CASE-BASED REVIEW

The Spectrum of Nonalcoholic Fatty Liver Disease

Case Study and Commentary, Peter Ghali, MD, and Jayant A. Talwalkar, MD, MPH

Nonalcoholic steatohepatitis (NASH) is a condition histologically similar to alcoholic steatohepatitis, yet while the latter has long been recognized as a cause of end-stage liver disease, the former was, until recently, discounted as having a benign course [1–3]. Indeed, it was felt that undisclosed alcohol use must account for those individuals with advanced fibrosis and steatohepatitis [4]. The first histologic account of a condition similar to alcoholic liver injury was made by Ludwig et al in 1980, at which time the term NASH was coined [5]. The condition is often first encountered as asymptomatic liver enzyme elevations or incidentally discovered fatty infiltration on ultrasound [6]. Liver enzymes do not necessarily correlate with the degree of underlying fibrosis [3]. There is a spectrum of disease ranging from asymptomatic steatosis to NASH to advanced liver disease [6,7]. The term nonalcoholic fatty liver disease (NAFLD) has been suggested to encompass both asymptomatic steatosis and steatohepatitis [6,8]. NAFLD is currently the most common clinical problem encountered by hepatologists and, with obesity reaching epidemic proportions, can be expected to increase further in significance [6]. The current estimated prevalence of NAFLD is about 20% [9–14], and the prevalence of NASH is about 5% [14]. Cirrhosis may be found in up to 1 out of 4 individuals with NASH [3]. Recent evidence suggests that NASH may account for a majority of individuals previously diagnosed with cryptogenic cirrhosis [15–17], and this diagnosis accounts for 7% to 14% of liver transplants performed [18,19].

There is currently no effective proven medical therapy for NASH [20,21]. Current treatment strategies focus on lifestyle modification, treatment of underlying risk factors, and avoidance of potential hepatotoxins [21]. A “metabolic syndrome” consisting of obesity, diabetes, hypertension, and hyperlipidemia has been associated with NASH and represents the potentially correctable risk factors for progression [3,22–24].

CASE STUDY

Initial Presentation

A 47-year-old white woman presents for a routine health examination. She feels that her health is not what it used to be and says she has gained weight steadily over the last 10 years, experiences frequent joint pains, and now gets out of breath quite easily. She has been followed by another physician for about 15 years for diabetes, hypertension, and high cholesterol.

From the Mayo Clinic College of Medicine, Rochester, MN.
NONALCOHOLIC FATTY LIVER DISEASE

**Table 1. Independent Predictors of Nonalcoholic Steatohepatitis or Fibrosis**

<table>
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<th>Predictor</th>
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<tr>
<td>Age &gt; 45 years</td>
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<td>Obesity (body mass index &gt; 30 kg/m²)</td>
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<tr>
<td>Diabetes mellitus, especially &gt; 15 years</td>
</tr>
<tr>
<td>Aspartate aminotransferase/alanine aminotransferase &gt; 1</td>
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<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Systemic hypertension</td>
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<tr>
<td>Hypertriglyceridemia</td>
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Data from references 3, 22, 24, and 29.

**History**

Review of systems is notable for polydipsia and polyuria. Her diet is high in fat and low in fiber. The patient takes oral medications for diabetes but is not on any lipid-lowering medications. She consumes 3 alcoholic beverages on weekends and admits to brief intravenous drug use as a teenager. She is in a monogamous longstanding relationship. Family history is unremarkable.

**Physical and Laboratory Examination**

Physical examination is notable for a blood pressure of 150/100 mm Hg and body mass index (BMI) of 33 kg/m². Results of examination are otherwise normal. Routine blood testing shows an elevated fasting glucose and glycated hemoglobin. Renal function is normal, but urinalysis shows microproteinuria. Complete blood count is normal. Liver enzymes are elevated, with an alanine aminotransferase (ALT) of 150 U/L (normal, 10–45 U/L), aspartate aminotransferase (AST) of 130 U/L (normal, 12–31 U/L); levels of alkaline phosphatase, bilirubin, albumin, and international normalized ratio (INR) are normal. Lipid studies show hypertriglyceridemia as well as elevated low-density lipoprotein cholesterol. A review of her previous records demonstrates a similar elevation in liver enzymes over the past 5 years.

