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Review Article

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New Perspectives in Pediatric Nonalcoholic Fatty Liver Disease: Epidemiology, Genetics, Diagnosis, and Natural History

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children. The global prevalence of pediatric NAFLD from general populations is 7.6%. In obese children, the prevalence is higher in Asia. NAFLD has a strong heritable component based on ethnic difference in the prevalence and clustering within families. Genetic polymorphisms of patatin-like phospholipase domain–containing protein 3 (*PNPLA3*), transmembrane 6 superfamily member 2, and glucokinase regulatory protein (*GCKR*) are associated with the risk of NAFLD in children. Variants of *PNPLA3* and *GCKR* are more common in Asians. Alterations of the gut microbiome might contribute to the pathogenesis of NAFLD. High fructose intake increases the risk of NAFLD. Liver fibrosis is a poor prognostic factor for disease progression to cirrhosis. Magnetic resonance spectroscopy and magnetic resonance proton density fat fraction are more accurate for steatosis quantification than ultrasound. Noninvasive imaging methods to assess liver fibrosis, such as transient elastography, shear-wave elastography, and magnetic resonance elastography are useful in predicting advanced fibrosis, but they need further validation. Longitudinal follow-up studies into adulthood are needed to better understand the natural history of pediatric NAFLD.

Keywords: Nonalcoholic fatty liver disease; Children; Epidemiology; Genetics; Microbiome; Liver fibrosis; Asia

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of fat in the liver in the absence of excessive alcohol consumption or other known liver pathologies. NAFLD has increased in prevalence and becomes the most common cause of chronic liver disease in children. NAFLD includes a wide spectrum of liver pathology ranging from steatosis to nonalcoholic steatohepatitis (NASH). Genetic and environmental factors are involved in the development and progression of the disease. NAFLD is associated with development of metabolic syndrome, type 2 diabetes, and cardiovascular disease. Studies on the long-term prognosis in the adult population demonstrate that simple steatosis follows a relatively benign clinical course, whereas steatohepatitis associated with increased fibrosis may progress to end-stage liver disease [1]. However, the natural history and prognosis of NAFLD

in children remains scant. This article reviews new perspectives in epidemiology, genetics, gut microbiomes, diagnostic modalities, and natural history of NAFLD in children.

EPIDEMIOLOGY

The pooled global prevalence of NAFLD was 7.6% in children from general population studies and 34.2% in obese children. In general population studies, there was no evidence that prevalence differed by geographical region. The prevalence of NAFLD in the pediatric populations from Asia, Europe, and North America was 5.9%, 5.7%, and 6.5% respectively. In clinical studies of obese populations, prevalence was higher in Asia than Europe and North America [2]. Using elevated serum ALT as a surrogate marker of NAFLD, data from Korean National Health and Nutrition Examination Surveys showed prevalence of NAFLD among adolescents was 5.3% and stable from 2001 to 2014. The risk factors for NAFLD were male gender, greater body mass index (BMI), and increased waist circumference [3]. Vitamin D deficiency was associated with pediatric NAFLD, independent of obesity and metabolic syndrome [4]. Studies using alanine aminotransferase (ALT) had a lower mean prevalence estimate than studies using ultrasound (US) or magnetic resonance imaging (MRI). In general population studies using US, prevalence estimates were 7.6% [2]. The prevalence of biopsy proven NAFLD in autopsy samples from children and adolescents was 9.6% in the United States [5].

GENETICS

NAFLD has a strong genetic component. Large multi-ethnic population-based studies showed ethnic difference in the prevalence of NAFLD, independent of adiposity, and insulin resistance [6]. Histologically confirmed NAFLD was present in 11.8% of Hispanic children, 10.2% of Asian children, 8.6% of European children, and 1.5% of African children [5]. There is the evidence that NAFLD tends to cluster in families. A familial aggregation study showed that in children without NAFLD, 17% of siblings and 37% of parents had NAFLD compared with 59% of siblings and 78% of parents of children with NAFLD. The heritability of fatty liver was 1.0 and of liver fat fraction was 0.39 after adjusting for age, gender, race, and BMI [7].

