Review
Pregledni članak

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Nelson's Syndrome after bilateral adrenalectomy: A comprehensive review of pathogenesis, diagnosis, and treatment approaches

Nelsonov sindrom nakon bilateralne adrenalektomije: sveobuhvatan pregled patogeneze, dijagnoze i pristupa liječenju

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Summary

Nelson's syndrome (NS) is a rare but serious condition that may develop in patients with Cushing's disease following bilateral adrenalectomy (BLA), a surgical intervention employed to control hypercortisolism. NS is characterized by the progressive enlargement of adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas, leading to markedly elevated circulating ACTH levels, diffuse skin hyperpigmentation, and neurological deficits secondary to local mass effects. The pathogenesis of NS primarily involves the removal of cortisol-mediated negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis, which promotes corticotroph tumor proliferation and unchecked ACTH hypersecretion. Genetic mutations, notably in *USP8* and *BRAF*, have been implicated in potentiating tumor aggressiveness. Recent advances in diagnostic practices emphasize dynamic contrast-enhanced magnetic resonance imaging (MRI) and sensitive biochemical assays, which have increasingly supplanted reliance on overt clinical features alone. Therapeutic modalities encompass transsphenoidal surgical resection, radiation therapy, and pharmacological agents such as pasireotide, a somatostatin receptor analogue. Novel therapies like temozolomide, inhibitors of the PI3K/AKT/mTOR signaling axis, and immune checkpoint inhibitors are currently under investigation for refractory or rapidly progressing cases. Nonetheless, management challenges persist, particularly regarding tumor recurrence, treatment resistance, and long-term complications, including hypopituitarism and infection-related morbidity, all of which significantly impair the quality of life. This review integrates contemporary understanding of NS, with emphasis on its molecular pathophysiology, evolving diagnostic landscape, clinical spectrum, and emerging treatment strategies. It further highlights the prophylactic utility of pituitary radiotherapy and the importance of vigilant ACTH surveillance post-BLA. Optimal outcomes necessitate a multidisciplinary, individualized approach focused on early detection, targeted interventions, and continuous follow-up.

Keywords: Nelson's syndrome, Cushing's disease, post-adrenalectomy, ACTH-secreting pituitary adenoma.

Sažetak

Nelsonov sindrom (NS) je rijetka, ali ozbiljna posljedica kirurškog liječenja Cushingove bolesti bilateralnom adrenalektomijom (BLA), kirurškom metodom liječenja hiperkortizolizma. NS je karakteriziran progresivnim povećanjem adenoma hipofize koji izlučuje adrenokortikotropni hormon

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(ACTH), što dovodi do izrazito povišenih razina ACTH-a u cirkulaciji, difuzne hiperpigmentacije kože i neuroloških ispada radi kompresivnog učinka na tkivo hipofize. Patogeneza NS prvenstveno nastaje jer dolazi do nestanka negativne povratne sprege na osovini hipotalamus-hipofiza-nadbubrežna žlijezda, što potiče proliferaciju kortikotropnog tkiva hipofize te posljedično nekontroliranu hipersekreciju ACTH-a te razvoj tumora hipofize. Genetske mutacije, osobito u genima USP8 i BRAF, doprinose agresivnosti tumora. Nedavni napredak u dijagnositici NS ističe dinamičku magnetsku rezonanciju (MRI) s pojačanim kontrastom i osjetljive biokemijske testove kao metode izbora koji sve više istiskuju oslanjanje isključivo na očite kliničke značajke NS. Terapijski, opcije liječenja NS su transfenoidalna kirurška resekcija tumora, zračenje te farmakoterapija pasireotidom (analog receptora somatostatina). Nove terapijske opcije kao npr. temozolomid, inhibitori PI3K/AKT/mTOR signalne osi i inhibitori imunoloških kontrolnih točaka, u studijama se ispituju za refraktorne ili brzonapredujuće slučajeve. Bez obzira na napredak u liječenju i dijagnostici, NS je izazovno stanje, osobito kod slučaja recidiva tumora, rezistencije na liječenje i kod pojave kroničnih komplikacija kao što su hipopituitarizam te infekcije nakon operativnog liječenja, što sve skupa značajno narušava kvalitetu života. Ovaj pregledni rad integrira suvremeno razumijevanje NS-a s naglaskom na njegovu molekularnu patofiziologiju, razvoj dijagnostičkih metoda, klinički spektar prikaza bolesti te nove strategije liječenja. Također ističe korist profilaktičke radioterapije hipofize i važnost praćenja razine ACTH-a nakon BLA. Optimalni ishodi liječenja NS zahtijevaju multidisciplinarni, individualizirani pristup usmjeren na rano otkrivanje, ciljane intervencije i kontinuirano praćenje bolesnika.