- How is a diagnosis of NASH established?
- Is a liver biopsy necessary?

**Differential Diagnosis of NASH**

This clinical presentation with asymptomatic mild to moderate elevation of liver enzymes in an individual with a metabolic syndrome is common. Prior to exhaustive investigation or referral, the persistence of elevated liver enzymes should be confirmed. In this case, liver enzyme elevation is persistent. While NASH is very common, other treatable causes of liver disease need to be excluded. Serologic testing for viral hepatitis is warranted in individuals with an illicit drug use history; hepatitis C has a high prevalence (1.8%) in the United States [25]. Iron studies are appropriate to screen for hereditary hemochromatosis, which is common in whites (0.5%) [26]. Screening for autoimmune liver diseases is suggested, especially in symptomatic females. Complete abstinence from alcohol is generally recommended to assess its impact on the liver enzyme abnormalities. Recently, the consumption of 3 alcoholic beverages or more on a single occasion by a woman has been classified as “risky” drinking behavior [27], although this amount of alcohol would be unlikely to cause liver disease. In clinical studies, NASH is not diagnosed unless significant alcohol intake is absent. In most studies, this refers to either 20 g or 40 g per day (2 or 4 standard alcoholic drinks per day).

The diagnosis of NAFLD is a clinical one. It is made in the appropriate clinical context, in individuals with risk factors (Table 1) after other etiologies of liver disease have been excluded. The confirmation of NASH requires the presence of necroinflammation on liver biopsy and thus is made histologically. A biopsy is usually attempted once NASH is suspected, both for diagnosis and staging. This is the most reliable way to accurately detect individuals with ongoing liver damage due to this disease.

**Specific Investigations for NASH**

Neither clinical signs nor degree of liver enzyme elevation can be used to predict individuals with active inflammation or fibrosis [3,28,29]. Cross-sectional imaging of the liver with ultrasonography may be performed to look for signs of steatosis. The sensitivity of ultrasound to detect steatosis is estimated to be 55% [30], although a range of 55% to 100% has been reported. Computed tomography scanning has a sensitivity of 56% to 88% [31,32] to detect steatosis. Magnetic resonance imaging to detect fatty liver is currently used mainly as a research tool [33]. No imaging modality can accurately distinguish between simple steatosis, steatohepatitis, or fibrosis [34]. Because of this, liver biopsy remains the only available method to distinguish NASH from benign steatosis and to determine the degree of fibrosis. Because fibrosis is found in 15% to 50% of individuals at diagnosis (with cirrhosis in 7%–26%), there is some rationale to perform liver biopsy in patients with fatty liver [3]. However, because liver biopsy is not without risk [35], its use is ideally targeted toward individuals at highest risk of fibrosis. Clinically, this may include those with thrombocytopenia, hypoalbuminemia, hyperbilirubinemia, or impaired coagulation. Older age, obesity (BMI > 30 kg/m²), longstanding diabetes, female gender, and an AST:ALT ratio of 1 or greater have been independently associated with advanced fibrosis on liver biopsy in various studies [3,6,21,29]. Significant fibrosis may be found in up to 30%
of individuals with an ALT or 2 or more times the upper limit of normal and/or an AST above the upper limit of normal [36]. Securing the diagnosis of advanced fibrosis can be important in guiding follow-up, treatment, and surveillance procedures for individual patients. In general, a persistent elevation of liver enzymes in older women affected by diabetes mellitus should prompt strong consideration for a liver biopsy. It should be noted that liver biopsies are subject to sampling error and, if negative, may not completely exclude NASH. It is also important to confirm with the involved pathologist that the specimen obtained for a liver biopsy is adequate for staging.

**Further Workup**

The results of a thorough evaluation for causes of liver disease in the case patient are negative. Ultrasoundography reveals an echogenic liver, compatible with fatty infiltration, and is otherwise normal. After discussion with the patient, a liver biopsy is performed, which shows moderate steatosis with lobular necroinflammation and ballooning degeneration. There is also evidence of bridging fibrosis (stage 3 disease). The patient inquires as to what caused her disease and what can be done.

