Nonalcoholic Liver Disease in Children and Adolescents

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KEYWORDS

• NAFLD • NASH • Pediatric • Steatohepatitis • Fatty liver disease

KEY POINTS

- Pediatric nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in children.
- The spectrum of NAFLD ranges from steatosis to nonalcoholic steatohepatitis (NASH) to fibrosis. Obesity rates in children continue to rise and, as a result, NAFLD in children is becoming more prevalent.
- The pathophysiology, natural history, and progression of disease are still being elucidated but NAFLD/NASH in children may represent a more severe phenotype that will benefit from early identification and management.

DEFINITIONS

Pediatric nonalcoholic fatty liver disease (NAFLD) is chronic hepatic steatosis in children, ages 18 years or younger, that cannot be attributed to a genetic or metabolic disorder, infection, steatogenic medications, ethanol, or malnutrition. NAFLD can further be divided into NAFL and nonalcoholic steatohepatitis (NASH), based on histology. NAFL is characterized by bland steatosis whereas NASH is characterized by steatosis with lobular inflammation and hepatocellular injury. Fibrosis, when present, may indicate a more severe disease phenotype, even in the absence of NASH. Pediatric NAFLD is most often diagnosed in children between the ages of 12 and 13; however, it has been reported in children as young as 2 years, with NASH-related cirrhosis noted as early as 8 years of age (**Table 1**).[1]

EPIDEMIOLOGY

Estimating the prevalence of NAFLD in pediatric populations is difficult due to differences in screening laboratory tests and imaging studies, thresholds for detection,

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Table 1
Nonalcoholic fatty liver disease definitions and phenotypes in children

Phenotype	Definition
NAFLD	Encompasses the full spectrum of disease from NAFL to NASH, without evidence of significant alcohol consumption, genetic or metabolic diseases, infection, or steatogenic medications
NAFL	Presence of ≥5% hepatic steatosis without evidence of hepatocellular injury
NASH	Presence of ≥5% of hepatic steatosis with inflammation, with or without ballooning injury to hepatocytes and fibrosis
NAFLD with fibrosis	NAFL or NASH with periportal, portal, sinusoidal, or bridging fibrosis
NAFLD with cirrhosis	Cirrhosis in the setting of diagnosed NAFLD

From Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr 2017;64(2):319–34; with permission.

and demographics of the region being sampled. A 2015 meta-analysis determined the pooled mean prevalence of NAFLD to be 7.6% in the general US pediatric population and 34.2% in studies based in pediatric obesity clinics.[2] A study of liver histology obtained at autopsy in 742 children ages 2 years to 19 years found an NAFLD prevalence of 9.6% after adjusting for age, gender, race, and ethnicity.[3]

This variation by race and ethnicity suggests that genetic factors likely play a large role in the pathogenesis and progression of NAFLD.[1] Hispanic adolescents have a 4-fold increased risk of developing hepatic steatosis compared with non-Hispanic adolescents ages 11 years old to 22 years old.[4] White and Asian children and adolescents also have high prevalence compared with African American children. NAFLD is also more prevalent in male children than female children.[1,5,6] Finally, prevalence is higher in obese children compared with those with normal weight; however, not all children with NAFLD are obese. NAFLD can occur in up to 5% of children with a normal body mass index (BMI).[1]

A single nucleotide polymorphism common variant allele in PNPLA3 has been associated with increased susceptibility to NAFLD.[7] Adult studies have demonstrated this variant allele associated with increased hepatic fat and histologic severity. Studies have been conflicting, however, regarding PNPLA3 association with histology of NAFLD in children.[8,9]

RISK FACTORS AND COMORBIDITIES

NAFLD is more common in children with metabolic syndrome.[10] Studies have shown that children with biopsy-proved NASH have increased risk for multiple cardiovascular factors, including high cholesterol, low-density lipoprotein, triglycerides, and systolic blood pressure compared with obese children.[11–13] Elevated ALT is more common in Hispanic children newly diagnosed with type 2 diabetes mellitus compared with African American children.[14]

NAFLD has been associated with obstructive sleep apnea. Hypoxia and oxidative stress from apnea are believed to contribute to progression of steatohepatitis and fibrosis because of ischemia-reperfusion injury. Two pediatric studies have shown an association of obstructive sleep apnea with the presence of NASH, independent