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Diagnosis and Treatment of Pediatric Nonalcoholic Steatohepatitis and the Implications for Bariatric Surgery

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Abstract

This review focuses on the diagnosis, risk factors, prevalence, pathogenesis and treatment of pediatric nonalcoholic steatohepatitis (NASH). NASH is a progressive form of nonalcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease in children. The factors that account for differences between children with NASH versus children with milder forms of NAFLD are unclear. The diagnosis of NASH requires interpretation of liver histology because no noninvasive markers predict the presence or severity of NASH. There is no proven treatment for NASH. Several clinical trials for NAFLD are in progress, however, clinical trials focusing on NASH are needed. Heightened physician awareness of NAFLD, NASH, and associated risk factors is important to identify and treat affected children.

Keywords

cirrhosis; histology; obesity; nonalcoholic fatty liver disease; pediatric; children

Nonalcoholic steatohepatitis (NASH) was first documented in children in 1983(1), and has since been recognized as a progressive form of nonalcoholic fatty liver disease (NAFLD). Liver histology in NAFLD ranges from simple steatosis, to steatosis with inflammation and cellular injury (NASH). Fibrosis, including cirrhosis, may also be present in NAFLD. NASH is included within the spectrum of NAFLD. In this review, the term 'NAFLD' is used to refer to the entire spectrum of histology, while 'NASH' refers only to the subset of NAFLD with histology consistent with NASH.

NAFLD is the most common cause of chronic liver disease in American children,(2) and has been described throughout much of the world.(3–8) Children with NAFLD can have advanced fibrosis or cirrhosis.(9–11) NAFLD in children is strongly associated with metabolic syndrome, greatly increasing the potential for future cardiovascular disease and diabetes mellitus.(12) Thus the potential for adverse outcomes coupled with the high prevalence of the disease makes for a considerable public health concern. Recent studies indicate that NAFLD is under-

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diagnosed by both pediatricians and pediatric subspecialists,(13,14) indicating a need to heighten physician awareness of this disease.

In the past 4 years, many reviews have described NAFLD in children;(15–21) however, these have not focused on NASH. Children with NASH are at the greatest risk for the most severe outcomes. However, not all children with NAFLD will develop NASH; thus, it is important to explore potential risk factors for NASH among children with NAFLD. Though NASH has been described in many adult reviews, increasing evidence has shown NASH manifests differently in children than in adults. Therefore, this review will specifically address NASH in children. PubMed was searched for studies between January 1995 and December 2008 using the terms “nonalcoholic fatty liver disease” or “nonalcoholic steatohepatitis,” with results limited to human studies, English language, and age group infant, child, or adolescent.

DIAGNOSIS

The diagnosis of NASH begins with the clinical suspicion of liver disease in a child. NAFLD may be suspected on the basis of an elevated serum alanine aminotransferase (ALT), hepatomegaly, or an abnormal imaging study consistent with fatty liver. However, none of these findings, either alone or in combination, is sufficient for the diagnosis of NAFLD. Each abnormality has a different differential diagnosis that must be appropriately evaluated. Interpretation of liver histology is required to confirm a diagnosis of NAFLD, and to identify the presence and severity of NASH.

NAFLD may be suspected based on several clinical abnormalities. Though many children with NAFLD are asymptomatic, some children experience right upper quadrant abdominal pain(4, 22) and/or fatigue. Most children with NAFLD are obese, defined as a body mass index (BMI) $\geq 95^{\text{th}}$ percentile for age and sex.(2,9) Upon examination, most affected children have hepatomegaly,(4,8,10,22) though this may be difficult to appreciate depending upon the degree of obesity. Insulin resistance is also common among children with NAFLD.(9,12,22) Acanthosis nigricans, a darkening and thickening of the skin around the flexoral surfaces associated with hyperinsulinemia, is a frequent finding in children with NAFLD.(10,22) Furthermore, based on ALT elevation, NAFLD is suspected in as many as 50% of children with type 2 diabetes mellitus.(23)