Ključne riječi: Nelsonov sindrom, Cushingova bolest, postadrenalektomija, adenom hipofize koji luči ACTH.

Introduction

Nelson's syndrome (NS), was first described in 1958, and represents a rare yet serious complication of bilateral adrenalectomy (BLA) undertaken for the treatment of Cushing's disease, and is characterized by progressive pituitary tumour enlargement, elevated adrenocorticotropic hormone (ACTH) levels, and diffuse skin hyperpigmentation.[1,2] The reported incidence of NS ranges from 8–43% in adults, and might reach up to 66% in pediatric populations post-BLA, with identified risk factors including preoperative ACTH elevation, invasive corticotroph adenomas, prolonged disease duration, and residual pituitary tumour burden.[3] The pathophysiology is primarily driven by the removal of cortisol-mediated negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis, which facilitates unchecked proliferation of corticotroph cells and excessive ACTH secretion, resulting in clinical manifestations such as hyperpigmentation, visual field defects, cephalea, and compressive neurological symptoms.[2,5]

Diagnostic approaches have evolved from reliance on classical clinical features and radiographic evidence to more refined criteria integrating dynamic magnetic resonance imaging (MRI) findings of pituitary tumour progression or new-onset adenoma, alongside biochemical parameters such as plasma ACTH concentrations exceeding 500 ng/L and a ≥30% increase across three separate measurements.[6-8] Diagnostic challenges are compounded by the potential for overlapping ACTH elevations observed in ectopic ACTH syndrome, necessitating comprehensive and multimodal assessment strategies.[5] MRI remains a cornerstone of evaluation, with sellar enlargement or visible pituitary lesions correlating strongly with clinical progression.[8] Furthermore, contemporary guidelines advocate the use of histopathological markers such as the Ki-67 labelling index to gauge tumor proliferative activity and aggressiveness.[5]

Given its potentially life-threatening nature, NS mandates early detection, individualized treatment planning, and sustained multidisciplinary surveillance. Continued research into molecular targets and novel therapeutic agents is essential to optimize patient outcomes and reduce the burden of recurrence.[4,9] This review aims to synthesize current evidence on the pathogenesis, diagnostic advancements, and therapeutic strategies of NS.

Clinical Features

NS is a rare but well-recognized complication arising after BLA performed for the management of Cushing's disease.[8] The syndrome is classically defined by a triad comprising progressive skin hyperpigmentation, markedly elevated plasma ACTH levels, and pituitary tumour enlargement.[8,10] Hyperpigmentation, present in approximately 42% of cases, results from ACTH-driven stimulation of melanocortin 1 receptors on melanocytes, most prominently affecting non–sun-exposed regions such as the linea nigra, surgical scars, and gingival mucosa.[5,9,10] ACTH concentrations in NS are characteristically elevated, with median morning values reported at 1176 pg/ml [interquartile range: 434–1713], and show minimal diurnal fluctuation, reflecting autonomous corticotroph hypersecretion that is largely uncoupled from corticotropin-releasing hormone.[11]

Pituitary tumour progression typically manifests

within 1 to 4 years following BLA, although delayed presentations have been reported up to 24 years postoperatively. Tumour expansion may precipitate neurological and visual disturbances, including headaches—reported in approximately 33% of affected individuals—bitemporal hemianopia due to optic chiasm compression, and cranial nerve palsies arising from cavernous sinus invasion.[12,13] As the tumour mass enlarges, compression of the normal pituitary gland frequently results in panhypopituitarism, with thyroid-stimulating hormone (TSH) and gonadotropin deficiencies among the most commonly observed endocrine sequelae.[10,12] Additional complications include diabetes insipidus, secondary to posterior pituitary involvement, and intracranial hypertension, which may arise from tumour necrosis or rapid growth.[12]

