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AAACE Clinical Case Reports

journal homepage: www.aaaceclinicalcasereports.com



Case Report

Nelson Syndrome: A Case Report and Literature Review

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ARTICLE INFO

Article history:

Available online 27 November 2020

Key words:

Nelson syndrome
ACTH
bilateral adrenalectomy
Cushing disease

ABSTRACT

Objective: Nelson syndrome (NS) is a rare clinical disorder that can occur after total bilateral adrenalectomy (TBA), performed as a treatment for Cushing disease. NS is defined as the accelerated growth of an adrenocorticotrophic hormone-producing pituitary adenoma. Our objective is to describe a case of NS and discuss it based on existing knowledge of this syndrome.

Methods: We describe the case of a woman diagnosed with NS at our facility in the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran and review published cases of NS.

Results: The patient, a 35-year-old woman with Cushing disease, had been diagnosed in 2006 at the endocrinology department in the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran. In 2007, a laparoscopic TBA was performed, and 2 years later, she presented with hyperpigmentation and adrenocorticotrophic hormone levels of up to 11 846 pg/mL. NS was suspected, and as magnetic resonance imaging showed macroadenoma, transsphenoidal surgery was performed. The patient remained asymptomatic until 2012, when she presented with a right hemicranial headache, photophobia, and phonophobia. A fresh magnetic resonance imaging was performed, which documented tumor growth. She was referred to the Instituto Nacional de Neurologia y Neurocirugia, where she underwent surgery. **Conclusion:** NS develops as a complication of TBA, which is used as a treatment of Cushing disease. The main treatment is surgery and radiotherapy.

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Introduction

Nelson syndrome (NS) is a rare clinical disorder first described by Dr. Don Nelson in 1958 and then in 1960 as a case series. NS may occur after total bilateral adrenalectomy (TBA), which is performed to treat Cushing disease. It has an incidence that ranges from 8% to 47% in patients who do not undergo pituitary radiation. Interestingly, it may appear up to 24 years after TBA.¹

After TBA, it is recommended that serum ACTH concentrations be measured 3 months after the surgery and then every 6 months for the first 2 years.² We can suspect the development of NS if serum ACTH concentration is found to be above 500 ng/L at any time during follow-up. Subsequently, magnetic resonance imaging (MRI) is recommended to identify the growing pituitary tumor. Despite early diagnosis, NS is characterized by poor treatment response and high recurrence of tumor growth.

Case Report

A 35-year-old woman from Zacapoaxtla, Puebla, Mexico, presented with the following symptoms after her third pregnancy in 2003: irritability, insomnia, polyuria, polydipsia, polyphagia, increased abdominal perimeter, skin hyperpigmentation, moon facies, and violaceous striae on the abdomen, thighs, and arms.

Abbreviations: ACTH, adrenocorticotrophic hormone; MRI, magnetic resonance imaging; NS, Nelson syndrome; TBA, total bilateral adrenalectomy; UFC, urinary free cortisol.

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<https://doi.org/10.1016/j.aaace.2020.11.034>

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Table 1
Initial Laboratory Test Results (November 2006)

Laboratory test	Results	Normal parameters
Cortisol (µg/dL)	49.39	8.7–22.4
ACTH (pg/mL)	49	10–100
CT3 (nmol/L)	0.38	0.32–0.48
T3 (nmol/L)	0.72	1.34–2.73
T4 (nmol/L)	48.34	78.38–157.40
TSH (nmol/L)	0.48	0.34–5.60
TG (ng/mL)	2.35	0.0–35.0
Glucose (mg/mL)	215	65–100
HbA1C (5)	9.3	<5.7
LH (mIU/mL)	0.51	1.8–8.6
FSH (mIU/mL)	5.25	0.3–10
Prolactin (ng/mL)	12.3	<25

Liddle's test			
Day	AM (8 am) µg/dL	PM (4 pm) (µg/dL)	Urine (µg/d)
1	39.12	26.42	2735.1
2	37.85	31.46	1711.5
3	34.74	26.12	
4	32.86	19.16	1106.6
5	38.80	15.72	1216.0
6	23.71	14.48	802.1
7	37.67		

Abbreviations: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; HbA1C = glycosylated hemoglobin; LH = luteinizing hormone; CT3 = T3 resin uptake test; T3 = triiodothyronine; T4 = tetraiodothyronine; TSH = thyroid-stimulating hormone; TG = thyroglobulin.

Laboratory results from the patient's cortisol determination in a 24-hour collection, showing over 50% reduction. This can be understood as a pituitary ACTH-producing adenoma due to negative feedback after dexamethasone administration.

