

# Hepatic disease in Turner syndrome

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**Abstract.** Liver test abnormalities are frequent in adult patients with Turner syndrome, but only few histological studies have been reported in the literature. The hepatic histological changes found in TS patients may be explained by one or more distinct physiopathological mechanisms. Marked architectural changes, including nodular regenerative hyperplasia, multiple focal nodular hyperplasia and cirrhosis, are observed in some patients and are associated with a risk of severe liver-related complications. These changes are frequently associated with vascular disorders that are probably related to congenitally abnormal vessels. Steatosis, steatofibrosis and steatohepatitis are frequent, caused by metabolic disorders. Finally, bile duct alterations resembling small duct sclerosing cholangitis are observed in several patients. There is no evidence for liver toxicity due to oestrogen replacement therapy. © 2006 Elsevier B.V. All rights reserved.

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## 1. Introduction

Liver involvement is frequent in adult patients with Turner syndrome (TS). The prevalence of liver test abnormalities (especially the elevation of aminotransferases, gamma glutamyl transferase and alkaline phosphatase) ranges from 20% to 80%, depending on the patient's age, with the highest values in the oldest patients [1–4]. Multiple causes may lead to liver test abnormalities in TS patients. Excess weight and estrogen replacement therapy have both been suggested to cause elevation of liver enzymes [2,3]. Beside biological abnormalities, a few studies had reported severe forms of liver involvement in TS patients,

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such as cirrhosis of unexplained origin and nodular regenerative hyperplasia (NRH) [5–9]. Recently, a cohort study with systematic histopathological examination analyzed the histological features, causes and prognosis of liver involvement in TS patients [10].

## 2. Hepatic lesions and mechanism of liver involvement

Liver involvement in TS patients is asymptomatic in most cases, discovered during systematic blood testing. In general, the diagnosis of TS precedes that of liver involvement, but, sometimes, abnormal liver tests can lead to the diagnosis of TS. In only few cases, liver biopsy data have been obtained, in patients with liver test abnormalities persisting for years or displaying signs of portal hypertension. The hepatic histological changes reported in TS patients are variable including minimal abnormalities [11], steatosis [12], steatohepatitis [3], biliary involvement [12–15], cirrhosis [5–7] and NRH [8,9,16,17]. Mechanisms and prognosis of liver disease have not been investigated in most cases, but it appears that the consequences of the hepatic involvement may sometimes be severe [11]. Accordingly, a five-fold increased risk of “cirrhosis” was reported in TS patients, compared to control patients [18].

### 2.1. Non-alcoholic fatty liver disease (NAFLD)

Overweight and insulin resistance syndrome have been recently recognized as a common cause of non-alcoholic fatty liver disease (NAFLD) [19,20]. Histopathological features of NAFLD, which include steatosis, steatohepatitis and steatofibrosis, have been found in several TS patients. Since overweight, defined by a body mass index (BMI) value above 25 kg/m<sup>2</sup>, and diabetes are frequent in TS patients [18,21,22], it is likely that these hepatic lesions reflect the same physiopathological mechanisms as in overweight patients without TS [23].

### 2.2. Liver architectural changes and vascular lesions

Marked liver architectural changes can be observed in some TS patients. They include cirrhosis, NRH and multiple FNH. Nodular regenerative hyperplasia (NRH) is defined as the presence of multiple small parenchymal nodules without annular fibrosis and with conserved portal tracts. Focal nodular hyperplasia (FNH) corresponds to the presence of a large nodule with or without intra-nodular fibrosis, alternating with fibrotic areas containing numerous abnormal arteries and ductules. Changes in the intrahepatic portal veins, including thrombosis, intimal thickening or complete obstruction and replacement by a fibrous scar containing numerous vessels, are frequently associated to liver architectural changes; they are considered as features of obliterative portal venopathy [24].

Several findings suggest that a primary vascular involvement is the cause of the architectural changes described above. NRH is currently thought to be an adaptation to microcirculatory disturbances that result in heterogeneous distribution of intrahepatic blood flow [25–27]. According to this view, NRH combines hepatocyte atrophy in areas of decreased perfusion, with hepatocyte hyperplasia in areas of normal perfusion. FNH is also considered as a focal hyperplastic hepatocellular response caused by focal deprivation of

portal perfusion and enhanced arterial perfusion in the corresponding area [28]. Finally, cirrhosis with no evidence for a known cause of chronic liver disease in TS patients may correspond to the final stage of a vascular disorder. Vascular abnormalities (including aortic coarctation, aortic bicuspidia, cerebral vessel aneurysm and gastrointestinal telangiectasia) are common in TS [29–31] and were found more frequently in patients with marked architectural changes of the liver [10]. Therefore, there is circumstantial but not compelling evidence to suggest that some hepatic changes in TS patients are part of a general disorder involving vessels of different sizes, types and locations. A congenital origin would be a likely hypothesis to explain this vascular disorder.

