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Clinical Features of Pediatric Nonalcoholic Fatty Liver Disease: A Need for Increased Awareness and a Consensus for Screening

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a metabolic disorder characterized by excessive fat accumulation in the liver not associated with infection, medication, or an autoimmune process. The majority of individuals with NAFLD are asymptomatic and are found to have elevated hepatic transaminases on blood work that has been drawn for screening purposes or as part of an entirely different evaluation. NAFLD is a spectrum of disease ranging from relatively benign nonalcoholic fatty liver (NAFL) to an inflammatory process affecting the hepatocytes called nonalcoholic steatohepatitis (NASH) that can ultimately lead to fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma.^{1–3} Currently, the only way to differentiate between NAFL and NASH is by determining the histopathology on liver biopsy. NAFLD is a common condition, affecting approximately 20% of Americans overall,^{4,5} and an estimated 3% to 17% of children.^{6,7} An obesity-associated condition, nearly 75% of overweight/obese adults⁵ and 38% of overweight/obese children have NAFLD.⁶ The prevalence of NASH is also rising as it affects approximately 1.1% to 14% of Americans,^{8,9} including 19% of individuals who are obese, and 50% of individuals who are morbidly obese.¹⁰ These numbers may ultimately lead to a rise in progressive liver scarring or NAFLD-associated cirrhosis and hepatocellular carcinoma.¹¹ In addition to adiposity, NAFLD is associated with the metabolic syndrome (MetS), a cluster of risk factors associated with cardiovascular disease and “type 2” diabetes mellitus (T2DM).^{6,7,12}

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NAFLD's associations with cardiovascular disease, type 2 diabetes mellitus, cirrhosis, and hepatocellular carcinoma make NAFLD a serious public health concern.

In this review, we will discuss emerging data regarding etiology and clinical features of NAFLD in childhood, particularly as they relate to the need for screening among children with obesity and increased metabolic risk.

Etiology

The etiology of NAFLD involves accumulation of stored fat in hepatocytes from both hepatic delivery of free fatty acids and de novo lipogenesis.¹³ This hepatic fat accumulation in NAFLD is most commonly seen in the setting of central adiposity, during which excess calories are stored as fat in visceral adipocytes, rather than subcutaneous adipocytes. Increased fatty acid delivery to the liver induces insulin resistance, paradoxically leading to an increase in de novo lipogenesis.^{14,15} Additionally, certain exogenous nutrients appear particularly linked to the de novo lipogenesis in the liver, including fructose, branch-chain amino acids and trans fats.¹⁶ The propensity to accumulate intrahepatic fat appears to be linked to activity of the enzyme patatin-like phospholipase domain-containing protein 3 (PNPLA3). PNPLA3 is upregulated in states of overnutrition. PNPLA3 is associated with fat accumulation and hepatic injury or inflammation.^{17,18} Polymorphisms of PNPLA3 differ by race, ethnicity, and may in part, account for racial and ethnic differences in NAFLD, discussed further below.¹⁶ The accumulation of intrahepatic fat contributes to hepatocyte injury most likely via mitochondrial dysfunction, production of reactive oxygen free radicals, and endoplasmic reticulum stress that ultimately activate the hepatocyte apoptosis pathway. This dysfunction and stress may lead to the release of alanine aminotransferase (ALT) and, to a lesser extent, aspartate aminotransferase (AST) as well as the production of inflammatory cytokines such as interleukin-1 β , interleukin-6, leptin and tumor necrosis factor- α .^{14,19} Kupffer cells, macrophages in the liver's sinusoids, also contribute to cytokine release and to recruitment of lymphocytes to portal and lobular areas.¹⁴ The damaged hepatocytes are less responsive to insulin, with subsequent insulin resistance. Concurrently, rising levels of systemic inflammatory cytokines and hormones/endocrine features (tumor necrosis factor- α , interleukin-6, adipokines, etc)²⁰ are associated with peripheral insulin resistance.^{21,22} In more progressed states, persistent hepatocyte inflammation and hepatocyte injury leads to fibrosis and ballooning of hepatocytes as part of NASH (Figure 1). Continued fibrosis then leads to cirrhosis and elevated hepatocellular carcinoma risks. On biopsy, some children have histological features similar to adults with NASH, including ballooning degeneration (type 1 NASH); while other children have a distinct histopathological pattern with portal inflammation²³ and less ballooning than in adult specimens (type 2 NASH).^{9,24,25} Type 1 NASH is more typical of white females, while type 2 NASH is more typical of non-white, younger, heavier males.^{9,24,25}