NAFLD may be suspected based on noninvasive tests, although none of these distinguish between children who have NASH versus children who have NAFLD but not NASH (i.e., milder forms of NAFLD). Liver biopsy is required for the definitive diagnosis of NAFLD and the determination of the presence of NASH. The diagnosis of NAFLD requires a finding of $\geq 5\%$ of hepatocytes with macrovesicular steatosis upon examination of liver histology, as well as the exclusion of other causes of hepatic steatosis. Although small droplet fat may be present, NAFLD is not characterized by microvesicular steatosis, which in isolation presents a different differential diagnosis. Other common histologic findings in adults include Mallory hyaline, lobular inflammation, ballooning degeneration, and perisinusoidal fibrosis.(24) In an appropriate clinical context, macrovesicular steatosis and inflammation, in addition to hepatocyte ballooning and/or fibrosis usually is sufficient for a diagnosis of NASH in adults. However, pediatric NASH has frequently been observed to show different patterns of inflammation and fibrosis than that seen in adults,(8,9,10,22) with predominantly portal histological changes.

In order to define histologic patterns of NASH in children, we applied hierarchical cluster analysis to liver biopsies from 100 children with NAFLD.(9) Two distinct histological subtypes of NASH were identified. Type 1 NASH was consistent with adult histology and defined as the presence of steatosis with ballooning degeneration and/or perisinusoidal fibrosis, without portal involvement. Type 2 NASH was defined as the presence of steatosis with portal

inflammation and/or fibrosis, in the absence of ballooning degeneration or perisinusoidal involvement. The majority of subjects (51%) had Type 2 NASH, and 8% had advanced fibrosis. Type 2 was more likely to be associated with advanced fibrosis. The predominance of portal features typical of type 2 NASH has been supported by subsequent studies of children with NASH.(6,25) Data from the National Institutes of Health NASH Clinical Research Network (NASH CRN) confirmed the heterogeneity of pediatric NASH subphenotypes (26), however, ballooning of hepatocytes was seen at a higher rate. Though the biological mechanisms behind the subtypes are currently unknown, these findings highlight a potentially important distinction between adult and pediatric NASH.

The NAFLD Activity Score (NAS), a histologic scoring system devised by the NASH CRN (27), was developed in order to assess the response of NAFLD to therapy in clinical trials. The score was defined as the sum of the scores for steatosis (scale 0 to 3), lobular inflammation (0 to 3), and ballooning (0 to 2). An additional fibrosis component was also developed that was not included in the NAS score. The pathology committee of the NASH CRN was explicit in stating that the NAS was not intended to replace a pathologist's interpretation of histology and diagnosis, as the score was designed to assess response to therapy only. The inter-observer agreement was superior when used for adult versus pediatric cases.

Noninvasive markers

Given the potential risks of liver biopsy and limited availability of pediatric hepatologists, many studies have attempted to find noninvasive means of differentiating NASH from milder forms of NAFLD, as well as mild fibrosis from severe fibrosis. Several studies have examined various parameters associated with specific features of NASH. Table 1 summarizes several such studies of noninvasive markers. Though many serum analytes have been reported to correlate with specific features, the difference in absolute values are too small and/or the overlap is too great to be of clinical use in noninvasively detecting NASH or fibrosis. In a recent study of children with known NASH, ultrasound transient elastography yielded promising results for the noninvasive assessment of liver fibrosis. However, elastography was not useful for patients with BMI ≥ 35 kg/m², limiting its potential role for moderately to severely obese adolescents.(29) Thus, despite a growing body of literature on noninvasive diagnosis, liver biopsy and assessment of liver histology are required for the diagnosis of NASH.

RISK FACTORS

Demographic and clinical risk factors for NAFLD are well established. However, risk factors for NASH among children with NAFLD are largely unknown. Thus, the following section will compare and contrast potential demographic and clinical differences between children with NAFLD and those with NASH. Since NASH is a histological diagnosis, only studies of children with biopsy-proven NAFLD are considered. A selection of these studies is summarized in Table 2, including a population-based study (Study of Child and Adolescent Liver Epidemiology, SCALE)(2), single center fatty liver clinic series (San Diego and Rome)(6,9, 22), a single center adolescent bariatric surgical series (Cincinnati)(30), and a multi-center pediatric cohort study of biopsy-proven NAFLD (NASH CRN)(26). The characteristics of children from single center studies differ widely. In the bariatric surgical series, all children were morbidly obese teenagers, most were white girls, and NAFLD was incidentally found upon intra-operative biopsy.(30) In contrast, children from the San Diego Fatty Liver Clinic were predominantly moderately obese Mexican-American boys.(9,22) In the Rome fatty liver clinic, all children were of white race, tended to be younger than those reported in series from the United States, and were much less obese.(6) The Study of Child and Adolescent Liver Epidemiology (SCALE) was performed to assess the prevalence of NAFLD among the general pediatric population in San Diego. Since NAFLD requires biopsy to accurately diagnose, it is

