PITUITARY TUMORS

New Endocrine Society guidelines for hyperprolactinemia—piecing together the pituitary puzzle

A task force appointed by the Endocrine Society has released new clinical practice guidelines for the diagnosis and treatment of hyperprolactinemia in a recent issue of the *Journal of Clinical Endocrinology and Metabolism*.

Hyperprolactinemia can be caused by pituitary tumors arising from lactotroph cells, so-called prolactinomas, but may also develop as a result of pharmacological or pathological disruption of hypothalamic–pituitary dopaminergic pathways. Regardless of its etiology, "hyperprolactinemia leads to infertility, hypogonadism and related secondary effects of low sex steroid levels in both women and men," points out Shlomo Melmed (Cedars-Sinai Medical Center, Los Angeles), lead author of the guidelines. Nonetheless, in some patients, hyperprolactinemia can be asymptomatic.

Using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system to describe both the strength of recommendations and the quality of evidence, the task force provide 20 recommendations or suggestions over six categories, including diagnosis and causes of hyperprolactinemia; management of drug-induced hyperprolactinemia and of prolactinomas; resistant and/or malignant tumors; and management of prolactinoma during pregnancy.

On the basis of strong evidence, the task force recommends a diagnosis of hyperprolactinemia with a single measurement of serum prolactin rather than dynamic testing of prolactin secretion. Moreover, serial dilution of serum samples should be performed in cases of very large pituitary tumors but only mildly elevated prolactin levels to eliminate the 'hook effect'—an artifact of some immunoradiometric assays that can yield a falsely-low prolactin value.

"Drug-induced hyperprolactinemia is very frequently encountered in clinical practice and should be considered as first-line differential diagnosis in all patients who present with hyperprolactinemia, before a diagnosis of prolactinoma is entertained," adds Melmed. "Even prolactin levels above 200 ng/ml may be caused by antipsychotic medications." Before embarking on expensive MRI of the pituitary gland, medication use and other secondary causes of hyperprolactinemia, such as renal failure, hypothyroidism and parasellar tumors, must, therefore, be excluded first.

Hyperprolactinemia caused by prolactinomas should be treated medically rather than by surgical excision. For the management of symptomatic prolactin-secreting microadenomas or macroadenomas, dopamine agonist therapy should be used to lower prolactin levels, decrease tumor size and restore gonadal function. Adverse effects of these drugs are critically evaluated, especially the concern that very high doses of cabergoline have been associated with cardiac valvular abnormalities in patients with Parkinson disease. Nevertheless, the task force strongly recommends the use of cabergoline over other dopamine agonists.

Before referral to surgery, dopamine agonist doses of patients with resistant prolactinomas—those who do not achieve normalization of prolactin levels or marked reduction in tumor size on standard doses—should be increased to maximum tolerable doses, and patients resistant to bromocriptine ought to be switched to cabergoline.

Moreover, the task force provides guidance for the medical management of prolactinomas during pregnancy. Dopamine agonist treatment should be discontinued as soon as pregnancy is confirmed. The authors do not advocate performing routine serum prolactin measurements or MRI scans during pregnancy, although these investigations should be undertaken immediately if signs of tumor regrowth, such as visual field defects or headaches, recur. Those who experience symptomatic regrowth of a prolactinoma during pregnancy, should be treated with bromocriptine.

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Suggestions for the management of drug-induced hyperprolactinemia, which are based on weaker evidence than the previously described recommendations, include discontinuation of medication for 3 days or substitution with an alternative drug, followed by remeasurement of serum prolactin; no discontinuation or substitution of antipsychotic agents unless confirmed with the patient's physician; no treatment of patients with asymptomatic medication-induced hyperprolactinemia; and estrogen or testosterone therapy in patients with long-term hypogonadism related to medication-induced hyperprolactinemia.

"This work should serve as an evidence-based guideline for the standard care of patients with hyperprolactinemia, written by experts in the field who critically evaluated and graded the literature and also provide extensive personal experience," concludes Melmed.

Linda Koch

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