Results of neurosurgical treatment by a transsphenoidal approach in 10 patients with Nelson's syndrome

JERZY WISŁAWSKI, M.D., ANNA A. KASPERLIK-ZALUSKA, M.D., WOJCIECH JESKE, M.D., BARBARA MIGDALSKA, M.D., JADWIGA JANIK, M.D., JÓZEF ZALUSKA, M.D., and WIESŁAW BONICKI, M.D.

Department of Neurosurgery, Academy of Medicine, and Departments of Endocrinology and of Biophysics and Biomathematics, Center of Postgraduate Medical Education, Warsaw, Poland

Ten patients with Nelson's syndrome, nine women and one man, aged 22 to 61 years, were treated neurosurgically by a transsphenoidal approach. In four patients, microadenomas were found, ranging in diameter from 4 to 10 mm. Microscopically, mixed adenoma was diagnosed in six cases, basophilic adenoma in three patients, and chromophobe adenoma in one patient. The presence of argyrophilic nerve fibers in the adenoma tissue was noted in one case. The time of observation after transsphenoidal surgery ranged from 6 months to 10 years. Clinical remission was achieved in eight patients; in two of them, radiation therapy was used to complement surgical treatment. In two patients, recurrence of the pituitary neoplasm was observed; anaplasia was revealed at the second operation in one of them. Radiation therapy might be a useful adjunct to neurosurgery in Nelson's syndrome, especially in patients with anaplastic adenoma.

KEY WORDS • Nelson's syndrome • pituitary tumor • Cushing's disease • transsphenoidal surgery • radiation therapy

Between 1958 and 1983, 130 patients with pituitary-dependent Cushing's syndrome (Cushing's disease) were treated at the Department of Endocrinology in Warsaw. Fifty-five of these patients underwent bilateral adrenalectomy. No sellar abnormalities were present at the time of operation. Fifty survivors were followed for an average of 13 years (range 2 to 23 years). In 15 patients (30%) undergoing bilateral adrenalectomy, the characteristics of a pituitary adenoma (Nelson's syndrome) appeared within 1½ to 12 years (mean 4.6 years). We report now the results of surgery by a transsphenoidal approach in 10 patients with Nelson's syndrome.

Clinical Material and Methods

Patient Population

The 10 patients included nine women and one man, ranging in age from 22 to 61 years (mean 36.6 years). Clinical data are summarized in Table 1. All the patients had markedly pigmented skin, nine had radiographic evidence of a pituitary tumor (Cases 1 to 8 and 10), and two had defects of the visual field (Cases 1 and 9). Headache was present in six cases. Secondary amenorrhea occurred only in the youngest patient (Case 3); she also had disturbances of accommodation and alternate convergent strabismus. Nine patients (Cases 1 to 9) were treated by transsphenoidal surgery 2 to 10 years prior to this study. The 10th patient was operated on in the last year of the study.

Endocrinological Studies

All the patients were treated with cortisone (12.5 mg three times/day) and fluorohydrocortisone (0.05 mg to 0.1 mg daily). Venous blood samples for the determination of adrenocorticotropic hormone (ACTH), cortisol, prolactin (PRL), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), growth hormone (GH), and thyroxine (T₄) were drawn at 8 a.m. (that is, 1 hour after the first dose of cortisone) for all the hormone estimations, and at 12 noon, 4 p.m., and 10 p.m. for the determination of ACTH and cortisol. Hormone estimates were carried out before and 6 to 12 months after transsphenoidal surgery. In some cases determinations were performed during the first postoperative month. In the long-term follow-up period, hormonal assessment was repeated every year.

Plasma ACTH levels were determined radioimmuno-
Surgical treatment of Nelson's syndrome

Operative Technique

The day before operation the patient receives hydrocortisone hemisuccinate, 100 mg intramuscularly, and neomycin spray to the nose. On the day of operation, 100 mg hydrocortisone is given intramuscularly every 8 hours. The operation is carried out in the sitting position, and the exposure of the sella is performed in the manner described by Hardy and Guiot and De-rome. As a rule, television monitoring and the operative microscope are used after the sphenoid sinus has been entered. After the dura is opened, the tumor is visualized and removed using suction, small punches, and spoons. When the whole tumor is removed, Gelfoam soaked in absolute alcohol is packed into the cavity for 5 minutes.

All the tumor specimens were stained by standard methods, including hematoxylin and eosin, orange, and Kratsay. For argyrophilic fibers, Bielschowsky's impregnation method was used.

