Nelson syndrome: comprehensive review of pathophysiology, diagnosis, and management

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✓Nelson syndrome (NS) is a rare clinical manifestation of an enlarging pituitary adenoma that can occur following bilateral adrenal gland removal performed for the treatment of Cushing disease. It is characterized by excess adrenocorticotropin secretion and hyperpigmentation of the skin and mucus membranes. The authors present a comprehensive review of the pathophysiology, diagnosis, and management of NS. Corticotroph adenomas in NS remain challenging tumors that can lead to significant rates of morbidity and mortality. A better understanding of the natural history of NS, advances in neurophysiology and neuroimaging, and growing experience with surgical intervention and radiation have expanded the repertoire of treatments. Currently available treatments include surgical, radiation, and medical therapy. Although the primary treatment for each tumor type may vary, it is important to consider all of the available options and select the one that is most appropriate for the individual case, particularly in cases of lesions resistant to intervention. (DOI: 10.3171/FOC-07/09/E13)

KEY WORDS • adrenalectomy • adrenocorticotrophic hormone • hyperpigmentation • Nelson syndrome • pituitary adenoma

NELSON syndrome is a rare clinical manifestation of an enlarging pituitary adenoma that can occur following bilateral adrenalectomy performed in the treatment of CD. It is characterized by skin and mucus membrane hyperpigmentation and excess ACTH secretion.

Diagnostic criteria for NS have been quite variable. Some authors⁷⁷ have defined NS as high levels of ACTH associated with skin hyperpigmentation after bilateral adrenalectomy regardless of pituitary enlargement,⁸⁰ whereas others consider the presence of an expanding pituitary adenoma causing visual field disturbance as a requirement for diagnosis.¹¹⁴ With modern day imaging, and for the purposes of this review, corticotroph tumor progression and high ACTH have been proposed as a basis for the diagnosis of NS.⁴

Abbreviations used in this paper: ACTH = adrenocorticotrophic hormone; CD = Cushing disease; CRH = corticotropin-releasing hormone; CT = computed tomography; GH = growth hormone; MR = magnetic resonance; MSH = melanocyte-stimulating hormone; NS = Nelson syndrome; TBA = total bilateral adrenalectomy; TSH = thyroid-stimulating hormone.

Historical Perspective

The first suggestion that the adrenal gland was essential for life came from Brown-Séquard, who showed in the 1850s that bilateral adrenalectomy in animals caused death within a few days.⁶⁶ Harvey Cushing¹³ was the first to link adrenal hypersecretion of cortisol to the presence of a pituitary tumor. The concept of the hypothalamic-pituitary-adrenal axis evolved further with the demonstration of the existence of ACTH-releasing factor in 1955 by Saffran and Schally.⁹⁸ The first case report of the characteristic triad of NS was published by Don Nelson in 1958.⁷⁸ He described a 33-year-old woman who developed marked skin hyperpigmentation, high plasma ACTH levels, and imaging evidence of a pituitary tumor (enlarged sella on skull radiographs) 3 years after bilateral adrenalectomy for CD. In 1960, Nelson and colleagues⁷⁹ formally described the syndrome of pituitary hypersecretion of ACTH and pituitary tumor enlargement, which has since become the eponymous syndrome. Corticotropin-releasing hormone was finally isolated and sequenced by Vale and coworkers in 1981,¹¹³ and with the availability of radioimmunoassay, the elevation of plasma ACTH levels after bilateral adrenalectomy became diagnostic for NS.

Historically, patients with CD were treated with bilateral

adrenalectomy.^{77,84} Transsphenoidal pituitary surgery has radically modified the management of pituitary-dependent hypercortisolism. It is currently the treatment of choice and has been reported to result in initial remission rates of 70 to 90%.^{28,61,92,93,96,108} The outcomes however, vary depending on tumor size and presence or absence of extrasellar invasion. Relapse rates of up to 20% have been reported, and long-term remission is achieved in only approximately 60 to 70% of patients with CD.^{15,81} For patients in whom transsphenoidal surgery is unsuccessful, four other treatment options exist: repeated transsphenoidal resection, radiation therapy, medical therapy, and bilateral adrenalectomy. Total bilateral adrenalectomy represents the ultimate treatment in severe cases of persistent hypercortisolism.¹² Adrenalectomy, performed nowadays with low rates of morbidity and mortality, is the only treatment option that offers immediate control of hypercortisolism with 96 to 100% certainty.^{24,116} Today TBA is typically performed in patients with nonresectable pituitary adenomas, pituitary tumors in which resection has failed to control symptoms and antihypertensive medications are either ineffective or not indicated (as in pregnancy), no evidence of a pituitary neoplasm despite strong biochemical evidence of CD (results of a high-dose dexamethasone suppression test, inferior petrous sinus sampling, or both), or life-threatening symptomatic CD.

