

EDUCATION PRACTICE

Abnormal Liver Tests and Fatty Liver on Ultrasound

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Clinical Scenario

A 56-year-old woman is noted to have slightly abnormal liver enzymes on 2 separate occasions obtained as part of a well woman clinic visit. Most recently, about 6 months after her first set of abnormal liver enzymes, the alanine transaminase (ALT) is 67 U/L, and the aspartate transaminase (AST) is 50 U/L. The patient denied any alcohol ingestion, herbal supplementation, or over-the-counter medications. Her current medications include Lipitor (atorvastatin) 40 mg daily, lisinopril 20 mg daily, and aspirin 325 mg daily. She has a medical history significant for obesity (body mass index, 32), hypertension, and hyperlipidemia. Her mother has diabetes. Results of a chronic hepatitis panel, fasting iron panel, ferritin, and antinuclear antigen are negative. A right upper quadrant ultrasound was obtained and demonstrated a hyperechoic liver consistent with fatty infiltration.

The Problem

This type of presentation is quite typical, occurs frequently in clinical practice, and will likely increase in the future as the prevalence of obesity and diabetes continues to increase in Western countries. The overall prevalence of nonalcoholic fatty liver disease (NAFLD) is between 20%–35%, but this increases dramatically in obese to morbidly obese patients, with the prevalence in some series being greater than 90%. Although most NAFLD follows a relatively benign natural history in relationship to the liver, numerous studies have now shown an increased cardiovascular disease risk in the presence of NAFLD. The presence of NAFLD also increases the odds of developing diabetes by more than 4-fold.

The more aggressive form of NAFLD, nonalcoholic steatohepatitis (NASH), has been estimated to occur in 6%–8% of the general population, increasing to ~35%–40% in morbidly obese patients undergoing bariatric surgery. This is problematic, because recent studies have suggested that about 10% of patients will progress to cirrhosis during an approximate 14-year period. Once cirrhotic, end-stage liver-related complications occur in 38%–45% of cases, and about 20% will succumb to a liver-related death during a 7- to 10-year period. Hepatocellular carcinoma has also been linked to NASH cirrhosis, but the exact prevalence remains unknown.

The pathogenesis of NAFLD is rooted in the development of insulin resistance and dysregulated energy metabolism that involves a complex interplay between adipose tissue, skeletal muscle, and liver. Hepatic steatosis has been shown to be primarily due to increased free fatty acid flux to the liver, which occurs as a result of either dietary fat intake or increased

lipolysis within insulin-resistant adipose tissue. Additional sources of hepatic steatosis include increased de novo lipogenesis, decreased free fatty acid oxidation, and impaired triacylglycerol export. The development of steatohepatitis is less clear but appears to involve an altered adipocytokine profile that includes increased proinflammatory cytokine production from visceral adipose tissue, Kupffer's cells, and hepatocytes with decreased production of the antisteatotic, anti-inflammatory, and antifibrotic cytokine adiponectin. Subsequent cellular injury, inflammation, apoptosis, and fibrosis lead to the characteristic histopathologic findings of NASH.

Management Strategies and Supporting Evidence

Elevated serum aminotransferase levels and a fatty liver on imaging should prompt the clinician to think about the possibility of NASH. Unfortunately, a liver biopsy is still required to make the distinction between isolated fatty liver and NASH. Specific histopathologic features of NASH include the presence of macrovesicular steatosis, lobular inflammation, and ballooning degeneration with or without the presence of perisinusoidal fibrosis. Noninvasive tests that accurately detect NASH and the various physiologic components of NASH to include oxidative stress, inflammation, apoptosis, and fibrosis are being actively investigated, and some show great promise. However, none of these tests correctly detect all patients at various stages of disease. Some are quite good for detecting advanced fibrosis and minimal to no fibrosis but lack efficacy in detecting those NASH patients with moderate disease. A recent review highlights some of the recent advances in this area. However, these noninvasive tests are still relatively novel and for the most part await validation in independent follow-up studies.