Nonalcoholic fatty liver disease, as previously noted, is frequently associated with obesity, and has been described as obesity manifested at the hepatic level.²⁶ The increase of NAFLD in developed countries has been associated with the increase in obesity in those same developed countries.^{26,27} Additionally, the relatively sudden increases in NAFLD support the role of environmental factors,²⁸ including overconsumption of high-fructose corn

syrup.²⁹ In addition, patients with NASH in a study in Japan ate more simple carbohydrates and had a lower ratio of intake of polyunsaturated fatty acid to saturated fatty acid than those with NAFLD,³⁰ suggesting that a diet high in simple carbohydrates and high in saturated fat may be linked with progression of NAFLD. A diet high in fructose has also been linked to worse clinical outcomes. In biopsy specimens of more than 400 adults, those with higher fructose consumption had worse fibrosis scores and higher hepatic steatosis and inflammation.²⁸ In addition to its association with insulin resistance, NAFLD has been linked to obstructive sleep apnea and hypothyroidism, though the reasons behind these associations independent of obesity are unclear.^{9,31}

Epidemiology

Because of a lack of standard diagnostic criteria²⁵ and the need for liver biopsy,¹² the exact prevalence of NAFLD in children is unknown. As in adults, tissue sample is needed to confirm a diagnosis of NAFLD. Thus, even though NAFLD is putatively the most common cause of liver disease in US children and adolescents,^{9,32} few data are available about its epidemiology, and natural history.^{9,33} The majority of data on NAFLD prevalence use elevated ALT as a proxy for NAFLD.³⁴ Using this proxy, it does appear the prevalence of NAFLD has increased significantly. A study from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994) indicated that 3% of US adolescents had an ALT >30 U/L^{9,32} while adolescents from the current cycles of NHANES (1999–2010), reported ALT elevations >30 U/L in 8% to 9% of adolescents aged 12 to 19 years,^{3,35} including 14.4% of males and 3.3% of females.³⁵ Estimates of NAFLD prevalence from liver biopsies on autopsy of children 2 to 19 years old who died in San Diego County 1993–2003 were 13%, including 17.3% of those aged 15 to 19 years, confirming a high prevalence among children.³⁶

Race/Ethnicity

Racial/ethnic variations for NAFLD have been reported in both adults^{4,37–40} and children (Figure 2).^{3,35,41} In a study of 127 twelfth graders, NAFLD was higher in Hispanic children (36%) as compared with white (22%) and black (14%) children. In another study analyzing NHANES data, being Mexican American conferred an odds ratio (OR) of 1.6 for ALT elevations as compared with non-Hispanic whites while being African American was protective (OR 0.4).⁴¹ In a large study of adults (n = 2971), African Americans were reported to having had the lowest hepatic triglyceride content, followed by Caucasians, and Hispanics in both genders.³⁷ Similarly, a large NASH study found an increased frequency of NASH histology among Latinos as compared with non-Latino blacks (63% vs 52%).³⁹ However, in a study in which Hispanic and Caucasian participants (n = 152) were matched for obesity, differences in hepatic steatosis (by magnetic resonance imaging and spectroscopy) were minimal and not significant overall; and there was no difference in severity of NASH by histology between the groups.⁴⁰ In a study of adolescents from NHANES 1999–2004, NAFLD (as indicated by elevated ALT) was present in 11.5% of Mexican Americans, 7.4% of non-Hispanic whites, and 6.0% of black adolescents.³ These racial/ethnic differences are notable given higher rates of diabetes mellitus but lower rates of MetS among in black adolescents.^{42–46} We recently demonstrated that, using unexplained