- **What are the causes of NASH?**

Traditionally, NASH has been classified as primary or secondary. Primary NASH is associated with the metabolic syndrome, but the exact pathogenesis remains unknown. A “2-hit” hypothesis for the development of NASH has been postulated [37]. The first “hit” refers to the development of steatosis, likely in relation to insulin resistance; potential causes include insulin resistance and adipokine imbalance [4]. The second “hit” refers to necroinflammation, which is felt to be due to oxidative stress. This ultimately may progress to fibrosis and cirrhosis.

Interestingly, obese individuals tend to have low levels of adiponectin and high levels of tumor necrosis factor-α (TNF-α). TNF-α stimulates the production of intracellular signaling molecules that in turn may cause insulin resistance. Adiponectin by contrast is an inhibitor of TNF-α; thus, a relative deficiency of TNF-α will tend to exacerbate its effects. The combination has been implicated in the development of steatosis. Leptin, in humans, may upregulate hepatic stellate cell activity and appears to be a factor in the development of fibrosis related to obesity. Noradrenaline and angiotensin also appear to be upregulated and may be fibrogenic [38]. In combination, these cytokines appear to play a role in the development of NASH and fibrosis, but the picture is as yet incomplete in humans [4].

<table>
<thead>
<tr>
<th>Table 2. Secondary Causes of Nonalcoholic Steatohepatitis</th>
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<tbody>
<tr>
<td><strong>Nutritional</strong></td>
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<tr>
<td>Total parenteral nutrition</td>
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<tr>
<td>Severe malnutrition</td>
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<td>Inborn errors of metabolism</td>
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<tr>
<td>Wilson disease</td>
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<tr>
<td>Abetalipoproteinemia</td>
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<td>Tyrosinemia</td>
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<tr>
<td>Hypobetalipoproteinemia</td>
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<tr>
<td>Galactosemia</td>
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<tr>
<td>Glycogen storage disease</td>
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<tr>
<td><strong>Weight loss/intestinal surgery</strong></td>
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<tr>
<td>Jejunoileal bypass</td>
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<tr>
<td>Biliopancreatic diversion</td>
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<tr>
<td>Gastric banding/bypass/gastroplasty</td>
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<tr>
<td>Extensive intestinal resection</td>
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<tr>
<td><strong>Drugs</strong></td>
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<tr>
<td>Amiodarone</td>
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<tr>
<td>Estrogens</td>
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<tr>
<td>Corticosteroids</td>
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<tr>
<td>Isoniazid</td>
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<tr>
<td>Perhexiline maleate</td>
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<tr>
<td>Tamoxifen</td>
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<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Lipodystrophy</td>
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<tr>
<td>Small bowel overgrowth</td>
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<tr>
<td>Inflammatory bowel disease</td>
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<tr>
<td>AIDS</td>
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</tbody>
</table>

Data from references 72–75.

Secondary NASH, while less common, must be excluded as it may be treatable. The term refers to both NASH associated with other disorders (eg, lipodystrophy) and NASH caused by medications. **Table 2** lists some secondary causes of NASH.

- **What are treatment options for NASH?**

Treatment options for secondary NASH include removing the inciting agent (in the case of medications or total parenteral nutrition) or treating the underlying cause. However, to date there is no proven effective therapy for the more common occurrence of primary NASH. Initial management includes dietary counseling and lifestyle modifications. However, there is no randomized trial proving the effectiveness of these types of interventions. Furthermore, data from the largest randomized controlled trial to date, in which both treatment and placebo groups were given dietary counseling,
demonstrate that at 2 years of follow-up there was no weight loss from baseline [39]. Various pharmacologic agents have been studied or are currently in trials. Although there are promising agents in terms of biochemical and histologic improvement, the achievement of clinically important end-points such as prevention or retardation of fibrosis and cirrhosis are still lacking (Table 3). Overall, the rationale underlying treatment of NASH has consisted of a balance between treating underlying risk factors and enhancing liver-protective factors. Initial interest in the latter led to studies of antioxidants and ursodeoxycholic acid. While promising at first, many earlier studies lacked both control groups and meaningful histologic endpoints. This was exemplified by studies of ursodeoxycholic acid, found to be promising in uncontrolled trials but when evaluated in a randomized control trial with histologic endpoints, it was found to be no better than placebo, at least in standard doses [39].