Several clinical factors, many of which are readily attainable on a routine clinic visit, have been shown to be associated with NASH and advanced fibrosis. Individually, none are sufficiently accurate to definitely diagnose the severity of disease. However, collectively, they do begin to paint a picture of the type of patient who is at greatest risk for having or developing NASH. These clinical factors include obesity, age, non-African American ethnicity, the presence of diabetes and hypertension, female

Abbreviations used in this paper: ALT, alanine transaminase; AST, aspartate transaminase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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1542-3565/08/\$34.00
doi:10.1016/j.cgh.2007.10.030

Table 1. Clinical Risk Factors for NASH With Advanced Fibrosis

(1) Obesity
(2) Age ≥ 50 y
(3) Non-African American ethnicity
(4) Female gender
(5) Diabetes mellitus, type II
(6) Hypertension
(7) AST ≥ 45 U/L
(8) AST/ALT ratio ≥ 0.8 –1.0
(9) Low platelet count

gender, AST/ALT ratio, the level of AST, and low platelet count (Table 1). Until clearly defined, highly accurate noninvasive testing becomes readily available, the clinician should consider these clinical factors in determining who should undergo a liver biopsy. Those patients not undergoing a liver biopsy should be counseled on proper lifestyle modifications aimed to improve the underlying insulin resistance that is inherently present in the vast majority of these patients.

Lifestyle modifications should include both dietary changes and increased exercise. The ideal diet has yet to be defined, but it is clear that patients with NASH consume on average more calories than their non-NASH counterparts; therefore, recommendations should be made to decrease total daily caloric intake. In addition, it is becoming clear that dietary intake of high fructose corn syrup and saturated fatty acids should be limited and replaced with diets higher in monounsaturated and n-3 polyunsaturated fatty acids. Examples of foods high in monounsaturated fatty acids (palmitoleic acid and oleic acid) include milk, peanut butter, and olive oil. Fish (salmon, herring, mackerel, trout), fish oil, flaxseed, and walnuts are examples of foodstuffs that contain large amounts of n-3 polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid).

Exercise improves insulin sensitivity, reduces visceral adiposity, increases adiponectin, and decreases hepatic steatosis. The good news is that significant amounts of exercise are not required to achieve these beneficial effects. Evidence supports that aerobic exercise performed 3–4 times per week to burn about 400 calories each session is sufficient, and the beneficial effects on energy regulation might be seen with minimal to no weight loss. Ideally, patients would combine the dietary and exercise recommendations in an effort to optimize lifestyle modification. Cumulative weight loss of 8%–10% baseline body weight is associated with histopathologic improvement of NASH.

Patients who are subsequently diagnosed with NASH should be counseled on the possibility of disease progression and should initially be treated with the same lifestyle modifications and weight loss goal as above. However, careful thought should be given to referral for clinical trials assessing different therapeutic agents currently under investigation. Bariatric surgery might also be considered if the patient has a body mass index ≥ 40 or ≥ 35 with comorbid illnesses. Numerous studies have demonstrated significant improvement and even resolution of NASH in a great majority of patients undergoing gastric bypass.

If this is not feasible and if the patient has histopathologic evidence of moderate to advanced disease (stage 2 fibrosis or greater), then a discussion about the use of alternative therapies might be warranted. The medication with the most promise in clinical trials is pioglitazone, a peroxisome proliferator-acti-

vated receptor (PPAR)- γ agonist that improves insulin sensitivity, reduces hepatic steatosis, and decreases hepatic necroinflammation. Two double-blind, randomized, placebo-controlled trials, albeit including a relatively small number of patients, have been performed and show a benefit in improving NASH. However, a longer-term study with more patients is still underway, and some physicians have advocated waiting for the conclusions from this study before making any recommendations on the use of pioglitazone to treat NASH, especially in nondiabetic patients. Untoward side effects including weight gain, peripheral fat deposition, lower extremity edema, and bone loss (particularly in diabetic female patients) have dampened enthusiasm for some. Patients with New York Heart Class III or IV condition should not be prescribed pioglitazone. Increased cardiovascular risk has not been shown with pioglitazone but has been identified with rosiglitazone, a drug in the same class.

