Current Concepts in Pediatric Nonalcoholic Fatty Liver Disease

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KEYWORDS

• Steatohepatitis • NASH • Obesity • Metabolic syndrome • Histopathology

KEY POINTS

- Nonalcoholic fatty liver disease (NAFLD) manifests as a spectrum of disease (steatosis to steatohepatitis to cirrhosis) and its increasing prevalence is a direct result of rapidly rising obesity rates.
- Pediatric NAFLD may be distinctly different from that found in adults by histologic evaluation; however, the cause of these differences is unknown.
- The exact pathophysiology of NAFLD is largely unknown, but histologic findings provide insight into possible mechanisms and targets for therapy.
- Few effective therapies are successful in treating NAFLD, and lifestyle modification remains the first-line of therapy in children.
- Randomized, controlled trials demonstrate resolution of NASH with vitamin E therapy, which is the current recommended treatment in pediatrics by expert guidelines.

PEDIATRIC EPIDEMIOLOGY AND RISK FACTORS

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in children and its increasing prevalence is associated with the concomitant rise in obesity.[1] Features of the metabolic syndrome criteria are each associated with NAFLD, including obesity, insulin resistance, and hypertriglyceridemia, and children with the metabolic syndrome have 5 times the odds of having NAFLD as overweight and obese children without metabolic syndrome.[2] Although the prevalence rates of pediatric obesity have remained stable over the past decade,[1] estimates on the prevalence of NAFLD in pediatrics vary widely.

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The variability in prevalence estimates is in part owing to a relative lack of sensitive screening methods. Alanine transaminase (ALT) is a marker of hepatic injury and when combined with imaging that has sensitivity to fat infiltration, and when combined with other laboratory tests to eliminate other causes of fatty liver clinical suspicion, can be used to diagnose NAFLD. However, ALT is not sensitive, and normal cutoff values are based on adult values; appropriate cutoffs have not yet been defined in children, and are likely lower than current cutoffs, because "normal" ranges have shifted upward with the trend in higher body mass index *z*-scores.[3] More work is needed to determine appropriate cutoffs in children, and to determine other more sensitive markers of disease.

Despite this challenge, attempts have been made to get accurate prevalence rates in children. The SCALE study conducted a retrospective review of 742 children from the San Diego, California area, between the ages of 2 and 19 years, who had an autopsy performed by a county medical examiner for reasons related to unnatural rapid death. In this study, 9.6% of all children and 38% of obese children were found to have NAFLD.[4] In contrast, in a large European cohort of children, the prevalence of elevated ALT was 11% of the study population, and 17% in the extremely obese children.[5] Finally, in an National Health and Nutrition Examination Survey cohort of children, 8% of the population had an elevated ALT.[6] Across all 3 studies, however, older, male, Hispanic children were found to be at greatest risk.[4–6]

NONALCOHOLIC FATTY LIVER DISEASE AS A SPECTRUM OF DISEASE

NAFLD results from an accumulation of excess free fatty acids and triglycerides, demonstrated by hepatocellular macrovesicular steatosis.[7] NAFLD is an all-encompassing term that refers to a spectrum of disease. Although nonalcoholic fatty liver refers to steatosis without inflammation or necrosis and is considered relatively benign, this condition may progress or present with inflammation, hepatocyte injury and cell death, called nonalcoholic steatohepatitis (NASH).[8] NASH may be present with or without fibrosis, with potential progression to cirrhosis and increasing the risk of hepatocellular carcinoma.[9]

THE ROLE OF LIVER BIOPSY

Liver biopsy is required for definitive diagnosis and staging of NAFLD owing to insufficiently validated or developed biomarkers or imaging techniques.[10] For example, pediatric ultrasound imaging has shown good correlation with steatosis but not with fibrosis or liver injury.[11] Liver biopsy is also required to rule out comorbid disease as cause of elevated ALT. Skelly and colleagues[12] found that one-third of patients with suspected NAFLD were diagnosed with a condition other than NAFLD by biopsy, reinforcing the role of biopsy and the lack of specificity of ALT. Furthermore, biopsy is required for determination of nonprogressive (NAFL) versus progressive (NASH) disease.[8]

Unfortunately, liver biopsy carries significant risks of morbidity and mortality, rendering it an unacceptable screening tool.[13] Therefore, guidelines have been developed to help clinicians balance possible risk with the need for accurate diagnosis. The American Association for the Study of Liver Disease published guidelines in 2012 that recommend clinicians reserve liver biopsy for only subjects who will benefit and for children with unclear diagnosis or consideration for medication.[14] Its European counterpart, the European for the Study of Liver Disease, released a position statement that acknowledged liver biopsy provides both diagnostic and prognostic information on fibrosis, and potential for progression if fibrosis is suspected by noninvasive methods. No specific pediatric recommendations were made.[15]