Blood pressure was high at 140/100 mm Hg. After evaluation, she was diagnosed with eclampsia and was prescribed multiple anti-hypertensive regimens; however, they elicited only a poor response.

Three years after the initial diagnosis (2006), the patient continued to have uncontrolled high blood pressure, violaceous striae on the abdomen as well as on the inner side of thighs and arms, dermatosis on both hands, papules, erythema, and residual spots on her feet that were compatible with mycosis, and Cushing syndrome was suspected based on these symptoms. The patient was admitted to our endocrinology department for further evaluation. Initial blood tests showed a serum ACTH concentration of 49 pg/mL with elevated cortisol (49.39 µg/dL), decreased serum thyroxine and triiodothyronine, and inappropriately normal thyroid-stimulating hormone (Table 1).

For diagnosis and determination of the origin of the hypercortisolism, it was decided to hospitalize the patient for a dynamic 7-day sequential low- to high-dose dexamethasone suppression test (Liddle's test). Our patient had a baseline mean serum cortisol concentration of 37.71 µg/dL and urinary free cortisol (UFC) of 2223.25 µg/day. After 2 days of low-dose dexamethasone, UFC was 1106.6 µg/day, demonstrating no suppression. The administration of high-dose dexamethasone reduced serum cortisol concentration to 14.48 µg/dL (61.6% reduction) while UFC reduced to 802.1 µg/day (63.9% reduction), thus confirming a diagnosis of Cushing disease and pituitary ACTH-producing adenoma due to negative feedback after high-dose dexamethasone administration.^{3–5} Further evaluation of serum follicle-stimulating hormone and prolactin concentration demonstrated values within normal parameters; luteinizing hormone values were low (Table 1).

In November 2006, an MRI was obtained, which showed homogeneous and intense reinforcement of the pituitary gland after contrast administration (Fig. 1 A). Due to the impossibility of performing a petrosal sinus catheterization, the patient was initially treated with levothyroxine 75 µg/day, ketoconazole 400 mg/day, enalapril 40 mg/day, metoprolol 300 mg/day, and rosuvastatin 10 mg/day. Further, as the patient had altered glucose metabolism, metformin 1500 mg/day and glyburide 7.5 mg/day were also