Areas of Uncertainty

Significant strides have been made in this field during the past 7–8 years. However, much is yet to be learned. Several critical questions remain and need to be answered in the near future. One such question concerns who progresses in disease severity. It does not appear that all NASH is created equal. One set of answers might lie in the understanding of why African Americans do not have the amount of fatty liver or the severity of NASH as their white or Hispanic counterparts, despite having more diabetes, hypertension, and metabolic syndrome. If the “protective” effects of African American ethnicity can be elucidated, significant strides in treating this disease will be made.

Another question involves the role of liver biopsy in the future. Will it still be necessary? Certainly with the development of noninvasive tests, the need to perform liver biopsies in patients with NAFLD will decrease and might be eliminated altogether.

What is the prevalence of hepatocellular carcinoma in NASH? Preliminary evidence suggests it is less than that seen with chronic hepatitis C, but longer-term natural history studies are needed to clarify. Even if the prevalence is much less, this still remains a significant problem as a result of the much higher prevalence of NASH in our society compared with chronic hepatitis C.

Effective therapies probably remain the largest area of uncertainty, however. The ideal diet and exercise combination has yet to be proved in prospective, randomized, controlled trials and warrants further investigation. The role of antioxidants such as vitamin E, betaine, and S-adenosylmethionine alone or in combination with other agents, as well as pentoxifylline, deserves further investigation. Uncontrolled pilot trials with metformin have been disappointing. The thiazolidinedione class of insulin sensitizers shows promise, but they are not effective in every patient and are associated with untoward side effects, and there are no long-term safety or efficacy data available. Other pharmacotherapies under investigation include glucagon-like peptide-1 receptor agonists, selective type 1 cannabinoid receptor antagonists, angiotensin receptor blockers, and the combination of metformin and the thiazolidinedione class of medications (either rosiglitazone or pioglitazone). It is likely that patients will be treated with combination therapy in the future as our understanding of the pathogenesis of NASH

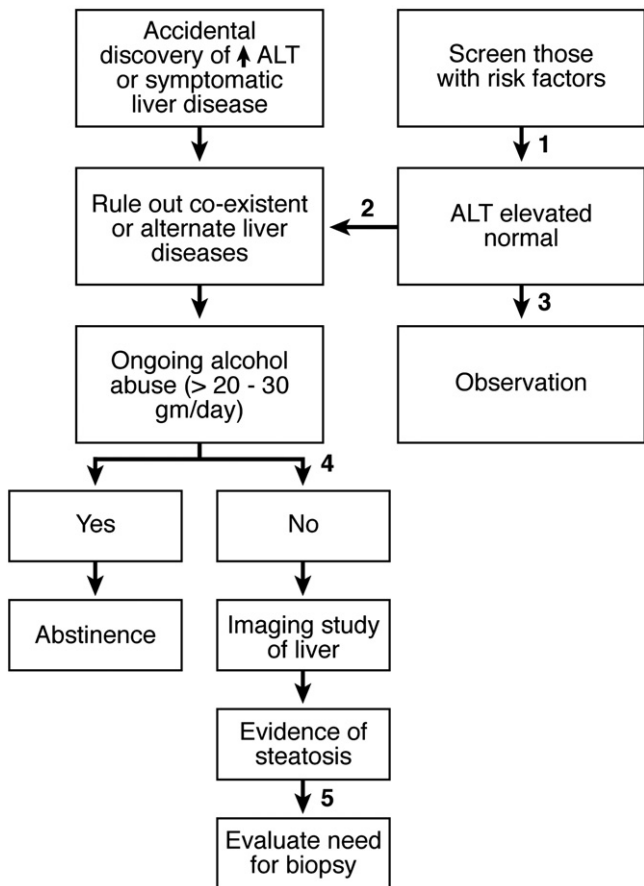


Figure 1. American Gastroenterological Association Institute 2002 guidelines for evaluation of NAFLD.

continues to evolve and specifically targeted therapy can be developed.

Published Guidelines

The AGA Institute medical position statement on NAFLD was published in 2002 (Figure 1). The recommendations at that time were to screen all patients with risk factors with a set of liver enzymes and rule out coexistent or alternate liver disease if the ALT was elevated. If no coexistent liver disease was found, then assess for alcohol intake and advocate abstinence if the patient consumed greater than 20-30 g of alcohol daily. Alternatively, if no significant alcohol history is obtained, then obtain an imaging study of the liver. If fatty liver is found, then evaluate the need for a liver biopsy.