difficult to obtain population-based data. Therefore, we designed an autopsy-based study.(2) After excluding children with insufficient data and other potential causes of liver disease, liver samples taken at autopsy from 742 children, ages 2 to 19 years, were reviewed. The distribution of age, sex, race, and ethnicity were standardized to match those of the County of San Diego. Each of these studies, therefore, reported findings from a demographically different subset of children. Thus, the findings of each study, while applicable to their respective subset, may not be fully generalizable to the full spectrum of children with NAFLD. Additional studies from other centers with carefully described populations and liver histology are greatly needed.

Demographic risk factors

Age and Gender—Age has been identified as a risk factor for NAFLD,(2) but has not been consistently associated with the likelihood of NASH.(2,9,30) NAFLD is also more common in boys than girls.(2,9,22) However, of those with NAFLD, boys and girls seem equally likely to have NASH. In SCALE, 23% of boys with NAFLD had NASH, versus 21% of girls.(2) In the San Diego Fatty Liver Clinic, of those children with biopsy proven NAFLD, NASH was present in 67% of boys and 71% of girls.(9) In the NASH CRN study, there was no difference in gender between children with and without NASH.(26) In one exception, 32% of girls undergoing bariatric surgery with NAFLD had NASH, versus 8% of boys.(30) However, as is typical for bariatric surgery case series, the majority of subjects (61%) were girls.

Race and Ethnicity—Multiple studies have shown that Hispanic children are more likely to have NAFLD than non-Hispanic children.(2,9,22,31) Though they frequently have many risk factors for NAFLD, African American children are less likely to be affected.(2,9,22,32) Whether race/ethnicity influences the likelihood of having NASH versus NAFLD is less clear. In the San Diego fatty liver clinic, 100% of Native American children, 86% of Hispanic children, 71% of non-Hispanic white children, and 60% of Asian children with NAFLD had NASH. In contrast, only 1 of 3 African American children demonstrated histology consistent with NASH.(9) In the Cincinnati bariatric surgery series, all children with NASH were white, and only 2 of 13 children with NAFLD were African American.(30) In contrast, in SCALE, 50% of both Asian and African American children with NAFLD had NASH, versus 24% of Caucasian and 11% of Hispanic children.(2) The distribution of NASH subtypes also differed by race and ethnicity. In one study from the San Diego fatty liver clinic, Type 1 NASH was more common in Caucasian children.(9) Type 2 NASH was more likely to be found in children of Asian, Hispanic, and Native American ethnicity.(9) This finding was supported in the NASH CRN study.(26) Thus, the ethnic risk for having NAFLD may differ from the risk for having NASH, but current studies have been limited by sample size. Further studies are needed to determine the role of race and ethnicity as risk factors for disease phenotype.

Clinical risk factors

Obesity and central adiposity—The majority of children with NAFLD and NASH are obese, defined as a body mass index (BMI) $\geq$ 95th percentile for age and sex.(2,4,8–10,22, 26) In addition, it appears that children with NASH may also be slightly more obese than children with NAFLD. In SCALE, children with NASH had a mean BMI percentile slightly greater than children with milder NAFLD.(2) In addition, the degree of obesity appears to vary between the subtypes of NASH. In one study from the San Diego fatty liver clinic, children with type 2 NASH were slightly more obese than children with type 1 (BMI z-score 2.3 vs. 2.1). However, children with type 1 NASH were no more obese than children with simple steatosis.(9) Neither the bariatric surgery(30) series nor the NASH CRN study(26) found a difference between BMI measures among adolescents with NASH and milder forms of NAFLD.