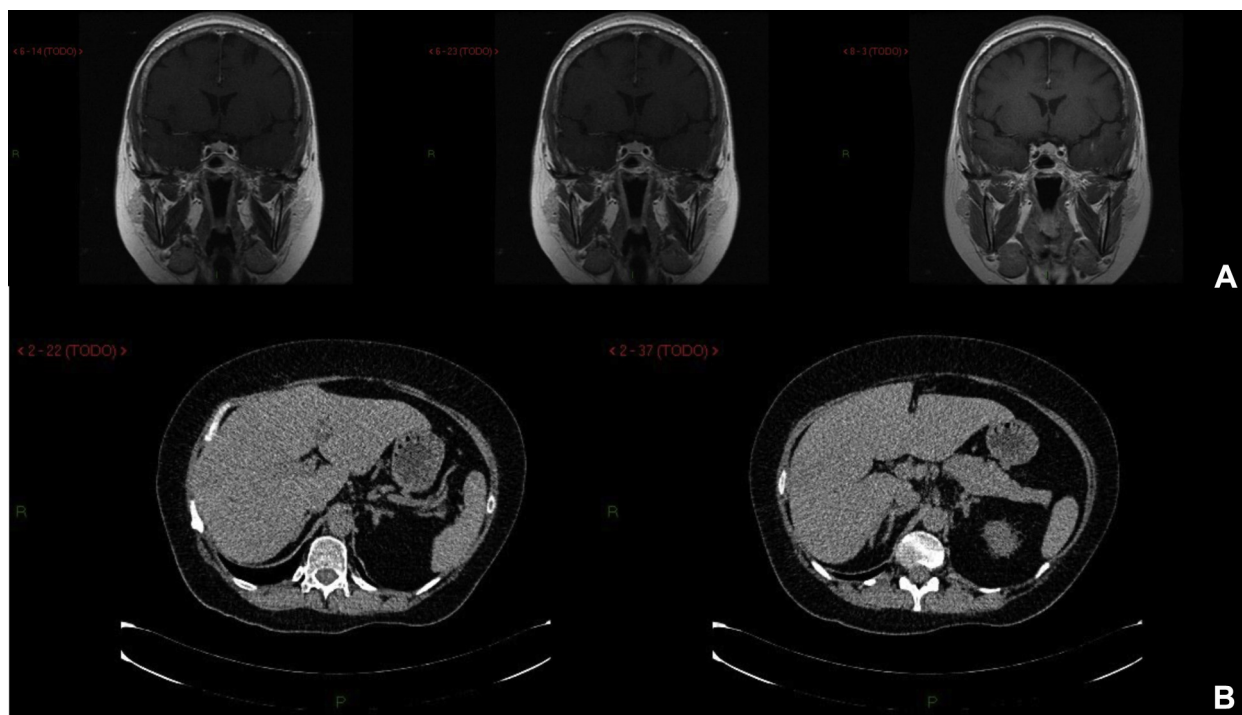


Fig. 1. A) Magnetic resonance imaging from 2006 showing a homogeneous pituitary gland, without intra- or extra-glandular lesion; homogeneous and intense reinforcement after administration of contrast material. B) Abdominal computed tomography from 2006. After TBA, the department of pathology reported a right adrenal gland with dimensions of 6 × 3 × 1 cm and a weight of 9.3 g, and a left adrenal gland with dimensions of 6.7 × 2 × 1.7 cm and a weight of 8 g.

Table 2
ACTH Evolution From 2006 To 2012

Date	ACTH serum concentration (pg/mL)
11/2006	49
01/2007	88
04/2007	70
08/2007	210
09/2007	325
05/2010	11 846
06/2010	15 250
06/2012	1383

Adrenocorticotrophic hormone (ACTH) serum concentration showing increasing values from the patient's admission to our institute in 2006 to 2010 when transsphenoidal surgery was performed. Higher values were seen again in 2012.

prescribed. Abdominal computed tomography was performed 1 month later and showed nephrolithiasis in the right kidney and a slight increase in the dimensions of the left adrenal gland (Fig. 1 B). A laparoscopic TBA was scheduled and performed on January 30, 2007. The pathology report identified an adenoma of the right suprarenal cortex and adenomatous hyperplasia in the left adrenal gland.

In August 2007, the patient presented with an 18-week pregnancy. Routine laboratory study results were normal. After her pregnancy, due to financial reasons, she was unable to continue follow-up treatments.

It was not until August 2009 that the patient returned to the hospital due to the presence of hyperpigmentation. Serum ACTH concentration was elevated and was suggestive of NS (Table 2). Another MRI was obtained, which revealed pituitary macroadenoma (Fig. 2 A). Transsphenoidal surgery was performed in December 2010, with no reported complications. A follow-up MRI at 6 months after surgery showed a decrease in the dimensions of the intraglandular lesion (Fig. 2 B).

In October 2012, she was admitted to the emergency department of our institute due to a hemicranial headache, photophobia, and phonophobia. She was treated with nonsteroidal anti-inflammatory drugs, which were only partially effective. Three days later, she developed diplopia, and 1 month later, she presented with right cranial nerve VI palsy. An MRI showed growth of the pituitary adenoma with compression of the right cranial nerve VI and the optic chiasm on its left side (Fig. 2 C). Her last known ACTH concentration was 1383 pg/mL, and subsequently, the patient was referred to Instituto Nacional de Neurología y Neurocirugía, where she underwent surgery in July 2012.

Discussion

Our patient was diagnosed with NS, which is a rare clinical manifestation that occurs in 8% to 47% of patients who undergo a TBA. TBA is a procedure used to control hypercortisolism in Cushing disease when resection of the primary tumor is not possible.¹ The pathophysiology of NS and the factors that influence its development and progression have not yet been fully identified. One hypothesis is that after TBA, a drop in previously elevated cortisol levels results in reduced negative feedback on the corticotrophs and restoration of hypothalamic corticotropin-releasing hormone production.

Clinical features of this syndrome include local compression by the tumor (visual defects in 10% to 57% or cranial nerve palsies), hyperpigmentation (42%), corticotroph metastases, headache, pituitary apoplexy, diabetes insipidus, panhypopituitarism, testicular pain or oligospermia, and paraovarian or paratesticular tumors.²

Given that 20% of pituitary tumors in NS develop in the first year and 35% in the first 2 years, some authors recommend performing an MRI at 3 months after TBA, while others recommend it every 6 months during the first 2 years and once a year thereafter.²

Surgery should be the first therapeutic option, particularly if there is compression of the nerves that control ocular function. The success of surgery ranges from 10% to 70%, and the initial approach should be transsphenoidal; however, a transcranial approach can be used if there is extrasellar extension, as seen in 33% of the cases. Surgical mortality in patients with NS is 5%, and panhypopituitarism presents in 69% of cases. Other surgical complications include cranial nerve palsy (5%), cerebrospinal fluid leak (15%), and meningitis (8%).² Radiation therapy represents another treatment option. Given the historically low rates of resolution after surgical intervention alone and the fact that progression of NS may occur in 20% to 30% of the patients, radiation therapy is often used to prevent tumor enlargement, reduce plasma ACTH levels, and control hyperpigmentation.⁶ Radiation therapy includes fractionated external beam radiotherapy or stereotactic radiosurgery, and both achieve control of hypercortisolism in approximately 50% to 60% of patients within 3 to 5 years. However, optimal radiotherapy for these patients has not yet been determined, and it remains to be elucidated whether stereotactic radiosurgery could result in more rapid biochemical control than conventional radiation.⁷