Since Nelson's original description, reports of over 50 series of NS cases have been published. These studies have had several limitations in that most included a small number of patients and the data in all were retrospective. Also, the definitions and diagnostic criteria have changed over time as the fields of neuroimaging and biochemistry have evolved. Prior to CT and MR imaging, pituitary microadenomas could not be visualized, and macroadenomas were identified by sellar x-ray tomography. Diagnosis initially relied on the physical examination and plasma ACTH measurements. High levels of ACTH secretion were defined based on qualitative assessment of associated cutaneous hyperpigmentation or on various arbitrary cut-off points for plasma ACTH concentration. Selective irradiation of pituitary adenomas only became feasible in the 1990s, after high-resolution CT and MR imaging became available for use in dose planning. Groups of patients received different treatments, some of which (for example, pituitary radiotherapy) may have directly impacted pituitary tumor growth. Finally, major technological and medical advances, such as pituitary MR imaging and the development of transsphenoidal surgical techniques, altered the diagnostic criteria and outcomes during the period of data acquisition. Consequently, data from these series can be difficult to compare, interpret, and apply to modern clinical practice.

Characteristics of Nelson Syndrome

Demographic Features

The ACTH-secreting adenomas represent approximately 10 to 12% of all pituitary adenomas and are seen predominantly in women (female/male ratio 8:1); the peak incidence is in the third to fourth decades of life.^{71,111} Middle-aged women, therefore, constitute the largest group at risk for NS. Although generally benign, ACTH-producing tumors are more invasive than most other pituitary adeno-

mas. The rates of NS in patients who had undergone adrenalectomy ranged from 8 to 42% in the largest series,^{12,46,48,72,106} and higher rates (up to 47%) have been reported in studies in which MR imaging and modified diagnostic criteria were used.^{4,85} In the largest pediatric case series NS was reported in 25 to 66% of children who had undergone adrenalectomy.^{33,109} The incidence of NS increased with prolonged follow-up, possibly indicating that there is a spectrum of disease ranging from small and slowly growing tumors to those that are more aggressive and produce symptoms earlier. A molecular mechanism for this variability has yet to be identified.

Pathophysiology of the Disease

Nelson syndrome usually occurs 1 to 4 years after TBA (range 2 months–24 years)^{24,77} and can be regarded an iatrogenic disease. The classical thinking was that NS results from the loss of feedback control of serum cortisol on the hypothalamus and pituitary gland. Following TBA, cortisol levels that had previously suppressed hypothalamic CRH production normalize, resulting in an increase in CRH production. Adrenalectomy in rats increases hypothalamic CRH transcription, and is followed by a moderate increase in corticotroph cell numbers.⁶⁸ Because most adenomatous corticotrophs still retain their responsiveness to CRH, elevation of the CRH level exerts a trophic effect on the residual tumor cells, stimulating their growth and increasing proopiomelanocortin production. Evaluating postadrenalectomy CRH production in humans has been more challenging; thus the role of CRH in stimulating the proliferation of corticotroph adenoma after adrenalectomy remains, to some extent, speculative.⁴

The corticotroph adenoma cells that are responsible for the CD in the first place are believed to be the source of the tumor that eventually grows and leads to NS development.³ In most corticotroph adenomas in patients with NS, the products of proopiomelanocortin transcription and processing are similar to those in normal anterior pituitary corticotrophs, except that in NS, these products are produced in greater amounts.⁷ The ACTH response to CRH in these patients also differs from the response in those who have adenomas of CD in two ways: the magnitude is greater, and the response is prolonged. These differences may be explained by the greater size of the tumor and the reduced glucocorticoid feedback in patients who have undergone adrenalectomies and have NS.⁸³ Cleavage of excessively produced proopiomelanocortin to ACTH and MSH is critical in NS; MSH is responsible for the increased pigmentation seen in these patients. In NS, plasma ACTH levels remain elevated in a stable fashion and demonstrate less diurnal fluctuation, indicating a process to some degree independent of phasically released CRH.^{40,42,101,122} Basal ACTH secretion was increased sixfold and pulsatile secretion was increased ninefold in patients with NS compared with patients with CD.¹¹³

