

An unusual presentation of Wilson's disease in childhood: nodular fatty infiltration in liver

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Wilson's disease is a rare inherited disorder characterized by progressive accumulation of copper in the body tissues. Liver and brain are the most commonly involved organs and the disease is presented predominantly by hepatic manifestations in childhood. Histopathological findings of hepatic involvement may vary from steatosis to end stage cirrhosis. Although diffuse fatty infiltration is a typical finding of Wilson's disease, it can very rarely present in nodular pattern. We report the first case with Wilson's disease who presented with nodular fatty infiltration in the liver in childhood.

Key words: Wilson's disease, nodular fatty infiltration, liver, children.

Wilson's disease (WD) is a hereditary chronic disorder due to toxic accumulation of copper in several tissues, especially the liver, brain, kidney and eyes¹. It is presented predominantly by hepatic manifestations in childhood. Liver disease ranges from mild elevation of serum aminotransferases in asymptomatic individuals to acute hepatitis, chronic hepatitis, cirrhosis and fulminant hepatic failure². Similarly, the spectrum of histopathological findings is greatly variable, from periportal glycogen-filled, swollen nuclei and hepatic steatosis to chronic active hepatitis and cirrhosis^{1,2}. Here, we report a child with WD presenting with nodular fatty infiltration in the liver.

Case Report

A 12-year-old male was admitted with jaundice and hepatomegaly. His medical history revealed ventriculoperitoneal shunt due to Dandy-Walker malformation. His parents were consanguineous. Physical examination revealed subicteric, 3.5 cm soft hepatomegaly, growth and motor-mental retardation, macrocephaly, cranial asymmetry, spasticity of lower extremities and bilateral Babinski reflex positivity. Complete blood count and blood smear were normal. Laboratory findings were as follows: aspartate aminotransferase

(AST) 50 U/L, alanine aminotransferase (ALT) 47 U/L, gamma-glutamyl transpeptidase (GGT) 28 U/L, alkaline phosphatase 590 U/L, total bilirubin 4.4 mg/dl, and conjugated bilirubin 2.2 mg/dl. Other biochemical measures were within normal limits. Prothrombin time, partial thromboplastin time, ceruloplasmin, alpha-1 antitrypsin, ferritin, alpha fetoprotein and sweat test were all normal. The serology for viral hepatitis (A, B, C, D, E, cytomegalovirus-CMV, Epstein-Barr virus-EBV, Rubella) and toxoplasma Ig M was negative. Arterial blood gases, blood sugar, serum lactic acid, pyruvic acid, serum and urine amino acids, urine organic acid, and thyroid function tests were normal. Reducing substance was negative in the urine, and ECG and ECHO did not reveal any abnormality. Skeletal survey was normal other than mild osteopenia. Hepatobiliary scintigraphy was normal. Abdominal ultrasonography revealed echogenic solid lesions in both lobes of liver, the largest being 3 cm in diameter. On dynamic contrast-enhanced tomography, lesions were seen as enhancing hypodense nodules in both arterial and portal phase (Fig. 1). Contrast enhancement pattern and density measurement of lesions were not compatible with hemangiomas, metastases or lipomas. On magnetic resonance imaging (MRI), lesions



Fig. 1. Portal venous phase of CT examination clearly demonstrates well-demarcated hypodense lesions in both lobes of liver.

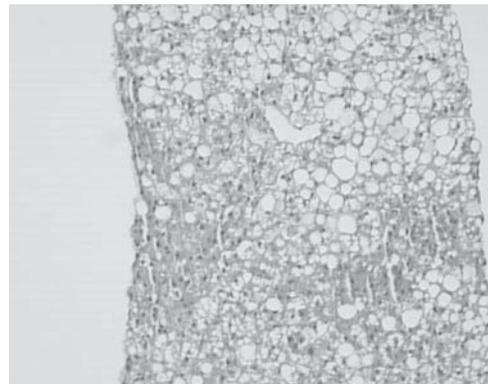


Fig. 3. Macrovesicular steatosis (hematoxylin and eosin, x200).

hepatocytes had intracytoplasmic yellow-brown colored pigment accumulation. It was shown with orcein stain that this pigment was copper (Fig. 4). Based on these histopathological

were hyperintense on both T₁- and T₂-weighted images compared to liver parenchyma. Lesion intensity was decreased on fat-suppressed images related with the fatty content (Fig. 2). Ultrasound-guided liver biopsy was performed on both normal liver parenchyma and nodular lesion. Histopathologic examination of both biopsies revealed that normal liver parenchyma was destroyed with bridging necrosis. Moderate mixed cellular infiltration was detected in portal, periportal areas and in the lobules. Multifocal, predominantly macrovesicular steatosis was seen (Fig. 3). Some hepatocytes had glycogenized nuclei. Most of the periportal



Fig. 4. Intracytoplasmic copper accumulation (orcein, x400).

