Nelson's syndrome: a review of the clinical manifestations, pathophysiology, and treatment strategies

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Nelson's syndrome is a rare clinical manifestation that occurs in 8%–47% of patients as a complication of bilateral adrenalectomy, a procedure that is used to control hypercortisolism in patients with Cushing's disease. First described in 1958 by Dr. Don Nelson, the disease has since become associated with a clinical triad of hyperpigmentation, excessive adrenocorticotropin secretion, and a corticotroph adenoma. Even so, for the past several years the diagnostic criteria and management of Nelson's syndrome have been inadequately studied. The primary treatment for Nelson's syndrome is transsphenoidal surgery. Other stand-alone therapies, which in many cases have been used as adjuvant treatments with surgery, include radiotherapy, radiosurgery, and pharmacotherapy. Prophylactic radiotherapy at the time of bilateral adrenalectomy can prevent Nelson's syndrome (protective effect). The most promising pharmacological agents are temozolomide, octreotide, and pasireotide, but these agents are often administered after transsphenoidal surgery. In murine models, rosiglitazone has shown some efficacy, but these results have not yet been found in human studies. In this article, the authors review the clinical manifestations, pathophysiology, diagnostic criteria, and efficacy of multimodal treatment strategies for Nelson's syndrome.

<http://thejns.org/doi/abs/10.3171/2014.10.FOCUS14681>

KEY WORDS Nelson's syndrome; Cushing's disease; ACTH; pituitary adenoma

THE primary treatment for Cushing's disease is transsphenoidal adenomectomy,^{12,22,76} remission rates are 70%–90%.^{6,12,72,79} In a meta-analysis of 50 studies performed by Roelfsema et al., biochemical remission was found for 4207 (72.7%) of 5787 patients who had undergone a single surgical procedure.⁷² However, refractory hypercortisolemia from persistent or recurrent Cushing's disease remains a therapeutic challenge.⁶⁵ Treatment options for Cushing's disease after unsuccessful transsphenoidal surgery include repeat transsphenoidal surgery, radiation therapy, medical therapy, and bilateral adrenalectomy.^{13,38,47} Bilateral adrenalectomy represents a safe and effective definitive procedure for patients who need immediate treatment for hypercortisolemia or who have been unresponsive to multiple therapies for refractory Cushing's disease.^{45,47}

In 1958, Dr. Don Nelson et al. reported a case in which a 33-year-old woman, who had undergone bilateral adrenalectomy for Cushing's disease 3 years earlier, experi-

enced skin hyperpigmentation, high plasma levels of adrenocorticotrophic hormone (ACTH), and ultimately a pituitary tumor.⁵⁹ By the 1960s, Nelson and other colleagues found that after bilateral adrenalectomy, ACTH-producing pituitary tumors appeared in several patients, thus leading to increased levels of ACTH and hyperpigmentation. Hence, these 3 symptoms have since become the clinical triad of Nelson's syndrome.^{60,61} Since its initial description in 1958,⁵⁹ Nelson's syndrome has caused concern for physicians treating refractory Cushing's disease with bilateral adrenalectomy. Although Nelson's syndrome is rare, therapies have varied. With the advancements in neuroimaging and endocrinology, Nelson's syndrome can be detected very early in its course. Treatment options include observation, surgery, radiation therapy, and pharmacotherapy. We review the clinical manifestations, pathophysiology, and incidence of Nelson's syndrome; delineate diagnostic methods; and outline the various treatment modalities that have been used to alleviate symptoms.

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; FSRT = fractionated stereotactic radiotherapy; GK = Gamma Knife; SRS = stereotactic radiosurgery; sst = somatostatin receptor.

SUBMITTED October 2, 2014. **ACCEPTED** October 30, 2014.

INCLUDE WHEN CITING DOI: 10.3171/2014.10.FOCUS14681.