Currently there is significant interest in modifying underlying risk factors. Early data regarding the use of insulin sensitizers is encouraging, in particular the thiazolidinediones
There is encouraging controlled data with regard to the effect of thiazolidinediones on biochemistry and histology, but sample sizes have been small; larger trials are underway. Limiting factors in most other trials to date have included small sample size, lack of blinding, and lack of control groups. A specific difficulty with the evaluation of histology has been that steatosis appears to regress as fibrosis progresses in this disease, and involvement within the liver may be patchy [43]. This, in association with the slowly progressive nature of the disease, makes it important to ensure adequate biopsy size and number as well as duration of follow-up in ongoing and future trials. At this time, there is no therapy for NASH that is approved by the U.S. Food and Drug Administration.

Weight Loss Strategies

There is general consensus that management of NASH should include a goal of weight loss. A combination of regular aerobic exercise in conjunction with a balanced low-calorie diet is effective in achieving weight loss in selected individuals and may be recommended [44–47]. This type of intervention may improve obesity-related conditions, such as insulin resistance [47]. Recently, the potential impact of bariatric (weight loss) surgery on NASH has been evaluated. Bariatric surgery has been shown to be effective in causing weight loss and improvements in diabetes and hyperlipidemia [48]; however, its effect on steatohepatitis remains unclear. Early bariatric procedures, such as jejun ileal bypass, were implicated in worsening steatosis, fibrosis, and even liver failure [49–53]. Rapidly increased mobilization of peripheral fat stores may be the cause of this worsening [54]. More recently, however, newer bariatric procedures have been found to potentially ameliorate NASH [55–58]. Adequately powered prospective studies are still pending.

Initiation of Therapy

A long discussion is undertaken with the patient. At the current time, there is no therapy approved for NASH outside of clinical trials. However, her diabetes and hyperlipidemia need to be managed aggressively. The patient mentions that she has previously been told not to start treatment for hyperlipidemia because of concern that statin therapy might worsen her already elevated liver enzymes.

• When is referral to a hepatologist indicated?

Referral to a hepatologist is often hampered by the lack of proven therapies. However, it must be realized that the treatment of individuals with NASH encompasses more than just targeting the disease itself. Indeed, the treatment comprises the evaluation and staging of the disease, periodic follow-up, and management of underlying risk factors. Furthermore, the timing of liver transplant in a subset of individuals suffering from this disease is best ascertained in conjunction with a hepatologist. In general, individuals with persistent elevation of liver enzymes 2 to 3 times above the upper limit of normal or with a degree of fibrosis on liver biopsy should begin evaluation by a hepatologist.

Follow-up

The patient is referred to a hepatologist and continues to be followed in primary care and by a subspecialist. Over a period of 5 years, the patient remains asymptomatic. Her weight is unchanged, but her diabetes, hyperlipidemia, and hypertension are well controlled. However, at her annual visit, she notes that she has been extremely fatigued and anorexic. Despite this, she has gained 15 lb. Her legs are also swollen. Physical examination reveals the presence of spider angiomata, palmar erythema, splenomegaly, shifting dullness in the abdomen, and mild pitting edema. Laboratory testing shows an increased INR of 1.5, total bilirubin of 1.7 mg/dL (normal, 0.1–1.0 mg/dL) and albumin of 3.1 g/dL (normal, 3.5–5.0 g/dL). Levels of serum ALT and AST values have actually improved, but the level of AST is now higher than ALT (55 and 45 U/L, respectively). Leukocyte and platelet counts are also reduced at 3.5 × 10⁹/L and 90 × 10⁹/L, respectively. An ultrasound is repeated and confirms the presence of splenomegaly and moderate ascites.
Clinically, the patient has now developed features of portal hypertension related to cirrhosis. Liver transaminases in NASH will often normalize or decrease as the degree of fibrosis becomes more advanced. The degree of steatosis and necroinflammatory activity generally decreases with the normalization of liver enzymes as liver fibrosis progresses [62]. In addition, individuals with cryptogenic cirrhosis by definition generally have minimal to no fat present on liver biopsy. Thus, this clinical presentation is compatible with cirrhotic-stage liver disease. There is no indication to repeat a liver biopsy, as it will not impact on management or consideration for liver transplantation. However, the patient will now need to be evaluated for liver transplantation. Further pretransplant workup will consist of screening for varices and hepatocellular carcinoma as well as managing complications of ascites. During the pretransplant period, close monitoring of electrolytes and renal function as well as for bleeding will be necessary. This is often coordinated with the patient’s primary care physician. Furthermore, it is important to avoid the unnecessary use of potentially hepatotoxic medications, such as nonsteroidal anti-inflammatory drugs, as well as potentially harmful surgical procedures, such as cholecystectomy or hernia repairs.

