

Differential Diagnosis of NAFLD- A Short Summary:

Almost a fifth of our general pediatric population is now classified as overweight in the United States. When such children present with elevated liver enzymes the most important consideration has to be obesity related fatty liver disease or NAFLD. However, it is possible that conditions that can mimic nonalcoholic fatty liver disease present with a similar hepatic phenotype (See **Table** at the end).

Such conditions in particular can occur in a mildly overweight or obese adolescent. The following are brief descriptions and diagnostic tools for such diseases that can easily “masquerade” as NAFLD:

Wilson’s Disease:

Wilson’s disease is an inherited disorder of the biliary excretion of copper metabolism and results in accumulation of copper in specific tissues¹. Clinical presentation varies widely but liver disease is one of the primary features. One of the unique features of the disease is the wide range of affects in the liver-from very mild elevated liver enzymes and minimal damage in the liver to acute liver failure or cirrhosis. Histologic findings include mild steatosis, glycogenated nuclei lobular inflammation that look very similar to NAFLD¹. Testing for Wilson’s disease includes sending a serum ceruloplasmin, Kayser-Fleischer rings, 24 hour urinary copper and measuring copper deposition in the tissue.

Medication Induced Steatosis

Medications can rarely cause steatosis in children and adolescents. These include but are not limited to, steroids, psychotropic and psychiatric medications.

Hepatitis C

Hepatitis C virus (HCV) is an important global health problem, especially in developing countries². Some children with chronic HCV will have elevated ALT levels although up to one third can have normal levels and another third will have fluctuating numbers³. HCV presentations can include insulin resistance and liver steatosis.⁴ The prevalence steatosis in HCV can be 40 to 80% in all patients⁴. Therefore patients with suspected fatty liver should be tested for HCV using Hepatitis C antibody.

Cholesterol Ester Storage Disease (Lysosomal acid lipase deficiency)

CESD is a rare genetic disease caused by a deficiency in lysosomal acid lipase that leads to accumulation of cholesterol esters (CE) and triglycerides (TG) in the lysosomes of liver cells. CESD has classically been described as presenting with two phenotypes; the more severe neonatal presentation Wolman's disease and a milder variant that may present later in life^{5,6}. Prevalence estimates vary, but a recent estimation in Germany using genetic testing found a carrier frequency of 1 in 200 persons⁷. Clinically, infants with Wolman's disease present with vomiting, diarrhea, anemia, failure to thrive, hepatosplenomegaly and adrenal calcification⁸. Milder variants of LAL deficiency can present in childhood or adolescence with a clinical scenario that is very similar to NAFLD; namely hepatomegaly, elevated serum liver enzymes, low HDL, hypercholesterolemia and a fatty liver on ultrasound⁸.

Diagnosis of LAL deficiency is made through either decreased LAL activity in cultured fibroblasts or in dried blood spots⁹. A suspicion for LAL deficiency is when low HDL is present in the setting of hepatomegaly and fatty liver.

Type 1 Diabetes and fatty liver:

Mauriac et al in 1946 described uncontrolled Type 1 diabetes (T1DM) leading growth failure, short stature and hepatic steatosis. The prevalence of steatosis in T1DM patients by ultrasound is 44%¹⁰. This hepatic steatosis is easily reversible with improved and tighter control of the diabetes. Diagnosis of T1DM associated hepatic steatosis can be made on the basis of a liver biopsy though an ultrasound showing increased liver echogenicity maybe sufficient to prove the presence of fatty liver disease. If the individual is not overweight or only slightly overweight and the T1DM diagnosis is well established this condition should be considered.

Mitochondrial dysfunction disorders:

There is a consistent pattern of hepatic steatosis when mitochondrial function is compromised. These include disorders of fatty acid oxidation resulting in macrovesicular steatosis especially if the biopsy is after a period of significant fasting¹¹. The different long-chain fatty acid oxidation defects present with multi-organ involvement including but bit limited to heart, liver, and skeletal muscles. Congenital mitochondrial hepatopathies on the other hand have more microvesicular hepatic steatosis and portal fibrosis such as seen in a patient with Alper's syndrome¹². These disorders may be confused with NAFLD, especially in recessive carriers for mutations in nuclear genes such as POLG, DGUOK, and MPV17 or mitochondrial DNA depletion. These are usually affecting multiple-systems including neurological and musculoskeletal systems not the case in simple NAFLD.

See table next page.

Table 1

Differential Diagnosis of Pediatric Fatty Liver Disease
Mitochondrial Hepatopathies
Kwashiorkor/ Anorexia nervosa
Wilson's Disease
CESD/ LAL Deficiency
Hepatitis C
Uncontrolled type 1 diabetes
Mitochondrial disorders

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