Operative Results

The pituitary tumors ranged in size from microadenomas of 4-mm diameter to large tumors invading the surrounding tissues, as in Case 3 (Table 1). Microscopically, six patients had a mixed adenoma (basophilic and chromophobe with predominance of basophilic cells), three patients had a basophilic adenoma, and one patient a chromophobe adenoma (Table 1). In one patient (Case 10), argyrophilic nerve fibers were found within the adenoma.

Neurosurgery was complemented by gamma radiotherapy in the patient with extrasellar invasion (Case 3) and in the first patient in this series (Case 1), who underwent surgery at the Neurosurgical Clinic at Foch Hospital, Paris, by Prof. G. Guiot. Clinical remission was achieved in all the patients following neurosurgery. Hyperpigmentation decreased markedly during the first 3 days after the operation, and in five patients normal pigmentation returned. Headache disappeared in all the patients. Regular menses returned in Case 3. One patient (Case 8) became pregnant 1 year after surgery, and delivered a 3200-gm boy. The child has developed quite normally. Before surgery, the patient had been treated for infertility for 6 years without success.

In two patients (Cases 4 and 5), the pituitary tumor recurred within 1½ and 1 year, respectively. In Case 5, the first sign of recurrence was anisocoria. There was a slight enlargement of the sella turcica. During the second operation via a transcranial approach, an anaplastic neoplasm with extrasellar extension was found. The patient underwent cobalt therapy as an adjunct to surgical exeresis. In Case 4, the recurrence of Nelson’s syndrome was manifested by headache, amenorrhea, and progressive cutaneous melanosis. The diagnosis was confirmed by routine radiography showing progressive enlargement of the sella turcica with erosion of the dorsum and by computerized tomography. About 6 months later, a clinical picture of intratumoral hemorrhage was seen, with transient bilateral paresis of the third, fourth, and sixth cranial nerves. Clinical remission of Nelson’s syndrome has been observed in this patient.

The plasma ACTH and serum cortisol findings at 8 a.m. and 10 p.m. are shown in Table 2. These values were representative of the diurnal ACTH rhythm, as the concentrations at noon and 4 p.m. did not differ significantly from those at 10 p.m. High plasma ACTH levels, 2000 ng/liter or above, were found in all the patients preoperatively, but decreased markedly in eight patients after neurosurgery.

Preoperative serum prolactin concentrations were increased above normal levels in five of nine patients studied. After surgery, they decreased and only in Case 3 was an increase noted. Serum LH levels ranged from

---

* ACTH antiserum (AS 215/E4) was kindly supplied by Prof. L. Rees and ACTH for iodination by Dr. P. Lowry of St. Bartholomew’s Hospital, London, England.

---

** TABLE 1 **

Clinical and postoperative data in 10 patients with Nelson’s syndrome (NS)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, Age (yrs)</th>
<th>Follow-Up Time (ys) After Adrenalectomy</th>
<th>Duration of NS (ys)</th>
<th>Tumor Size (mm)</th>
<th>Histological Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 42</td>
<td>12½</td>
<td>10</td>
<td>11</td>
<td>14 basophilic</td>
</tr>
<tr>
<td>2</td>
<td>F, 34</td>
<td>7</td>
<td>6</td>
<td>6½</td>
<td>12 mixed</td>
</tr>
<tr>
<td>3</td>
<td>F, 22</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>25 mixed</td>
</tr>
<tr>
<td>4</td>
<td>F, 29</td>
<td>7</td>
<td>4</td>
<td>5</td>
<td>18 basophilic</td>
</tr>
<tr>
<td>5</td>
<td>F, 39</td>
<td>11½</td>
<td>4</td>
<td>6</td>
<td>15 mixed anaplastic</td>
</tr>
<tr>
<td>6</td>
<td>F, 28</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>11 basophilic</td>
</tr>
<tr>
<td>7</td>
<td>M, 32</td>
<td>11½</td>
<td>2</td>
<td>3</td>
<td>4 mixed</td>
</tr>
<tr>
<td>8</td>
<td>F, 37</td>
<td>15</td>
<td>2</td>
<td>3</td>
<td>10 mixed</td>
</tr>
<tr>
<td>9</td>
<td>F, 42</td>
<td>15</td>
<td>2</td>
<td>7</td>
<td>4 mixed</td>
</tr>
<tr>
<td>10</td>
<td>F, 61</td>
<td>5½</td>
<td>2</td>
<td>7</td>
<td>chromophobe</td>
</tr>
</tbody>
</table>

* Finding at the second operation.
TABLE 2
Plasma ACTH, cortisol, and prolactin levels in 10 patients with Nelson's syndrome before and after neurosurgery