The AGA Institute guidelines were based on data available in 2002 and now seem relatively vague and outdated. A significant amount of research has yielded abundant knowledge in this field since 2002, albeit much is still to be learned. It is apparent that NAFLD represents the hepatic manifestation of metabolic syndrome, and thus those patients who exhibit features of metabolic syndrome are at risk for NAFLD. Data have shown that among obese patients with NAFLD, more than two thirds have metabolic syndrome. Subsequently, Figure 2 includes a modified evaluation scheme that identifies the specific risk factors for NAFLD to be those of metabolic syndrome. In addition, more specific data are available for the definition of

elevated ALT. Patients with an abnormal ALT, as defined by the newer criteria of >30 IU/mL in men and >19 IU/mL in women, should be considered for evaluation.

If the liver enzymes are chronically (>6 months) elevated, then a work-up to exclude other causes of chronic liver disease should be performed. If this history is unremarkable and laboratory testing does not demonstrate other types of chronic liver disease, then an imaging study such as a right upper quadrant ultrasound should be considered to diagnose NAFLD. The published guidelines then suggest that these patients should be evaluated for the need for liver biopsy, but they do not give specific details as to who should undergo biopsy.

Newer data published since 2002 clearly describe specific clinical risk factors for NASH with advanced fibrosis (Table 1). Identifying these patients is critical, because data suggest these are the patients who are at risk for liver-related morbidity and mortality. Until accurate, noninvasive testing becomes available, a liver biopsy should be considered in patients with these risk factors.

Summary

This case illustrates a common problem seen in clinical practice and one that will likely continue to increase in frequency. Patients with metabolic syndrome are at greatest risk for NAFLD. Given the prevalence of NAFLD in the population, it is imperative that clinicians be able to recognize those pa-

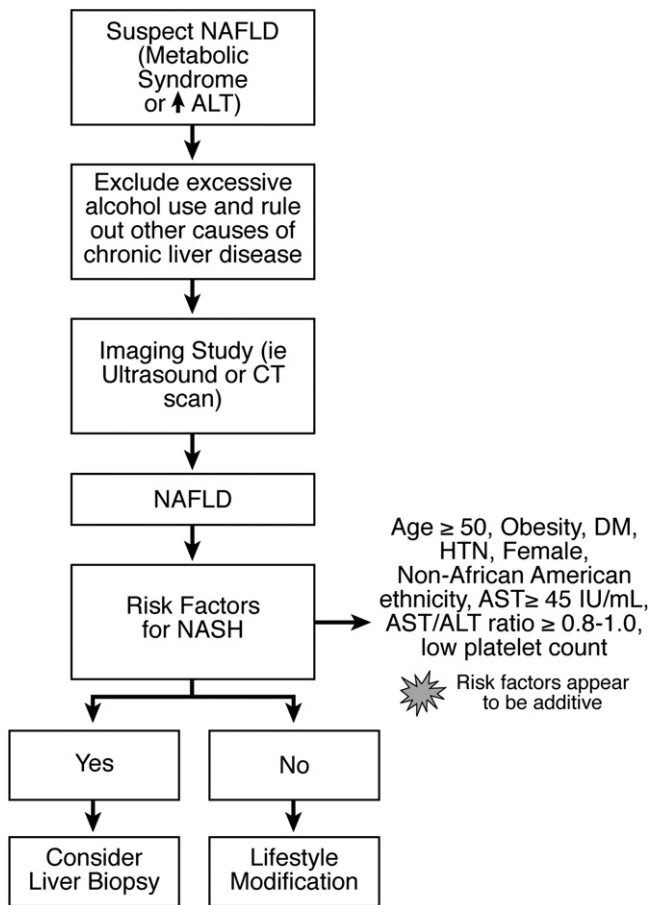


Figure 2. Modified evaluation of NAFLD.

tients who might benefit from a liver biopsy. Treatment is still based on a foundation of diet and exercise, but adjuvant therapies for patients with more advanced disease should be considered.

Suggested Reading

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