All patients who undergo TBA are treated with physiological steroid replacement, typically an equivalent of 30 mg of hydrocortisone per day. Some authors have speculated that differences in the maintenance dose and frequency of glucocorticoid administration after bilateral adrenalectomy might account in part for the variable prevalence of NS after adrenalectomy for CD.^{41,77,85,90} When the inhibitory

influence of steroids is insufficient for longer periods, as in cases in which replacement of glucocorticoid hormones has not been adequate, pituitary ACTH-producing cells can be stimulated excessively, which in turn can lead to adenomatous transformation of these cells, resulting in NS.^{77,111,114}

What remains intriguing in the pathophysiology of NS is the lack of responsiveness of adenocorticotroph cells to steroid hormone replacement therapy. Partial resistance to glucocorticoids in a monoclonal pituitary adenoma has been found in corticotroph adenomas.⁷ The NS adenomas, like the corticotroph adenomas in general, show a defective response or a partial resistance to glucocorticoid hormones. This has been demonstrated by the results of in-vivo studies showing that ACTH plasma levels are not normally suppressed by glucocorticoid hormone administration in patients with NS.¹²⁰ Regulatory gene mutations and mutations in the glucocorticoid receptor may also be important in determining the behavior of the tumor leading to local resistance to negative glucocorticoid feedback. It has been suggested that a somatic glucocorticoid receptor defect might play a pathophysiological role in the tumorigenesis of the corticotroph adenoma bearing this mutation.³⁹

Controversy remains as to whether the pituitary ACTH adenoma tumor progression in NS is a result of the lack of cortisol feedback after adrenalectomy or reflects corticotroph tumors that were programmed to behave in an aggressive manner.²⁴ The search for the possible molecular mechanisms responsible for the pathogenesis of corticotroph adenomas has been recently reviewed.¹⁴ A number of possible mechanisms have been investigated, including oncogenes, tumor suppressor genes, growth factors, transcription factors, various signaling pathways, cell-cycle associated genes, and angiogenic factors. Unfortunately, no definitive information is yet available on the molecular pathogenesis of corticotroph adenomas. The pathophysiology of accelerated tumor growth remains poorly understood,³ and it is still unclear whether adrenalectomy accelerates corticotroph tumor growth.⁶⁹ Somatic modification may play an important role in the pathogenesis of corticotroph adenomas, allowing monoclonal expansion of a genetically aberrant cell.²³

Histopathological Findings

Although pituitary tissue obtained in patients with NS has been found to show molecular features essentially identical to those observed in CD,⁸ NS-associated adenomas are often larger, more invasive, and more aggressive than those causing CD.⁷⁷ These tumors are of monoclonal origin³² and are basophilic as well as periodic acid–Schiff-positive. Immunostaining also demonstrates the presence of ACTH, MSH, and related peptides in the cytoplasm of these tumors. The few ultrastructural features different from those of adenomas in CD are inconspicuous or absent Type 1 filaments and a lack of Crooke hyaline changes (present only with excess cortisol). None of the pathological features of the tumors have thus far correlated with prediction of corticotroph tumor progression.⁴

The tumors of NS may have cytological features that include increased cellular proliferation, with mitoses and cellular and nuclear pleomorphism. At the molecular level, this aggressive behavior may reflect the development of genetic mutations in oncogenes and genes regulating pituitary growth and differentiation, although this has not been elucidated.

Molecular studies on p53 expression have found nuclear and/or cytoplasmic accumulation of p53 in 50% of noninvasive and 69% of invasive ACTH-secreting tumors. Nuclear accumulation of p53 protein is associated with a significantly lower apoptotic index indicating a failure of p53 protein to exert its apoptotic action in at least a subset of this tumor type.^{11,52} Other authors have not been able to reproduce these results,³⁹ and the implications of this molecular expression remain to be determined.

Machado et al.⁵⁹ studied DNA flow cytometry of pituitary adenomas in NS and CD and found the highest proliferation rates in NS tumors. Histological invasiveness was directly associated with increased proliferation rates. These authors proposed that DNA flow cytometry could be used to identify those patients with pituitary tumors with a higher invasive potential and risk of NS.

