Case report : practical management of hepatopathy in Turner syndrome

A propos d'un cas : Prise en charge pratique de l'hépatopathie au cours du syndrome de Turner

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ABSTRACT :

Turner syndrome (TS) is a genetic disease attributable to the complete or partial absence of one X chromosome in a female individual. Hepatic disturbances are commonly encountered in TS and yet their pathophysiological mechanisms as well as their management are to be ascertained. Herein, we report a case of a 10-year-old patient with TS, who had cytolysis and cholestasis. Etiological assessment was negative. She was treated with hormonal replacement therapy. Despite this, her liver enzymes remained elevated. Ursodesoxycholic acid was thus administered. The evolution was marked by the normalization of her biological tests. This case raises intriguing points of discussion: pathophysiology and management of the hepatic derangements found in TS.

Key words : Turner Syndrome, Liver diseases, pathophysiology, estrogen replacement therapy

RÉSUMÉ :

Le syndrome de Turner est une pathologie génétique rare due à l'absence totale ou partielle d'un chromosome X chez un sujet de sexe féminin. Il englobe un large éventail d'atteintes, dominées par le syndrome dysmorphique, le retard de croissance ainsi que l'insuffisance ovarienne primitive. Parmi les pathologies associées à ce syndrome, on trouve l'hépatopathie. Nous rapportons le cas d'une patiente ayant un syndrome de Turner et qui s'est présentée avec une atteinte hépatique : cholestase et cytolyse hépatique. Nous discutons à travers ce cas, les différents mécanismes physiopathologiques impliqués dans la genèse de l'atteinte hépatique associée au ST ainsi que sa prise en charge.

Mots clés : syndrome de Turner, affections hépatiques, pathophysiologie, hormonothérapie oestrogénique substitutive

INTRODUCTION :

Turner syndrome (TS) is a genetic disease attributable to the complete or partial absence of an X chromosome in female individuals. It is characterized by the association of short stature, hypergonadotropic hypogonadism and dysmorphic features as well as a higher incidence of autoimmune and metabolic diseases. Additionally, hepatic disturbances are often found in TS [1]. However, gaps remain in our comprehension of the underlying pathophysiological mechanisms of this latter manifestation of TS.
Through this case report, we aim to discuss the etiopathogenesis relating X chromosomal abnormalities and hepatic disorders along with its management.

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CASE REPORT :

A 10-year-old girl was referred to our Endocrinology Departement for short stature. She was the offspring of a non-consanguineous marriage. Her past medical as well as her family history was unremarkable. She had a body weight of 24 kg, a height of 118 cm (-3 standard deviations) and a body mass index of 20.54 kg/m2. Physical examination also revealed a minor dysmorphic syndrome associating short neck, pigmented naevi and short fourth metacarpal. She had a female phenotype with underdeveloped external genitalia (Tanner stage I). She also presented an alopecia universalis. Hormonal investigations unveiled a hypergonadotropic hypogonadism demonstrated by high levels of FSH (181.4 mIU/ml), LH (41mIU/ml) and low estradiol level (9 pg/ml). Pelvic ultrasonography showed a hypoplastic uterus and absence of the ovaries. Cytogenetic testing confirmed the diagnosis of TS showing a monosomy of the X chromosome. Fluorescence in situ hybridization analysis identified a small ring X chromosome that was found in all examined cells, therefore confirming the karyotype of 45, X, r(X) (Figure1).

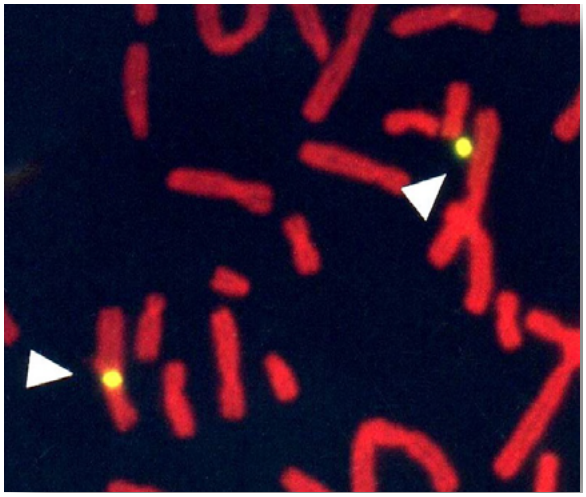

Figure 1 : FISH analysis showing hybridization of X chromosome probe to normal X and a small ring X in a 46, X, r(X) metaphase

Hematological and biochemical assessment were normal except for Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Alkaline phosphatase (AP), that were elevated (107 IU/l > 45 IU/l), (87 IU/l > 45 IU/l) and (819 IU/l > 200 IU/l), respectively. In contrast, γ-Glutamyl transferase and serum bilirubin levels were normal. Regarding the etiology of the disturbed liver function, we first ruled out hepatotoxic medications and alcohol consumption. An abdominal ultrasound excluded the diagnosis of vesicular lithiasis and showed a normal liver morphology. Viral hepatitis serologies were negative, thus eliminating this diagnosis. Furthermore, negative anti-mitochondrial, anti-smooth muscle and anti-Liver and kidney microsome (anti LKM1) antibodies dismissed autoimmune hepatitis. Wilson disease and alpha-1 anti-trypsin deficiency were also eliminated since clinical findings were inconsistent with these pathologies.

