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Clinical Advances in Pediatric Nonalcoholic Fatty Liver Disease

Jeffrey B. Schwimmer, M.D.

[1]Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Diego School of Medicine, La Jolla, California

[2]Department of Gastroenterology, Rady Children's Hospital San Diego, San Diego, California

[3]Liver Imaging Group, Department of Radiology, University of California, San Diego School of Medicine, San Diego, California

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The importance of nonalcoholic steatohepatitis (NASH) was first formally recognized at an NIH Consensus Symposium in December 1998 (1). Since then, there has been a rapid growth of knowledge regarding nonalcoholic fatty liver disease (NAFLD) in children. The greatest advances have been made in the realms of awareness, diagnosis, and understanding of associated comorbidities. Challenges that lie ahead are centered on clinical management —the ongoing search for valid non-invasive diagnostic tools and effective therapy. This review addresses key clinical questions for which progress has been made.

Liver Chemistry in Pediatric NAFLD

What is the upper of limit of normal for ALT in children?

Serum alanine aminotransferases (ALT) is the laboratory assay most used in the evaluation of NAFLD. Unfortunately, there are extreme differences in the cutoffs in use by clinical laboratories for the upper limit of normal (ULN) for ALT in children. In the United States, the Screening ALT for Elevation in Today's Youth (SAFETY) study used data from the National Health and Nutrition Examination Survey to determine biologically-based thresholds for the ULN of ALT (2). The 95th percentile for ALT in children who had normal body mass index (BMI), glucose and lipids, and the absence of infection or use of hepatotoxic medications was 26 U/L for boys and 22 U/L for girls. Park et al. used data from participants in the Korea National Health and Nutrition Examination Survey who were at low risk for liver disease to determine the ULN for ALT in Korean adolescents. The 97.5th percentile for ALT was 33 U/L for boys and 25 U/L for girls (3). The Canadian Laboratory Initiative in Pediatric Reference Intervals (CALIPER) determined that the normal range for

Correspondence: Jeffrey B. Schwimmer, M.D., Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of California, San Diego, 3020 Children's Way, MC 5030 San Diego, CA 92123, jschwimmer@ucsd.edu, phone: 858-966-8907, fax: 858-560-6798.

liver chemistry varied not only by sex, but also by age. (4). For children age 1 through 12 years, the ULN for ALT was 25 U/L for both boys and girls. For children age 13 to 18 years, the ULN for ALT was 24 U/L for boys and 22 U/L for girls. When taken in aggregate, these studies make it clear that the ULN for ALT in children is approximately 25 U/L with small variations related to age and sex.

How well does ALT perform in the detection of NAFLD in children?

In the SAFETY study, utilizing the biology-based ALT cut-points for detection of hepatic steatosis determined by magnetic resonance imaging (MRI) yielded a sensitivity of 80% in boys and 92% in girls, and a specificity of 79% in boys and 85% in girls (2). The diagnostic accuracy of ALT was also tested in children with suspected NAFLD identified in primary care by screening according to pediatric guidelines (2). For the diagnosis of NAFLD in overweight and obese children ≥ age 10, screening ALT of ≥ 80 U/L had a sensitivity of 57% and a specificity of 71%. As a comparison, using two times the biology-based ALT thresholds (ALT ≥ 50 for boys and ≥ 44 for girls) had a sensitivity of 88% and a specificity of 26%. Finally, Molleston and colleagues analyzed 483 children with NAFLD enrolled in the NASH CRN, of whom 3.5% (17/483) had normal ALT (boys < 26 U/L, girls <23 U/L) and 15.3% (74/483) had mildly elevated ALT (boys 26–50 U/L, girls 23–44 U/L) (5).

Liver Imaging in Pediatric NAFLD

Is there a role for ultrasound in the management of NAFLD in Children?

The presence of lipid droplets within hepatocytes can cause scatter and attenuation of ultrasound waves. Changes due to scattering and attenuation are used to infer hepatic steatosis, but currently available ultrasound-based techniques do not permit a direct quantifiable measurement of liver fat content. In aggregate, there are 492 children documented who had an estimate of liver steatosis by ultrasonography compared to an estimate of grading of steatosis by liver histology or liver fat fraction by MRI (6). The overall positive predictive value of ultrasound in the detection of hepatic steatosis was 47–62%. In the one study with available data, the accuracy for grading the severity of steatosis was 32% (7). Thus, an evidence based assessment concluded that ultrasound does not meet the standard clinical threshold required to be used to diagnose fatty liver, grade hepatic steatosis, monitor disease, or be used as an outcome measure in clinical trials (6). However, it should also be noted that there are promising ultrasound-based technologies for the assessment of hepatic steatosis and fibrosis that are being developed (8–10). It will be important that these be properly evaluated in children with NAFLD.