Patient Identification and Treatment

Diagnosis

The presentation of patients with NS is variable and the criteria used in the diagnosis of the syndrome have evolved over time. Historically, tumor enlargement was diagnosed by radiographic evidence of sellar enlargement, and increased ACTH production was often inferred from diffuse hyperpigmentation. Today, with modern neuroimaging techniques and the wide availability of immunoassays, the clinical diagnosis of NS is easier. The majority of authors refer to a triad of a plasma ACTH level above 200 ng/L (normal levels are below 54 ng/L), imaging (MR imaging, unless contraindicated) evidence of pituitary mass enlargement, and hyperpigmentation. Hyperpigmentation, which occurs later in the disease process, is present in only 42% of cases in modern series,⁴⁶ probably reflecting the fact that NS is now generally diagnosed at an earlier stage. The mere presence of a pituitary adenoma postoperatively, even with mild elevations of plasma ACTH levels, is not always followed by the disastrously progressive problems that some patients experience. Therefore, evidence of tumor progression is a necessary requirement for the diagnosis of NS.⁸⁵

Signs and Symptoms. Complications related to NS are essentially due to tumor growth. The spectrum of clinical features observed relates to the local effects of the tumor on surrounding structures and the secondary loss of pituitary hormones. Compression by the tumor can inhibit the release of any of the anterior pituitary hormones and may also occasionally lead to diabetes insipidus.⁹⁴ A large tumor can cause visual deficits through compression of the optic pathways; such visual deficits have been reported in 10 to 57% of cases.^{26,37,43,48,62,65,77,109,121} The high rates of visual deficits seem to be in accordance with the lesion's well-documented aggressive behavior.^{77,96} If a tumor invades the cavernous sinus it can cause diplopia and cranial nerve lesions by involving the oculomotor, trochlear, abducent and V1 and V2 branches of the trigeminal nerve.⁶⁵ Tumor necrosis with sudden intracranial hypertension has also been described.^{18,41} Features of raised intracranial pressure can occur late and are uncommon as they require a tumor large enough to obstruct the flow of cerebrospinal fluid. Headaches can occur and are probably the result of stretch-

ing of the diaphragma sellae. Malignant conversion to pituitary carcinoma with distant metastases, while rare, has also been described.^{43,55,58,72,86,121} Brain invasion is associated with aggressive adenomas that have been resistant to prior interventions.⁴⁶

Hyperpigmentation of the skin is usually obvious and is not limited to sun-exposed areas. The degree of pigmentation varies depending upon ethnicity as well as levels of MSH. Patients with hyperpigmentation usually present with a linea nigra and pigmentation of the extensor surfaces, scars, gingivae, and areolae.

Paratesticular and paraovarian tumors producing cortisol or androgens in an ACTH-dependent manner have been described.^{5,82,107} During embryogenesis, adrenal cortical cells may migrate along the line of gonadal descent or become sequestered in the hilum of the testes, giving rise to adrenal rest tissue. In NS, this adrenal rest tissue may become stimulated. When in the testes, it can result in painful testicular enlargement and oligospermia. Rarely, the adrenal rest tissue can produce sufficient cortisol to normalize levels or even cause recurrence of CD.^{38,82,100}

Predictive Risk Factors. Much effort has been directed towards the identification of predictive factors for the development of NS. The ability to forecast which patients are at risk would facilitate earlier detection and treatment of a smaller tumor burden with a lower morbidity rate. Also, other treatment options could be weighed against adrenalectomy in higher risk patients.

The presence of high basal plasma ACTH levels after adrenalectomy is the best validated risk factor.^{4,6,24,37,41,48,73,77,85} No unique threshold value has been defined. Assie et al.⁴ found levels above 100 ng/L in the year following adrenalectomy to be predictive of NS. Young age at the time of adrenalectomy, with a corresponding higher incidence of NS in children, has been reported,^{33,36,49,109} but this is not universally accepted.⁴ A shorter duration of CD^{4,48} and the presence of a pituitary tumor prior to adrenalectomy have also been identified as predictive in several series.^{4,29,37,85,105} High urinary cortisol excretion before adrenalectomy was seen in some studies^{77,105} but not all.^{6,48,85} Likewise, residual cortisol secretion was found predictive in some^{62,85} but not all reports.⁴ The results of a few recent retrospective studies^{41,77,90} have suggested that an insufficient dose of glucocorticoid substitution treatment after adrenalectomy may be linked to the development of NS. This hypothesis, however, is not supported by the results of a number of earlier studies.^{6,43,48} The presence of mitoses or a high percentage of Ki 67-immunopositive nuclei in the adenoma has also been identified as a potential predictor of corticotroph tumor progression (Ki 67 $\geq$ 3%),^{4,74} but this finding remains controversial.⁴