Aiming to promote her growth, the patient was given somatropin at a dose of 1 IU / kg / week at a chronological age of 10 years and a bone age of 8 years, which resulted in a significant gain of 30 cm in stature, after a duration of 7 years.

After attaining a bone age of 14 years, a low dose estrogen therapy was started, administered transdermally. The evolution of the hepatic enzymes was marked by their high fluctuation.

The persistence of the altered liver function led us to the use of Ursodeoxycholic acid therapy 250 mg twice a day, while continuing the estrogen replacement therapy. Consequently, a substantial improvement in her liver function was noted after one month as clarified in table 1. The patient was thereafter lost to follow-up.

Table 1 : Evolution of the liver function test before and after the administration of Ursodeoxycholic

Liver function tests	Before Ursodeoxycholic acid therapy	After Ursodeoxycholic acid therapy
AST (IU/L)	107	22
ALT (IU/L)	87	24
AP (IU/L)	819	270

DISCUSSION :

TS encompasses a wide range of clinical features comprising short stature, dysmorphic phenotype and premature ovarian insufficiency. Another very common finding often seen in TS is liver function abnormalities that can be detected in 20 to 80 % of cases [1]. From an epidemiological perspective, liver impairment is more frequently encountered in older patients with TS, with an increasing incidence of 3.4 % per year [2] [3].

Hepatic involvement in patients with turner TS is often asymptomatic and thus the frequent incidental detection of this anomaly on biological exams. Rarely, this condition precedes the diagnosis of TS and therefore leads to its diagnosis [4]. The histopathological findings reported in patients with TS include: minor histological alterations, biliary abnormalities, nodular regenerative hyperplasia, steatohepatitis, cirrhosis and steatosis; the latter feature being the most frequently encountered [2].

Regarding its etiology, non-alcoholic fatty liver disease is the most incriminated in the genesis of liver disturbances in patients with TS. In fact, TS subjects are more prone to develop overweight, insulin resistance and metabolic syndrome than normal individuals [1]. El-Mansoury et all conducted a 5-year longitudinal study, in which they demonstrated that elevated total cholesterol correlated significantly with elevated liver enzymes [3], and therefore cor-

roborating this hypothesis. These metabolic abnormalities are ascribable to estrogen deficiency [9].
Additionally, vascular abnormalities seem to play a pivotal role in the hepatic derangement found in TS. Susceptibility to thrombosis [10], venous malformations and vascular thickening could lead to hepatic microcirculatory defects and thus local hypoxia and compensatory hyperplasia, resulting in nodular regenerative hyperplasia and focal nodular hyperplasia [10] [11] [4].
Biliary diseases such as primary biliary cirrhosis, bile duct paucity and biliary atresia have been outlined in previous reports within the context of TS. Inflammatory bowel diseases, which represent a risk factor of primary sclerosing cholangitis (PSC), are over delineated in TS, explaining partially the frequency of biliary lesions. The particularity of PSC in TS is the predominant intrahepatic lesions as opposed to the involvement of extrahepatic ducts in patients without TS [12].
Autoimmunity is thought to be also involved in the liver dysfunction associated with TS, albeit modestly, mainly through autoimmune hepatitis and primary biliary cirrhosis. Conversely, specific liver antibodies (anti liver kidney, anti-mitochondrial and anti-smooth muscle) were not more frequently observed in TS [13].
Hepatotoxicity of estrogens has been incriminated in the development of liver function alterations in women with TS. However, this hypothesis has been invalidated by several research that proved that liver disturbances can be present even in girls who were not treated with estrogen therapy. Moreover, hormonal replacement therapy proved to have a beneficial effect on liver enzymes as demonstrated by several studies. Given these facts, its actually recommended to continue treatment with estrogen therapy in patients with liver biochemical abnormalities [1].
Overall, the hepatic abnormalities seen in TS are multifactorial involving metabolic syndrome, vasculopathy, biliary lesions, autoimmune predisposition and estrogen deficiency.
Otherwise, Ursodesoxycholic acid is a potent drug, commonly used in liver diseases. In fact, it protects the impaired cholangiocytes from the toxic effect of bile acids, stimulates the secretion of bile and hampers the apoptosis of hepatocytes, thus it halts the progression of liver disease. It's also indicated in the treatment of cholestasis in TS [15]. In our case, it resulted in the resolution of the liver function impairment.
Relating to the spontaneous evolution of liver enzymes, they tend to rarely revert to normal [1], as was the case of our patient. Intriguingly, the risk of developing cirrhosis in TS is six times more important than the general population, imputable mainly to estrogen deficiency and hypoxia which is consequential to the vascular malformations in TS such as coarctation of the aorta [12]. Accordingly, recent recommendations endorse the systematic screening for abnormal hepatic function yearly in patients with TS after the age of six. Hepatic ultrasound and transient elastography in patients is indicated in patients with persistently elevated liver enzymes [1].

CONCLUSION :

Hepatic derangement is frequent in TS. However, differential diagnosis should be ruled out before retaining TS as it's etiology. Many factors have been incriminated in the genesis of this abnormality; nevertheless, metabolic syndrome seems to be the main player. Estrogen treatment should be continued as it's cessation can be detrimental to these patients' health. Usodesoxycholic acid may be helpful. A long-term follow-up is required to detect in time rare, but serious complications of liver disease such as cirrhosis.

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