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Before ACTH (ng/liter)</th>
<th>After ACTH (ng/liter)</th>
<th>Before Cortisol (µg/dl)</th>
<th>After Cortisol (µg/dl)</th>
<th>Before Prolactin (µg/liter)</th>
<th>After Prolactin (µg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 A.M.</td>
<td>10 P.M.</td>
<td>Time†</td>
<td>8 A.M.</td>
<td>10 P.M.</td>
<td>8 A.M.</td>
</tr>
<tr>
<td>1</td>
<td>6600</td>
<td>—</td>
<td>1 yr</td>
<td>5300</td>
<td>—</td>
<td>16.5</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 3000</td>
<td>—</td>
<td>7 yrs</td>
<td>1200</td>
<td>—</td>
<td>4.8</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 4000</td>
<td>3250</td>
<td>1 mo</td>
<td>1850</td>
<td>1687</td>
<td>11.8</td>
</tr>
<tr>
<td>4</td>
<td>2500</td>
<td>2500</td>
<td>3 yrs</td>
<td>465</td>
<td>300</td>
<td>14.1</td>
</tr>
<tr>
<td>5</td>
<td>&gt; 3000</td>
<td>2050</td>
<td>1 yr</td>
<td>1333</td>
<td>&gt; 1333</td>
<td>12.0</td>
</tr>
<tr>
<td>6</td>
<td>2000</td>
<td>8000</td>
<td>15 mos</td>
<td>1500</td>
<td>19.7</td>
<td>33.3</td>
</tr>
<tr>
<td>7</td>
<td>6000</td>
<td>3500</td>
<td>10 days</td>
<td>125</td>
<td>215</td>
<td>6.1</td>
</tr>
<tr>
<td>8</td>
<td>2000</td>
<td>2000</td>
<td>2 yrs</td>
<td>420</td>
<td>420</td>
<td>12.1</td>
</tr>
<tr>
<td>9</td>
<td>&gt; 2000</td>
<td>&gt; 2000</td>
<td>5 mos</td>
<td>375</td>
<td>16.8</td>
<td>16.3</td>
</tr>
<tr>
<td>10</td>
<td>2000</td>
<td>2000</td>
<td>6 mos</td>
<td>500</td>
<td>700</td>
<td>31.1</td>
</tr>
</tbody>
</table>

* Cortisol and prolactin estimations before and after neurosurgery were performed concomitantly with adrenocorticotropic hormone (ACTH) measurements.
† Time indicates the interval between neurosurgery and endocrine measurements.
‡ Assays performed before and after the second operation.

The original description defined Nelson's syndrome as a pituitary tumor with progressive cutaneous melanosis occurring after bilateral adrenalectomy for Cushing's disease. Some authors require only hyperpigmentation for the diagnosis; however, this sign may be due to inadequate replacement therapy and is not considered to be a sufficient indication for neurosurgical treatment. In the past 20 years, the treatment for Nelson's syndrome has been surgery of large tumors that enlarge further and destroy the sella turcica.

The recent diagnosis of ACTH-producing adenomas by hormone analysis allows these tumors to be treated at an earlier stage. In four of our patients (Cases 7 to 10), microadenomas, ranging in diameter from 4 to 10 mm, were found during the operation. The size of these tumors did not depend on the duration of clinical signs, as the patient with the smallest lesion (Case 9) had suffered hyperpigmentation and visual disturbances for a period of 6 years. This patient had undergone bilateral adrenalectomy 15 years before. This was the longest time of observation in this group, 4 months longer than in Case 8.

In eight of our patients, the results of neurosurgery were good. In Case 10, with very recent surgery, the time of the observation was too short to make possible an unequivocal judgment as to the outcome; however, as the first spectacular sign of remission, cutaneous melanosis decreased within 72 hours postoperatively. In two patients with recurrent pituitary neoplasm, the hyperpigmentation reappeared within 1 to 1½ years after surgery.

Before the operation, high plasma ACTH concentrations were found which decreased following treatment in all of the patients but one. However, the morning ACTH levels were higher than the evening ones, probably due to cortisol deficiency depending on an overnight interval in cortisone therapy. The dose of cortisone given about an hour before the blood samples were taken for hormonal measurements was probably not sufficient to suppress ACTH hypersecretion. Low serum cortisol levels at 8 a.m. supported this supposition. It would be very important to prevent hypercortisolism in Nelson's syndrome because it may be that insufficient feedback inhibition could stimulate not only ACTH hypersecretion but also tumor growth. Elevated ACTH levels following neurosurgery for Nelson's syndrome have been observed in some patients by other authors. However, in the series of Lüdecke, et al., a reduction in plasma ACTH concentrations was observed, especially in the group of intrasellar adenomas.