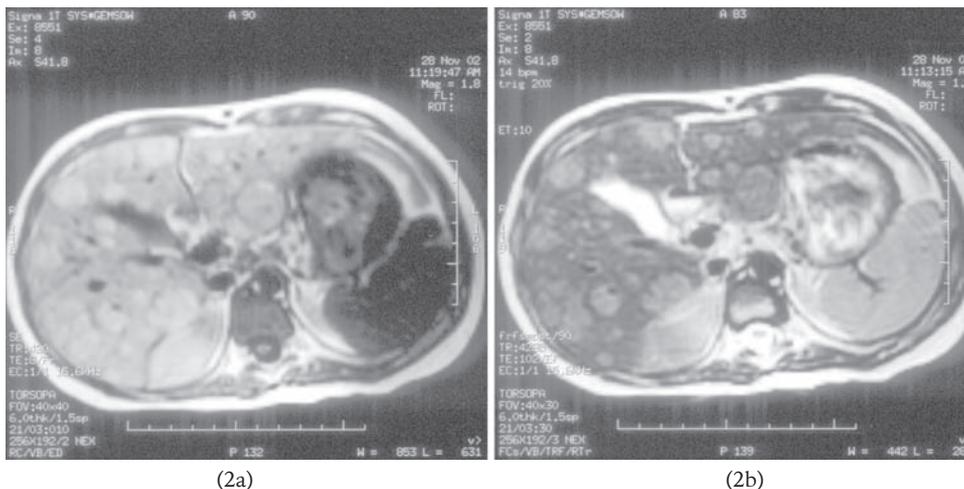


Fig. 2. On fat-suppressed T1-(A) and T2-weighted (B) images, lesions are seen hypointense.

findings, he was investigated for WD in more detail. Kayser-Fleischer rings were negative, serum ceruloplasmin was normal (0.6; normal 0.2-0.6 g/L), 24-hour urine excretion of copper was 350 $\mu\text{g}/\text{day}$ (normal $<40 \mu\text{g}/\text{day}$) and hepatic copper concentration was 681 μg per gram of dry weight (normal $<50 \mu\text{g}$). Response of urinary copper output to 500 mg D-penicillamine stimulation was observed. In conclusion, the diagnosis of WD was established and D-penicillamine was instituted.

Discussion

Multiple lesions in the liver are rare in childhood. The diseases which cause multiple lesions in the liver are hepatoblastoma, hemangioma, hemangioendothelioma, lymphoma, hamartoma, extramedullary hematopoiesis, myelolipoma, tuberous sclerosis associated with multiple hepatic lipomatous tumors, nodular regenerative hyperplasia, tyrosinemia and hemochromatosis³⁻⁵. Besides clinical and laboratory evidences, imaging methods are important in the differential diagnosis of these disorders. In the patient presented here, hepatoblastoma, lymphoma, extramedullary hematopoiesis, tuberous sclerosis, tyrosinemia and hemochromatosis were eliminated by clinical and laboratory findings. Sonographic and computed tomographic (CT) images of lesions were not found compatible with hemangioma, hemangioendothelioma, metastatic liver tumors or nodular regenerative hyperplasia⁶.

The lesions in the liver of this child were fatty in nature as shown by liver MRI and biopsy. Metabolic disorders such as cystic fibrosis, tyrosinemia, hereditary fructose intolerance and fatty acid oxidation defects and clinical conditions such as obesity, diabetes mellitus, hyperlipidemia, toxic hepatitis and kwashiorkor may cause liver steatosis^{7,8}. In these disorders, fatty infiltration is frequently diffuse, but also rarely occurs in a focal pattern, which leads to nodular lesions with well-defined borders mimicking metastatic tumor⁸. All these metabolic and clinical conditions were eliminated by clinical and laboratory findings in this patient.

In WD, the earliest histologic findings which may be present in asymptomatic children include periportal glycogen-filled, swollen nuclei and hepatic steatosis, initially microvesicular and developing into macrovesicular fat⁸.

Hepatic steatosis may relate to ultrastructural abnormalities of mitochondria and peroxisomes that may lead to diminished lipid oxidation and accumulation of triglyceride in hepatocytes. With progression, portal fibrosis and inflammation are seen. If injury continues, liver cirrhosis develops⁸. Copper may be detected by specific stains for copper such as rhodanine, orcein and Timm's silver sulfide staining⁸. Our patient had macrovesicular steatosis, glycogen-filled, swollen nuclei, positive copper staining in liver histopathology and elevated hepatic copper concentration. These findings were highly suggestive of WD.

Although diffuse steatosis of liver, especially macrovesicular fat deposition, is a well-known histological finding in WD, to the best of our knowledge, there are only two cases of WD diagnosed with nodular lesions reported in the literature^{9,10}. In the first case, multiple nodular lesions in the liver were not fatty in nature, and were due to paramagnetism of copper accumulation in liver⁹. Our patient's radiological findings were different from this case, because signal change in MRI was caused by fat accumulation in these nodular lesions.

The other case was a 20-year-old man who was found to have multiple focal lesions by chance in the liver on abdominal ultrasonography and CT¹⁰. These focal lesions were found to be nodular fatty infiltrations by histopathological examination. Our case is similar to that patient. However, in contrast to Pascual's¹⁰ report, we were able to demonstrate the fatty nature of the lesions before the biopsy. These findings demonstrate that MRI is very helpful in the differential diagnosis of focal nodular lesions.

Our patient, to the best of our knowledge, is the first case with WD who presented with nodular fatty infiltration in the liver in childhood. Moreover, it is the first report in which fatty content of the lesions was demonstrated by MRI in WD. However, as in the previous report¹⁰, we could find no conclusive explanation as to why the usual histological changes caused unusual CT/MRI findings.

In conclusion, we want to emphasize that in WD, steatosis may present in different patterns. Although a very rare occasion, WD should be kept in mind in the differential diagnosis of multiple nodular lesions in the liver in children.

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