

Asymptomatic Intrahepatic Cholestasis with Turner's Syndrome

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Turner's syndrome is a genetic disorder that affects females. It is a condition in which full sexual development is not achieved and pubertal amenorrhea occurs secondary to gonadal dysgenesis. In 1938, the American physician, Henry H. Turner, became the first to describe this disorder, and it was subsequently named after him.

The genotype of an individual with this disorder is characterized by the absence of 1 of the X chromosomes. For this reason, the syndrome is also referred to as 45,X and sometimes called gonadal dysgenesis (45,X), Bonnevie-Ulrich syndrome, and monosomy X.

Low birth weight can be suggestive of the diagnosis, with infants often having facies characterized by micrognathia, epicanthal folds, prominent low-set ears or deformed ears, a fish-like mouth, and ptosis. Turner's syndrome leads to a webbed neck, lymphedema of the hands and feet, abnormal hairline, cardiovascular abnormalities (eg, coarctation of the aorta), genital hypoplasia, shortened metacarpals, a high arched palate, a broad chest with widely spaced nipples, tibial extosis, cubitus valgus, and osteoporosis and short stature (rarely exceeding 5 ft) in adulthood. About half of all births that are associated with Turner's syndrome involve conjoined twins, and the vast majority of these twins have monosomia.

Associated conditions include pigmented nevi, hypoplastic nails, renal malformation, keloid formation, perceptive hearing loss, unexplained hypertension, hypothyroidism, and other autoimmune disorders. Spatial disorientation and learning disorders of a moderate degree are common, also.

This article describes a patient with asymptomatic intrahepatic cholestasis associated with Turner's syndrome. This is an uncommon association and has been reported in the literature only rarely.

CASE PRESENTATION

Initial Presentation and History

The patient is a 31-year-old woman with a confirmed diagnosis of Turner's syndrome. Onset of menstruation was delayed, occurring when she was 18 years old. Chromosomal studies performed at that time revealed the patient's karyotype to be 45,XO, consistent with Turner's syndrome.

During a routine physical examination, laboratory studies were performed, and she was found to have elevated liver enzyme levels, with an alanine aminotransferase (ALT) level of 73 U/L (normal, 1 to 40 U/L), γ -glutamyltransferase (GGT) level of 299 IU/L (normal, 10 to 45 IU/L), 5'-nucleotidase level of 83.3 U/L (normal, 3 to 15 U/L), and alkaline phosphatase level of 126 U/L (normal, 30 to 115 U/L).

Clinic Visit

Owing to her abnormal laboratory results, the patient was admitted to our institution for further evaluation. Upon evaluation, the patient was asymptomatic and denied any fever, nausea, vomiting, abdominal pain, jaundice, or pruritus. She was taking no medications (prescription or over-the-counter) and denied any history of allergies, smoking, illicit drug use, or alcohol intake.

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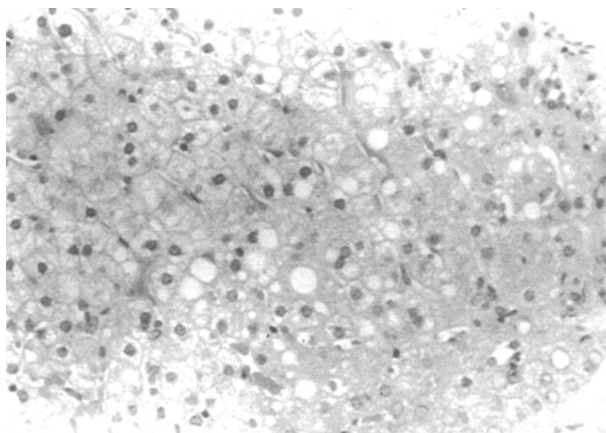


Figure 1. Low-power view of liver biopsy specimen showing the patient's overall mild hepatocytic steatosis (hematoxylin and eosin stain; magnification $\times 130$).

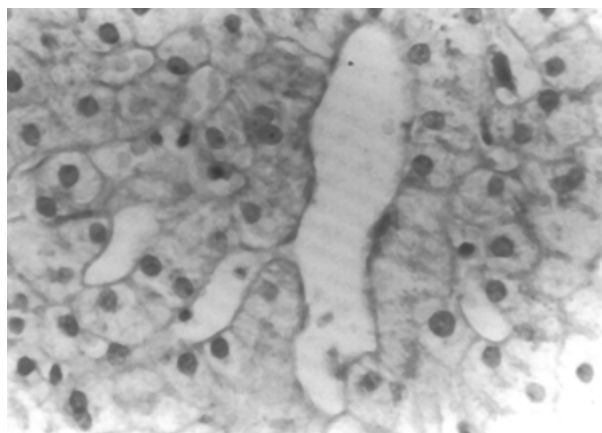


Figure 2. High-power view of liver biopsy specimen showing focal sinusoidal dilatation and hepatocytes containing cytoplasmic bile granules (hematoxylin and eosin stain; magnification $\times 400$).

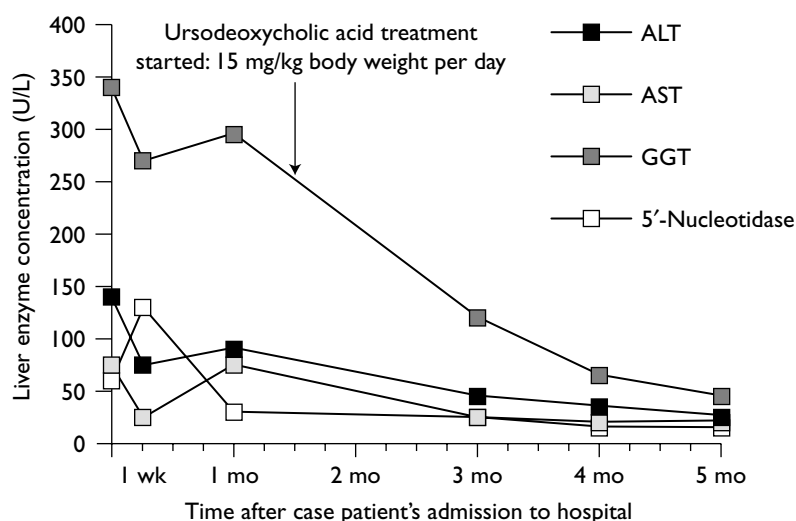


Figure 3. Liver function test results before and after treatment of the case patient with ursodeoxycholic acid until liver enzyme concentrations normalized. ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ -glutamyltransferase.