A negative predictor for the development of NS has been the use of prophylactic radiotherapy after adrenalectomy,^{24,37,46,77} although neither the predictive value nor the clinical significance of the association is universally accepted.^{62,64,72,85,105}

Some factors that have never been demonstrated to have predictive value for development of NS include gender^{49,72,77,105} and plasma ACTH concentration prior to adrenalectomy.^{6,36,49,105}

Laboratory Studies. The only laboratory investigation required for the diagnosis of NS is a plasma ACTH level.

Normal values are below 54 ng/L and levels above 200 ng/L have been generally considered diagnostic for NS.^{37,50} (Authors of several studies used pmol/L units; 1 ng/L is equivalent to 0.225 pmol/L.) The plasma ACTH levels in CD are normal or only slightly elevated, whereas in NS they are markedly elevated, usually in the range of thousands of ng/L. Pereira et al.⁸⁵ found that levels of 154 pmol/L or greater were only present in patients with NS. Other derivatives of the precursor peptide, proopiomelanocortin, are also elevated, although their measurement is not required for diagnosis. Patients with NS will also often have an exaggerated ACTH response to CRH. Although blood levels of ACTH are generally markedly elevated in patients with NS, hypercortisolemia is absent.

Other laboratory investigations that should be considered as part of the evaluation of a patient with possible NS include a general pituitary panel to evaluate preexisting and/or identify new pituitary dysfunction as well as to address the adequacy of hormone replacement therapy. These studies may include (as clinically indicated) evaluation of blood levels of free thyroxine (T4) and TSH, prolactin, GH, insulin-like growth factor-1, gonadotropin-releasing hormone, luteinizing hormone, follicle stimulating hormone, and testosterone, and urine osmolality or specific gravity.

Imaging Studies. There are no specific imaging studies for the diagnosis of NS. Magnetic resonance imaging provides the best means of visualizing the sellar region and can be considered a reliable guide for surgeons before and during the operation.

The diagnosis of NS requires demonstration of corticotroph tumor progression. Because the majority of patients have previously undergone at least one transsphenoidal procedure, comparison with postoperative images is of major importance. This comparison is particularly critical in the presence of residual tumor after incomplete resection of a pituitary adenoma.

The progression of a corticotroph tumor is best identified with MR imaging. Magnetic resonance imaging techniques that facilitate detection of ACTH-secreting adenomas responsible for CD and NS include high-resolution (3-mm cuts) coronal T1- and T2-weighted sequences, dynamic MR imaging, and post-gadolinium administration delayed images with gadolinium dose adjustment for each sequence. Protocols such as this can routinely demonstrate pituitary adenomas smaller than 3 mm in diameter.^{9,10} Smaller ACTH-secreting pituitary adenomas may evade detection with MR imaging.

Ectopic corticotroph adenomas are extremely rare, and ectopic pituitary adenomas causing symptoms of NS are even rarer.^{19,89} These tumors frequently extend beyond the boundaries of the sella turcica. Infiltration of the cavernous sinus, sphenoid sinus, or clivus, compression of the optic chiasm, and encasement of the internal carotid artery can all be present. Over 90% of macroadenomas lead to enlargement of the osseous pituitary fossa. Intratumoral hemorrhage may also be seen. Microadenomas are best seen on coronal images and usually appear hypo- or isointense relative to normal pituitary tissue on unenhanced T1-weighted images. After the administration of a contrast agent, the microadenoma usually remains hypointense due to the earlier and more intense enhancement of normal pitu-

itary tissue. Indirect imaging features of microadenomas may be a one-sided elevation of the diaphragm or prolapse of the pituitary fossa. In dynamic sequences after rapid injection of contrast medium, a diminished and delayed enhancement of the adenoma may be seen. Some microadenomas demonstrate an early arterial enhancement, occurring simultaneously with enhancement of the posterior lobe, but compared with normal pituitary tissue most microadenomas display slightly lower signal intensity.⁹⁷ For those patients in whom MR imaging is contraindicated, thin-cut CT with coronal and sagittal reconstructions and intravenous administration of a contrast agent can be used instead.