Metabolic factors—Overweight children with NAFLD have higher absolute values of cardiovascular risk markers, such as elevated fasting glucose and triglycerides, low high-density lipoprotein (HDL) cholesterol, and elevated blood pressure than equally obese children without NAFLD.(12) Children with NAFLD are also more likely to exceed dichotomous thresholds for cardiometabolic factors used to determine metabolic syndrome. Furthermore, children with NAFLD are more insulin resistant than children without NAFLD. In fact, most children with NAFLD are insulin resistant.(9,12,19,30) In addition, a recent prospective multi-center study found children with definite NASH had a significantly greater degree of insulin resistance than children with “borderline” or “no NASH”.(26) Hypertriglyceridemia is also common in children with NAFLD,(9,12,22) though it is unclear whether children with NASH have a greater degree of triglyceride elevation than children with milder forms.(9,12,26,30)

Importantly, children with hypothalamic and pituitary disorders are at high risk for the most severe forms of NASH. The large, rapid weight gain common with these disorders leads to a concomitant development of NAFLD. These children have been observed to have the most severe disease, including cirrhosis.(34–37) Thus, physicians should have a heightened awareness of this association.

Risk factors for fibrosis

Investigators have attempted to find correlations between demographic and clinical risk factors and the presence or severity of fibrosis in pediatric NAFLD. One study from the fatty liver clinic in Rome found a significant association between age and the presence of fibrosis,(6) although most studies have not.(22,33) However, pubertal stage was recently shown to be higher in children without fibrosis than those with bridging fibrosis.(26) Gender has not been shown to be significantly different between children with and without fibrosis.(22,26) However, children with fibrosis may be more obese than children without.(6,22,33) In a second study from Rome, waist circumference was moderately correlated with fibrosis.(38) A NASH-CRN study did not find an association with fibrosis and BMI, but did find that children with fibrosis had a greater percent body fat than children without fibrosis.(26) The association between metabolic risk factors and fibrosis is less clear. Some studies have shown an association between triglycerides and fibrosis;(6,28) others have not.(22,33) Children with moderate fibrosis may have a greater degree of insulin resistance than those with mild fibrosis.(26)

PREVALENCE

Overall NAFLD prevalence

In SCALE, after standardization to age group, sex, race, and ethnicity distribution of the county, we estimated NAFLD prevalence to be 9.6% in San Diego. It is likely that the prevalence of NAFLD within the United States falls within our 95% confidence interval of 7.4% to 11.4%. In addition, NAFLD is more prevalent in obese children. In SCALE, 38% of obese children had NAFLD.(2)

Prevalence of NASH

The prevalence of NASH varies depending on the setting. Figure 1 shows the prevalence of NASH among children with NAFLD in two fatty liver clinics, a bariatric surgery series, and a population-based sample (SCALE). In the San Diego and Rome fatty liver clinics, the majority of children (84%(22) and 86%(6), respectively) with a biopsy had NASH. Of these, 5 to 8% of children had advanced fibrosis. However, in the SCALE study, 23% of children with NAFLD had NASH, with 2% showing advanced fibrosis.(2) In the NASH CRN study, 36% of children with NAFLD had Definite NASH, and 43% of children with NAFLD had

Borderline NASH.(26) In the bariatric surgery series, an intraoperative biopsy showed NASH in 24% of those with NAFLD, with no cases of advanced fibrosis.(30)

TREATMENT

The pathogenesis of NAFLD is not fully understood. Insulin resistance, caused or exacerbated by obesity, appears to be a major factor in the development of NAFLD. Hepatocyte injury or apoptosis occurs secondary to the deranged metabolism and high cytokine levels characteristic of the insulin resistant state.(39) Oxidative damage may induce further cell injury and insulin resistance. Thus, current treatments focus on weight loss, improving insulin sensitivity, and/or decreasing oxidative damage.

The determination of specific therapies for NASH await adequately powered, controlled clinical trials based on appropriate endpoints. Most studies to date have been targeted to the broader spectrum of NAFLD, rather than the specific entity of NASH. However, therapeutic trials should consider targeting therapy for NASH, as these are the children at greatest risk for severe outcomes. Only one treatment trial to date has required NASH for entry. In addition, only one treatment study has used histology as an end point. Clinical trials will be discussed below in order to provide what information is available, with the acknowledgment of these limitations.