**Preventive Health Strategies**

Individuals with cirrhosis are at risk for malnutrition, bone disease, and further deterioration with superinfections of the liver. Indeed, malnutrition was initially included in the Child-Turcotte model for estimating mortality in cirrhotic patients undergoing portocaval shunt surgery, prior to the Pugh modification [63]. A low threshold is needed for nutritional evaluation and assessment of bone density [64]. Furthermore, it is recommended that all patients with cirrhosis undergo vaccination for hepatitis A and B if not immune. Individuals with NASH are also at risk for cardiac and vascular disease as well as complications of diabetes. Aggressive control of diabetes and cholesterol is warranted, as is application of appropriate periodic health assessments and investigations.

**Liver Transplant Assessment**

Ultimately, the most effective therapy for end-stage liver disease is liver transplantation. The decision to proceed with liver transplantation is based on indication for the procedure and the patient being an acceptable candidate for liver transplantation with a reasonable likelihood of favorable outcome. Individuals should be referred to a liver transplant center if the following criteria are met:

1. Cirrhosis with a Child-Pugh score of at least 7 or greater (Table 4)
2. Major complication of cirrhosis (eg, ascites, variceal bleeding, encephalopathy, hepatocellular carcinoma, hepatopulmonary syndrome, hepatorenal syndrome) [65]

Priority for liver transplantation is currently based on the Model for End-Stage Liver Disease (MELD) score. This is calculated using a logarithmic formula based on levels of bilirubin, INR, and creatinine and ranges up to a maximum of 40. Liver transplantation is most beneficial when a MELD score of 15 or more is attained [66]. A liver biopsy is not absolutely required to confirm histologic cirrhosis if clinical features are present. It is also important to be certain that no other effective form of therapy is available to individuals prior to considering transplantation. In the case of this patient, she clearly requires consideration for liver transplantation based on the development of ascites. Individuals with hepatocellular carcinoma are not automatically excluded from transplant. In fact, for individuals with cirrhosis and single tumors under 5 cm in size or no more than 3 lesions under 3 cm in size, liver transplantation is considered the therapy of choice when available [67–69]. Morbid obesity should be

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**Table 4. Child-Pugh Classification of Cirrhosis**

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<tr>
<th>Ascites</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
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<tr>
<td>None/slight</td>
<td>Moderate/controlled by diuretics</td>
<td>Severe/refractory</td>
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<tr>
<td>Albumin, g/dL</td>
<td>&gt; 3.5</td>
<td>2.8–3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Bilirubin (noncholestatic disease), mg/dL</td>
<td>1–2</td>
<td>2–3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Bilirubin (cholestatic disease), mg/dL</td>
<td>1–4</td>
<td>4–10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt; 1.7</td>
<td>1.7–2.3</td>
<td>&gt; 2.3</td>
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<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Stage 1 + 2</td>
<td>Stage 3 + 4</td>
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Interpretation: 5–6 pts = Class A; 7–9 pts = Class B; 10+ pts = Class C. (Adapted with permission from reference 98.)
considered a contraindication to liver transplantation [65]. If a liver transplant is undertaken, it is important to advise patients that NASH can recur [15,70,71].

