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Clinical Case Study

Increased Prolactin Concentrations in a Patient with Bipolar Disorder

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CASE

A 58-year-old woman in the depressive phase of bipolar disorder (BPD)[3] type 1 enrolled in a clinical study of the efficacy of a new form of electroconvulsive therapy (ECT) for her depression, because ECT has not been commonly used for the treatment for BPD or depression. BPD is any of several mood disorders characterized by alternating episodes of depression and mania or by episodes of depression alternating with mild nonpsychotic excitement. BPD type 1 is distinguished from type 2 according to the severity of increased mood symptoms *(1)*. At study enrollment, the patient reported severe sadness, a lack of motivation, fatigue, general malaise, feelings of guilt, and an increased need for sleep, but she had no suicidal or homicidal thoughts. She had no history of galactorrhea. A physical examination revealed nothing outstanding except decreased tendon reflexes in the patellar and the achilles, and a small nodule on the closure site from a previous hysterectomy. A cranial computed axial tomography (CAT) scan was performed to assess for increased intracranial pressure before proceeding with ECT; no unusual findings were noted. Initial blood tests showed a serum sodium concentration of 135 mEq/L (135 mmol/L; reference interval, 135–145 mmol/L), a high triglyceride concentration [217 mg/dL (2.45 mmol/L); reference interval, <150 mg/dL (<1.69 mmol/L)], and a VLDL cholesterol concentration of 43 mg/dL [1.11 mmol/L; reference interval, <30 mg/dL (<0.78 mmol/L)]. The results of a urine drug screen for amphetamines, barbiturates, benzodiazepine, cannabinoids, cocaine, opiates, and phencyclidine were negative.

As per the study protocol, a baseline blood sample was drawn 5 min before treatment, and at 5, 15, 30, 45 min after seizure termination. Prolactin (PRL) concentrations were assessed from these blood draws during the second and fourth treatments of the study by means of a 2-site sandwich immunochemiluminometric assay (Siemens ADVIA Centaur® System). These assessments revealed unexpected and markedly increased baseline PRL concentrations (Table 1). PRL concentrations increased further after ECT treatment and were still increased 45 min after the seizure. Although an increase in PRL concentrations after seizure initiation was expected, the increased baseline concentrations were not, and a clinical investigation was conducted to determine the cause of the asymptomatic hyperprolactinemia in this patient.

QUESTIONS TO CONSIDER

1. How is PRL measured in clinical laboratories, and what analytical interferences can lead to a falsely increased PRL result?
2. What are the physiological and pathologic conditions characterized by hyperprolactinemia?
3. Can medications cause hyperprolactinemia?

DISCUSSION

PRL is a pituitary hormone that causes breast enlargement during pregnancy and milk production during lactation. The hypothalamus exerts a predominantly

Table 1. PRL concentrations before and after the ECT treatment (from baseline to 45 min after seizure termination).[a]

	PRL concentration, μg/L				
Treatment	Baseline	5 min after seizure	15 min after seizure	30 min after seizure	45 min after seizure
Second	164.1	188.5	170.8	197.5	177.6
Fourth	177.5	186.9	196.7	218	196.5

[a] Reference interval, 1.8–20.3 μg/L (78–883 pmol/L) for postmenopausal women. For PRL, 1 μg/L = 43.48 pmol/L.

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[3] Nonstandard abbreviations: BPD, bipolar disorder; ECT, electroconvulsive therapy; CAT, computed axial tomography; PRL, prolactin.

inhibitory influence on PRL secretion through dopamine. Dopamine attaches to D2 receptors, thereby causing arrest of PRL release by lactotrophs. Disruption of the pituitary stalk can lead to a moderate increase in PRL secretion. PRL-releasing factors include thyrotropin-releasing hormone and vasoactive intestinal peptide.

Normal PRL is a polypeptide of 199 amino acid residues with a molecular weight of 23 kDa; it is known as monomeric or "little" PRL. It is the product of the PRL gene and is the major secretory product. Another circulating form of PRL has a molecular weight between 50 kDa and 60 kDa and is termed "big" PRL. Big PRL is believed to be a complex of monomeric PRL and a 32-kDa binding protein that is identical to the extracellular domain of the human PRL receptor *(2)*. PRL can also be bound to immunoglobulins (most commonly IgG) to form macro-PRL or "big-big" PRL, which has a molecular weight of 150–170 kDa *(3)*.

During pregnancy, estrogen-stimulated lactotroph hyperplasia leads to a progressive increase in serum PRL and a 10-fold increase at term. In postpartum lactating women, PRL concentrations remain increased until about 6 weeks after delivery and gradually return to normal. The woman in the present case had undergone a hysterectomy, so the increased PRL concentrations were not due to pregnancy.

Hyperprolactinemia can also be found in patients with macro-PRL. In most patients, macro-PRL constitutes <1% of circulating PRL. Serum from a hyperprolactinemic patient containing mainly macro-PRL is termed "macroprolactinemia." Macroprolactinemia is suspected when a hyperprolactinemic patient lacks clinical symptoms directly ascribable to the hormone excess (although some patients with macroprolactinemia do have signs and symptoms of PRL excess). In patients with asymptomatic hyperprolactinemia, the Endocrine Society Clinical Practice Guideline suggests assessing for macro-PRL as an initial step *(4)*. In addition, many commercial assays do not readily separate macro-PRL from monomeric PRL *(4)*. Several methods, including gel filtration chromatography, ultrafiltration, polyethylene glycol precipitation, and protein A, protein G, or antihuman IgG antibody binding can be used to recognize big-big PRL *(5)*. To rule out macroprolactinemia, one of the patient's serum samples was treated with polyethylene glycol precipitation *(6)*. PRL concentrations in untreated and treated samples were 215 μg/L (9350 pmol/L) and 200 μg/L (8696 pmol/L), respectively; therefore, no notable amount of macro-PRL was detected.