Accurate diagnosis of NS necessitates careful exclusion of alternative conditions. ACTH-driven pigmentation without primary adrenal failure helps differentiate NS from Addison's disease,[5] while the absence of cortisol production following BLA distinguishes it from recurrent or persistent Cushing's disease.[8, 9] Atypical presentations have been described, including cases of hyperpigmentation in the absence of radiologically detectable pituitary adenomas and rare occurrences of pituitary apoplexy, involving haemorrhage or infarction within the adenoma.[14, 15]

Pathophysiology

In refractory Cushing's disease, BLA eliminates endogenous cortisol production and the HPA axis by removing cortisol-mediated negative feedback. This disinhibition leads to unchecked secretion of ACTH by corticotroph adenomas, driving the development of NS. [5,8,11,16–19] Under normal physiology, cortisol suppresses corticotropin-releasing hormone (CRH) and ACTH release through mineralocorticoid (MR) and glucocorticoid receptors (GR). The absence of GR-mediated suppression after BLA results in overproduction of CRH and pro-opiomelanocortin (POMC), culminating in corticotroph cell hyperplasia and progressive ACTH hypersecretion.[16-19]

Genetic mutations further modulate this dysregulation. Variants in *USP8* (e.g., *p.Pro720Gln*, found in ~45% of corticotroph adenomas), *BRAF* (notably V600E), and *NR3C1* (encoding GR) have been implicated in the pathogenesis of NS. These mutations are associated with enhanced POMC transcription, aberrant mitogen-activated protein kinase (MAPK) signaling, and impaired cortisol feedback, though they do not consistently predict tumor size or recurrence risk. [4] Following BLA, compensatory CRH and arginine vasopressin (AVP) secretion from the hypothalamus further stimulate ACTH release. Overexpression of CRH and vasopressin V3 receptors in corticotroph tumors exacerbates this process, promoting tumor proliferation. [5, 8]

Clinically, NS tumors are aggressive, ACTH-secreting macroadenomas. Tumor growth may cause compressive symptoms such as bitemporal hemianopia and cranial nerve deficits. Hyperpigmentation, a hallmark feature, results from ACTH interaction with melanocortin 1 receptors on melanocytes, activating the cAMP/protein kinase A (PKA) pathway to increase melanin synthesis. [8, 20] Corticotroph adenomas comprise 10–15% of all intracranial tumors and are categorized by size (microadenomas <10 mm; macroadenomas ≥10 mm) and function. ACTH-producing adenomas underlie Cushing's disease and its post-adrenalectomy sequelae. A rare subset, ectopic ACTH-producing pituitary adenomas (EAPAs), may arise from ectopic Rathke's pouch remnants, posing unique diagnostic challenges.[22,23] NS typically results from the monoclonal expansion of pre-existing corticotroph adenomas rather than de novo formation. CRH and AVP remain central to tumor stimulation in the absence of adrenal feedback.[5]

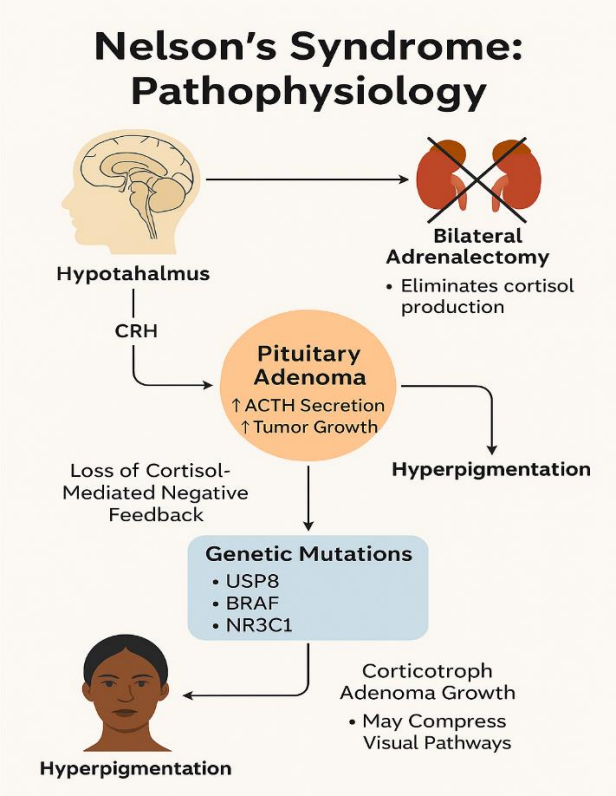

Figure 1: Pathophysiology of Nelson's Syndrome following Bilateral Adrenalectomy: BLA abolishes cortisol-mediated negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis, resulting in disinhibition of corticotropin-releasing hormone (CRH) and increased