SUMMARY

NASH is a highly prevalent disorder in Western society and will likely become more prominent as the epidemic of obesity continues. The cause of NASH is uncertain, but an association with obesity, hypertension, hyperlipidemia, diabetes, and female gender exists. Initial presentation may be with asymptomatic elevation of liver enzymes or incidental radiologic evidence of steatosis. Some individuals presenting with cirrhosis may in fact have had longstanding NASH. This population likely explains a large proportion of individuals diagnosed with cryptogenic cirrhosis. Often, a liver biopsy is required to establish the diagnosis and obtain prognostic information. While no specific therapy currently exists for this condition, there are several promising agents under investigation. However, some of the limitations for studying this disease include its slowly progressive nature, the absence of a reliable, easily obtained gold standard in measuring disease progression, and the absence of large controlled trials to date. Follow-up is required for individuals with NASH, as it may progress to a fibrotic or cirrhotic stage. In this case, consideration should be given to referral for liver transplantation, but this may depend on the patient being an acceptable candidate. Specific risks in this population include morbid obesity, undetected cardiac disease, undetected vascular disease, and severe complications of diabetes and hypertension. Because NASH can recur, risk factors for the disease, such as diabetes and hypertension, should be aggressively managed both before and after liver transplantation.

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References

NONALCOHOLIC FATTY LIVER DISEASE


CASE-BASED REVIEW


CME EVALUATION: The Spectrum of Nonalcoholic Fatty Liver Disease

DIRECTIONS: Each of the questions below is followed by 4 possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following statements about diagnosing non-alcoholic steatohepatitis (NASH) is TRUE?
   (A) NASH is diagnosed if an individual with the metabolic syndrome and elevated liver enzymes has no other identifiable cause of liver disease
   (B) NASH is a histologic diagnosis based on the presence of steatosis and necroinflammation
   (C) NASH is diagnosed radiologically by the presence of fatty liver with signs of cirrhosis
   (D) NASH is diagnosed only if both steatosis and fibrosis are identified on liver histology

2. Which of the following statement regarding NASH is TRUE?
   (A) NASH may be found in at-risk individuals with normal liver enzymes
   (B) A minority of patients with NASH will have fibrosis at the time of diagnosis
   (C) A negative liver biopsy excludes the diagnosis of NASH
   (D) The prevalence of NASH in the general population is extremely low and should only be suspected in the morbidly obese

3. Which of the following may occur as NASH progresses to fibrosis and/or cirrhosis?
   (A) The degree of steatosis will tend to increase
   (B) Liver enzyme levels will rise acutely
   (C) Aspartate aminotransferase levels will normalize
   (D) The degree of steatosis will tend to decrease

4. Which of the following individuals has the best indication for a liver biopsy to evaluate for NASH? (All have negative etiologic workups for liver disease)
   (A) A 25-year-old man with liver enzymes 4 times the upper limit of normal 1 year ago and again this year
   (B) A 56-year-old man with liver enzymes normal 1 year ago but 4 times the upper limit of normal today
   (C) A 72-year-old woman with liver enzymes intermittently elevated at 1.5 times the upper limit of normal
   (D) A 55-year-old woman with obesity and family history of NASH

5. Which of the following statements is TRUE?
   (A) Statin therapy is likely to cause an exacerbation in liver enzymes if NASH is present and is therefore contraindicated
   (B) Ursodeoxycholic acid (13–15 mg/kg) has been shown to improve the histology of NASH when compared with placebo
   (C) Pioglitazone is the drug of choice for treating NASH
   (D) Bariatric surgery has been shown to improve liver histology in some individuals with NASH
EVALUATION FORM: The Spectrum of Nonalcoholic Fatty Liver Disease

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Circle your answer to the CME questions below:

1. A  B  C  D
2. A  B  C  D
3. A  B  C  D
4. A  B  C  D
5. A  B  C  D

Please answer the following questions:

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   _ Excellent   _ Good   _ Fair   _ Poor

2. This article was fair, balanced, free of commercial bias, and fully supported by scientific evidence.
   _ Yes   _ No

3. Please rate the clarity of the material presented in the article.
   _ Very clear   _ Somewhat clear   _ Not at all clear

4. How helpful to your clinical practice was this article?
   _ Very helpful   _ Somewhat helpful   _ Not at all helpful

5. What changes will you make in your practice as a result of reading this article?

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6. What topics would you like to see presented in the future?

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