Is MRI ready for use in the management of NAFLD in children?

Increasingly MR methods are used to measure liver fat. Most studies have measured the signal fat fraction (SFF), the proportion of the MR signal that comes from fat. Because the fat signal is influenced by multiple factors, the SFF may not reliably reflect actual fat content. A newer method, proton density fat fraction (PDFF), is the SFF corrected for major confounding effects, and thus, more closely represents the actual fat content (11). The MRI Rosetta Stone Project showed that liver PDFF is strongly correlated with the histologic steatosis grade (12). This correlation was influenced by both sex and fibrosis stage.

Moreover, there was not a singular cutoff for PDFF that separated children with and without NAFLD sufficient for diagnostic use. Thus as this time MRI is well suited to use in clinical research, but further studies are needed prior to its use in patient care for children with NAFLD.

Liver Histology in Pediatric NAFLD

How safe is liver biopsy as a test for NAFLD in children?

The AASLD position paper on Liver Biopsy estimates that the risk of clinically significant bleeding following liver biopsy is between 1/2500 and 1/10,000 (13). There are over 2000 children with biopsy-proven NAFLD reported in the literature, and there have been no reports of any serious adverse events related to the liver biopsy procedure. However, most publications did not specifically detail adverse events. In a retrospective study, Harwood et al demonstrated that liver biopsy in obese children was not associated with a higher rate of complications than for non-obese children (14). In a prospective study, 255 children had an outpatient percutaneous liver biopsy for suspected NAFLD (15). There were no serious adverse events. In the immediate recovery period 3% of children experienced mild pain or nausea. Once at home, an additional 3% of children noted minor self-limited discomfort.

What is the role of liver biopsy as a diagnostic test for NAFLD in children?

The AASLD practice guideline on NAFLD states that, “liver biopsy in children with suspected NAFLD should be performed in those where the diagnosis is unclear, where there is possibility of multiple diagnoses, or before starting therapy with potentially hepatotoxic medications. A liver biopsy to establish a diagnosis of NASH should be obtained prior to starting children on pharmacologic therapy for NASH.” (16). The guideline does not address what makes the diagnosis *clear* in the absence of liver biopsy. Certainly elevated ALT alone does not. Algorithms such as the Fatty Liver Index have proven invalid in children (15, 17). Liver ultrasound does not reliably determine hepatic steatosis in children. There is not a specific threshold for MRI fat fraction that accurately separates between all children with and without NAFLD. The value of a liver biopsy in NAFLD evaluation was recently demonstrated in a prospective study of 347 overweight or obese children identified as having suspected NAFLD by screening in primary care and referred to pediatric gastroenterology(15). The combination of histology, clinical, and laboratory features yielded a diagnosis of NAFLD in 55% (193/347) of those children. However, a total of 17 different liver diseases other than NAFLD were present in 24% of those who underwent liver biopsy. Finally, there are nearly 100 medications that can be considered as potentially hepatotoxic (2). These medications are most commonly used in dermatology, infectious disease, neurology, oncology, and rheumatology. The clinical challenge is to determine who needs how much of a work-up. The greater potential for hepatotoxicity and the more advanced the disease is believed to be, the greater the need to be certain of the diagnosis and to properly grade and stage the disease.

Although there is great passion in the debate over the role of liver biopsy in the diagnosis of NAFLD and NASH, no other diagnostic modality has shown sufficient accuracy to be appropriate for clinical use in the place of biopsy. One can choose not to do a biopsy, but

then rather than declaring a diagnosis of NAFLD, a child should be considered to have suspected NAFLD. There will be some children who are misclassified if a diagnostic certainty is proclaimed. We have observed this leading to a delay in diagnosis of important alternative diagnoses, such as autoimmune hepatitis. The benefits of liver biopsy will continue to need to be balanced against the potential risks on a case-by-case basis.

How is liver histology evaluated in children with NAFLD?

Histology is the most sensitive means of obtaining pertinent, comprehensive information to identify steatohepatitis and stage liver fibrosis, which have important prognostic implications. Moreover, histology provides complex and integrated information at a cellular level, and can therefore refine a diagnosis. NAFLD is a heterogeneous disorder with at least 3 patterns in children: those with steatosis and relatively mild features overall, those with portal features, and those with typical adult features of NASH (18). In contrast to the zone 3 predominance of lesions in adults, children are more likely to have zone 1 steatosis, inflammation, fibrosis and greater severity of steatosis. It is unclear whether these patterns represent sub-phenotypic variations, or are different disease processes altogether.