Lifestyle

Diet and exercise have been a focus of treatment for NASH due to the association with obesity and insulin resistance. In a recent study in adults undergoing one year of intense nutritional counseling and end-of-treatment biopsy, 9 of 15 patients had improvement in NAS score. (40) Notably, those with histologic improvement lost significantly more weight and had a greater decrease in waist circumference than those whose histology was unchanged.

Nobili and colleagues performed the only pediatric lifestyle intervention study thus far in which all participants had biopsy-proven NAFLD.(6) Seventeen of the 52 participants lost at least 10% of their body weight. Of these 17 children, 5 had a normal ultrasound at year's end. Children with weight loss of less than 10% did not show improvement in liver ultrasonography. Thus, moderately intensive interventions can yield substantial weight loss in children with NAFLD. However, even in the majority of those with a $\geq 10\%$ loss of body weight, this was not sufficient to alleviate evidence of disease. To what extent there may be improvement remains to be demonstrated by end-of-treatment liver biopsy in a controlled trial. However, lifestyle interventions have been shown to benefit other obesity-related co-morbidities and thus should be recommended.

Pharmacological

To date two targets for pharmacological intervention have been tested based upon the proposed pathophysiology of NASH. The first involves the use of medications to treat associated metabolic disorders, particularly insulin resistance. The second involves the use of antioxidants such as vitamin E.

Medications targeting insulin resistance—In the only published treatment study requiring biopsy-proven NASH for entry, the effects of metformin on serum aminotransferase levels and hepatic fat fraction (determined by magnetic resonance spectroscopy) were evaluated.(41) Ten non-diabetic children received metformin 500 mg by mouth twice daily for 6 months in an open-label pilot trial. After treatment, ALT normalized in 40% and AST in 50% of subjects, and magnetic resonance spectroscopy results demonstrated a significant reduction in hepatic fat. Though the data suggested improvement, the treatment duration was short-term

and an end-of-treatment biopsy was not performed. A recent observational study from Italy of children with biopsy-proven NAFLD who had very low baseline liver chemistry (ALT 21–43 U/L) and mild histology, tested the effects of metformin added to a lifestyle intervention. After treatment with metformin, 12 out of 30 children had a follow-up liver biopsy which demonstrated improvement from baseline, but was not able to demonstrate a difference between children treated with lifestyle therapy alone. (42) Certain thiazolidinediones, such as pioglitazone, have also shown promising results in adult treatment trials.(43) However, the safety of these medications is not established in children. Thus, in the U.S., thiazolidinediones are not considered a treatment option outside of a FDA-approved clinical trial.

The Treatment of NAFLD in Children (TONIC) trial, a large, multi-center, randomized, double blind, controlled trial conducted by the NASH CRN, is currently in progress to test the effects of metformin and vitamin E on serum aminotransferases and liver histology.(44) Children with biopsy proven NAFLD, ages 7 to 17 years, are receiving metformin, vitamin E, or placebo for 96 weeks. An end-of-treatment biopsy assesses histological changes.

Hepatoprotective agents—Vitamin E, vitamin C, and ursodeoxycholic acid (UDCA) are potentially hepatoprotective agents that have been tested in preliminary clinical trials. These compounds may slow the progression of steatosis to steatohepatitis by reducing oxidative damage to hepatocytes. Two treatment trials(45,46) have investigated the efficacy of supplemental vitamin E, or vitamin E and C in normalizing serum aminotransferases. The TONIC trial will assess the histologic response to supplemental vitamin E treatment.

Surgery

Because of the association between obesity and NASH, bariatric surgery has been proposed as a potential treatment.(47) Adolescents are increasingly undergoing surgical treatment of obesity, though the guidelines for eligibility are not standardized.(48,49) Whether NASH should be a major or minor criterion has not been determined. Furthermore, whether NASH-related cirrhosis should preclude surgery, or conversely, accelerate the decision to perform surgery has not been established. As shown by Figure 2, children with a clinical diagnosis of NAFLD are different than those typically undergoing bariatric surgery. Children with a clinical diagnosis of NAFLD tend to be younger and less obese than adolescents undergoing surgical treatment of obesity.(6,9,22,26,37) Whether requirements for bariatric surgery should be modified in the context of NAFLD needs to be determined. Key questions to be addressed regarding bariatric surgery as a treatment for adolescent NAFLD are presented in Table 3. Though in some cases bariatric surgery in adults has been shown to improve histology,(50, 51) outcomes data in adolescents are needed, along with untreated natural history data for comparison. Physicians performing bariatric surgery on adolescents should be aware of the potential for undiagnosed steatohepatitis.