DISCLOSURE The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Diagnosis and Clinical Features

After a patient undergoes bilateral adrenalectomy for Cushing's disease, the chance of Nelson's syndrome development ranges from 8% through 47%.^{2,4,8,19,31,34,38,47,51} The presentation of Nelson's syndrome is variable and depends on the extent of adrenalectomy, length between surgery and presentation, and the source of hypercortisolemia (potentially ectopic sources).³¹ When radiation therapy is used to treat an ACTH-secreting pituitary tumor after Nelson's syndrome has developed, it is considered as a therapeutic measure for Nelson's syndrome. However, when pituitary radiation therapy is undertaken before or immediately after bilateral adrenalectomy but before Nelson's syndrome has developed, it is considered a prophylactic measure that can potentially prevent the development of Nelson's syndrome.^{21,25,33,39} The signs and symptoms used to diagnose Nelson's syndrome are elevated plasma ACTH levels, hyperpigmentation, and tumor progression (Figs. 1–3). These tumors are capable of invading the cavernous sinus and compressing cranial nerves and optic pathways. In a recent case, bilateral oculomotor palsy was present in a patient with Nelson's syndrome.²³

Pathophysiology

Cortisol is a steroid hormone produced in the zona fasciculata of the adrenal cortex. In normal physiological systems, it provides negative feedback on the release of corticotropin-releasing hormone produced by the hypothalamus. Bilateral adrenalectomy is meant to curb hypercortisolemia in patients with Cushing's disease, thus releasing the system from the negative-feedback loop. Along the same line, without negative feedback, it is hypothesized that corticotropin-releasing hormone levels increase, leading to increased production of proopiomelanocortin and its subsequent products ACTH and melanocyte-stimulating hormone. In a study of pituitary tissue from patients with Nelson's syndrome, the tumor was monoclonal

FIG. 1. Photograph of 51-year-old woman with Nelson's syndrome (on right), taken 15 years after undergoing bilateral adrenalectomy for Cushing's disease. Hyperpigmentation of her skin was very noticeable, as distinguished from the lighter skin of her daughter (on left).

FIG. 2. Preoperative post-Gd MR images (sagittal [A] and coronal [B]) of the patient in Fig. 1, showing an ACTH-secreting pituitary macroadenoma with optic chiasm compression. Postoperative postgadolinium MR images (sagittal [C] and coronal [D]) after endoscopic endonasal transsphenoidal resection. A small remnant can be seen at the base of the pituitary stalk. Plasma ACTH dropped from over 2000 pg/ml to 418 pg/ml. The residual tumor was further treated with SRS.

and proopiomelanocortin mRNA and gene products were unaltered.^{2,14,20,29,69} In murine models, adrenalectomy led to increased corticotroph cell numbers, corticotroph cell hyperplasia, increased expression of arginine vasopressin, and increased levels of corticotropin-releasing hormone and proopiomelanocortin-derived gene products.^{10,52,89} In a previous work, ACTH-secreting pituitary tumors were shown to overexpress vasopressin V3 and corticotropin-releasing hormone receptor genes; this finding is crucial because it was previously shown that both arginine vasopressin and corticotropin-releasing hormone induce proliferation in a corticotrophic tumor cell line.^{15,82} Also with regard to negative feedback, in the aforementioned in vitro model, proliferation of the tumor cell line was significantly inhibited by cortisol, and ACTH secretion by the tumor cell line was increased after incubation with corticotropin-releasing hormone but not with arginine vasopressin.⁸² In a separate in vitro study, cortisol suppressed RNA and DNA synthesis in ACTH-secreting human pituitary tumor cell lines, which also confirms the negative-feedback loop.⁷¹ Of note, somatostatin-14 and somatostatin-28 suppressed secretion of proopiomelanocortin-derived peptides from a pituitary adenoma causing Nelson's syndrome, but arginine vasopressin, vasoactive intestinal peptide, and oxytocin stimulated secretion of proopiomelanocortin-derived peptides.⁷⁴ In patients with Nelson's syndrome, continuous infusion of synthetic ovine corticotropin-releasing hormone at 1 µg per kilogram per hour led to increased plasma ACTH, without desensitization of ACTH secretion.⁶² In contrast, ovine corticotropin-releasing hormone did not stimulate ACTH secretion at concentrations from

FIG. 3. Major treatment options for Cushing's disease and Nelson's syndrome (not all of the possible treatments for Cushing's disease are included). Prophylactic radiotherapy at the time of bilateral adrenalectomy may have a highly protective effect in preventing Nelson's syndrome. Transsphenoidal surgery remains the primary treatment for the management of Nelson's syndrome. Nonsurgical treatments can either be stand-alone or used as adjuvants to surgery. Temozolomide, octreotide, and pasireotide show the most promise as pharmacotherapies, but they are often administered after transsphenoidal surgery. The usefulness of sodium valproate is still inconclusive. The usefulness of cabergoline has been shown in some studies, but that of other dopamine agonists is inconclusive. Rosiglitazone has shown some efficacy in murine models, but these results have not yet been found in human studies. PPARG = peroxisome proliferator-activated receptor γ .

