What is the recommended evaluation and treatment for elevated serum prolactin?

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EVIDENCE-BASED ANSWER

History and physical examination can distinguish among most physiologic, pharmacologic, or pathologic causes of an elevated serum prolactin level (SPL) (strength of recommendation [SOR]: **C**, expert opinion). Patients with unexplained elevations of serum prolactin or with a level above 200 ng/mL should undergo imaging of the sella turcica (SOR: **C**, expert opinion). Mildly elevated SPL due to physiologic causes may be managed expectantly (SOR: **B**, cohort studies) and pharmacologic elevations may be treated by discontinuing the causative medication (SOR: **C**, expert opinion). Elevated SPL due to pathologic causes requires both monitoring for complications and treatment of the underlying condition (SOR: **C**, expert opinion).

Dopamine agonists are effective for patients requiring drug treatment (SOR: **B**, systematic review of cohort studies), and cabergoline is more effective and better tolerated than bromocriptine (SOR: **B**, randomized controlled trial [RCT]). Surgery is reserved for symptomatic patients not controlled medically (SOR: **C**, expert opinion).

CLINICAL COMMENTARY

Patients with mildly elevated SPLs can be safely watched with testing and symptom monitoring

Most elevated prolactin levels in my practice have been mild and often secondary to medication, though there are a host of causes, as listed in the **TABLE**. This Clinical Inquiry reassures us that patients with mildly elevated SPLs can be safely watched with serial testing and monitoring symptoms. Obtaining SPLs only on fasting specimens can help improve test accuracy. The feared risk of vision loss due to a macroadenoma seems to be quite small. Patients with significantly elevated SPLs with amenorrhea or infertility deserve referral to clinicians comfortable with using dopamine agonists because of the high rate of success with this treatment.

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Evidence summary

An expert guideline recommends a history and physical examination to determine whether an elevated SPL is due to physiologic, pharmacologic, or pathologic causes (**TABLE**).[1] The fasting morning SPL is least variable and correlates best with a disease state.[1] Clinical correlation is necessary to reveal false positives (due to biologically inactive forms of prolactin) or false negatives (due to very high SPLs that exceed the ability of the assay). If an elevated SPL is suspected despite a normal laboratory report, retesting with serum diluted 1:100 can identify a false-negative value.[2]

A detailed drug history is important since drug-induced elevated SPL is common.[1] Laboratory evaluation includes thyroid-stimulating hormone, blood urea nitrogen, and creatinine, as well as pregnancy testing when applicable. If no cause of elevated SPL is identified by initial clinical evaluation or if the SPL is greater than 200 ng/mL, experts recommend imaging of the sella turcica with computed tomography or magnetic resonance imaging.[1]

Physiologic causes. For patients with a mildly elevated SPL due to a physiologic

TABLE

Physiologic, pharmacologic, and pathologic causes of an elevated serum prolactin level[1]

PHYSIOLOGIC
Pregnancy
Ectopic pregnancy
Lactation
Nipple stimulation
Stress
Sleep disorder
PHARMACOLGIC
Dopamine receptor antagonists: phenothiazines, butyrophenones, thioxanthene, risperidone, metoclopramide, sulpiride, pimozide
Dopamine-depleting agents: α-methyldopa, reserpine
Hormones: estrogens, antiandrogens
Others: danazol, isoniazid, verapamil, cyproheptadine, opiates, H2-blockers (cimetidine), cocaine and marijuana, tricyclic antidepressants
PATHOLOGIC
Acromegaly
Alcoholic cirrhosis
Chest wall trauma or tumor
Herpes zoster
Hypothalamic and pituitary stalk disease
Hypothyroidism
Pituitary tumors: prolactinomas, adenomas
Polycystic ovarian syndrome
Renal failure
Sarcoidosis

cause, experts recommend expectant management. Patients should be monitored for symptoms of hypogonadism (amenorrhea, infertility, or sexual dysfunction) and have SPL measured at 6- to 12-month intervals.[1] In cohort studies, treatment of the underlying cause of elevated SPL reverses secondary physiologic changes of low estrogen or testosterone, and hypogonadism.[3–5]

Pharmacologic causes. Eliminating a pharmacologic cause may lead to normalization of SPL, although experts recommend psychiatric consultation before discontinuing neuroleptic medications.[1]

Pathologic causes. Experts advise treating the underlying cause of a pathologic elevation of SPL. Patients with microadenoma should have SPLs monitored to prevent complications of decreased bone mineral density and sexual dysfunction due to persistently elevated SPL. Patients with a macroadenoma (>1 cm) are at risk for tumor growth and require serial imaging studies in addition to treatment of SPL, according to expert opinion.[1–3]

Medical therapy. Medical therapy with a dopamine agonist is indicated for patients with either symptoms of hypogonadism due to elevated SPL, or neurologic symptoms due to the size of a macroadenoma.[1] In a review of 13 cohort studies, bromo-criptine improved symptoms and reduced SPLs to normal for 229 of 280 women (82%).[6] A cohort study of 27 patients with macroadenomas treated with bromocriptine found 10% to 50% reductions of tumor size.[7] A randomized controlled trial treating 459 women having hyperprolactinemic amenorrhea with either cabergoline or bromocriptine achieved a stable normal SPL in 83% and 59%, respectively ($P<.001$). Adverse effects were common but were less common with cabergoline (68% vs 78%) and resulted in fewer discontinuations (3% vs 12%).[8]

Surgical therapy. Surgery is indicated for patients unresponsive to or intolerant of medical therapy, or who have visual field loss, cranial nerve palsy, or headache due to macroadenoma.[1] A retrospective review of patients who underwent surgical resection found a 40% recurrence rate.[9]

Recommendations from others

Williams Textbook of Endocrinology includes the recommendations above and advises seeking consultation for patients with mass effects of macroadenomas such as visual field loss, cranial nerve palsy, or headaches; for patients with progressive elevation of SPL despite medical treatment; and for pregnant women.[4] Conventional antipsychotic agents are commonly associated with elevated prolactin due to dopamine agonist activity. Some atypical antipsychotics may lead to lower levels of elevated prolactin, transient elevations or marked elevations.[10] Experts recommend following serial SPLs, if antipsychotics are truly needed. Psychiatric consultation may assist in making decisions about medication selection. Patients with

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symptoms (galactorrhea, amenorrhea, headaches, visual disturbances, sexual dysfunction) or levels of 200 or more, should undergo an MRI or CT. Experts recommend monitoring levels every 1 to 3 months.[1]

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