historical aspects. Pituitary 2000; 3: 97–104.
7. Kasperlik-Załuska AA, Bonicki W, Jeske W et al. Nelson's syndrome — 46 years later: clinical experience with 37 patients. Neurochirurgie 2006; 67: 14–20.
8. De Tommasi C, Vance ML, Okonkwo DO et al. Surgical management of ACTH-secreting macroadenomas: outcome and challenges in patients with Cushing's disease or Nelson's syndrome. J Neurosurg 2005; 103: 825–830.
9. Kelly PA, Samandouras G, Grossman AB et al. Neurosurgical treatment of Nelson's syndrome. JCEM 2002; 87: 5465–5469.
10. Pereira MA, Halpern A, Salgado LR et al. A study of patients with Nelson's syndrome. Clin Endocrinol 1998; 49: 533–539.
11. Fukushima T. Trans-sphenoidal microsurgical treatment of Nelson's syndrome. Neurosurg Rev 1985; 8: 185–194.

12. Xing B, Ren Z, Su C et al. Microsurgical treatment of Nelson's syndrome. Chin Med J 2002; 115: 1150–1152.
13. Tindall GT, Herring CJ, Clark RV et al. Cushing's disease: results of transsphenoidal microsurgery with emphasis on surgical failures. J Neurosurg 1990; 72: 363–369.
14. Kemink L, Pieters G, Hermus A et al. Patient's age is a simple predictive factor for the development of Nelson's syndrome after total adrenalectomy for Cushing's disease. JCEM 1994; 79: 887–889.
15. Mauermann WJ, Sheehan JP, Chernavvsky DR et al. Gamma Knife surgery for adrenocorticotropic hormone-producing pituitary adenomas after bilateral adrenalectomy. J Neurosurg 2007; 106: 988–993.
16. Assié G, Bahurel H, Bertherat J et al. The Nelson's syndrome revisited. Pituitary 2004; 7: 209–215.
17. Fisher BJ, Gaspar LE, Stitt LW et al. Pituitary adenoma in adolescents: a biologically more aggressive disease? Radiol 1994; 192: 869–872.
18. Mampalam TJ, Tyrrell JB, Wilson Ch. Transsphenoidal microsurgery for Cushing's disease. A report of 216 cases. Ann Int Med 1998; 109: 487–493.
19. Partington MD, Davis DH, Laws ER et al. Pituitary adenomas in childhood and adolescence. Results of transsphenoidal surgery. J Neurosurg 1994; 80: 209–216.
20. Lüdecke DK, Breustedt HJ, Brämswig J et al. Evaluation of surgically treated Nelson's syndrome. Acta Neurochir 1982; 65: 3–13.
21. Kim LJ, Klopfenstein JD, Cheng M et al. Ectopic intracavernous sinus ACTH-secreting microadenoma: could this be a common cause of failed transsphenoidal surgery in Cushing's disease? Case report. J Neurosurg 2003; 98: 1312–1317.
22. Scheithauer BW, Kovacs KT, Laws ER et al. Pathology of invasive pituitary tumors with special reference to functional classification. J Neurosurg 1986; 65: 733–744.
23. Scheithauer BW, Gaffey TA, Lloyd RV et al. Pathobiology of pituitary adenomas and carcinomas. Neurosurg 2006; 59: 341–353.
24. Simmons NE, Alden TD, Thorner MO et al. Serum cortisol response to transsphenoidal surgery for Cushing disease. J Neurosurg 2001; 95: 1–8.
25. Fahlbusch R, Buchfelder M, Müller OA. Transsphenoidal surgery for Cushing's disease. J R Soc Med 1986; 79: 262–269.
26. Esteban F, Ruiz-Avila I, Vilchez R et al. Ectopic pituitary adenoma in the sphenoid causing Nelson's syndrome. J Laryn Otol 1997; 111: 565–567.
27. Wilson Ch. Surgical management of the pituitary tumors. JCEM 1997; 82: 2381–2385.
28. Hashimoto N, Handa H, Yamagami T. Transsphenoidal extracapsular approach to pituitary tumors. J Neurosurg 1986; 64: 16–20.