A baseline MR imaging study is recommended 3 months after surgery, as maximal extension of the pituitary mass does not return to normal immediately postoperatively (even with total tumor removal). This interval allows postoperative changes to resolve while still not risking significant growth from any residual tumor. Contrast-enhanced images obtained immediately (on the first postoperative day) following resection may also be reliable for visualization of residual tumor, with fat-suppressed sequences enabling discrimination between a fat pad and enhancing adenoma.⁹⁷

Ophthalmological Testing. All patients who have large masses in the region of the pituitary or the optic nerves should be referred for formal visual field assessment by an ophthalmologist. Children do not always report visual symptoms and therefore benefit from periodic ophthalmological evaluations.

Treatment Options

Today, with greater awareness of NS and with the availability of modern neuroimaging and immunoassays, tumor progression can be detected much earlier and thus at a smaller lesion size. Surgery remains the primary mode of therapy. Radiotherapeutic protocols offer additional options for treatment.⁶⁰ Although not widely accepted, some pharmacotherapeutic measures can also be offered to patients with resistant lesions. If untreated, NS adenomas often become markedly aggressive and may cause death in some patients, usually through brain invasion.

Surgery. Still the best hope for cure in cases of NS, surgery is the treatment of choice for large tumors that produce acute compression of the optic apparatus and other vital structures.^{27,41,46,123} The goal of surgery is to remove all macroscopic tumor tissue without compromising vital structures. The choice of transsphenoidal or cranial approach depends on the degree of extrasellar extension, which is demonstrated in 33% of cases at the time of NS diagnosis.¹⁵ As in other pituitary adenomas, surgical treatment of NS tumors is more effective when the tumors are relatively small, and when surgery is performed before extrasellar expansion of the tumor occurs, it may result in long-lasting remissions.⁵⁰ Other determinants of surgical success include the degree of tumor invasion of brain parenchyma, optic apparatus, cavernous sinuses, dura mater, and bone, as well as the experience of the surgeon.

In a recent study involving long-term follow-up of 56 patients with NS, 13 patients required surgical intervention because of an expanding pituitary mass (nine transsphenoidal hypophysectomies and four craniotomies). Control

of the neoplasm was achieved in 70% and the disease remained stable in 15%. No visible tumor was found in 85% on postoperative MR images. In 15% of the patients, the disease persisted and led to tumor progression and death. Also, 85% of patients recovered normal pigmentation, and all experienced at least partial improvement. The plasma ACTH levels decreased in all patients (median decrease 84%, range 56–99%).⁴⁶ Xing et al. surgically treated 23 patients with NS (performing 21 transsphenoidal procedures and two craniotomies) and reported curative and remission rates of 57 and 26%, respectively.¹²¹ De Tommasi et al.¹⁵ reported that among six patients with NS treated with surgery alone or surgery and radiation, only one (16.6%) experienced remission. General efficacy rates of neurosurgery for NS have been reported at between 10 and 70%.^{15,21,46,50,120} In cases of incomplete removal or where invasion is present, adjunctive irradiation reduces the rate of recurrence and improves the prognosis.

Surgical complications are similar to those for initial or repeated transsphenoidal pituitary resection or craniotomy. Reported rates of perioperative complications remain relatively low, with a documented mortality rate of 5% (a single patient in one study), visual loss 0%, cranial nerve deficits 5%, cerebrospinal fluid leak 15%, and meningitis 8%.^{46,63,121} Occurrence of treatment-associated hypopituitarism can be as high as 69%, particularly with large tumors. Permanent diabetes insipidus was reported in 38% of patients. Frequently, the aggressive and locally invasive nature of tumors in NS necessitates radical hypophysectomy. Not surprisingly, an increased prevalence of panhypopituitarism and diabetes insipidus results. Nevertheless, the procedure is relatively safe and well tolerated and offers rapid and long-lasting resolution of the mass effect.⁴⁶