Patatin-like phospholipase domain–containing protein 3 (*PNPLA3*) encodes a transmembrane protein known as adiponutrin. PNPLA3 is expressed predominantly in adipose tissue and may be involved in the hydrolysis of triglycerides (TG). The rs738409 (G/C) single nucleotide polymorphism (SNP), which causes a I148M protein variant, had a strong association with increased hepatic fat content. This allele frequency was 0.48 in Hispanics, 0.23 in Europeans and 0.17 in Africans, which is consistent with different prevalence of NAFLD by ethnicity [8]. The minor allele frequency of rs738409 is 0.51 in Koreans [9]. Studies in adults have shown that I148M is associated with histologic severity of steatosis, NASH, and fibrosis [10,11]. *PNPLA3* SNP appears to be more important in the development of NAFLD in the non-obese population. In a study in Hong Kong, *PNPLA3* variant was found in 78.4% of the non-obese NAFLD group and in 59.8% of the obese NAFLD group [12]. Genetic susceptibility rather than metabolic risk factors might play an important role in the development of NAFLD in the Asian population [9]. Several pediatric studies have demonstrated association of the I148M genotype with elevated ALT in Asian, Hispanic, and European children who are obese [13-17].

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A nonsynonymous SNP in the transmembrane 6 superfamily member 2 (*TM6SF2*) gene is associated with NAFLD but a clinically favorable lipid profile. This variant (rs58542926) is resulting in glutamic acid to lysine substitution at codon 167 (E167K). TM6SF2 is required for secretion of very low-density lipoprotein (VLDL) from the liver. The E167K variant results in impaired VLDL secretion and intrahepatic TG accumulation [18]. This variant is associated with pediatric NAFLD but may protect cardiovascular disease by lowering total cholesterol and TG in obese children [19,20]. Glucokinase regulatory protein (*GCKR*) regulates de novo lipogenesis by controlling the influx of glucose in hepatocytes. The *GCKR* rs780094 SNP is associated with an increased risk of NAFLD, and this allele frequency is higher in Asian population [21]. Membrane bound O-acyl transferase domain-containing protein 7 (*MBOAT7*) is involved in phospholipid remodeling [22]. Variants in *GCKR* and *MBOAT7* gene contribute to the risk of pediatric NAFLD [23,24].

Studies evaluating multiple genetic polymorphisms have demonstrated that different ethnic groups have different risk genes [22,23,25,26]. Synergistic effects of the risk alleles of *PNPLA3*, *TM6SF2*, and *GCKR* on intrahepatic fat accumulation suggested that multiple risk genotypes have an additive effect on hepatic fat content [19]. Addition of genotypes to clinical risk factors including ethnicity, weight gain, and insulin resistance improved prediction of NALFD in obese children [26,27]. Adiposity amplifies the effect of the risk alleles of *PNPLA3*, *TM6SF2*, and *GCKR*, indicating gene-adiposity interaction has a major role in the development and progression of NAFLD [28].

GUT MICROBIOME

The composition of gut microbiome at phylum level demonstrated that a significant increase in Bacteroides and decrease in Firmicutes was found in the obese and NASH children, compared to the healthy children. Proteobacteria was significantly increased in NASH group, compared to obese group. Patients with NASH had not only more alcohol producing *Escherichia*, but also higher elevated blood ethanol levels. This study suggests that microbiomes rich in ethanol-producing *Escherichia* may be involved in the disease progression from obesity to NASH [29]. In a metagenomics and metabolomics study of children with simple steatosis, NASH, obesity, and healthy controls, 26 of 292 volatile organic compounds were increased in patients with NAFLD. The combination of a low abundance of *Oscillospira* with high levels of 2-butanone was intestinal microbiota signatures of liver steatosis, and high abundance of *Ruminococcus* and *Dorea* were associated with progression of simple steatosis to NASH [30]. Gut microbiota is associated with advanced fibrosis in adults with NAFLD and gut microbiome model can be used as a non-invasive test to accurately diagnose advanced fibrosis [31]. In a study of children with obesity or NAFLD, gut microbiomes of children with NAFLD had lower α-diversity than obese children without NAFLD. Increases in *Prevotella copri* were associated with more severe fibrosis. Bacterial genes for lipopolysaccharide biosynthesis were enriched in children with NASH, and genes for flagellar assembly were enriched in moderate to severe fibrosis [32]. Alterations of the intestinal microbiome might contribute to the pathogenesis of NAFLD and be used as markers of disease or severity.

