Published in final edited form as:

Gastroenterol Nurs. 2011 ; 34(6): 434–437. doi:10.1097/SGA.0b013e3182371356.

Predictors of Nonalcoholic Steatohepatitis in Obese Children

Stacee Marie Lerret, PhD, RN, CPNP,

Medical College of Wisconsin, Department of Gastroenterology, Milwaukee, Wisconsin

Laura Garcia-Rodriguez, BA,

Medical College of Wisconsin, Department of Gastroenterology, Milwaukee, Wisconsin

Joseph Skelton, MD,

Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina

Vincent Biank, MD,

Medical College of Wisconsin, Department of Gastroenterology, Milwaukee, Wisconsin

Denise Kilway, RN, CPNP, and

Medical College of Wisconsin, Department of Gastroenterology, Milwaukee, Wisconsin

Grzegorz Telega, MD

Medical College of Wisconsin, Department of Gastroenterology, Milwaukee, Wisconsin

Abstract

As the prevalence of childhood obesity increases, the incidence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH) also escalates. This study's purpose was to identify the clinical criteria to aid in determining when a liver biopsy is indicated for this growing population because currently no guidelines exist. We performed a retrospective chart review on all patients who were seen in the Nutrition Exercise and Weight Loss Kids™ Program at the Children's Hospital of Wisconsin from July 2003 through December 2004. We analyzed only individuals who underwent liver biopsy with the following criteria: (1) no evidence of other liver disease and (2) aspartate transaminase or alanine aminotransferase greater than 200 IU/L or any elevation of or for more than 6 months. Of the 284 patients reviewed, only eight patients (3%) met the criteria for analysis. Biopsy results demonstrated that 100% had histological evidence of NASH with steatosis, and seven of the eight (87.5%) had NASH with fibrosis, cirrhosis, or both. Obese children with an aspartate transaminase or alanine aminotransferase greater than 200 IU/L or any elevation of aspartate transaminase or alanine aminotransferase for more than 6 months, have a strong likelihood of having NASH with or without fibrosis, cirrhosis, or both.

As the prevalence of childhood obesity has risen, so too has the incidence of nonalcoholic fatty liver disease and its more severe form, nonalcoholic steatohepatitis (NASH). First described by Ludwig, Viggiano, McGill, and Oh (1980), NASH was associated with obesity related diseases such as cholelithiasis and diabetes mellitus, and thus was felt to be a benign disease of adult women (Ludwig, Viggiano, McGill, & Oh, 1980). More recently, the prevalence of fatty liver disease in children was documented as 2.6% in the general population, increasing to 53% in obese children (Alisi, Manco, Vania, & Nobili, 2009).

© 2011 Society of Gastroenterology Nurses and Associates

Correspondence to: Stacee Marie Lerret, PhD, RN, CPNP, Medical College of Wisconsin, 8701 West Watertown Plank Road, Milwaukee, WI 53226 (slerret@chw.org).

The authors declare no conflict of interest.

Today, based on the current trends, NASH is expected to become one of the most common causes of end-stage liver disease in both children and young adults (Iacobellis et al., 2006).

Despite the development of noninvasive measures to evaluate for evidence of liver fibrosis (Iacobellis et al., 2006), NASH remains a clinicopathological entity characterized by the development of histological changes of inflammation and fibrosis in the liver. Currently, there are no universally accepted criteria for the selection of patients who should undergo diagnostic liver biopsy. Accordingly, the aim of this study was to evaluate the utility of specific laboratory criteria in identifying the presence of NASH on liver biopsy.

Methods

We performed a retrospective chart review on all patients who were seen in the Nutrition Exercise and Weight Loss Kids™ (NEW Kids™) Program at the Children's Hospital of Wisconsin from July 2003 through December 2004. The NEW Kids™ program treats children aged 2 to 18 years with a body mass index (BMI) of 95th percentile or greater for age with one or more weight related comorbidities including asthma, dyslipidemia, insulin resistance, musculoskeletal complaints, or elevated liver enzymes.

We retrospectively analyzed only those individuals who underwent liver biopsy with the following criteria: (1) no evidence of other liver disease and (2) aspartate transaminase (AST) or alanine aminotransferase (ALT) greater than 200 IU/L or any elevation of AST (>46 IU/L) and ALT (>35 IU/L) for more than 6 months. Liver biopsy was obtained percutaneously with one core biopsy that was subsequently analyzed via histology. A total of eight individuals met these criteria. Data recorded included age, gender, race, weight, height, BMI, AST, ALT, as well as, fasting lipid panel and insulin level. Liver biopsy results were analyzed for the presence or absence of NASH to calculate the percentage of individuals meeting the above criteria that had evidence of NASH on liver biopsy. Subjects with incomplete laboratory data were excluded from the study. Descriptive statistics of the sample and the frequency of NASH were calculated using SPSS 16 statistical package (SPSS Inc, Chicago, IL). This protocol was approved by the institutional review board of the Children's Hospital of Wisconsin.