There are a constellation of histopathologic lesions required for the diagnosis of steatohepatitis. Because of differences in the pattern of liver injury between children and adults with NAFLD, the diagnosis of steatohepatitis remains somewhat controversial in children. The determination of steatohepatitis is best made by an experienced pathologist reviewing the histology in aggregate. Scoring systems have been developed for clinical trials, but not for the diagnosis of NASH. There is a need for a consensus as to what constitutes steatohepatitis in children as determined by knowing which features are most associated with the risk for progression of disease, development of cirrhosis, and liver-related morbidity and mortality.

Associated Conditions

What is the relationship between NAFLD and Obesity?

Obesity is a consistent risk factor for NAFLD in children. However, NAFLD and obesity are not interchangeable. Most obese children do not have NAFLD. In SCALE, only one-third of obese children had NAFLD (19). Even many severely obese adolescents do not have NAFLD. In the Teen LABS study of 242 severely obese adolescents (mean BMI 50.5 kg/m^2) undergoing weight loss surgery, NAFLD was suspected in 37% (20). NAFLD was then diagnosed in 87 of the 148 patients that had a liver biopsy at the time of bariatric surgery, representing 59% of those biopsied and 36% of those who had weight loss surgery (21). When assessed from the other vantage point, most children with NAFLD are obese. In SCALE, 60% of children with NAFLD were obese. In reports of children diagnosed with NAFLD in pediatric hepatology centers, approximately 70 to 90% were obese. However the severity of obesity differs by region and center. In reports from Europe and Asia the mean BMI of children with NAFLD was 25 to 27 kg/m^2, compared to 30 to 32 kg/m^2 in reports from North America (22). Thus, there may be differences in the risk for NAFLD or the severity of NAFLD among children around the globe. For example, the rate of advanced fibrosis among children with NAFLD ranged from 5–10% in Europe, 8–10% in Asia, and 8–

20% in the United States (5, 15, 23–29). However in the Teen LABS study, advanced fibrosis was observed in only 1% of adolescents with NAFLD (21).

Is NAFLD associated with cardiovascular disease in children?

NAFLD is also associated with numerous serious health conditions over and above the expected rates attributable to obesity. Adults with NAFLD have increased rates of coronary heart disease, congestive heart failure, atrial fibrillation, and cardiovascular mortality (30, 31). These associations are independent of traditional risk factors and led many to speculate that NAFLD is a contributor to cardiovascular pathology via a combination of hepatic insulin resistance, atherogenic dyslipidemia, and liver derived inflammation.

The association between NAFLD and cardiovascular disease is also present in childhood. In a case-control study of 300 overweight children, we established that NAFLD was associated with metabolic syndrome independent of BMI (32). Children with NAFLD had higher rates of abnormal glucose, insulin, triglycerides, and HDL cholesterol than overweight children matched for age, sex and BMI. Overall, dyslipidemia is present in approximately half of children with NAFLD. Moreover, hepatic steatosis has been linked to higher rates of atherogenic small dense LDL particles that promote endothelial dysfunction and a hypercoagulable state (33).

Pediatric NAFLD is also associated with hypertension. In a study of 494 children with NAFLD, the estimated prevalence of high blood pressure was 36% (34). Children with high blood pressure had more severe steatosis than children with NAFLD who did not have high blood pressure. Over one year of follow-up, girls with NAFLD had two-fold greater odds of having persistent high blood pressure than boys with NAFLD.

Hepatic steatosis in children, independent of degree of obesity, is associated with significant overall cardiac dysfunction. Sert el al reported that obese adolescents with abnormal liver echotexture and ALT > 40 U/L had greater left ventricular mass and impaired diastolic function compared to obese adolescents with normal liver echotexture and ALT < 40 U/L. (35). Similarly, in a study of 400 obese children, Alp et al demonstrated systolic and diastolic impairment in children with abnormal liver echotexture compared to children with normal liver echotexture.(36). Singh et al reported that obese adolescents with elevated hepatic SFF had decreased left ventricular global longitudinal strain (systolic dysfunction) and decreased early diastolic longitudinal strain (diastolic dysfunction) compared with obese adolescents with normal hepatic SFF. (37). Finally, Pacifico et al showed that obese children with NASH had more severe left ventricular systolic and diastolic dysfunction compared to obese children with NAFLD but not NASH or obese children without NAFLD (38). Thus, in children, there is a greater severity of cardiovascular structural and functional abnormalities associated with the presence and severity of NAFLD.

Is obstructive sleep apnea directly or indirectly associated with NAFLD in children?

