Galactorrhea with menstrual irregularity: something other than a prolactinoma?

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Abstract
We report the case of a 29-year-old female who presented with galactorrhea and irregular menstrual periods. Laboratory tests showed elevated levels of serum prolactin, raising the possibility of a prolactinoma. However, further evaluation revealed an unusual and unexpected cause for her illness.

Keywords galactorrhea, hyperprolactinemia, prolactinoma, Wilson's disease

Introduction
Galactorrhea and menstrual irregularity are typical manifestations of hyperprolactinemia. In the absence of a demonstrable pituitary mass on MRI imaging, the condition is usually labeled as idiopathic hyperprolactinemia and presumed to be due to microadenomas too small to visualize. As our case will demonstrate, however, there are a number of other causes that should be considered in any patient with otherwise unexplained hyperprolactinemia.

Case report
A 29-year-old female with no premorbidities was admitted with complaints of galactorrhea for the past week and menstrual irregularities over the past six months. Her last childbirth six years ago had been uneventful. She denied any history of substance abuse. There was no significant family history. General physical examination showed mild pallor. Systemic examination was entirely normal. Routine laboratory investigations showed elevated serum prolactin (190 ng/mL). Liver enzymes were minimally elevated, while albumin-globulin ratio was reversed (serum albumin: 2.3 gm/dL, serum globulin: 4.1 gm/dL). Renal and thyroid function tests were normal (serum urea: 34 mg/dL, serum creatinine: 1.4 mg/dL, TSH: 2.6 mIU/L). Prothrombin time was prolonged (patient: 20.9 sec, control: 14.8 sec; INR: 1.49). Abdominal ultrasound demonstrated coarse echotexture of the liver, a dilated portal vein (12 mm) and mild splenomegaly (12.3 cm), features consistent with hepatic cirrhosis. Although stool examination was negative for occult blood, upper GI endoscopy revealed grade I esophageal varices and mild portal hypertensive gastropathy. MRI imaging of the brain was performed and ruled out the presence of any pituitary mass.

As the patient continued to have galactorrhea, gynecological consultation was sought. Transvaginal ultrasonography was unremarkable; serum levels of gonadotrophins were normal (serum FSH: 11.82 mIU/mL, serum LH: 2.51 mIU/mL) and expectant management was advised.

The patient was now evaluated for the cause of cirrhosis. Serologic markers for hepatitis B and C infections were negative, as were tests for anti-nuclear antibodies. However, serum ceruloplasmin was low (9.0 mg/dL); 24-hour urine copper estimation was significantly elevated (758 mcg). Slit lamp microscopy revealed Kayser-Fleischer rings (Fig. 1) and sunflower cataracts (Fig. 2). A diagnosis of compensated hepatic cirrhosis secondary to Wilson’s disease with symptomatic hyperprolactinemia was made. Retrospectively, the patient displayed no evidence of neurological involvement, either clinical or radiological, despite the presence of Kayser-Fleischer rings. Therapy with d-penicillamine was initiated at 300 mg TID, and subsequently increased to 600 mg TID. On follow-up she reported significant improvement in symptoms including cessation of galactorrhea within 3 months and regularization of her menstrual cycle.

Discussion
Also known as progressive hepatolenticular degeneration, Wilson’s disease is a genetic disorder of copper metabolism first described by Kinnier Wilson in 1912 [1]. Since that time,
our understanding of the disease has steadily progressed, so that we can now trace the disease to a mutation in the ATP7B gene on chromosome 3. Although inherited, Wilson's disease can result from over 300 mutations of the gene in question [2], and affected individuals may be heterozygous for two different mutations that manifest in combination. Consequently, a positive family history is often not elicited, as was the case in our patient.

Clinical manifestations of the condition can be diverse [2] including both acute disease such as fulminant hepatitis and Coomb's negative hemolytic anemia, and chronic disease such as hepatic cirrhosis, Parkinsonism-like syndromes, neuropsychiatric illness and aminoaciduria. Diagnosis depends on the demonstration of a copper-overload state as evidenced by the presence of Kayser-Fleischer rings within the cornea, and high levels of urinary and hepatic copper [3], estimated respectively by a 24-hour sample, and by means of liver biopsy. Treatment modalities include elemental zinc [4], which interferes in copper absorption, and chelators such as d-penicillamine [5], trientine and ammonium tetrathiomolybdate. Liver transplantation remains the only curative therapy available [6].

Although hyperprolactinemia is known to occur in patients with cirrhosis [7], it is most often asymptomatic. We suggest that this paradox might be due to the preponderance of male patients included in such studies. It is well known that the physiologic action of prolactin is potentiated by the presence of high levels of estrogen and progesterone. Therefore, for a given degree of hyperprolactinemia, a female subject is more likely to develop symptoms such as galactorrhea than a male patient. In particular, endocrine manifestations of Wilson's disease remain poorly understood. Gonadal dysfunction can produce amenorrhea, oligomenorrhea and recurrent abortions in females, although true infertility is rare [8]. Similarly, there have been case reports of hypoparathyroidism, possibly secondary to copper deposition within the parathyroid glands [9].

It is pertinent to note that there is no clear relationship between the severity of liver disease and the degree of hyperprolactinemia [10]. As shown in our case, as a direct consequence of this discrepancy, hyperprolactinemia can manifest well before other more classical complications of cirrhosis, such as variceal bleeding and ascites, appear. This is especially important in the context of patients with a potentially treatable cause of cirrhosis, such as Wilson's disease, where the rapid and timely institution of appropriate therapy can significantly alter the natural history of the disease.

In conclusion, unexplained hyperprolactinemia can be a marker for underlying systemic disease, and therefore warrants careful investigation before being labeled as idiopathic.
Galactorrhea and metrorrhagia but not a prolactinoma

References