POSTINFANTILE GIANT CELL HEPATITIS ASSOCIATED WITH LONG-TERM ELEVATED TRANSAMINASE LEVELS IN TREATED GRAVES' DISEASE

To the Editor:

A 64-year-old woman presented with a 3-month history of fatigue, jaundice, abdominal distension, and orthopnea. She had persistently elevated transaminase levels that had been incidentally discovered 8 years before during thyroidectomy for Graves' disease. They were attributed to her thyroid disease and remained elevated over the subsequent years.

Her examination revealed icterus, stigmata of chronic liver disease, and an abdominal fluid wave without hepatosplenomegaly. Medications included thyroxine and a multivitamin. Laboratory data disclosed the following values: total bilirubin, 7.3 mg/dL (4.5 mg/dL conjugated); aspartate aminotransferase, 646 U/L; alanine aminotransferase, 372 U/L; alkaline phosphatase, 281 U/L; total protein, 4.5 mg/dL; albumin, 2.2 mg/dL; and ferritin, 500 ng/mL. Hepatitis B and C, antinuclear antibodies, and antimitochondrial serologies were negative, but anti–smooth muscle antibody serology was positive (1:80 titer). Thyroid-stimulating hormone level was 14 μIU/mL. Abdominal ultrasound revealed a normal heterogeneous liver, and a spleen sized at the upper limits of normal. Ascites analysis confirmed a noninfected transudative fluid. A liver biopsy revealed giant cell hepatitis and cirrhosis (Figure). Treatment for autoimmune hepatitis was initiated with oral prednisone, administered daily at 1.5 mg/kg. The patient's transaminase levels improved initially; however, her clinical status deteriorated rapidly, and she died.

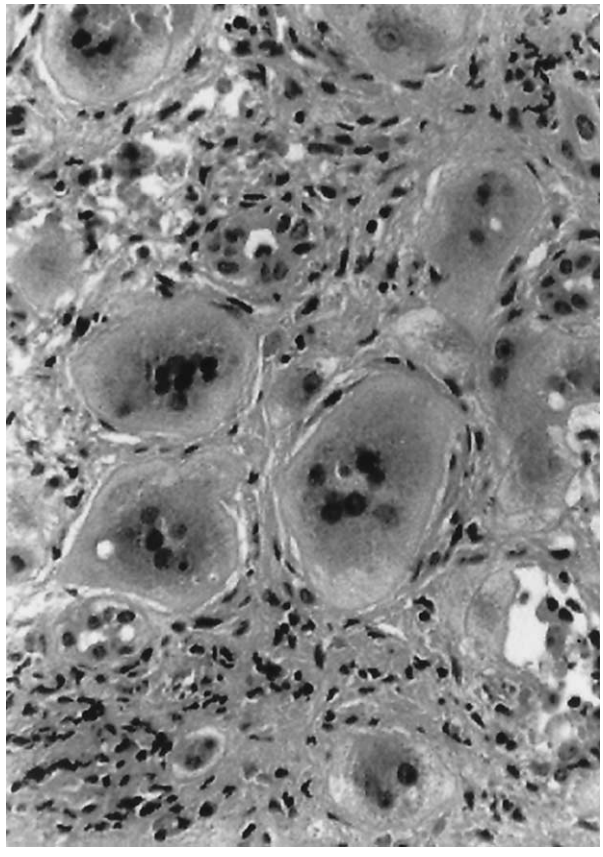

Figure. Liver biopsy showing giant cell hepatitis and cirrhosis.

Giant cell hepatitis encompasses a group of disorders with varying clinical presentations, etiologies, and other specific histologic findings (1,2). Etiological factors include drugs (e.g., methotrexate), viruses (e.g., hepatitis A, B, and C; Epstein-Barr virus; paramyxoviruses), and autoimmune disorders, such as systemic lupus erythematosus (2–6). Adult hepatitis with extensive giant cell change is referred to as postinfantile giant cell hepatitis (1), which has been associated with high mortality and a rapidly progressive course in about half of patients, leading to death or the need for orthotopic liver transplantation (4).

We hypothesize that our patient had autoimmune hepatitis that eventually led to postinfantile giant cell hepatitis. What was striking was the 8-year history of asymptomatic elevated transaminase levels. In 29 patients with postinfantile giant cell hepatitis, only 3 had elevated transaminase levels for more than 1 year (1,2). Most patients had elevated transaminase levels from 2 weeks to 8 months before diagnosis (2).

