NELSON'S SYNDROME: PATHOPHYSIOLOGY, DIAGNOSIS, AND MANAGEMENT STRATEGIES

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Abstract: Nelson's Syndrome (NS) is a rare but serious complication arising after bilateral adrenalectomy (BA) in patients with Cushing's disease. The progressive enlargement of a pituitary adenoma and excessive secretion of adrenocorticotropic hormone (ACTH), which can lead to hyperpigmentation, visual disturbances, and potentially life-threatening complications characterize this condition. Despite advances in endocrine surgery and pituitary imaging, NS remains a diagnostic and therapeutic challenge. This article reviews the current understanding of the pathophysiology of NS, presents clinical findings from recent studies, evaluates diagnostic criteria, and discusses treatment options including surgery, radiotherapy, and medical therapy. The study also proposes recommendations for early detection and prevention strategies to minimize the development of NS post-adrenalectomy.

Keywords: Nelson's Syndrome, Cushing's disease, bilateral adrenalectomy, ACTH-secreting pituitary tumor, pituitary macroadenoma, hyperpigmentation, pituitary surgery, radiotherapy, endocrinology, rare diseases

Aim of the Study: The aim of this study is to explore the underlying mechanisms, clinical features, and current treatment modalities for Nelson's Syndrome, with an emphasis on improving early diagnosis and enhancing management outcomes. Furthermore, the study aims to consolidate findings from existing research to provide evidence-based recommendations for clinicians dealing with post-adrenalectomy patients at risk of developing NS.

Materials and Methods: This is a retrospective, literature-based review complemented by a case series from endocrinology departments of two tertiary care hospitals between 2018 and 2024. The inclusion criteria involved patients diagnosed with Nelson's Syndrome following bilateral adrenalectomy for Cushing's disease. Data collection involved review of patient records, imaging studies, histopathological findings, ACTH levels, and clinical symptoms such as hyperpigmentation and neurological changes. Additionally, peer-reviewed journals, clinical trials, and meta-analyses indexed in PubMed, Scopus, and Web of Science were reviewed to consolidate global findings. Keywords used in the search included "Nelson's Syndrome," "Cushing's disease," "ACTH-secreting tumors," and "pituitary adenoma."

Results: Out of 28 patients with a history of bilateral adrenalectomy for Cushing's disease, 10 (35.7%) developed Nelson's Syndrome within a mean duration

of 3.6 years post-surgery. The median age of diagnosis was 42.5 years, with a female predominance (70%). Clinically, all patients presented with progressive hyperpigmentation. Visual field defects were noted in 4 patients due to tumor expansion.

MRI imaging revealed pituitary macroadenomas (>10 mm) in 9 of the 10 patients. The mean plasma ACTH level was significantly elevated (average: 950 pg/mL, normal <50 pg/mL). Histopathological examination of surgically removed tumors confirmed aggressive corticotroph adenomas with Ki-67 indices ranging from 5-15%.

Therapeutic interventions included transsphenoidal surgery (n=6), stereotactic radiosurgery (n=3), and medical therapy with pasireotide and cabergoline (n=4). Three patients required a combination of modalities. Post-treatment follow-up showed tumor size stabilization in 80% of cases and significant reduction in ACTH levels in 70%.

A review of global literature revealed a declining incidence of NS with improved monitoring and prophylactic pituitary irradiation, although cases remain underreported in developing countries due to lack of regular follow-up and advanced imaging capabilities.

Recommendations:

1. Prevention and Surveillance: Patients undergoing bilateral adrenalectomy should be closely monitored with serial ACTH measurements and pituitary MRIs every 6–12 months to detect early signs of NS.

2. Patient Education: Educating patients about the symptoms of NS, particularly skin pigmentation changes and visual issues, can aid in earlier self-reporting and diagnosis.

3. Prophylactic Radiotherapy: Consideration should be given to prophylactic pituitary radiotherapy at the time of BA in patients at high risk for NS, especially those with residual tumor visible on MRI.

4. Multimodal Treatment Approach: A combination of surgical debulking, radiotherapy, and pharmacological therapy tailored to tumor size and ACTH levels provides the most effective management outcomes.

5. International Registry: Establishing a global registry for NS could facilitate better understanding of disease patterns and help refine diagnostic and treatment guidelines.

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