Radiation Therapy. Radiation is another alternative treatment for patients in whom surgery has been unsuccessful or is not an option.¹¹⁰ Radiotherapy administered to the pituitary at the time of adrenalectomy has been correlated with a lower risk for NS in some series.^{24,37,46,77} Once NS occurs, prophylactic pituitary irradiation cannot prevent the disease from progressing, especially in patients with adenomas that secrete large amounts of ACTH.¹²¹ While the use of prophylactic radiotherapy at the time of adrenalectomy has been proposed, the suggestion has not been translated into common practice. Given the risks of sellar radiation, the inconsistent protective relationship, and the relatively low rates of NS in patients who have undergone adrenalectomy, routine prophylactic irradiation is not justified based on currently available data. Thus far there has been no agreement on the optimal time of intervention in patients with NS. Some advocate early treatment,^{37,50} whereas others are proponents of close follow-up and intervention only with evidence of disease progression.³

Fractionated radiation therapy has been used to control ACTH secretion and tumor growth in patients in whom surgical intervention for CD and NS has failed and in those with recurrent tumors.^{20,34,60} The typical total dose of 45 to 54 Gy is delivered in 1.8- to 2-Gy daily fractions.²⁰ After fractionated radiation therapy, a decrease in circulating ACTH levels and improved hyperpigmentation was observed in 14 (93%) of 15 patients with NS.³⁴

Stereotactic radiosurgery has been frequently used to cure or control pituitary adenomas during the past 2

decades. The differences in the imaging used for locating the target, the radiation source, dosimetry, length of follow-up, and the method of defining tumor remission make comparison of the data across studies difficult.⁶⁷ Other shortcomings of the data are the lack of prospective randomization and the short follow-up periods in the studies. Nevertheless, stereotactic radiosurgery has been shown to be an effective tool in controlling tumor growth in the majority of patients who have residual tumor after transsphenoidal surgery for CD.^{16,20,22,35,51,63,90,99}

Gamma Knife surgery has also been successfully used in NS.^{22,51,63,90,119} Initial results reported by Pollock et al.⁹⁰ seemed very promising, with rates of tumor control reported at 82% in 11 patients treated, at a median of 37 months' follow-up. The median plasma ACTH level decreased 66%, and approximately one half of the patients with hyperpigmentation had improvement in their skin coloration. Complications in this series occurred exclusively in patients who had undergone prior fractionated radiation therapy (diplopia in two patients and ipsilateral blindness, hormone deficiency, and temporal lobe radiation necrosis in one each). Of six patients treated with Gamma Knife surgery by Kobayashi et al.,⁵¹ a partial response in tumor size was achieved in two (33%), a minor response was achieved in two (33%), and no change occurred in two (33%). A decrease in hormone levels occurred in two cases, and hormone levels remained unchanged in two cases. The rates of response in patients with NS were noted to be lower than in those with CD. Mauermann et al.⁶³ treated 20 patients with NS by means of Gamma Knife surgery. Of those, 67% experienced reduction of plasma ACTH levels (mean reduction 75%) and 17% experienced normalization of plasma ACTH levels. Decrease in tumor size was observed in 50% and stabilization in 40%, for an overall tumor control rate of 90%. Mean imaging follow-up was 20 months (range 0–124 months). Complication-related follow-up was incomplete, but in five of 10 cases in which there was endocrinological follow-up, new hormone deficiencies were observed (including one case of diabetes insipidus). One patient developed a permanent third cranial nerve palsy.

Radiotherapy is associated with serious long-term consequences, including learning and memory difficulties, hypopituitarism, visual damage, and risk of secondary tumors.¹¹⁰ Radiation-related complication rates are widely discussed in articles analyzing outcomes of CD treatment. High rates of radiation-induced hypopituitarism in NS—up to 82%—have been described.^{35,63,67,110} Some abnormalities did not become evident until 10 years after treatment.³⁵ Optic neuropathy occurs in fewer than 2% of patients who have undergone radiosurgery, especially when doses to optic structures are limited to less than 8 Gy.²⁵ Higher rates have been described for conventional radiotherapy. Although there is an associated risk of secondary neoplasm, no instances have been reported in the patients who underwent radiosurgery for NS, which is probably related to the limited number of patients studied and relatively short follow-up windows. The treatment-related mortality rate is essentially zero.³⁵