ALT elevation >30 U/L as a surrogate for NAFLD, non-Hispanic black adolescents had a lower association between NAFLD, insulin resistance and MetS than other ethnicities.³⁵ We divided the adolescents into quartiles of insulin resistance (estimated via the homeostatic model assessment of insulin resistance, HOMA-IR) and compared odds of ALT elevations between those in the lowest quartile and those in the highest quartile. Non-Hispanic blacks in the highest quartile did not have as big of an increase in risk of ALT elevations (OR = 2.9) as their white (OR = 8.5) and Hispanic (OR = 9.6) counterparts. The same was true when comparing non-Hispanic blacks in the highest versus lowest quartile of waist circumference. This suggests that the presence of insulin resistance, central obesity, or MetS may perform poorly as triggers for screening tests for the presence of NAFLD in non-Hispanic black adolescents. Conversely, there was a similar correlation between risk of NAFLD and triglyceride elevations among non-Hispanic blacks as with whites, suggesting the presence of elevated triglycerides may be a better indicator of NAFLD among non-Hispanic blacks.

Clinical Features

The most striking clinical feature of NAFLD is that, despite some individuals having ongoing hepatocyte damage, most patients are asymptomatic. In adults and children, NAFLD is most frequently first suspected in overweight or obese individuals when elevations are noted in ALT on routine screening. Laboratory evaluation may also be triggered by complaints of malaise, a vague pain in the upper right quadrant of the abdomen or hepatomegaly on exam.¹² On recognition of elevated transaminases, further evaluation must be done to rule out other common causes of hepatitis such as infection, drug-induced injury, metabolic disease (Wilson), or an autoimmune process. Often this is accomplished with coordinated care with a subspecialist. Imaging with ultrasound or magnetic resonance imaging is often used as a noninvasive method of evaluating fatty liver. On ultrasound, children with fatty liver will have increased liver echotexture and impaired visualization of hepatic vessels.⁴⁷ Although ultrasound does provide useful information about presence of fatty liver, it has only fair sensitivity/specificity and there is a degree of subjectivity with interpretation and increased interobserver variability.^{47,48} Magnetic resonance imaging is a less subjective imaging modality that can quantify hepatic steatosis and has the potential to provide additional information about fibrosis with magnetic resonance elastography.^{49,50} Although noninvasive biomarkers for hepatocyte apoptosis and fibrosis are currently being studied to identify and follow those individuals with NAFLD, unfortunately, liver biopsy with histopathology is the only way to determine the presence of inflammation and extent of scarring or fibrosis.⁵¹

The most significant threat of NAFLD is the increased potential for liver failure, and increased morbidity and mortality. Patients with NASH have an increased mortality of 35% to 85% (controlled for age and gender).⁵² Cirrhosis occurs as the major risk factor, with 38% to 45% of adults with NASH developing liver failure over 7 to 10 years.⁵² Factors for the progression to cirrhosis include insulin resistance, alterations in liver fat metabolism, systemic inflammation, and oxidative stress (from diet, environment, infection, drugs, and/or toxins).³³ Causes of death in patients with NASH include sepsis, portal hypertension with variceal hemorrhage, hepatocellular carcinoma, cardiovascular disease— related mortality,

and liver mortality, which is increased 9- to 10-fold.⁵² Given the high rate of morbidity and mortality over time, NAFLD, as other chronic diseases, incurs great psychological, behavioral, and pharmacological costs in quality of life.¹⁶ This further underscores the need for investigations into its etiology, and potential interventions.⁵³ Effective therapy for NAFLD remains elusive.²⁸

Management

There are no treatments for NAFLD; however, diet and exercise to reduce obesity and overweight have resulted in a decrease in fetuin A, a liver protein that appears to be a mediator of hepatic insulin resistance and is a potential biomarker for NAFLD.⁹ Much emphasis has been placed on weight loss to benefit the liver and overall health. However, the evidence is limited and of the evidence to date, the amount of weight loss and the process to attain that level have not been specified.²⁷ One review found only 4 prospective studies of weight loss and dietary interventions (without exercise counseling) in adults with NAFLD; the results indicated improvement of liver enzymes after weight loss.⁵⁴ One study of 9 obese children showed improvements in transaminitis after weight loss.⁵⁵ A similar study of 75 obese adolescents who received a moderate hypocaloric diet and exercise program indicated that of the 25% who had elevated ALT, there was rapid decline with weight loss.⁵⁶ In a prospective study of 84 children with biopsy-confirmed NAFLD, and increased ALT, weight loss and exercise significantly improved the liver disease.⁵⁷ The study indicated that providing lifestyle advice concerning diet and exercise led to improvements in liver enzymes, and reduced visceral fat in children. In overweight or obese children, the loss of 5% of body weight resulted in decreases in ALT. However, this study was somewhat limited by its small size. Other studies have demonstrated improvement with diet and exercise, but these also have had limited numbers of participants, making it difficult to compose evidence-based recommendations about dietary modification and exercise to treat NAFLD and NASH.³³