Results

A total of 284 obese pediatric patients were seen in the NEW Kids™ Program over the 17-month period. The sample was mostly female with a mean age of 11.3 years ($SD = 3.6$, range = 2–19) and mean BMI of 34.9 kg/m² ($SD = 8.9$); (Table 1). Descriptive statistics regarding the population's total and fractionated cholesterol, as well as their triglycerides and insulin levels, are described in Table 2. Of the 284 children, eight children (3%) underwent liver biopsy and met the criteria for analysis.

Descriptive statistics regarding these eight children's total and fractionated cholesterol, triglycerides, and insulin levels, are described in Table 3. Histological evaluation of the biopsy samples identified that all eight children (100%) had histological evidence of NASH with both macrovesicular and microvesicular steatosis, hepatocyte ballooning, and spotty necrosis associated with hepatocyte injury or death, respectively. Furthermore, seven of the eight children (87.5%) demonstrated NASH with fibrosis or cirrhosis.

Discussion

In the United States, the prevalence of pediatric obesity has tripled during the last four decades (Crocker & Yanovski, 2009). Consequently, the rise in pediatric NASH has

mirrored this increase. Despite this increase, there remain no universally accepted criteria for the selection of individuals who should undergo diagnostic liver biopsy.

Currently, NASH remains a clinicopathological entity characterized by the development of the histological changes of inflammation and fibrosis in the liver, which is becoming more prevalent in the pediatric population due to rising levels of obesity. The gold standard means of diagnosing NASH is via liver biopsy (Bedossa & Carrat, 2009); however, the invasive nature of a liver biopsy along with the current deficiency in management options for NASH has resulted in a controversy surrounding when and on whom a liver biopsy should be performed.

On one hand, the procedure is expensive and on the other, it has been associated with significant morbidity and even mortality (Lichtman, Guzman, Moore, Weber, & Roberts, 1987). Specific risks include transient hypotension, hematoma at the biopsy site, and significant bleeding requiring transfusion (Lichtman et al., 1987). Other more serious complications include pneumothorax, biliary peritonitis, or both (Piccinino, Sagnelli, Pasquale, & Giusti, 1986). Death, although infrequent (9/100,000), has also been reported, but is more commonly associated with cases where a malignant disease is present (Piccinino et al., 1986).

Another problem is sampling error. It is estimated that the samples obtained by liver biopsy account for only 1/50,000 of the liver mass, and thus, may not accurately represent the entire organ (Adams & Angulo, 2007). Consequently, one study documented that sampling error resulted in a difference of at least one fibrosis stage in 30% of the patients (Adams & Angulo, 2007). As a result the patients may not be treated as aggressively as required, or unfortunately may be treated more aggressively than needed.

More recently, the utility of noninvasive imaging methodologies such as ultrasound or magnetic resonance spectroscopy have also questioned the benefit of liver biopsy. Unfortunately, these modalities currently focus on the consequences of chronic liver disease such as hepatosplenomegaly or portal hypertension (Lefton, Rosa, & Cohen, 2009) and fail to identify the degree of inflammation or cirrhosis within the liver parenchyma.

Despite the problems associated with liver biopsy, it remains the only reliable means for diagnosing and staging steatohepatitis, fibrosis, and/or cirrhosis (Ramesh & Sanyal, 2005). Although limited treatment options currently exist, establishing the diagnosis of NASH versus other treatable disorders has significant benefits regarding treatment and outcomes. For example a diagnosis of seronegative autoimmune hepatitis established via liver biopsy would allow the physician to treat the underlying cause for the patient's persistently elevated liver transaminases and potentially prevent further liver damage. More importantly, knowledge of the extent of liver injury or evidence of cirrhosis on liver biopsy may provide the individual and family with additional motivation to change their current lifestyle behaviors which is the only proven treatment for NASH (Neuschwander-Tetri, 2009). Consequently, liver biopsy is essential in establishing the etiology of clinical liver disease as well as staging the degree of fibrosis or cirrhosis associated with the disease process (Brunt, 2009).

Regardless of one's opinions regarding the utility of liver biopsy, the development of clinical guidelines on whom and when a liver biopsy is necessary to decrease unnecessary morbidity and risk associated with the procedure. Results of our data suggest that by following the criteria of: (1) no evidence of other liver diseases and (2) AST or ALT greater than 200 IU/L or any elevation of AST (>46 IU/L) and ALT (>35 IU/L) for more than 6 months, one can more accurately predict whether an individual will have NASH on liver biopsy. Specifically, using these criteria, 100% of these eight patients had patho-histological

evidence of NASH with nearly 90% also demonstrating NASH with fibrosis or cirrhosis. Consequently, one may argue that these criteria for liver biopsy are too strict and that a significant number of individuals with disease may be missed considering the increasing frequency of NASH within the general population. Given the limited treatment options currently available, however, using the criteria that limit the number of unnecessary liver biopsies may be acceptable. These criteria provide a guideline for whom and when a liver biopsy should be considered in relationship to the diagnosis and management of pediatric NASH.