In a follow-up study of 15 patients treated with adjuvant radiotherapy, 93% showed a reduction in hyperpigmentation. Even

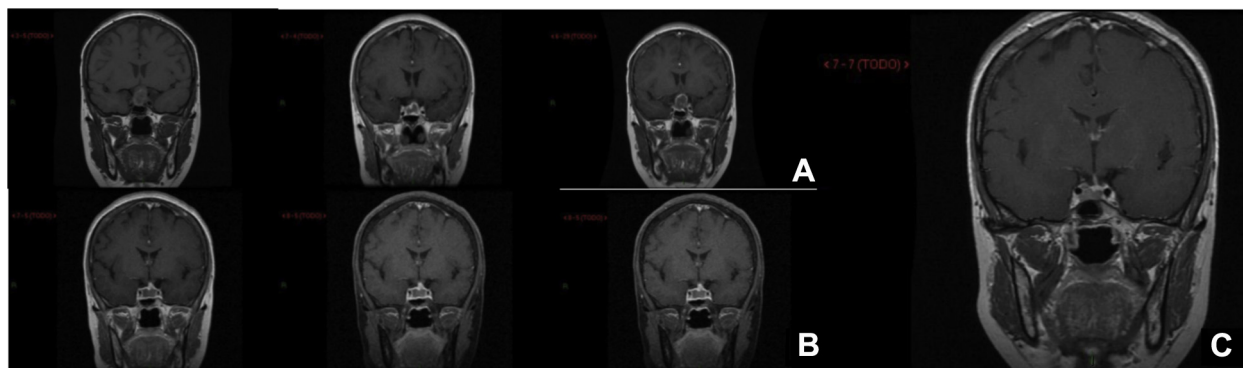


Fig. 2. A) Magnetic resonance imaging from 2010 showing an extra axial and intraglandular lesion measuring $20 \times 17 \times 13$ mm with heterogeneous signal and areas of necrosis inside, as well as with hemosiderin or calcium deposits. The lesion is in contact with the cavernous sinuses and displaces the optic chiasm as well. B) Follow-up magnetic resonance imaging shows a decrease in the dimensions of the intraglandular lesion at 6 months after surgery: $6 \times 12 \times 11$ mm (396 mm^3) at the dorsal-ventral, lateral, and caudal faces. C) Magnetic resonance imaging from 2012. Tumor had grown and was measured as $15 \times 11 \times 16$ mm (1320 mm^3). The image suggested compression of the right cranial nerve VI, as well as displacement of the optic chiasm on the left side.

though current evidence regarding adjuvant radiotherapy in patients undergoing TBA is limited, this treatment seems to be reasonable in patients with remnants of corticotropic tissue. Moreover, in patients with residual Cushing disease, radiosurgery can be performed.^{7,8}

Treatment by radiosurgery offers a variety of procedures that result in effective management rates of up to 70%, as measured by reduction in ACTH levels, and up to 90% control of tumor growth. Further, over a period of some years, it can lead to cessation of hypersecretion.⁶ With radiosurgery for NS, a 21.6% incidence of panhypopituitarism (up to 7 years later) has been reported. Prior radiation for treatment of Cushing disease will shorten the time-to-presentation of hypopituitarism. New visual problems and cranial nerve palsy are important complications following radiotherapy, and it cannot be used in tumors located adjacent to the optic nerves, or in tumors that invade the cavernous sinus.^{6,8,9} Radiation is an option for the treatment of NS if surgical treatment fails to control the disease.⁹ Medical treatment is limited, but some results have been obtained with somatostatin-analogs (octreotide and pasireotide), dopamine agonists (bromocriptine and cabergoline), sodium valproate, and temozolomide.⁹

Conclusion

We present the case of a patient with Nelson syndrome, who unfortunately suffered 2 recurrences. It is important to offer our patients timely radiotherapy to prevent NS complications because sometimes, many of the tumors do not develop clinically meaningful symptoms or have a slow growth pattern of less than 5 mm per year. Further, it is recommended to measure serum ACTH concentration 3 months after the surgery and then every 6 months for the first 2 years after TBA.

Acknowledgment

This study was funded by the department of Endocrinology and Metabolism of the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran.

Disclosure

The authors have no multiplicity of interest to disclose.

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