In addition to macro-PRL, PRL concentrations can be falsely increased in the presence of heterophilic antibodies or human antimouse antibodies *(7)* via the bridging of the capture antibody and the tracer antibody used in the assay. We used a heterophilic antibody–blocking reagent (Scantibodies Laboratory) to treat the sample. There was no notable difference between the treated and untreated samples in PRL concentrations [175.2 μg/L (7617 pmol/L) before treatment vs 196.8 μg/L (8556 pmol/L) after treatment], thereby ruling out heterophilic antibody interference.

The most common pathologic condition causing hyperprolactinemia is a PRL-secreting pituitary tumor. In general, the serum PRL concentration parallels tumor size, so PRL-secreting pituitary macroadenomas are typically associated with concentrations >250 μg/L (>10 870 pmol/L). In many cases, concentrations exceed 1000 μg/L (43 480 pmol/L). In patients with large, nonfunctioning pituitary adenomas, PRL concentrations are usually <250 μg/L (<10 870 pmol/L). Hyperprolactinemia is also seen in patients with renal failure, primary hypothyroidism, polycystic ovarian syndrome, cirrhosis, and chest trauma. In some individuals, no cause of the hyperprolactinemia can be identified. When other causes of hyperprolactinemia have been ruled out, the final diagnosis of PRL-secreting pituitary tumors can be confirmed by gadolinium-enhanced MRI *(8)*. In the present case, a cranial CAT scan had been performed, and no abnormalities were revealed. We did not perform an MRI because we had not excluded other possibilities, and the patient did not have any clinical indications of prolactinoma, such as menstrual irregularity, amenorrhea, or galactorrhea. Of note is that men and postmenopausal women with hyperprolactinemia may be asymptomatic, because they do not experience the subtle sign of an irregular menstrual period.

After we had ruled out that the increased PRL concentration was due to pregnancy and analytical interferences, we tried to ascertain whether the hyperprolactinemia was due to medications. Neuroleptic/antipsychotic agents commonly cause hyperprolactinemia *(4)*. The mechanism of neuroleptic- or antipsychotic-induced hyperprolactinemia is the dopamine-antagonist effects of these medications *(4)*. Any disruption in dopaminergic pathways or D2 receptor binding sites can increase the PRL concentration. High-potency typical antipsychotic medications, such as phenothiazines, butyrophenones, and thioxanthenes are associated with hyperprolactinemia, whereas atypical antipsychotics, such as molindone, clozapine, olanzapine, quetiapine, ziprasidone, and aripiprazole are thought to have little if any effect. However, risperidone, which is classified as a high-potency atypical antipsychotic, has been shown to markedly increase the serum PRL concentration *(9)*. Of the patients taking phenothiazines or butyrophenones, 40%–90% have hyperprolactinemia, whereas

50%–100% of patients on risperidone have significantly increased PRL concentrations *(10)*. Other drugs, such as verapamil, can also cause hyperprolactinemia by blocking hypothalamic dopamine *(9)*, whereas opiates and cocaine increase PRL through the μ receptor *(4)*. We reviewed the patient's medications and found that she was taking 5.5 mg risperidone per day, 3 mg lorazepam per day, omeprazole, dietary supplements of Conjointin (glucosamine), zinc, biotin, folate, bisoprolol, and aldactone. Among these drugs, risperidone was the most likely cause of the hyperprolactinemia *(4)*. To determine whether the increased PRL concentration in this patient was induced by risperidone, we slowly decreased the risperidone dose after discussion with the attending physician. The PRL concentration reached 4 μg/L (174 pmol/L) 1 week after risperidone had been completely discontinued and replaced with quetiapine, a less antidopaminergic medication. This result suggests that risperidone caused the hyperprolactinemia in this patient.

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POINTS TO REMEMBER

- PRL is commonly measured with sandwich immunoassays that use chemiluminescent or electrochemiluminescent techniques. Similar to any sandwich immunoassay, heterophilic antibodies can bridge the capture antibody and the tracer antibody to produce a falsely increased PRL. The interference can be identified with heterophilic antibody–blocking reagents. In addition, patients with macro-PRL, a complex of PRL and antibody, can have highly increased PRL concentrations. Macro-PRL can be identified with gel filtration chromatography, ultrafiltration, protein A binding, protein G binding, antihuman IgG antibody binding, and polyethylene glycol precipitation.
- PRL greatly increases during pregnancy and lactation. Pathologically, hyperprolactinemia is often found in patients with PRL-secreting pituitary macroadenomas, which are typically associated with concentrations $>$250 μg/L ($>$10 870 pmol/L); in many cases, concentrations exceed 1000 μg/L (43 480 pmol/L). In patients with large, nonfunctioning pituitary adenomas, PRL concentrations are usually $<$250 μg/L ($<$10 870 pmol/L). Hyperprolactinemia is also seen in renal failure, primary hypothyroidism, polycystic ovarian syndrome, cirrhosis, and chest trauma patients. In some individuals, no cause of hyperprolactinemia can be identified.
- The most common medications that cause hyperprolactinemia are the antipsychotic agents. Other medications causing hyperprolactinemia include antidepressants, antihypertensive agents, and drugs that increase bowel motility. Opiates, cocaine, and estrogen can also increase blood PRL concentrations. The mechanism of neuroleptic drug– and antipsychotic drug–induced hyperprolactinemia is the dopamine-antagonist effect of these medications. Drug-induced hyperprolactinemia can be identified by stopping the medication temporarily or by switching temporarily to another medication in the same class that does not cause hyperprolactinemia to see if PRL concentrations return to normal.

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