Limitations

Two major limitations to this study are the limited sample size and the patient population. In this study, the population examined was from the NEW Kids™ Program at Children's Hospital of Wisconsin, which provides health maintenance and recuperation for obese and morbidly obese children. Consequently, this population is not typical of a general pediatric population and therefore these results may not be generalized to the general pediatric community. In addition, only eight patients met the criteria for analysis. Although this accounted for more than 3% of the total sample analyzed, the patho-histological findings associated with this small patient number meeting criteria may not accurately represent the frequency of NASH identified on liver biopsy in the general population. Accordingly we would recommend that a prospective study using the same criteria be pursued to provide more definitive criteria of whom and when a liver biopsy should be performed.

Conclusions

In conclusion, NASH is a chronic progressive liver disease and is expected to become one of the most common causes of end-stage liver disease in both children and young adults. Our results demonstrate that obese individuals with no evidence of liver disease with an elevation of AST or ALT greater than 200 IU/L or any elevation of AST (>46 IU/L) and ALT (>35 IU/L) for greater than 6 months identified the presence of NASH in 100% ($n = 8$) of individuals with nearly 90% of the individuals demonstrating fibrosis or cirrhosis. These results underscore the importance of establishing pediatric guidelines for NASH and the necessity for development of treatment protocols for what is expected to become the most common cause of end-stage liver disease.

References

- Adams LA, Angulo P. Role of liver biopsy and serum markers of liver fibrosis in non-alcoholic fatty liver disease. *Clinical Liver Disease*. 2007; 11:25–35.
- Alisi A, Manco M, Vania A, Nobili V. Pediatric nonalcoholic fatty liver disease in 2009. *Journal of Pediatrics*. 2009; 155:469–474. [PubMed: 19772998]
- Bedossa P, Carrat F. Liver biopsy: the best, not the gold standard. *Journal of Hepatology*. 2009; 50:1–3. [PubMed: 19017551]
- Brunt EM. Histopathology of non-alcoholic fatty liver disease. *Clinical Liver Disease*. 2009; 13:533–544.
- Crocker MK, Yanovski JA. Pediatric obesity: etiology and treatment. *Endocrinology & Metabolism Clinics of North America*. 2009; 38:525–548. [PubMed: 19717003]
- Iacobellis A, Marcellini M, Andruilli A, Perri F, Leandro G, Devito R, Nobili V. Non invasive evaluation of liver fibrosis in paediatric patients with nonalcoholic steatohepatitis. *World Journal of Gastroenterology*. 2006; 12:7821–7825. [PubMed: 17203527]
- Lefton HB, Rosa A, Cohen M. Diagnosis and epidemiology of cirrhosis. *Medical Clinics of North America*. 2009; 93:787–799. [PubMed: 19577114]

- Lichtman S, Guzman C, Moore D, Weber JL, Roberts EA. Morbidity after percutaneous liver biopsy. *Archives of Diseases in Children*. 1987; 62:901–904.
- Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clinic Proceedings*. 1980; 55:434–438. [PubMed: 7382552]
- Neuschwander-Tetri BA. Lifestyle modification as the primary treatment of NASH. *Clinics in Liver Disease*. 2009; 10:649–665. [PubMed: 19818311]
- Piccinino F, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. *Journal of Hepatology*. 1986; 2:165–173. [PubMed: 3958472]
- Ramesh S, Sanyal AJ. Evaluation and management of non-alcoholic steatohepatitis. *Journal of Hepatology*. 2005; 42:S2–S12. [PubMed: 15777569]

Table 1Population Demographics (*N* = 284)

Age	
Mean $\pm$ <i>SD</i>	11.3 $\pm$ 3.6 years
Median	11.3 years
Range	2–19
BMI, kg/m ²	
Mean $\pm$ <i>SD</i>	34.9 $\pm$ 8.9
>40	27%
Gender, <i>n</i> (%)	
Male	124 (43.6%)
Female	160 (56.4%)
Race, <i>n</i> (%)	
Caucasian	116 (41%)
African American	108 (38%)
Latino	26 (9%)
Other	34 (12%)

Note. BMI = body mass index.

Table 2

Population Laboratory Values

Serum Test (Reference Range)	<i>n</i>	Mean ($\pm$ SD)
Total cholesterol (<170 mg/dl)	257	189 ($\pm$ 32.2)
LDL (<110 mg/dl)	257	124.4 ($\pm$ 30)
HDL (>35 mg/dl)	256	48.0 ($\pm$ 10.3)
Triglycerides (<125 mg/dl)	262	114.1 ($\pm$ 72.6)
Insulin level (<15 mU/L)	223	14.8 ($\pm$ 22.8)

Note. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 3

Sample Patient Laboratory Values

Patient	Age (years)	Race	Cholesterol (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	AST (IU/L)	ALT (IU/L)
1	10	Hispanic	167	100	40	107	475	231
2	8	Hispanic	183	218	42	79	265	388
3	14	Caucasian	182				32	64
4	10	Caucasian	141	112	38	81	74	108
5	8	African American	235				105	228
6	13	Caucasian	167				37	56
7	16	Caucasian	234	194	45	151	23	26
8	15	Hispanic	199	191	33	127	111	204
Mean			188.5	163	39.6	109	140.3	163.1

Note. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride.