Advances in Pediatric Nonalcoholic Fatty Liver Disease

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- Nonalcoholic fatty liver disease (NAFLD)
- Nonalcoholic steatohepatitis (NASH) • Pediatric • Obesity
- Metabolic syndrome • PNPLA3

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in children and its increase is coincident with the obesity epidemic. NAFLD is defined as the presence of macrovesicular steatosis in greater than 5% of hepatocytes in the absence of significant alcohol consumption, drug use, or other recognized disorders that may result in fatty liver. The disease includes a range of disease severity from simple steatosis, which is thought to have a relatively benign prognosis, to nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis. Among children, it is estimated that 5% of normal or overweight and 38% of children who are obese have evidence of NAFLD.[1] Given that obesity rates in the United States approach 30% in many areas, the prevalence of the disease is staggering.[2] Obesity trends in children are not isolated to the United States and are found worldwide.[3–8] Among those patients with NAFLD, a subset will develop NASH. Current evidence suggests that 1% to 3% of the Western population has NASH, making this disease a significant public health problem.[9]

Clinically, NAFLD is primarily a silent disease that is often suspected incidentally on physical examination or on routine blood testing. On physical examination, most patients will be overweight or obese and will commonly have acanthosis nigricans on the back of the neck, intertrigenous areas, or joints. Hepatomegaly can usually be appreciated, although palpating the liver is often challenging in obese individuals. Alanine aminotransferase (ALT) and aspartate aminotransferases (AST) can be abnormal in NAFLD, usually less than 200 U/L. Patients can also complain of abdominal pain as a presenting symptom, which may relate to stretching of the liver capsule as the liver expands or may be the result of other known obesity-related

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gastrointestinal comorbidities, such as reflux, constipation, or biliary tract disease. Abdominal pain often prompts the clinician to order an abdominal ultrasound, which sometimes demonstrates echogenicity of the liver that is highly suggestive of fatty infiltration.

Although the diagnosis of NAFLD may be strongly suspected based on clinical parameters, liver function tests and ultrasound, staging and grading of the disease still requires liver biopsy. Liver biopsy not only can confirm NAFLD but can differentiate between simple steatosis and NASH, which is relevant given differences in natural history. Laboratory testing to exclude other forms of liver disease, such as viral hepatitis, alpha-1 antitrypsin deficiency, Wilsons disease, hemochromatosis, and autoimmune hepatitis should be performed before liver biopsy as part of a general hepatitis evaluation in patients with persistently abnormal liver function tests.

This review endeavors to provide a clinically relevant general overview of pediatric NAFLD by using the most up-to-date literature on the topic. Our understanding of this disease has improved significantly in the last several years, and there have been many interesting advancements in the areas of diagnosis, pathophysiology, genetics, and management.

EPIDEMIOLOGY AND NATURAL HISTORY

The true prevalence of pediatric NAFLD is difficult to determine because screening guidelines are not established and the diagnosis can only be made definitively by liver biopsy. ALT is a nonspecific marker of liver injury in NAFLD, which can be easily obtained; unfortunately normal ALT values have not been clearly established in children.[10] Furthermore, it has been shown that up to 23% of children with NAFLD can have a normal ALT with liver fibrosis.[11] Although abnormal ALT is seen in numerous other liver diseases, most abnormal ALT levels in large populations are attributable to NAFLD. Despite limitations in sensitivity and specificity, ALT can be a valuable screening tool and has been used in numerous studies looking at the prevalence of NAFLD.[12] Data collected from the National Health and Nutrition Examination Survey on 5586 adolescents found elevated ALT in 8% of the study population. Elevated ALT correlated with male sex, Mexican American ethnicity, waist circumference, and fasting insulin levels.[13] The metabolic syndrome, which includes overweight or obesity, insulin resistance, elevated blood pressure, and abnormal waist circumference, has been strongly correlated with the development of NAFLD and disease severity.[14,15] In a European cohort of 16,390 overweight children and adolescents, 11% of the study population was found to have abnormal liver function tests that significantly correlated with high insulin levels, older age, increasing obesity, and male gender.[16] NAFLD prevalence in Asia seems to be as high or higher, although pediatric data is limited.[17] No official position statement by the major pediatric professional societies recommend routine screening for NAFLD, but plasma ALT may be an easily obtainable, although nonspecific, screening tool in patients considered high risk.

NAFLD is a clinicopathologic diagnosis and, therefore, liver tissue is required to determine true prevalence data in children. The only practical means to obtain this data has been to obtain autopsy specimens from children who had an accidental death. In a landmark article using 742 autopsy specimens from children in San Diego County, 17.3% of the children were aged from 15 to 19 years, were found to have the disease.[1] NAFLD was also found to be more common in boys and children of Asian (10.2%) and Hispanic (11.8%) background. African Americans had the lowest rates of NAFLD at 1.5%. Of note, most Hispanic subjects in this study were of Mexican