Idiopathic Liver Involvement in Turner Syndrome

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Turner syndrome is a relatively common chromosomal abnormality with a frequency of 1:2,500 liveborn female infants. The most common chromosomal aberration is the complete loss of one X chromosome (45X0), but many other chromosomal abnormalities result in the same phenotype – 45X0/46XX, 45X0/46 Xi (Xp), 45X0/46Xi(Xq), 45X0/46Xr(X), 45X0/46XX/47XXX and 45X0/46XY. Only 0.3% of the embryos with the 45X0 genotype survive to term [1]. Typical findings include low hair line, small suture, epicanthal fold, webbed neck, shield chest, cubitus valgus, multiple pigmented nevi, peripheral edema, streak ovaries, left-sided heart defect (coarctation of the aorta), and renal abnormality (horseshoe kidney). There is also a relatively high prevalence of Hashimoto thyroiditis, inflammatory bowel disease, insulin resistance and ovarian malignancy [1]. The association of liver involvement in Turner syndrome is not well understood. We present a patient with Turner syndrome and idiopathic liver involvement, and a review of 55 medical charts.

Patient Description

A 49 year old patient with Turner syndrome, known to have elevated liver enzymes for 5 years, was admitted for evaluation of jaundice. Her past medical history was remarkable for Turner syndrome and an aortic coarctation repair 22 years earlier. She also presented with hypertension and hypothyroidism. Physical examination revealed jaundice, small suture, webbed neck, shield chest and peripheral edema. Laboratory tests showed aspartate aminotransferase of 1,098 u/L, alanine aminotransferase 1,349 u/L, alkaline phosphatase 413 u/L and bilirubin 4.8 mg/dl. Viral serology for hepatitis A, B and C, as well as cytomegalovirus/Epstein-Barr virus and *Toxoplasma* was negative. The immunologic workup revealed anti-smooth muscle antibodies; antinuclear factor, antimitochondrial and antiparietal cell antibodies were negative, and immunoglobulin levels were normal.

Abdominal computerized tomography and ultrasound showed no evidence of biliary tract obstruction. Endoscopic retrograde cholangiopancreatography was normal. Liver biopsy demonstrated a few neutrophils and eosinophils in the portal space and intrahepatic cholestasis, in addition to feathery degeneration and fibrosis around the central veins. The final diagnosis was idiopathic cholestasis.

A review of 55 medical charts

To determine the frequency of liver involvement in patients with Turner syndrome, we retrospectively reviewed 55 medical charts of patients with Turner syndrome admitted to Hadassah University Hospital between 1980 and 2000. Results of AST, ALT, gamma-glutamyltransferase, and ALP were available for 25 of them. The charts were reviewed for all causes of liver function disturbances. Abnormality in one of the enzymes was observed in 24 of the 25 patients. Nine of them had isolated elevation of alkaline phosphatase at a young age. Four patients received hormonal therapy and three others had unrelated disorders associated with liver function disturbances. Eight patients (32%) – 6 adults and 2 children with a mean age of 28.5 years (range 1–49) – had idiopathic liver involvement. Their liver enzymes were elevated as follows: GGT with a mean of 197 IU (range 41–479) in seven of the eight patients, ALP with a mean of 158 IU (range 153–161) in four, AST with a mean of 153 IU (range 56–206) in five, and ALT patients with a mean of 189 IU (range 142–265) in four.

AST = aspartate aminotransferase
ALN = alanine aminotransferase
ALP = alkaline phosphatase
GGT = gamma-glutamyltransferase

Comment

We describe a case of idiopathic cholestatic liver involvement in a patient with Turner syndrome and present a retrospective review of 55 medical charts. Thirty-two percent of these patients had idiopathic liver dysfunction.

The first case report of Turner syndrome and liver disease was reported in 1959 by Bridwell [2]. The patient manifested with melena. Esophageal varices were demonstrated and a liver biopsy revealed periportal fibrosis. No etiology was found. In 1973, a patient with Turner syndrome was diagnosed with osteomalacia secondary to celiac disease. Laboratory results revealed elevated liver enzymes, which were attributed to hormone replacement therapy but did not improve after discontinuation of the drug [2]. Grandner [1,2] described two patients with Turner syndrome and intrahepatic cholestasis. He suggested that the hepatic syndrome could be the result of an expression of a mutant allele whose locus was on the homologous pairing of the X or Y chromosome, or that the hepatic disease is a rare X-linked trait of the classic Mendelian variety with the expression both in monosomy X patients or XY patients. Another possibility was an unexplained association between aneuploidy and hepatic disease [1]. Friedman et al. described a patient who had jaundice at age 15 months that was treated with steroids, but developed liver cirrhosis 5 years later. Susceptibility to infections, or a common pathway that causes the chromosomal abnormality and liver injury, was suggested [1].

Recently, Salerno et al. [3] reviewed 70 patients with Turner syndrome. The rate of elevated liver enzyme was 14/70. Ten of these patients were treated with hormone replacement therapy. Two patients had evidence of autoimmune disease. The authors concluded that the most common cause of elevated liver enzymes is hormonal therapy – namely, estrogen, oxandrolone or growth hormone [3]. Larizza and colleagues [4] compared 22 patients with elevated liver enzymes to 48 patients without liver dysfunction, and concluded that while estrogens were not a major risk factor for liver abnormality in Turner syndrome, autoimmunity is the cause of the abnormality in many patients, and obesity is also a risk factor. Albareda et al. [5] followed 16 patients with Turner syndrome and found an incidence of 43.7% for disturbed liver functions. All were treated with hormone replacement therapy, but biochemical abnormalities appeared 1–14 years following initiation of treatment and did not improve following cessation of treatment. A follow-up of adult Turner patients noted that liver disorder was common (81.6%) but not progressive. Liver biopsy had been performed in 4 of 49 patients and did not reveal significant changes [3,5].

In summary, liver involvement is relatively common in patients with Turner syndrome and occurs in 20–80% of patients. Hormone replacement therapy, autoimmune disease, or fatty liver associated with overweight, may account for the majority of cases. In about a third of the patients, cholestatic liver involvement of unknown etiology may occur. The pathogenesis and prognosis of this disorder are still unknown.

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