Obstructive sleep apnea (OSA) may be associated with NAFLD in children over and above its association with obesity. There have been two studies to date that have performed polysomnography in a combined total of 90 children with NAFLD (39, 40). These studies reported a prevalence of OSA of approximately 60% in children with NAFLD. Moreover,

OSA was associated with the diagnosis of NASH and the severity of fibrosis. The pediatric hepatology community will need to work closely with pediatric sleep specialists to develop a validated strategy to guide which children with NAFLD should undergo polysomnography, and to learn whether the appropriate treatment of OSA in children will improve NAFLD.

What about Quality of Life in Children with NAFLD?

Quality of life (QOL), a subjective measure of a disease's overall impact from an individual's perspective, is an important component for the complete understanding of disease burden. Children with NAFLD have lower QOL than healthy children. The decrements have been reported in both physical health and psychosocial health. Kistler et al reported that QOL was impaired in 39% of children with NAFLD (41). There were four symptoms most associated with impaired QOL: fatigue, trouble concentrating, sadness, and nausea. In addition, case-control studies have shown that children with NAFLD have a greater degree of negative mood and more symptoms of anxiety than obese children without NAFLD (42, 43).

Treatment of Pediatric NAFLD

What is the treatment for children with NAFLD?

Treatment of NAFLD in children is a major gap. To date, there is not an available, proven, safe, and effective treatment for NAFLD in children. One complicating factor is that there is not a universal definition of what represents a treatment success.

What treatment improves ALT in children with NAFLD?

The most studied outcome measure in clinical trials has been ALT. Based upon multiple studies, including the large randomized controlled trial TONIC, there is sufficient evidence to conclude that neither vitamin E nor metformin improve ALT in children with NAFLD (44). In pilot studies, there was no improvement in ALT with docosahexaenoic acid, ursodeoxycholic acid, combination probiotic (VSL #3), or a low fructose diet (45–48). There are no definitive trials showing a therapeutic improvement in ALT, but preliminary studies have shown the potential for improvement with cysteamine bitartrate, Lactobacillus GG, diets low in fat or glycemic Index, and weight loss (49–53). Although lifestyle interventions have demonstrated the potential to improve ALT, they have been limited by study design, including confirmation of diagnosis, low baseline ALT, and multi-modal interventions without adequate controls. Thus, which diet or what exercise or how much weight loss is effective are unknowns.

What treatment results in improved histological pattern?

There are no supplements or medications that have been shown to improve steatosis in children with NAFLD. In contrast, there is some evidence that steatosis may be improved by diet, exercise or weight loss (54–58). To date, no therapy has been shown to improve inflammation (portal or lobular) or fibrosis. Both vitamin E and metformin had similar efficacy in improving ballooning compared to placebo over two years in the TONIC study; ballooning was improved in 38% (22/58) taking vitamin E, 39% (22/57) taking metformin, and 17% (10/58) taking placebo (44). The development of effective therapies for children

with NAFLD and their demonstration of effectiveness in large, well-designed clinical trials is an urgent need.

What about bariatric surgery as a treatment for NAFLD in pediatrics?

Because of the lack of an established treatment for NAFLD in adolescents and the overlap with severe pediatric obesity, in 2015 ESPGHAN released a detailed statement on bariatric surgery in adolescents including those with NAFLD (59). Although substantial weight loss can be achieved via weight loss surgery in adolescents (60), there are not yet data on the direct effect of weight loss surgery on NAFLD in this population. Therefore, adolescents with NAFLD undergoing bariatric surgery should be cared for in centers with appropriate pediatric multidisciplinary expertise and a commitment to rigorously phenotype NAFLD histology at baseline and to follow outcomes prospectively as long as possible(61).

Summary

NAFLD is the most common cause of chronic liver disease in children. National studies have provided stable estimates for the appropriate reference ranges for ALT in children. Clinical laboratories should be encouraged to use these data to improve the standardization of pediatric care. Non-invasive blood-based and imaging markers for NAFLD and NASH in children are an active research area, but have yet to provide a tool validated for clinical use. Liver biopsy is safe in children with suspected NAFLD and has been shown to provide clinically meaningful data for children with chronic liver chemistry elevation. NAFLD has the potential to progress to cirrhosis and the need for liver transplantation in childhood and early adulthood (62, 63). Beyond the risk for adverse hepatic outcomes, NAFLD is associated with dyslipidemia, hypertension, and early cardiac dysfunction in children. NAFLD is also associated with impaired QOL. Current treatment is individualized and focused on optimizing lifestyle including nutrition, physical activity, and mental well-being. The search for pharmacologic therapies for pediatric NAFLD is ongoing.

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Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CALIPER, GGT	gamma-glutamyltransferase
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease

NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
PDFF	proton density fat fraction
QOL	quality of life
SAFETY	Screening ALT for Elevation in Today's Youth
SCALE	Study of Child and Adolescent Liver Epidemiology
SFF	signal fat fraction
ULN	upper limit of normal

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