Another question raised was the association of thyroid disease and hepatitis, since our patient's long-term elevated transaminase levels had been attributed to Graves' disease. In hyperthyroidism, excess thyroid hormone causes hepatic tissue hypoxia owing to an increase in hepatic and splanchnic oxygen requirement (7). Abnormalities of hepatic enzymes have been reported in as many as 76% of hyperthyroid patients, but the incidence of overt clinical hepatitis is less than 1% (8). Hypothyroidism also affects the liver by increasing bilirubin UDP-glucoronyl transferase activity, reducing p-nitrophenol transferase activity, reducing bile flow and excretion, and increasing the proportion of conjugated bilirubin (8). Notably, abnormalities in liver tests normalize once the thyroid disease is recognized and treated.

Postinfantile giant cell hepatitis encompasses a heterogeneous group of disorders and should be considered in patients with long-standing hepatitis of unclear etiology, especially if associated with antecedent autoimmune disease.

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ANOREXIA NERVOSA AND THE RISK OF SUDDEN DEATH

To the Editor:

Anorexia nervosa affects 0.5% to 1% of young women, and is characterized by a refusal to maintain a minimum body weight, an abnormal perception of body size and shape, and an intense fear of weight gain (1). Patients who have anorexia nervosa can be divided into two subtypes: a restricting type, which is characterized by a constant avoidance of food, and a binge/purging type, which is characterized by weight loss, binge eating, and compensatory behavior. Mortality in women with anorexia nervosa is 12 times greater than in age-matched normal women, and is often due to cardiac complications (2). We describe two women with anorexia who underwent cardiac arrest shortly after admission to the Toxicology Unit of our hospital.

The first case was a 33-year-old woman diagnosed as having had the binge/purging form of anorexia since adolescence, who was admitted because of a suicide attempt. She had ingested approximately 21 g of potassium chloride and 700 mg of flurazepam monohydrochloride; she had a body mass index of 17.5 kg/m^2. After 1 hour, she underwent 2 cardiac arrests due to ventricular fibrillation, but was treated successfully with direct-current cardioversion. In spite of the potassium overdose, her kalemia was very low (1.6 mEq/L), and she subsequently received an intravenous infusion of potassium chloride. After 5 hours, she experienced several episodes of torsade de pointes, followed by ventricular fibrillation, which were resolved by cardioversion. Continuous intravenous therapy with potassium chloride, lidocaine, and magnesium sulfate was maintained during the following days. No further alteration in heart rhythm was observed after kalemia reached 4.5 mEq/L.

Hypokalemia, which is caused by vomiting, starvation, and abuse of potassium-depleting drugs, is common in patients with the binge/purging form of anorexia. The relative surplus of potassium in the myocardial cells determines an increase in inward currents during the repolarization phase, generating an early after-depolarization phenomenon. The electrocardiogram (ECG) shows a prolonged QT interval, which facilitates arrhythmias, torsade de pointes, and ventricular fibrillation, especially when heart frequency is low, as in patients with anorexia nervosa (3).

In the second case, a 39-year-old woman with a body mass index of 16.1 kg/m^2 and who had the restricting form of anorexia for the last 20 years, was admitted because she had attempted suicide by ingesting about 1400 mg of trazodone and 575 mg of thioridazine hydrochloride. She was treated immediately with gastric lavage and an intravenous infusion of mannitol. After 10 hours, she underwent a cardiac arrest (torsade de pointes followed by ventricular fibrillation), which was reversed by a single direct-current cardioversion. The ECG showed a sinus rhythm of 75 beats per minute, diffused alterations of the ST tract, and a prolonged QT interval of 520 ms. Continuous infusion of lidocaine was started. A few hours later, she had several episodes of polymorphic ventricular extrasystoles, followed by 2 episodes of ventricular fibrillation, each reversed by cardioversion and administration of lidocaine. Her kalemia was always normal (range, 3.2–5 mEq/L; 3.3–3.6 mEq/L during cardiac arrest), but her QT interval was markedly prolonged, often over 600 ms, and her serum albumin level was very low (2.6 g/dL).

Hyponutrition is a consequence of patients who suffer from the restricting form of anorexia for a long time. Prolongation of the QT interval, which is not associated with hypokalemia, can occur because of the anatomical remodeling of the heart; autoptic studies report extreme atrophy of cardiac muscle determining sinus bradycardia and QT prolongation (4). In addition, drugs that interfere with a delayed outward rectifier K^+ current can prolong QT interval and facilitate cardiac arrhythmias.

Sudden death is a serious risk for patients with anorexia nervosa, particularly if the following conditions are present: a long duration of illness, hypokalemia, or chronic hypoalbuminemia with QT prolongation (absolute QT $\geq$600 ms) (3,4). Therefore, serum albumin levels should be