WebLog Journal of Endocrinology and Diabetes

Case Series
Published: 24 Dec, 2025

Nelson's Syndrome: About 3 Cases

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WebLog Open Access Publications
Article ID : wjed.2025.I2402
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Abstract

Nelson's syndrome is a severe complication that may develop in patients with Cushing's disease treated with bilateral adrenalectomy. Since pituitary tumors in Nelson's syndrome are often aggressive, early diagnosis and careful management are essential. We report three cases illustrating this syndrome.

Keywords: Nelson's Syndrome; Pituitary Adenoma; Corticotroph Tumor; Adrenocorticotropic Hormone (ACTH); Bilateral Adrenalectomy; Cushing's Disease; Hyperpigmentation

Case 1

A 32-year-old woman, followed in our department since age 26 for Cushing's disease (Figure 1), underwent two surgical interventions: the first via a subfrontal approach and the second via a transsphenoidal route. A rescue bilateral adrenalectomy was then performed due to persistent deep hypokalemia, despite a normal hypothalamic–pituitary MRI.

Two years after adrenalectomy, she developed features consistent with Nelson's syndrome, including generalized hyperpigmentation (Figure 2) and elevated ACTH levels. MRI revealed a left-lateralized intra- and suprasellar adenoma measuring 11 × 13 × 20 mm (Figure 3).

Superiorly, it displaced the optic chiasm; laterally, it encased the intracavernous left internal carotid artery for less than 180°; inferiorly, it bulged into the left sphenoid hemisinus.

Transsphenoidal excision was recommended but refused by the patient. Gamma knife radiosurgery was proposed but not performed due to financial reasons. She has been under clinical and radiological surveillance for two years with stable findings.

Superiorly: displacing the optic chiasm; laterally: encasing the intracavernous left internal carotid artery for less than 180°; inferiorly: bulging into the left sphenoid hemisinus.

Case 2

A 23-year-old woman, followed since age 18 for Cushing's disease—characterized by ACTH-dependent hypercortisolism with a positive high-dose dexamethasone suppression test and a normal pituitary MRI (Figure 4)—was initially treated medically with mitotane (OP'DDD). Due to treatment failure (persistent hypercortisolism and complications), a bilateral adrenalectomy was performed.

Seven years later, she developed Nelson's syndrome with hyperpigmentation, elevated ACTH levels, and a 7 mm left-lateralized microadenoma. Transsphenoidal surgery was advised but initially refused. Tumor progression (18 mm at 12 months, then 20 mm at 18 months) led the patient to

Figure 1: Patient before bilateral adrenalectomy.

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Received Date: *12 Dec 2025*
Accepted Date: *22 Dec 2025*
Published Date: *24 Dec 2025*

Citation:
Gorgi K, Chaouche M. Nelson's Syndrome: About 3 Cases. WebLog J Endocrinol Diabetes. wjed.2025.I2402. https://doi.org/10.5281/zenodo.18058857

Figure 2: Clinical appearance of the patient with hyperpigmentation after bilateral adrenalectomy.

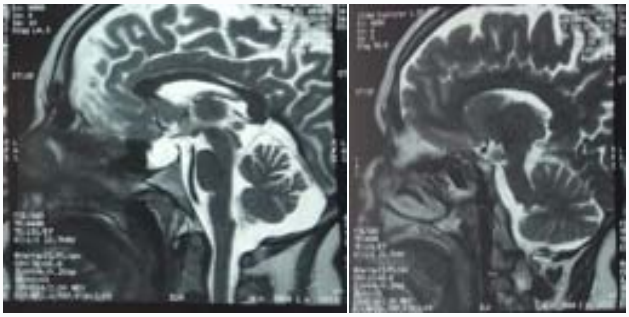

Figure 3: Pituitary MRI showing a left-lateralized intra- and suprasellar adenoma measuring 11 × 13 × 20 mm, with deviation of the pituitary stalk.

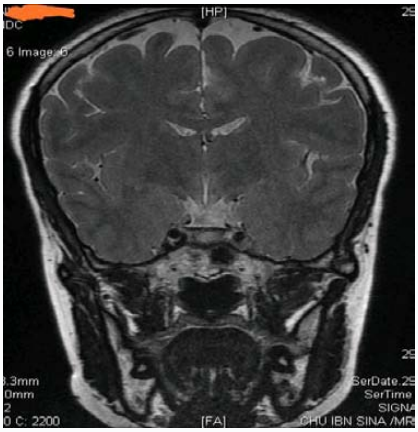

Figure 4: Pituitary MRI showing the pituitary adenoma.

accept surgery. She underwent a successful transsphenoidal excision with good clinical and biochemical evolution.