1×10^{-13} M through 1×10^{-7} M in pituitary adenomas resected from patients with Nelson's syndrome.⁷⁵ Based on these studies, an additional hypothesis can be developed, suggesting that if a patient with Cushing's disease had a residual corticotroph adenoma and underwent bilateral adrenalectomy, then the resulting increased arginine vasopressin and corticotropin-releasing hormone would lead to the corticotroph tumor progression that has now become characteristic of Nelson's syndrome.

Predictive Factors

Multiple factors have been linked to onset of Nelson's syndrome. As mentioned, presence of a residual pituitary adenoma before bilateral adrenalectomy has been associated with the development of Nelson's syndrome.^{21,33,66,77} Presence of an adenoma at the time of surgery or on neuroimages has been shown to predict the onset of Nelson's syndrome, particularly in patients with larger tumors (macroadenomas with cavernous sinus involvement). In one series, among 20 patients who had undergone adrenalectomy after hypophysectomy, residual tumor was documented in 9; of these 9 patients, Nelson's syndrome developed in 2 (22%).²¹ These 2 patients did not receive prophylactic radiotherapy, which brings this discussion to the next predictive factor. It has been suggested that prophylactic pituitary radiotherapy at the time of bilateral

adrenalectomy might serve a protective role in reducing the risk for development of Nelson's syndrome or possibly delaying its onset.^{21,25,33,39} In a study by Gil-Cárdenas et al., Nelson's syndrome developed in 11 patients, none of whom had received prophylactic radiation therapy.²¹ One of the best predictive factors for Nelson's syndrome is high levels of ACTH after adrenalectomy, but no definitive threshold value has been established.^{5,18,33,34,51,55,66} A rapid rise of plasma ACTH levels in the first year after bilateral adrenalectomy seems to be a strong predictor because of its association with tumor progression.^{5,51} Some studies have suggested young age at the time of bilateral adrenalectomy as a predictive factor, but this finding has not been consistent.^{32,42,54,58,77,78} Also, the duration of Cushing's disease before bilateral adrenalectomy might have some role in the development of Nelson's syndrome; however, in many case series, this association has not been shown.^{41,42,58,77} Patient sex could be a predictive factor,^{16,21,42,58,66,77} and in several studies, high urinary cortisol has been associated with Nelson's syndrome.^{25,58,77}

Treatment Strategies

Observation

Although some clinicians may consider initial observation with repeat imaging for Nelson's syndrome patients

harboring smaller, stable tumors that have not grown or that have demonstrated limited progression, observation is generally not the first line of treatment. If left untreated, most of these tumors will probably progress and warrant treatment. In a study by Kemink et al., observation was the treatment modality for 8 of 15 patients.⁴³ In these 8 patients, ACTH levels increased between the time of diagnosis and the time of the last follow-up visit, and in all 8 patients, the tumor progressed with parasellar extension or suprasellar extension. Of these 8 patients, 6 underwent elective pituitary surgery.

Surgical Treatment

The first line of treatment for Nelson's syndrome is resection, which is performed primarily via a transsphenoidal approach or, less commonly, via a transcranial approach. One of the first reports of pituitary surgery for Nelson's syndrome was by Espinoza et al., who described 3 patients who had undergone transsphenoidal surgery for the removal of the ACTH-secreting pituitary adenomas (Table 1).¹⁸ Surgical treatment enables potentially curative resection of the expanding corticotroph tumor and decompression of the optic chiasm, if needed. Unfortunately, considering the rarity of Nelson's syndrome, not many long-term case series for this surgery have been studied, and with the current advancements in nonsurgical therapies, the likelihood of finding any such series will decrease. Kelly et al. attempted total hypophysectomy on 13 patients with Nelson's syndrome³⁹; 9 patients underwent transsphenoidal resection and 4 underwent transcranial resection (2 by subfrontal approach and 2 by pterional approach). Tumor recurred in 2 patients, both of whom had undergone transsphenoidal resection; however, no regrowth occurred in patients who had undergone transcranial resection. De Tommasi et al. reported on 6 patients with Nelson's syndrome who had undergone transsphenoidal surgery.¹⁶ Two patients had extrasellar extension. In all 6 patients, the adenoma persisted after the first transsphenoidal surgery; half of these patients subsequently underwent repeat transsphenoidal surgery and half underwent Gamma Knife (GK) radiosurgery. Remission occurred in only 1 patient; disease persisted for the remainder. The range of efficacy of resection for treatment of Nelson's syndrome is 10%–70%. Complications can include CSF leaks, cranial nerve deficits, meningitis, and visual field defects.^{3,24,39,49}