### *2.3. Biliary lesions*

Whereas biliary atresia has been reported in only one child with TS [14], non-inflammatory, concentric fibrosis of small intra-hepatic bile ducts, resembling primary sclerosing cholangitis, has frequently been found in TS adult patients. TS patients have a higher than expected incidence of inflammatory bowel disease [32], a condition that is frequently associated with primary sclerosing cholangitis. However, sclerosing cholangitis mostly involves extra-hepatic bile ducts, whereas only intra-hepatic bile ducts were found to be involved in TS patients. In addition, associated inflammatory bowel disease was not reported in TS patients with biliary lesions. The findings above indicate that the ductal fibrosis in TS patients is caused by a different physiopathological mechanism than primary sclerosing cholangitis. Ductal fibrosis frequently occurs in patients with damaged peribiliary arterioles [33]. Thus, the concentric biliary fibrosis might be related to an altered blood supply. If this hypothesis is correct, biliary lesions found in patients without marked architectural alterations could correspond to one end of a spectrum of vascular-related anomalies, with the marked architectural changes described above on the other end.

Cholangitis and ductopenia, which have also been described in patients with TS [10], are common features in patients with primary biliary cirrhosis (PBC). The prevalence of PBC in TS has never been studied, despite the fact that TS and PBC share some similarities [34]. In both diseases, cholestasis is age-related and both diseases are strongly associated with autoimmune disorders. Moreover, a recent study reported significantly more frequent X chromosome monosomy in patients with PBC than in controls [35].

### *2.4. Role of oestrogen therapy*

Oestrogen-induced hepatotoxicity has been considered as the main cause of liver test abnormalities in TS patients receiving hormone replacement therapy [36,37]. However, the causative role of oestrogens has never clearly been established. Both, alterations in liver tests and liver architectural changes have been reported whether TS patients were treated with estrogens or not [10]. In addition, these alterations were not improved by cessation of replacement therapy [1,9]. Therefore, the definitive discontinuation of replacement therapy is not necessary unless interruption followed by a re-challenge shows improvement in liver test anomalies followed by recurrence. Moreover, several studies demonstrated a beneficial effect of natural oestrogens on liver function of TS patients [4,38,39].

### **3. Evolution**

#### *3.1. Natural history of liver involvement in TS patients*

To date, only one study reported long term follow-up of TS patients with liver involvement. In this cohort study, patients referred to liver departments for abnormal liver tests were followed for an average of 9 years [10]. In most cases, liver involvement did not progress to overt hepatic disease. Major complications were observed in 3 patients who all displayed liver architectural changes. One patient died of uncontrolled refractory ascites with pleural effusion and cardiac failure. The second patient experienced uncontrolled variceal bleeding and intractable cholestasis, requiring orthotopic liver transplantation 6 years after the diagnosis of liver involvement. The third patient underwent surgical portocaval shunting for recurrent variceal bleeding. In conclusion, major liver complications are uncommon in TS patients (10%) and are only observed in case of marked architectural changes.

#### *3.2. Evolution after ursodeoxycholic acid treatment*

Ursodeoxycholic acid (UDCA) is commonly recommended in biliary disease, mainly in patients with PBC [40]. As biliary involvement may occur in about two-third of TS patients with elevated liver enzymes, particularly in case of a cholestatic profile, UDCA treatment has often been prescribed. This treatment proved to be effective at least on biological tests. In one study, serum aminotransferase and alkaline phosphatase levels returned to normal after a few weeks of treatment in most patients receiving UDCA, although GGT remained slightly increased [10]. UDCA treatment had no beneficial effect on biological tests in patients with liver architectural changes. A positive effect of UDCA on anatomical lesions could not be documented so far since a second liver biopsy was only performed in two patients treated with UDCA for 8 and 7 years, respectively, and did not show histological changes [10]. In the absence of a case-control study, however, it cannot be ruled out that the progression of liver lesions may be delayed by the UDCA treatment. Taken together, the findings above indicate that UDCA therapy may have some beneficial effect in TS patients with biliary lesions and no alteration of liver architecture.

### **4. Managing of TS patients with persistent elevated liver enzymes**

#### *4.1. Initial evaluation*

The initial evaluation of TS patient with abnormal liver tests should include abdominal ultrasound (US) with assessment of blood flow by Doppler to detect hepatic nodules, portal hypertension and/or liver steatosis. In case of isolated cholestatic syndrome with normal US examination, UDCA should be proposed. In case of ultrasonographic signs of hepatic steatosis, the treatment of the metabolic syndrome is required to avoid NAFLD-related complications.

When ultrasonographic signs of portal hypertension are present, the histological examination of the liver should be performed. If liver architectural changes are present,

upper gastrointestinal endoscopy will establish the presence or absence of esophageal varices, which require either long-term  $\beta$ -blocker treatment or variceal elastic ligation. The treatment of steatohepatitis and of biliary lesions is based on the correction of the metabolic syndrome and on long-term prescription of UDCA.

#### 4.2. Subsequent monitoring

Liver blood tests and blood tests count are recommended twice a year for all patients. For patients who did not undergo liver biopsy at the initial evaluation, persistently elevated liver enzymes for more than 6–12 months despite the correction of the metabolic syndrome and or UDCA treatment, liver biopsy should be considered.

In case of liver architectural changes, abdominal ultrasound must be performed once a year and upper gastrointestinal endoscopy every 3 years to detect portal hypertension signs.

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