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DIETARY FACTORS

There is growing evidence that fructose contributes to the development and severity of NAFLD. In an epidemiologic study, energy-adjusted higher fructose intake was associated with NAFLD in adolescents with obesity [33]. Fructose promotes increased hepatic de novo lipogenesis, production of uric acid, visceral adiposity, and decreased insulin sensitivity [34,35]. Hepatic de novo lipogenesis is a major contributor of intrahepatic fat accumulation [36]. Visceral obesity and insulin resistance are the most important risk factors for pediatric NAFLD [37]. Children with NAFLD had higher fasting insulin and glucose compared with children with obesity alone [38]. Visceral adipose tissue is the main source of free fatty acids for hepatic TG synthesis [39]. Fructose may alter intestinal microbiome or its products such as endotoxin [40]. Adolescents with NAFLD had higher endotoxin levels than obese controls and the endotoxin level correlated with insulin resistance and inflammatory cytokines [41].

DIAGNOSIS

Liver biopsy

Liver biopsy is the gold standard to define the presence and severity of NAFLD and to rule out alternative and/or concurrent diagnoses [42]. However, liver biopsy is invasive and samples only a very small portion of the liver and thus may not be ideal for clinical monitoring. Hepatic steatosis is histologically graded on biopsy according to the proportion of hepatocytes containing fat macrovesicles on hematoxylin and eosin staining (grade 0, <5%; grade 1, 5–33%; grade 2, 34–66%; and grade 3, >66%). Fibrosis is scored as stage 0-none; stage 1-periportal or perisinusoidal fibrosis; stage 2-perisinusoidal and portal/periportal fibrosis; stage 3-bridging fibrosis; and stage 4-cirrhosis [43]. Two types of histologic patterns have been described in pediatric NASH. Type 1, more common in adults, is characterized by steatosis, ballooning degeneration, and perisinusoidal fibrosis. Type 2, more common in Asian children, is characterized by steatosis, portal inflammation, and portal fibrosis [44]. In a study of 80 children with NAFLD in Korea, type 1 NASH was present in 34%, and type 2 NASH in 44% [45]. The significance of portal predominant type 2 NASH for future clinical events is unknown. About 10 to 25% of children with biopsy proven NAFLD have advanced fibrosis at initial presentation [46,47]. Severity of fibrosis is associated with higher BMI and increased waist circumference [48,49]. Reliable noninvasive tests are required, as liver biopsy cannot be performed in all patients suspected of having NAFLD.

Detection of steatosis

US is the most commonly used imaging tool used to detect hepatic steatosis. Semiquantitative estimation of steatosis by US is based on hepatorenal echogenicity contrast and visualization of vasculature, parenchyma, and diaphragm. The area under the curve (AUC) for ultrasonographic detection of moderate-to-severe steatosis was 0.87 in children [50]. The sensitivity of US to detect hepatic steatosis is low when the liver contains less than 30% fat.

Magnetic resonance spectroscopy and MRI proton density fat fraction (MRI-PDFF) are more accurate for the hepatic fat quantification [51]. MRI-PDFF has high diagnostic accuracy to predict histological steatosis grade in children with NAFLD [52]. Cost effectiveness of MRI needs to be addressed.

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Assessment of fibrosis

Liver fibrosis is a poor prognostic factor for risk of disease progression to cirrhosis. Several noninvasive serologic scores to assess fibrosis use readily available laboratory tests. These include fibrosis-4 index (FIB-4), Forn's index, AST to platelet ratio index (APRI), pediatric NAFLD fibrosis score, and pediatric NAFLD fibrosis index. FIB-4 can predict significant fibrosis (stage 2) with an AUC of 0.81 in children with NAFLD [53]. External validation is needed before they are implemented in clinical practice [53,54].