5.5 to 23.5 µU/ml prior to treatment and from 5.0 to 26.0 µU/ml postoperatively. Serum TSH concentrations ranged from 1.4 to 3.2 µU/ml before and from 2.0 to 4.0 µU/ml after the operation. Serum GH levels were 1.0 to 4.0 µg/liter before and 1.2 to 3.3 µg/liter after treatment. Only in one patient (Case 3) was the serum thyroxine level (45 nmol/liter) below the lowest normal limit before the operation.

Discussion

The original description defined Nelson's syndrome as a pituitary tumor with progressive cutaneous melanosis occurring after bilateral adrenalectomy for Cushing's disease. Some authors require only hyperpigmentation for the diagnosis; however, this sign may be due to inadequate replacement therapy and is not considered to be a sufficient indication for neurosurgical treatment. In the past 20 years, the treatment for Nelson's syndrome has been surgery of large tumors that enlarge further and destroy the sella turcica.

The recent diagnosis of ACTH-producing adenomas by hormone analysis allows these tumors to be treated at an earlier stage. In four of our patients (Cases 7 to 10), microadenomas, ranging in diameter from 4 to 10 mm, were found during the operation. The size of these tumors did not depend on the duration of clinical signs, as the patient with the smallest lesion (Case 9) had suffered hyperpigmentation and visual disturbances for a period of 6 years. This patient had undergone bilateral adrenalectomy 15 years before. This was the longest time of observation in this group, 4 months longer than in Case 8.

In eight of our patients, the results of neurosurgery were good. In Case 10, with very recent surgery, the time of the observation was too short to make possible an unequivocal judgment as to the outcome; however, as the first spectacular sign of remission, cutaneous melanosis decreased within 72 hours postoperatively. In two patients with recurrent pituitary neoplasm, the hyperpigmentation reappeared within 1 to 1½ years after surgery.

Before the operation, high plasma ACTH concentrations were found which decreased following treatment in all of the patients but one. However, the morning ACTH levels were higher than the evening ones, probably due to cortisol deficiency depending on an overnight interval in cortisone therapy. The dose of cortisone given about an hour before the blood samples were taken for hormonal measurements was probably not sufficient to suppress ACTH hypersecretion. Low serum cortisol levels at 8 a.m. supported this supposition. It would be very important to prevent hypercortisolism in Nelson's syndrome because it may be that insufficient feedback inhibition could stimulate not only ACTH hypersecretion but also tumor growth. Elevated ACTH levels following neurosurgery for Nelson's syndrome have been observed in some patients by other authors. However, in the series of Lüdecke, et al., a reduction in plasma ACTH concentrations was observed, especially in the group of intrasellar adenomas.
Surgical treatment of Nelson’s syndrome

In five patients, hyperprolactinemia was found preoperatively, probably due to β-endorphin hypersecretion. It is noteworthy that the secretion of other pituitary hormones was not disturbed significantly before or after the operation.

A very interesting finding was the presence of argyrophilic nerve fibers in the adenoma tissue in Case 10. This was found first by Lamberts, et al., in patients operated on for active Cushing’s disease. The authors suggested that these adenomas originated from the pars intermedia. Our experience shows that this kind of pituitary adenoma may exist in Nelson’s syndrome.

Transsphenoidal neurosurgery appears to be the method of choice in the treatment of Nelson’s syndrome. In small intrasellar adenomas, selective tumor excision is preferred. The recurrence of pituitary adenomas after the operation in two patients in our series led us to consider adjunctive postoperative radiation therapy in Nelson’s syndrome, especially in patients with anaplastic tumors. Radiation therapy following neurosurgical treatment of Nelson’s syndrome, especially in large tumors, is also recommended by Lüdecke, et al. An alternative method could probably be treatment with sodium valproate; however, a long-term study would be necessary to evaluate the results of this pharmacotherapy.

References


Manuscript received May 4, 1984. This work was supported by Grants PR-VI and RM2-VII/9.

Address for Dr. Kasperlik-Załużska: Department of Endocrinology, Center of Postgraduate Medical Education, 01-809 Warsaw, Ceglowska 80, Poland.

Address reprint requests to: Jerzy Wisławski, M.D., Department of Neurosurgery, Academy of Medicine, 02-097 Warsaw, Banacha 1, Poland.