CONCLUSION

NAFLD is the most common cause of chronic liver disease in children, with much less known about the subphenotype of NASH. In some children, NASH progresses to advanced fibrosis and cirrhosis. Given the large number of children with NASH, this represents a largely unrecognized public health crisis. The determinants of more severe NAFLD are unknown. A liver biopsy is required to determine the diagnosis of NASH. Studies to determine the natural history of pediatric NAFLD sub-types and the predictive value of particular histological features are needed. Future treatment trials should focus on treatment of children exhibiting steatohepatitis. Heightened physician awareness of NAFLD and NASH will improve recognition and potential treatment of this prevalent and potentially devastating disease..

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Figure 1. Prevalence Distribution of Histology among Children with NAFLD

The prevalence of NASH among children with NAFLD varies on the setting. The highest prevalence of NASH among children with NAFLD is seen in fatty liver clinics. In a population-based study, SCALE (Study of Child and Adolescent Liver Epidemiology), fewer children with NAFLD had NASH. A lower rate of NASH was also reported in the bariatric surgery series.

Figure 2.

Mean age and BMI of children diagnosed with NAFLD at a liver clinic versus those undergoing bariatric surgery. Children with a clinical diagnosis of NAFLD tend to be younger and less obese than children undergoing bariatric surgery. NAFLD studies references 6,9,22,26,37. Bariatric surgery studies references 30,52–55.

Table 1

Summary of studies of noninvasive means of assessing NAFLD disease severity.

Study	Steatosis	Inflammation	Cellular Injury	Fibrosis
Schwimmer et al (2003)22	QUIKI ↑ age race/ethnicity	↑ ALT ↑ fasting insulin	--	RUQ pain - periportal HOMA-IR - periportal AST - perisinusoidal Insulin - perisinusoidal BMI Z-score - perisinusoidal
Schwimmer et al (2005)9	--	--	--	↓ age ↑ GGT ↑ insulin resistance
Nobili et al (2006)6	--	--	--	↑ age ↑ BMI
Nobili et al (2006)28	↑ leptin	↑ leptin	↑ leptin	↑ leptin ↑ BMI Z-score
Manco M et al (2008)38	--	--	--	↑ waist circumference ↓ age
Nobili et al (2008)29	--	--	--	Ultrasound-based transelastography
Patton et al (2008)26	--	--	--	↑ AST ↑ GGT ↑ WBC

QUIKI, quantitative insulin sensitivity check index; ALT, alanine aminotransferase; RUQ, right upper quadrant; HOMA-IR, homeostasis model assessment of insulin resistance; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; BMI, body mass index; WBC, white blood cell count

Table 2
Selected studies of pediatric NAFLD with separate analysis of patients with NASH.

Study	Number of Subjects	Study Type	Sex (% M)	Asian, NH	Black, NH	Race/Ethnicity (%)			White, NH	Other
						Hispanic	NA			
San Diego 200322	43	Clinical series	70	0	5	53	0		25	17
San Diego 20059	100	Clinical series	65	10	3	67	5		14	1
SCALE 20062	742	Population-based	72	9	11	34	0		44	2
Rome 20066	84	Clinical series	70	0	0	0	0		100	0
Cincinnati 200630	41	Bariatric surgery series	39	0	17	0	0		83	0
NASH CRN (2008)26	176	Clinical series	77	0	0	59	0		41	0

SCALE, Study of Child and Liver Epidemiology; NASH CRN, Nonalcoholic Steatohepatitis Clinical Research Network; M, male; NH, Non-Hispanic; NA, Native American

Table 3
Key questions regarding bariatric surgery as a treatment for NAFLD.

<p>At what threshold should surgery be an option for the treatment of NAFLD, both in terms of BMI criteria and histological criteria?</p> <p>Does bariatric surgery have the same treatment outcomes in adolescents with clinical NASH as those with incidental findings at the time of surgery?</p> <p>Is there a level of disease severity (e.g. cirrhosis, portal hypertension) that changes whether surgery will be performed, or the timing at which it is performed?</p>
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