Radiotherapy and Radiosurgery

Radiotherapy can be considered as an option for patients in whom surgery for Nelson's syndrome was unsuccessful or patients who are not optimal surgical candidates. One pitfall of radiotherapy is that it does not immediately reduce and normalize ACTH levels. Achieving normal ACTH levels can take weeks to months, depending on the size of the tumor; in the interim, control of excessive ACTH must be achieved by another manner such as medical therapy. Potential complications of radiation therapy include radiation-induced optic neuropathy, hypopituitarism, radiation necrosis, cerebral edema, and vasculopathy.⁸³ Radiation therapy can also be used as an adjunctive treat-

ment.³⁹ More conformal techniques such as fractionated stereotactic radiotherapy (FSRT) or proton beam therapy can help reduce the adverse effects of disseminated radiation. For prevention of optic nerve injury, brain necrosis, and damage to surrounding tissues, the typical radiation dose (approximately 45–50 Gy) is given at 1.8- to 2.0-Gy fractions.^{3,46,64} Some investigators suggest that neoadjuvant radiation therapy after bilateral adrenalectomy may protect and possibly delay development of Nelson's syndrome.^{33,39} According to a review of 39 patients followed up over 15 years after bilateral adrenalectomy, Nelson's syndrome did not develop in any patients who had received neoadjuvant radiation therapy but did develop in 50% of those who did not.²¹ Although there is currently no consensus as to the role of neoadjuvant prophylactic radiation therapy, it has been the practice at the University of Oxford to administer it to patients with residual pituitary tissue who will undergo bilateral adrenalectomy.⁴ However, further definitive follow-up data are pending.

Stereotactic radiosurgery (SRS) directs several beams of low-powered radiation to a specific target in the brain by a 3D coordination system. Although the low-powered beams prevent collateral radiation injury to the brain, a strong radiation dose is delivered to the point of convergence. One of the more common radiosurgical techniques used to manage Cushing's disease is GK radiosurgery.^{7,43,50,85,70} Vik-Mo et al. published a study in which 10 patients with Nelson's syndrome underwent GK treatment.⁸⁴ On average, tumor volume decreased by 32% for 9 patients but not at all for 1 patient. Of these 10 patients, ACTH levels decreased for 8 (range 2.0–278 pmol/L) and reached normal range for only 1 patient. However, the authors do not define their normal range for ACTH nor reveal the plasma ACTH levels for this patient. Recently, Marek et al. reported a study of 14 patients with Nelson's syndrome treated by GK radiosurgery in which the average follow-up period was 10.4 years.⁵⁰ Of these 14 patients, plasma ACTH levels decreased gradually in 12 and achieved normal levels 13–14 years later in 2. At approximately 2–5 years postirradiation, adenoma volume had decreased in 7 patients, remained unchanged in 6 patients, and completely disappeared in 1 patient. At 5–10 years after irradiation, among 11 patients reassessed, tumor volume decreased in 5 patients, remained unchanged in 3 patients, completely disappeared in 2 patients, and regrew in 1 patient. Most recently, Wilson et al. published a report about use of a linear accelerator for SRS (5 patients) and FSRT (2 patients).⁸⁷ After SRS, tumor volume decreased for 2 patients, increased in another 2 patients, and did not change in 1 patient. After FSRT, tumor volume decreased for 1 patient and increased after 15 months for the other. Unfortunately, no data concerning posttreatment ACTH levels were available. For patients in whom residual tumor is adjacent or in close approximation to the optic apparatus (< 2–3 mm), it might be safer to use FSRT rather than SRS to avoid radiation-induced optic nerve injury.

Medical Therapy

Medicinal therapy aims to control ACTH levels and curb tumor growth; however, no consistent series have confirmed its efficacy. Pharmacotherapies include sodium

TABLE 1. Treatment modalities for Nelson's syndrome stratified by year of publication

Authors & Year	No. of Pts	Mean Age (yrs)	Treatment Modality	Outcome	Mean FU	Dosage
Espinoza et al., 1973	3	NA	Transsphenoidal microsurgery	ACTH at reference levels (5 mU/100 ml plasma) for 2 pts, levels reduced (from 25 to 7 mU/100 ml plasma) for 1 pt	NA	
Tyrell et al., 1975	5	31.8	Somatostatin	ACTH levels decreased avg 52% from baseline	NA	500 µg/1 hr
Dornhorst et al., 1983	10		Sodium valproate	ACTH drop from 2460 to 480 ng/L in 3 wks, back to pretreatment values by 5–12 wks; reduced tumor size (1/10 pts)	NA	600–1200 mg, 5–12 wks
Kelly et al., 1988	11	45	Sodium valproate	No significant ACTH changes in 1 yr	NA	600–1200 mg/day
Kelestimur et al., 1996	1	27	Octreotide	Approx 54% decrease in plasma ACTH	NA	100 µg/3× day/7 days
Mercado-Asis et al., 1997	6	41	Bromocriptine	52% decrease in plasma ACTH	NA	2.5 mg
			Cyproheptadine	17% decrease in plasma ACTH	NA	8 mg
			Valproic acid	37% decrease in plasma ACTH	NA	1 g
			Cyproheptadine + valproic acid	19% decrease in plasma ACTH	NA	8 mg + 1 g
			All 3 combined	58% decrease in plasma ACTH	NA	2.5 mg + 8 mg + 1 g
			Placebo	6% decrease in plasma ACTH	NA	
Wolffenbuttel et al., 1988	1	50	GK	Minor reduction in tumor size	>2.0 yrs	40 Gy
Kemink et al., 2001	15	40.3	Observation only (2 pts)	Remission (0/2 pts)	4.0 yrs	
			Elective pituitary surgery (11 pts)	Remission (4/11 pts)	10.1 yrs	
			RT only (2 pts)	Remission (0/2 pts)	9.5 yrs	40–50 Gy
Kelly et al., 2002	13	35 at 1st op	Transsphenoidal surgery (9 pts)	Regrowth (2/9 pts)	15.2 yrs	
			Transcranial surgery (4 pts)	Regrowth (0/4 pts)	16.8 yrs	
Pollock & Young, 2002	11	42	GK (11 pts)	Stable tumor size (6/11 pts), decreased tumor size (3/11 pts), increased tumor size (2/11 pts)	3.08 yrs	Avg 40 Gy
Casulari et al., 2004	1	26	Cyproheptadine	ACTH drop from 2850 to 112 pg/ml but no change in tumor size	>4.0 yrs	12 mg/day for 18 mos
			Cabergoline	ACTH drop to 38 pg/ml & tumor regression		0.5 mg/2× wk/1 yr
			Bromocriptine	ACTH increase from 38 to 247 pg/ml		7.5 mg/day/6 mos
De Tomassi et al., 2005	6	55.5	Transsphenoidal surgery (repeated 2–3 times)	Remission (1/3 pts)	NA	
			Transsphenoidal surgery (repeated 3 times) + GK	Remission (0/3 pts)	NA	
Mullan et al., 2006	7	55.8	Rosiglitazone	No significant ACTH drop in 12 wks	12 wks	7 mg/day/12 wks
Gil-Cárdenas et al., 2007	11	28	RT only (3 pts), RT + valproic acid (3 pts), hypophysectomy (3 pts), valproic acid (1 pt), RT + valproic acid + hypophysectomy (1 pt)	Tumor stable in 6/8 pts not treated surgically	NA	
Vik-Mo et al., 2009	10	47	GK (10 pts)	32% decrease in avg tumor vol (9/10 pts)	7.0 yrs	Avg 53.4 Gy
Moyes et al., 2009	1	64	Temozolomide	ACTH drop 2472 to 389 pmol/L; decreased tumor size	NA	200 mg/m ² orally for 5 days, 28-day cycle

(continued)

TABLE 1. Treatment modalities for Nelson's syndrome stratified by year of publication (continued)

Authors & Year	No. of Pts	Mean Age (yrs)	Treatment Modality	Outcome	Mean FU	Dosage
Katznelson, 2013	1	55	Pasireotide	Decreased plasma ACTH from 42,710 pg/ml to 4272 pg/ml; tumor reduction	19 mos	60 mg intramuscularly, 28-day cycle
Wilson et al., 2014	19	49	SRS (5 pts)	Reduced tumor vol (2/5 pts)	4.40 yrs	20.0 Gy total
			FSRT (2 pts)	Reduced tumor vol (1/2 pts)	6.72 yrs	49.3 Gy total
			Conventional RT (12 pts)		3.15 yrs	50.0 Gy total
Marek et al., 2014	14	39.8	14 GK	Decrease plasma ACTH (12 pts), normalization (2 pts); tumor decrease (10 pts), stable (3 pts), regrowth (1 pt)	10.4 yrs	Avg 56.0 Gy
Arregger et al., 2014	1	59	Octreotide	ACTH drop from 235 pM to 71 pM by 21 mos	1.8 yrs	20 mg/mo

Approx = approximately; avg = average; FU = follow-up; NA = not applicable; pt = patient; RT = radiation therapy.

valproate, temozolomide, selective somatostatin analogs, dopamine agonists, and peroxisome proliferator-activated receptor γ agonists (Fig. 4).

Sodium valproate works as a therapeutic agent for Nelson's syndrome by inhibiting reuptake of γ -aminobutyric acid, which would decrease corticotropin-releasing hormone release by the hypothalamus. In a study by Dornhorst et al., 10 patients with Nelson's syndrome received 600–1200 mg of sodium valproate per day for 5–32 weeks. Although initial treatment successfully decreased plasma ACTH levels, when treatment was discontinued, ACTH returned to pretreatment levels within 5–12 weeks.¹⁷ In another study, 11 patients with Nelson's syndrome were given 600 mg of sodium valproate per day. At 6 weeks, plasma ACTH levels had decreased slightly ($p < 0.05$). Of these 11 patients, sodium valproate was continued for 6 patients (600 mg/day for 5 patients and 1200 mg/day for 1 patient). At 1 year, ACTH levels had not changed significantly from pretreatment or 6-week levels for the 6 patients taking sodium valproate or the 5 patients not taking sodium valproate.⁴⁰ Even when other reports are taken into consideration, effectiveness of sodium valproate for Nelson's syndrome remains inconclusive.^{35,48,70}

Temozolomide is an orally administered alkylating agent capable of crossing the blood-brain barrier. Its active form is methyl-triazeno-imidazole-carboxamide, which methylates DNA at the O⁶ position of guanine. Methylation leads to mispairing with thymine, and continual mispairing eventually leads to apoptosis of the affected cell. The standard dosage of temozolomide is 150–200 mg/m² for 5 days in a 28-day cycle. Temozolomide was first used as a treatment for a prolactin-secreting pituitary adenomas.⁴⁴ Temozolomide has been used in over 30 cases of pituitary adenomas; for patients whose tumors respond to this treatment, hormone levels decrease almost immediately.⁶³ Recently, Moyes et al. described a case in which a 64-year-old woman with Nelson's syndrome was given 200 mg/m² of temozolomide orally for 5 days in a 28-day cycle.⁵⁶ By the end of the fourth cycle, MR images showed markedly decreased tumor volume and plasma ACTH lev-

els had fallen from 2472 to 389 pmol/L. However, the patient experienced complications of CSF leakage from the ears and nostrils from tumor shrinkage, which abated after a bout of bacterial meningitis. Although temozolomide seems to be an effective and well-tolerated treatment for Nelson's syndrome, further studies with larger series and longer-term follow-up are warranted.

Somatostatin analogs such as octreotide have been used in the treatment of Nelson's syndrome.⁶⁷ ACTH-secreting pituitary adenomas primarily express somatostatin receptor (sst) 5, sst1, and sst2.^{30,81} Octreotide has a strong binding affinity to sst2 and only a moderate binding affinity to sst5.^{9,73} One of the earliest reports was made in 1975, when Tyrrell et al. described a progressive decline in plasma ACTH levels (40%–71% of pretreatment basal values) in 5 patients who had been given somatostatin.⁸⁰ After infusion cessation, ACTH values rose back to baseline levels. In a separate study, octreotide was given to a 27-year-old Nelson's syndrome patient. Plasma ACTH levels fell 54% from pretreatment values (from 66.7 pmol/L to 36 pmol/L), and tumor diameter decreased by 3 mm.³⁷ In a very recent quality of life assessment, the effect of long-acting repeatable octreotide was assessed in a 59-year-old woman with Nelson's syndrome.¹ Pretreatment plasma ACTH levels of 235 pM decreased to 116 and 71 pM at 18 and 21 months, respectively, after the patient received long-acting repeatable octreotide. Hyperpigmentation also decreased. Even after 3 months without receiving octreotide, the patient remained stable but ACTH levels began to increase (266 pM), thus corroborating the effects of octreotide.