Several concerns in planning radiosurgery for NS arise from the propensity of NS adenomas to grow faster and invade more readily than do most ACTH-secreting tumors

in CD. Tumor progression can occur before the delayed effect of radiosurgery (mean 1 year) takes place. The minimum effective dose to the tumor margin is the main element determining tumor response.¹¹⁰ Proximity to the optic nerves or chiasm may exclude some larger tumors from radiosurgical treatment, unless the nerve is already non-functional. Cavernous sinus invasion can be subtle even on MR images, and the borders of an invasive adenoma, particularly the borders of a subtotally resected tumor admixed with postoperative fibrosis, can be difficult to delineate with enough certainty to protect adjacent brain from radio-toxicity. A history of prior irradiation of the sella, commonly encountered in patients with NS, may limit the dose possible in radiosurgery.³⁷

Pharmacological Therapy. Much progress has been made in recent years in the pharmacological control of pituitary tumors, with prolactinomas and GH- and TSH-secreting adenomas being successfully treated with dopaminergic and somatostatinergic drugs. Unfortunately, none of the drugs tested thus far have consistently provided reproducible efficacy in the treatment of NS and no well-established medical therapy for CD or NS currently exists.^{81,115} Nevertheless, the following agents have shown some positive effects and may be useful options when all other treatments fail.

Dopamine Agonists. Bromocriptine, cabergoline, and cyproheptadine have all been studied, but variable results have relegated these agents to be used for adjunctive therapy to lower plasma ACTH levels in select cases.^{53,70,88,102,103,118}

Valproic Acid. Sodium valproate may lower, but not normalize, plasma ACTH levels by inhibiting the release of CRH without reducing tumor size, but the results of studies to date have been inconsistent and inconclusive.^{1,17,44,47,54,56,57,70,95}

Somatostatin Analogues. Octreotide and other somatostatin analogues have been shown to reduce plasma ACTH levels in NS but not in patients with untreated pituitary-dependent CD, and the results of some studies have even suggested stabilization of tumor growth with some agents.¹¹² For now, these agents may provide a useful short-term measure, to be used as a bridge before other therapies can be implemented.^{44,45,87,117}

Rosiglitazone. Peroxisomal proliferator-activated receptors- γ are expressed abundantly in ACTH-secreting pituitary tumors.⁷⁵ Data from animal studies has suggested that high-dose peroxisomal proliferator-activated receptors- γ agonists, such as rosiglitazone, retarded tumor growth and lowered ACTH and cortisol levels, but only modest reductions in plasma ACTH levels and no tumor regression have thus far been seen in human studies.^{2,30,31,75,76}

Serotonin Antagonists. Ketanserin and cyproheptadine have demonstrated transient reductions in plasma ACTH levels and possible reduction in tumor size,^{91,104} but this effect has not been consistently reproduced.⁵⁰

Follow-Up Studies

There is currently no widely accepted follow-up schedule for patients with NS. Most cases of corticotroph tumor progression can be diagnosed within 3 years of adrenalectomy.

tomy,³⁷ so patients should be monitored more closely during this initial postoperative period.⁴

Tumor volume can be indirectly monitored with measurements of circulating ACTH levels.⁵⁰ This method offers a simple and rather inexpensive means of screening, which can be used every 3 to 6 months during the first year, every 6 months during the 2nd and 3rd year, and yearly after that. Serial MR imaging is also essential to monitor for any adenoma progression. In the vast majority of patients, yearly MR imaging studies were found to be sufficient to identify disease progression prior to evolution of clinical symptoms related to tumor enlargement. Plasma ACTH values above 100 ng/L should prompt an MR imaging study of the pituitary to look for tumor progression.⁴ If plasma ACTH levels remain low, the imaging interval can be extended to every other year, after the initial 3 years of annual monitoring.

Conclusions

Adrenalectomy performed for CD carries significant but not uniform risk for corticotroph tumor progression. Currently, plasma ACTH levels above 200 ng/L along with MR imaging or CT evidence of tumor growth are sufficient for the diagnosis of NS. Tumors in NS are typically large, invasive pituitary macroadenomas that present a major therapeutic challenge. The only preadrenalectomy predictive factor strongly linked to increased risk for NS development is the presence of a residual corticotroph adenoma following attempted resection. Postadrenalectomy, elevated levels of ACTH during the first year help to identify those at high risk. The most effective and safe treatment option for NS is surgical intervention, which can then be augmented by radiosurgery if complete resection is not possible. So far, the results of pharmacotherapeutic interventions have been disappointing and inconsistent, but pharmacotherapy may provide a last resort option in cases of resistant tumors. Future molecular characterization and a better understanding of the pathophysiology of pituitary corticotroph tumors may lead to the development of tumor-targeted therapies.

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