While lifestyle modification and weight reduction remains the cornerstone of therapy for NAFLD and NASH, concomitant medical therapy to address oxidative stress associated with steatosis and improve insulin resistance has been studied in children. In adults, vitamin E has been shown to not only reduce ALT but also improve steatohepatitis compared with placebo.⁵⁸ The Treatment of NAFLD in Children (TONIC) trial was a randomized control trial comparing vitamin E, metformin, and placebo in children with biopsy-proven NAFLD.⁵⁹ Subjects were followed for 2 years with a primary outcome being reduction of ALT and a secondary outcome of histologic improvement on biopsy. The TONIC trial revealed that neither vitamin E nor metformin resulted in decreased ALT at the conclusion of the trial. There were improvements in histopathology and even resolution of NASH in the group taking vitamin E but not in the group taking metformin.⁶⁰ There are ongoing trials using other antioxidants such as cysteamine and fish oil with promising preliminary results.^{60,61} Future targets for therapy include peroxisome proliferator-activated receptor (PPAR) and farnesoid X receptor (FXR). PPAR agonists are nuclear receptors that not only influence both lipid and glucose metabolism but also seem to be integral in hepatic inflammation and fibrosis. Both rosiglitazone and pioglitazone have been shown in adults to improve steatohepatitis, but not fibrosis.^{58,62} There are, to date, no pediatric studies

evaluating the effects of PPAR agonists in children with NAFLD, and the potential cardiovascular effects of thiazolidinediones makes their future use in NAFLD unclear.⁶³ FXR is a transcription factor regulated by bile acids that may play a role in glucose and lipid metabolism and function as an immune modulator. Use of FXR agonists have been shown in NASH animal models to ameliorate hepatic inflammation, and modulation of FXR with semisynthetic bile acids are in phase 1 trials in adults.⁶⁴ Clinicians should continue to focus efforts on treatment of overweight and obesity, though vitamin E is a therapeutic option, and more options are likely becoming available in the future.

Screening

There are varying opinions from national societies about how to best identify children with NAFLD. Although the European Association for the Study of Liver Disease; European Society for Pediatric Gastroenterology, Hepatology and Nutrition; Asian-Pacific Working Party for NAFLD; the Chinese Liver Disease Association; and the Endocrine Society all recommend screening high-risk patients with liver function tests and/or ultrasound, the American Association for the Study of Liver Disease (AASLD) does not recommend any *routine screening*.⁶⁵ The most recent American Academy of Pediatrics obesity guidelines in 2008 suggest twice yearly checks of AST/ALT in *obese* children further complicating physicians' choices on whom to screen.⁶⁶ The AASLD points to the "lack of understanding of knowledge related to the long-term benefits and cost-effectiveness of screening."⁶⁵ Although this position is understandable with our current level of knowledge, it is also important to remember that children with NAFLD have a shorter long-term survival compared with children who do not have NAFLD. Children with NAFLD have a 13.8-fold higher risk of dying or requiring a liver transplant.⁶⁷ Despite ambiguous recommendations about screening, we know that the majority of general pediatricians and subspecialist are inadequately addressing obesity; nor are they widely screening for NAFLD.⁶⁸ One study indicated that only 36.7% of overweight children, or their parents, were told by their physician/healthcare provider of their overweight.⁶⁹ Since NAFLD is linked with obesity, the lack of screening for obesity potentiates the lack of screening for NAFLD, with potential long-term health consequences.⁶⁹ Without consensus regarding screening, clinicians must take it upon themselves to determine who to screen and how.