ACTH secretion from residual pituitary adenomas. Genetic mutations, including USP8, BRAF, and NR3C1, contribute to enhanced pro-opiomelanocortin (POMC) transcription, tumor progression, and sustained hypersecretion of ACTH. This leads to characteristic hyperpigmentation through melanocortin 1 receptor (MC1R) activation on melanocytes and potential mass effects such as visual pathway compression.

Slika 1.: Patofiziologija Nelsonovog sindroma nakon bilateralne adrenalektomije: *BLA ukida negativnu povratnu informaciju posredovanu kortizolom na hipotalamičko-hipofizno-adrenalnoj (HPA) osi, što rezultira deinhibicijom kortikotropin-oslobađajućeg hormona (CRH) i povećanim lučenjem ACTH iz rezidualnih adenoma hipofize. Genetske mutacije, uključujući USP8, BRAF i NR3C1, doprinose pojačanoj transkripciji pro-opiomelanokortina (POMC), progresiji tumora i produljenoj hipersekreciji ACTH. To dovodi do karakteristične hiperpigmentacije putem aktivacije receptora melanokortina 1 (MC1R) na melanocitima i potencijalnih učinaka na masu poput kompresije vidnog puta.*

Diagnosis

NS is diagnosed by progressive enlargement of an ACTH-secreting pituitary adenoma and rising plasma ACTH levels following BLA, most often performed for refractory Cushing's disease. Diagnostic confirmation integrates biochemical, radiologic, and histopathological criteria. [24, 25] Plasma ACTH concentrations exceeding 500 ng/L, particularly when showing a ≥30% increase over three serial measurements, are considered diagnostic, though isolated elevations may reflect physiological post-BLA fluctuations. [4, 5]

Dynamic contrast-enhanced MRI remains the gold standard for detecting pituitary adenomas. It enables early identification of tumor progression, particularly when combined with functional imaging sequences that highlight delayed contrast uptake.[26, 27] A minimum threshold of more than 10 mm tumor enlargement has been proposed to reduce interobserver variability and enhance reproducibility in radiological assessments. [28] MRI also allows for differentiation from other ACTH-related pathologies, such as ectopic ACTH syndrome or persistent Cushing's disease, both of which can present with elevated ACTH levels. [5, 10] Endocrine testing plays a pivotal role in diagnostic refinement.

High-dose dexamethasone suppression and CRH stimulation tests help distinguish NS from ectopic ACTH production or residual pituitary activity by evaluating ACTH responsiveness patterns. [10, 29] Failure to suppress ACTH with high-dose dexamethasone, combined with an exaggerated CRH-stimulated response, is characteristic of NS. Histopathological analysis remains a cornerstone of diagnosis, especially in surgically resected specimens. Immunohistochemistry confirms ACTH positivity, while the Ki-67 labeling index offers insights into tumor proliferative potential. [30] Molecular testing for somatic mutations such as *USP8* variants can further elucidate disease mechanisms, though these findings are not currently incorporated into standard diagnostic algorithms.[4]

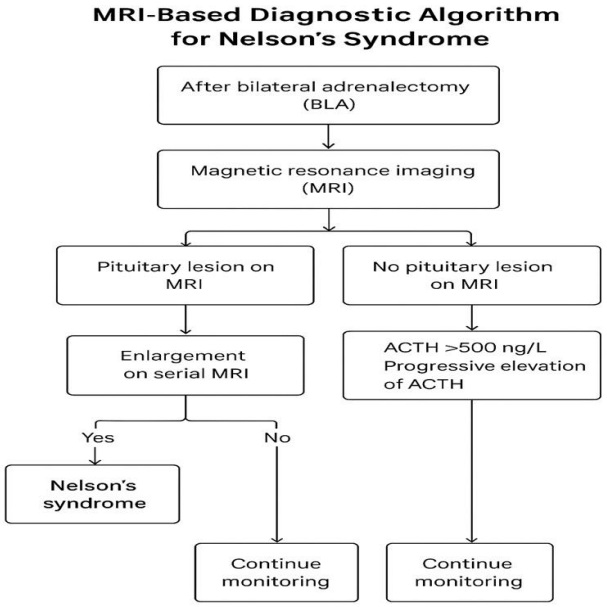

Figure 2: Magnetic Resonance Imaging- based diagnostic algorithm of NS: This algorithm outlines post-adrenalectomy surveillance, integrating ACTH trends and pituitary MRI findings to support early identification, differentiation, and timely intervention in suspected NS.