On physical examination, she looked well, and her heart rate was 80 bpm and regular. Her blood pressure was 160/100 mm Hg. Her temperature was 97.8°F. Her respiratory rate was 18 breaths/min. Her weight was 140 lb, and her height was 5 ft. Mild neck webbing was apparent, but no lymphadenopathy was present. Chest examination showed equal bilateral air entry. Cardiac examination showed normal heart sounds, with no S₃, murmurs, or jugular venous distention. An abdominal examination showed a soft abdomen with positive bowel sounds and no palpable organomegaly. Extremity examination showed cubitus valgus but no edema. No rashes were noted.

The results of the laboratory studies performed at our institution were as follows: leukocyte count,

$12.2 \times 10^3/\text{mm}^3$; hemoglobin level, 13.5 g/dL; hematocrit, 39.9%; mean corpuscular volume, 91.2 μm^3 ; red cell distribution width, 12.4%; and platelets, $303 \times 10^3/\text{mm}^3$. Serum electrolyte levels were within normal range. The patient's liver enzyme levels were still elevated: alkaline phosphatase level, 138 U/L; lactate dehydrogenase, 166 U/L; ALT level, 143 U/L; GGT level, 344 IU/L; 5'-nucleotidase level, 58.2 U/L; aspartate aminotransferase level, 73 U/L; α -fetoprotein level, 7.7 ng/mL; and serum aldolase level, 1 U/L (normal 0 to 6 U/L). Serologic evaluations for hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis A antibodies (total and immunoglobulin M [IgM] class), and hepatitis C antibody had negative results. Urinalysis showed 27 leukocytes/high-power

field. The patient's follicle-stimulation hormone, luteinizing hormone, and gonadotropin levels were elevated. Adrenocorticotrophic hormone, 17-ketosteroid, and 17-hydroxyketosteroid levels were normal.

An electrocardiogram showed a normal sinus rhythm. A radiograph of the chest showed no active pulmonary disease. An abdominal ultrasonogram showed left renal hydronephrosis. A renal scan showed normal flow and function with partial proximal obstruction of the left kidney but dilatation of the collecting system.

Electron microscopic evaluation of a liver biopsy specimen that was obtained percutaneously showed cytoplasmic lysosomal, bile-like bodies in the majority of hepatocytes in the vicinity of the bile canaliculi. Histologic examination showed mild steatosis and sinusoidal ectasia, without evidence of ductopenia (Figures 1 and 2). It also showed cholestasis, which was predominantly centrolobular, with occasional foci of sinusoidal ectasia. No inflammation, fibrosis, ductopenia, iron stains, or α_1 -antitrypsin was seen.

Ursodeoxycholic acid has been used to normalize abnormal results on biochemical liver tests.^{1–3} We initiated a trial of ursodeoxycholic acid (15 mg/kg body weight daily) and observed the patient for the ensuing 3 months. During treatment, periodic evaluation of her liver enzymes revealed marked decreases in their levels, with eventual normalization (Figure 3).

DISCUSSION

This report presents a 31-year-old woman with Turner's syndrome whose routine liver function test results indicated a mixed pattern of cholestasis and hepatocellular injury. Examination of the liver biopsy specimen revealed mild steatosis, sinusoidal ectasia, and no evidence of ductopenia. The patient's abdominal ultrasonogram and hepatitis A and B serologic profiles did not indicate acute or chronic viral hepatic liver disease.

Gastrointestinal abnormalities associated with Turner's syndrome include inflammatory bowel disease and celiac disease.^{4–6} A review of literature showed only a few adult cases of Turner's syndrome associated with chronic asymptomatic intrahepatic cholestasis (Table 1). We suggest that asymptomatic intrahepatic cholestasis presenting in combination with Turner's syndrome is a true association but an unexplained phenomenon. Physician awareness of this rare association

Table 1. Published Case Reports of Turner's Syndrome With Asymptomatic Intrahepatic Cholestasis

Report	Description
Thatcher et al 1973*	A patient with Turner's syndrome, abnormal liver function test results, and chronic cholestasis
Gardner 1974†	Two patients with Turner's syndrome and intrahepatic focal bile stasis
Loria et al 1993‡	Four patients with Turner's syndrome and asymptomatic chronic cholestasis

*Data from Thatcher N, Stephens AD, Besser GM. Turner's syndrome with coeliac disease, thin bones, and abnormal liver function tests. *Postgrad Med J* 1973;49:738–41.

†Data from Gardner LI. Letter: Intrahepatic bile stasis in 45,X Turner's syndrome. *N Engl J Med* 1974;290:406.

‡Data from Loria A, Serfaty L, Giral P, et al. Chronic cholestasis associated with Turner's syndrome: a report of four cases. *J Hepatol* 1993;18(Suppl):141.

is important. A simple observation of a patient's liver enzyme levels may be sufficient to identify this condition. Treatment with ursodeoxycholic acid may normalize liver enzyme levels. Clinical observations and long-term outcomes of patient with these disorders should be reported and investigated. **HP**

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