The next question in this dilemma is the best means of screening. It is important to recognize that no one method is perfectly sensitive or specific, and that all screening has cost involved, both monetary and emotional. Screening for abnormal ALT in obese children or children with MetS can potentially capture a number of children with NAFLD. It should be noted that ALT elevations may miss some individuals with NAFLD, as the level of ALT elevation does not correlate with findings on biopsy and there are even a small percentage of children with advanced liver disease who have normal laboratory values.⁷⁰ Interpreting the laboratory values for ALT can often be based on individual laboratory normative values. A recent publication from the SAFETY (Screening ALT for Elevation in Today's Youth) study demonstrated that the upper limit of normal was set too high to detect pediatric liver disease.⁷¹ This study found that clinicians should adjust what they consider normal, and instead consider any ALT elevated if it is >25 U/L for boys and >22 U/L for girls,⁷¹ whereas many laboratories use 40 U/L as their upper limit of normal.⁷² A recent study evaluated the

sensitivity and specificity of using ALT levels 2 times the upper limit of normal as an indicator of biopsy-proven NAFLD among a group of adolescents referred to a pediatric gastroenterology clinic for “ALT elevations” or “suspected NAFLD.”⁷² They found that the use of 2 times the upper limits from the SAFETY trial (50 U/L for boys and 44 U/L for girls) yielded better sensitivity (88%) but worse specificity (26%) than 2 times the upper limits of laboratories (80 U/L for both sexes), which yielded a sensitivity of 57% and a specificity of 71%. Notably, there were a relatively high number of non-NAFLD cases found on biopsy (16%), underscoring that not all ALT elevations among obese children are NAFLD related. Additionally, 21% of those children referred had normalized the ALT at the time of subspecialty evaluation suggesting that repeating laboratory values after a period of time may decrease the need for referral in those children who had a transient ALT elevation.

The use of imaging as an adjunct to biochemical screening also remains controversial. It can identify liver steatosis and complications of end stage fibrosis like portal hypertension, but ultrasound is only modestly sensitive, is user dependent and identifies only those individuals with moderate to severe steatosis. Its use as a screening technique—including cost-to-benefit ratio— should be considered carefully.

Based on the available data, it is our recommendation that clinicians consider screening all children with a body mass index 95th percentile by assessing levels of ALT. If the levels are 2-fold higher than the laboratory’s upper limit, physicians should refer to for evaluation to pediatric gastroenterology for evaluation of chronic liver disease. For values less than 2-fold higher than the upper limit, we recommend that the physician counsel the patient and family regarding weight loss efforts. If ALT abnormalities persist after 6 months of effort, children should then be referred for subspecialty evaluation.

Conclusions

Pediatric NAFLD is a complex and chronic condition for which the prevalence is increasing. All overweight or obese children are at risk for NAFLD and physicians should consider screening these children via measurement of transaminases. Future research should focus on improved biomarkers as initial screening tools to reduce cost and improve the decision-making process as to when to proceed with imaging and liver biopsy. In caring for children at risk for NAFLD, it is important to collect an accurate and complete health history and physical exam. Treatment remains controversial but clearly involves targeted weight loss via lifestyle, behavior modification, dietary changes, and exercise. More research is needed to understand NAFLD in children, the reason some cases progress to NASH and cirrhosis, and treatment interventions appropriate for children. There is a need for international consensus about NAFLD definitions, normative laboratory values, and appropriate screening measures.

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Figure 1.

Spectrum of liver changes related to pediatric nonalcoholic fatty liver disease (NAFLD). See text for details.

Figure 2.

Prevalence of elevated alanine aminotransferase (ALT; >30 U/L) by race/ethnicity and sex among adolescents. The prevalence of unexplained elevations in ALT >30 U/L (a common surrogate for nonalcoholic fatty liver disease [NAFLD]), varies by race/ethnicity (A) and sex (B), being highest in Hispanics, lowest in non-Hispanic blacks, and more common in males. Adapted from data from 13- to 19-year old adolescents from the National Health and Nutrition Examination Survey (NHANES) 1999–2010, presented in DeBoer et al.³⁵ ** $P < 0.01$, *** $P < 0.001$.