Transient elastography (TE) using the Fibroscan apparatus has been used to estimate hepatic stiffness and liver fibrosis. It was most useful in predicting advanced fibrosis (stage 3), whereas differentiation between no fibrosis and stage 1 or 2 was less accurate in Italian children with NAFLD. TE values of at least 9 kPa were associated with the presence of advanced fibrosis [55]. Optimal cutoff TE value for predicting advanced fibrosis was 8.6 kPa in a United States cohort [56]. Shear-wave elastography (SWE) by using conventional US machine efficiently detects the presence of significant liver fibrosis and, less accurately, mild fibrosis (stage 1) in children with NAFLD. The AUC for differentiating significant fibrosis from fibrosis of less than stage 2 was 0.97, with an optimal cutoff value of 6.7 kPa [57].

Magnetic resonance elastography (MRE) is a promising noninvasive method for assessing fibrosis that has demonstrated excellent results in adults with liver fibrosis. A study in which healthy children were compared with healthy adults using MRE demonstrated that liver stiffness increased with age during normal development and approached adult values during adolescence. Applying pediatric liver stiffness to adult baseline values may underestimate severity of liver disease [58]. MRE in children had an overall accuracy for discriminating between any versus no fibrosis of 72% and 87% to 90% for classifying advanced fibrosis. The results of this study did not show the degree of diagnostic performance reported in adult-based studies due to breath holding difficulties in children [59].

A meta-analysis to compare the performance of APRI, FIB-4, BARD score, NAFLD fibrosis score, TE, SWE, and MRE for assessing liver fibrosis in adults with NAFLD showed that MRE and SWE may have the highest diagnostic accuracy for staging fibrosis [60]. Further pediatric studies of US-based tools and MRE are needed to validate these imaging studies.

NATURAL HISTORY

In a retrospective longitudinal adult studies of biopsy confirmed NAFLD, fibrosis stage at baseline, but no other histologic features of steatohepatitis, were associated independently with long-term overall mortality, liver transplantation, and liver-related events [61]. Adolescents with NAFLD may have more advanced fibrosis compared with adults [62]. There are few longitudinal studies on natural history of pediatric NAFLD. In a retrospective study with a follow-up liver biopsy after a mean interval of 28 months, 7 of 18 patients had progression of fibrosis, and 3 patients had regression or disappearance of fibrosis after losing weight. Advanced fibrosis might be seen in patients in the absence of liver enzyme abnormalities [63]. The natural history of pediatric NAFLD in the setting of lifestyle counseling was represented by the placebo arm of a randomized control trial designed to compare vitamin E, metformin, and placebo with liver biopsies at baseline and at 2-year follow-up. In the placebo cohort, 28% had resolution of NASH, 40% improved fibrosis, 40% improved steatosis, and 43% improved lobular inflammation [64]. Lifestyle modification

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with diet and increased physical activity for 2 years improved grade of steatosis, lobular inflammation, hepatocyte ballooning, and NAFLD activity score [65]. Baseline hepatic fat fraction and weight loss predicted resolution of NAFLD at 2 years follow-up [26].

Children with NAFLD have a very high risk of type 2 diabetes and persistence of obesity at follow-up in young adulthood [66]. A retrospective longitudinal study over time periods up to 20 years showed that progression of fibrosis on follow-up liver biopsy was noted in 4 of 5 patients, and 2 patients with decompensated cirrhosis underwent liver transplantation. Children with NAFLD had a 13.8-fold higher risk of dying or requiring liver transplantation than the general population of the same age and sex [67]. Severe fibrosis and cirrhosis can occur within a few years of diagnosis in the most severe cases. There are insufficient data to predict which children are at higher risk of rapid disease progression [68]. Because death, cardiovascular disease, and liver transplantation from pediatric NAFLD typically do not occur in childhood, studies determining health outcomes from pediatric NAFLD will require longitudinal follow-up into adulthood.

CONCLUSION

NAFLD is the leading cause of chronic liver disease in children. Multiple genetic factors, intestinal microbiomes, and fructose intake have been identified as risk factors for pediatric NAFLD. A better understanding of NAFLD pathophysiology may help to identify children at risk of the progression of NAFLD and efficient personized therapeutic approaches. Noninvasive imaging modalities, such as US and MRI are used to estimate the steatosis and fibrosis, but they require further validation in children. Additional larger pediatric longitudinal studies are needed to investigate the progression and natural history of pediatric NAFLD.

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