In contrast to octreotide, pasireotide is a multireceptor ligand with high binding affinity to sst1, sst2, sst3, and sst5. In 2012, the US Food and Drug Administration approved the use of pasireotide for the treatment of Cushing's disease.^{9,73} In 2013, Katznelson³⁶ reported favorable biochemical and clinical responses in a patient with Nelson's syndrome treated with pasireotide. The patient was a 55-year-old woman with an aggressive and persistent pituitary corticotroph adenoma previously treated with multiple transsphenoidal surgeries and fractionated radio-

FIG. 4. Illustration depicting some of the pharmacological therapies that have been used in the treatment of Nelson's disease.

therapy. The patient received an intramuscular injection of 60 mg of pasireotide every 28 days. The pretreatment baseline plasma ACTH level of 42,710 pg/ml (reference range 5–27 pg/ml) declined significantly, almost a thousand-fold, to 4272 pg/ml, a month after treatment and remained around this level for approximately 19 months. In addition, the patient's skin hyperpigmentation decreased markedly. Follow-up MR imaging at 9 months showed a reduced size of the suprasellar component of the adenoma. Perhaps the greater binding affinity of pasireotide to sst5 makes it more effective than octreotide for treatment of Nelson's syndrome. Additional studies are warranted to corroborate the existing data for pasireotide as a treatment for Nelson's syndrome, and studies comparing octreotide with pasireotide should be considered.

Dopamine agonists such as bromocriptine and cabergoline have also been used in the medical management of patients with Nelson's syndrome. One study assessed the effects of bromocriptine, cyproheptadine (serotonin antagonist), and valproic acid on ACTH levels in 6 female patients with Nelson's syndrome.⁵³ Only bromocriptine at 2.5 mg caused a significant (52%) decrease in plasma ACTH levels. In a different study, bromocriptine was ineffective at reducing plasma ACTH levels in a 26-year-old female Nelson's syndrome patient, but cabergoline successfully

reduced levels from 247 pg/ml to 64 pg/ml.¹¹ According to MRI analysis, cabergoline also led to complete remission of the pituitary adenoma. The single and combined effects of cyproheptadine and bromocriptine were also tested in 12 patients who had raised plasma ACTH levels but no pituitary macroadenoma after bilateral adrenalectomy for Cushing's disease; plasma ACTH levels did not change significantly after treatment with this combination.⁸⁶

Rosiglitazone, a thiazolidinedione, is a selective ligand of peroxisome proliferator-activated receptor γ . These receptors are abundantly expressed in human ACTH-secreting pituitary adenomas. Heaney et al. showed that rosiglitazone effectively prevented corticotroph tumors and suppressed ACTH secretion in murine models (150 mg/kg/day).^{26–28} In *in vitro* studies, rosiglitazone induced G₀/G₁ cell-cycle arrest and apoptosis in human and murine corticotroph, somatolactotroph, and gonadotroph pituitary tumor cells and further suppressed hormone secretion.²⁶ However, the favorable effects of rosiglitazone have not been successfully replicated in human studies. Mullan et al. presented a series of 7 patients with Nelson's syndrome for whom 8 mg of rosiglitazone orally, once daily for 12 weeks, led to no statistically significant decrease in plasma ACTH levels.⁵⁷ Of note, the US Food and Drug Administration limits the maximal dose of rosiglitazone in humans

to 8 mg, but the murine models tested by Heaney and colleagues received 150 mg.

Conclusions

Nelson's syndrome remains a challenging neuroendocrine condition associated with significant morbidity after bilateral adrenalectomy for Cushing's disease. As treatments for Cushing's disease become more refined and shift away from bilateral adrenalectomy, the incidence of Nelson's syndrome will naturally decrease. This review should facilitate the diagnosis and understanding of the criteria of Nelson's syndrome. This description of therapies should be used to determine the best treatment strategy for a patient with Nelson's syndrome and should influence future investigations that may clarify current controversies with multimodal management.

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