Slika 2.: Dijagnostički algoritam NS-a temeljen na magnetskoj rezonanciji: *Ovaj algoritam ocrtava nadzor nakon adrenalektomije, integrirajući trendove ACTH-a i nalaze magnetske rezonancije hipofize kako bi se podržala rana identifikacija, diferencijacija i pravovremena intervencija kod sumnje na NS.*

Barber et al.'s criteria define NS as either radiologic evidence of a growing pituitary lesion or ACTH levels persistently above 500 ng/L with progressive increase post-BLA. [4, 5] These thresholds, while widely cited, require contextual interpretation, particularly in the early postoperative period when ACTH fluctuations are common. Routine MRI surveillance is recommended beginning three months post-BLA, followed by annual imaging, to detect early signs of tumor recurrence or growth. [5] Predictors of NS development include the presence of residual pituitary adenomas before adrenalectomy, rapid ACTH elevation during the first postoperative year (e.g., ACTH >100 pg/mL), and high

preoperative urinary free cortisol (UFC >1,000 µg/day). [5] Although hyperpigmentation is frequently observed and linked to ACTH excess, it lacks diagnostic specificity and should not be used in isolation to confirm NS. [5] Diagnosis requires the integration of biochemical progression and radiologic findings, supported by histopathology where applicable.

Treatment and Management

Surgical management

Transsphenoidal resection is the cornerstone of therapy for corticotroph adenomas in NS, achieving biochemical remission in 10 – 70 % of unselected series and only 0 – 60 % when the cavernous sinus is invaded. [8, 32, 33]. Recurrence is common after subtotal excision of macroadenomas, underscoring the need for prolonged surveillance. Postoperative morbidity remains high: panhypopituitarism affects up to 69 %, diabetes insipidus 20 %, cerebrospinal-fluid leakage 15 %, cranial-nerve deficits 5 %, and perioperative mortality 5 %. [30] Transcranial surgery, reserved for tumours inaccessible via the sphenoid sinus, carries even greater morbidity. [32] In a single-surgeon cohort (n = 10), only half of the patients achieved combined biochemical and radiological remission at follow-up. [34]

Radiotherapy

Radiotherapy is indispensable when resection is incomplete or contraindicated. Fractionated stereotactic radiotherapy (FSRT) delivered at 45 – 50 Gy in 1.8 – 2.0 Gy fractions provides durable tumour control while sparing the optic apparatus. [8] In a small linear accelerator (LINAC)-based series, tumour volume tracked hormonal response, and no new endocrine deficits were observed. [35] Gamma-Knife radiosurgery (GKRS) offers particularly robust long-term control. A multicentre International Radiosurgery Research Foundation study (n = 51) reported radiological control in 92.2 %, a median ACTH reduction of 62.7 %, and endocrine remission in 29.4 % after a single 25 Gy margin dose.[33] A separate single-centre series (n = 28) demonstrated 10-year progression-free survival of 91.7 % (95 % CI 80.5 – 100). [36] New hypopituitarism arises in roughly 22 % of GKRS-treated patients. [33, 36] Prophylactic pituitary irradiations at the time of BLA have reduced NS incidence from 39 – 50 % to nearly zero. [8, 32]

Pharmacologic therapies

Somatostatin analogues. Pasireotide, which binds somatostatin receptor subtype-5 (SSTR-5) with high affinity, lowered morning ACTH from ~1,823 ng/L to ~829 ng/L over 28 weeks in an open-label trial; however, tumour volume was unchanged, and 57 % of participants discontinued because of hyperglycaemia. [37] Case reports confirm rapid biochemical responses—ACTH fell from 5,935 to 609 pg/mL and from 42,710 to 4,272 pg/mL—yet also document persistent metabolic toxicity. [38, 39] *Dopamine agonists* such as Cabergoline achieve sustained biochemical control in roughly 30 % of patients but are prone to late "escape." [40]