Case 3

A 33-year-old woman, followed since age 16 for Cushing's disease based on clinical signs of hypercortisolism with hyperpigmentation, a positive high-dose dexamethasone suppression test, and elevated ACTH, underwent transsphenoidal adenoma resection. Persistent hypercortisolism and cardiovascular complications prompted bilateral adrenalectomy.

Eight years later, she presented with generalized hyperpigmentation, elevated ACTH levels, and a 13 × 10 mm pituitary adenoma on MRI. She underwent adenoma resection combined with radiotherapy, which was complicated by panhypopituitarism.

Table 1: Diagnostic criteria for Nelson's syndrome according to expert recommendations [1].

Primary (mandatory) criteria	Secondary criteria (optional)
• New appearance of a pituitary adenoma on MRI, **or** • Radiological evidence of corticotroph tumor progression	• Clinical hyperpigmentation after adrenalectomy • Progressive rise in plasma ACTH levels after adrenalectomy

Discussion

Nelson's syndrome is a rare endocrine condition diagnosed by the presence of hyperpigmentation, elevated ACTH, and a pituitary adenoma (micro- or macroadenoma) on MRI after bilateral adrenalectomy for Cushing's disease.

Given advances in imaging, tumors may be detected earlier, before clinical symptoms appear. A recent expert consensus recommended that radiological evidence of corticotroph tumor progression or the new detection of a visible pituitary tumor be considered the **primary diagnostic criterion** (Table 1) [1].

Nelson et al. described the first case in 1958 in a 33-year-old woman who developed an ACTH-secreting pituitary tumor after bilateral adrenalectomy [2, 3].

The pathophysiology remains unclear. One hypothesis suggests that the loss of cortisol after adrenalectomy removes negative feedback on the hypothalamus, leading to CRH-driven stimulatory overactivation of corticotroph cells and subsequent tumor growth [1]. Another hypothesis supports the progression of pre-existing corticotroph tumor cells responsible for the original Cushing's disease.

Bilateral adrenalectomy is generally reserved for patients with severe or refractory hypercortisolism because of the risks associated with the procedure, including Nelson's syndrome [4].

After adrenalectomy, ACTH levels should be measured three months postoperatively, then every six months for two years. Some authors recommend pituitary MRI at three months, while others suggest every six months for two years, then annually [5].

Predictive factors for tumor aggressiveness after adrenalectomy include young age at diagnosis, visible residual tumor on imaging, cytological markers of aggressiveness (Ki-67 > 3%, mitoses, nuclear PTTG expression), and a marked rise in ACTH levels shortly after surgery [6].

In our three cases, several predictive factors were present: young age (mean age 16 years at initial diagnosis), abrupt elevation of ACTH after adrenalectomy, and residual tumor on imaging.

The first-line treatment of Nelson's syndrome is pituitary surgery, particularly in the presence of mass effect. Transsphenoidal endoscopic surgery is preferred, with success rates ranging from 10% to 70% [5].

A transcranial approach may be required for extensive extrasellar tumors, as in Case 1. Surgical complications include mortality (5%), panhypopituitarism (69%), cranial nerve palsy (5%), CSF leak (15%), and meningitis (8%) [5].

Remission is defined as ACTH levels < 200 pg/mL two hours after morning hydrocortisone dosing [1].

Radiotherapy (fractionated or stereotactic radiosurgery) is an alternative for residual or progressive tumors. Both modalities control hypercorticotropism in approximately 50–60% of patients within 3–5 years [1]. Panhypopituitarism is a late complication, occurring in up to 21.6%, as seen in Case 3 [7].

Prophylactic radiotherapy at the time of adrenalectomy has been proposed, but evidence remains inconsistent [8].

Medical therapy is used for invasive or unresectable tumors or while awaiting radiotherapy effects. Somatostatin analogues show limited efficacy, although pasireotide appears more effective than octreotide. Dopamine agonists (bromocriptine, cabergoline) remain therapeutic options [9].

Conclusion

Nelson's syndrome is a rare endocrine complication appearing after bilateral adrenalectomy for Cushing's disease. Diagnostic and therapeutic challenges persist, emphasizing the importance of long-term follow-up. The three cases presented highlight the need for vigilant monitoring and multidisciplinary management.

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