Alkylating chemotherapy. Temozolomide, valued for its ability to cross the blood–brain barrier, has been reported in six NS cases, with partial responses ranging from transient tumour shrinkage to sustained ACTH suppression. [41] In a pooled series of aggressive pituitary tumours (n ≥ 24), the response rate is 40 – 60 %, although NS-specific data remain sparse. [41] Combination protocols such as capecitabine–temozolomide (CAPTEM) show early promise in refractory disease.[42]

The therapeutic landscape is shifting toward molecularly targeted options. Agents directed at PI3K/AKT/mTOR, cyclin-dependent kinases, and immune checkpoints are in early-phase trials.[11] Given the rarity of NS, enrolment in collaborative studies is essential.

Long-term outcomes and complications

Despite multimodal therapy, NS imposes a heavy chronic burden. Up to two-thirds of surgically managed patients develop panhypopituitarism.[31] Radiotherapy, particularly GKRS, adds an ≈ 20 % risk of new hormone deficits. [33, 36] Structural complications, such as cerebrospinal-fluid leaks, cranial-nerve palsies, and diabetes insipidus, reflect tumour invasiveness and surgical complexity. Although tumour control is highest with GKRS (≈ 90 % at 10 years) [33, 36] and high-precision FSRT [8], durable endocrine remission remains modest (≤ 50 % after surgery; ≈ 30 % after GKRS). Care must therefore balance aggressive disease control against cumulative treatment toxicity, endocrine replacement needs, and quality-of-life considerations.

Future Directions

Therapeutic frontiers

Pharmacological control of NS remains nascent. Pasireotide has produced clinically relevant ACTH suppression and measurable tumour regression in small, heterogeneous cohorts. [39] Yet, in the absence of randomised controlled trials, its long-term efficacy and safety remain uncertain. [25] Hyperglycaemia is the

predominant adverse event, necessitating structured metabolic-monitoring protocols. [8] In parallel, characterisation of corticotroph dopamine-receptor subtypes has revived interest in dopamine agonists: cabergoline has yielded favourable biochemical and radiological responses in case reports and limited series, but methodological constraints and small sample sizes preclude definitive guidance. [10, 11] Debate also persists over prophylactic radiotherapy at the time of bilateral adrenalectomy; while some studies suggest a reduced incidence of NS, robust long-term outcome data are lacking.[8]

Biomarker-driven risk stratification

Accurate risk prediction is pivotal to tailoring surveillance and timely intervention. Persistent or rising ACTH concentrations within the first post-adrenalectomy year reliably herald future NS.[11] Nevertheless, ACTH lacks specificity, underscoring the need for complementary molecular or advanced-imaging biomarkers that refine risk stratification and pinpoint candidates for pre-emptive therapy or intensified follow-up.

Diagnostic gaps and pathway standardisation

A clinically challenging subset of patients exhibits florid hyperpigmentation and marked ACTH excess in the absence of radiologically demonstrable adenoma. The capacity of sparse corticotroph cell clusters to generate disproportionate ACTH remains poorly elucidated and warrants focused molecular investigation. [43] Closing this knowledge gap—together with harmonising diagnostic thresholds and treatment algorithms across centres—will require coordinated, multinational research networks and consensus statements. Only through such collaborative efforts can clinicians achieve consistent, evidence-based management and improve outcomes for individuals affected by this complex post adrenalectomy syndrome.

Conclusion

NS represents a rare but serious sequela of BLA for Cushing's disease, characterized by ACTH hypersecretion and progressive pituitary tumor growth. Its pathogenesis is driven by disrupted hypothalamic-pituitary-adrenal feedback and is further modulated by somatic mutations in genes such as *USP8*, *BRAF*, and *NR3C1*. Diagnostic accuracy has improved with serial ACTH monitoring, high-resolution MRI, and histopathological markers; however, standardized criteria are still evolving. Management typically involves transsphenoidal surgery, with adjunctive radiotherapy and pharmacological agents like pasireotide or temozolomide employed in refractory cases. Despite therapeutic advances, recurrence and treatment-related morbidity remain significant concerns. Further research is needed to identify reliable biomarkers, evaluate prophylactic strategies, and clarify the pathobiology in patients with biochemical NS but no radiological evidence of disease. Multidisciplinary and individualized approaches are essential to improving long-term outcomes in this complex and understudied condition.

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