

CLINICAL VIGNETTE

Nonalcoholic Fatty Liver Disease in the Geriatric Patient

Hong-Phuc Tran, M.D. and Elizabeth Whiteman, M.D.

Case Report

A 72-year-old male with insulin dependent diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease Stage 3, bipolar disorder, and recent septic colitis was readmitted to the hospital for worsening altered mental status for three days. His delirium worsened despite broad spectrum antibiotics for pneumonia. On exam, he was hemodynamically stable, chronically ill appearing, and alert but oriented only to person. His body mass index was 27.5, and remainder of his physical exam was unremarkable. Laboratory exam included high ammonia level of 125, elevated lactate of 31, WBC of 2.78, and low albumin of 2.6. Basic metabolic panel, depakote level, urine culture, viral hepatitis panel, and other liver function tests were normal. Abdominal ultrasound showed echogenic liver and splenomegaly. Chest xray and head imaging with CT and MRI showed no acute changes that would explain his altered mental status. He was treated empirically with broad spectrum antibiotics, IV fluids, and lactulose. Mirtazapine was held, and his mentation improved when ammonia level improved to 53. Antibiotics were discontinued on hospital day 3 without worsening symptoms. His ammonia level increased to 157 on hospital day 4 and lactulose was continued. His altered mental status was thought to be from hepatic encephalopathy from underlying nonalcoholic steatohepatitis with possible contribution from Mirtazapine. He was discharged on hospital day 5 to a skilled nursing facility for rehab with outpatient hepatology consultation.

Initial hepatology consultation noted mild bilateral hand tremor but no overt asterixis or other stigmata of liver disease. Repeat labs showed mild anemia, normal platelets, normal liver function tests except for hypoalbuminemia of 2.9, elevated prothrombin time of 13.4, and INR of 1.3. A recent ferritin was normal at 91. The hepatologist raised questions about underlying chronic liver disease given "good" liver function function tests, and ordered additional imaging.

MR Elastography showed markedly elevated liver stiffness of 9.6kPa, consistent with underlying F4 fibrosis / cirrhosis. There was also evidence of portal hypertension, including splenomegaly, small ascites, and a recanalized paraumbilical vein. FIBROspect II showed an Index of 77, which was consistent with METAVIR F2-F4. The probability of F2-4 was 89.6%. At the follow-up, he was diagnosed with "cirrhosis likely due to nonalcoholic steatohepatitis" with a low MELD (Model for End-Stage Liver Disease) score, and metabolic

syndrome. He was started on Rifaxamin 550mg twice daily and was recommended to decrease lactulose as tolerated. Abdominal ultrasound every 6 months was recommended for hepatocellular carcinoma surveillance, and an esophagogastro-duodenoscopy was recommended for variceal surveillance.

Discussion

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease and elevated liver function tests in the United States. Its prevalence is 30%, affecting about 75 to 100 million people,¹ and is increasing in the aging population,² – with higher prevalence in males¹ and Hispanics. This is greater than 40% of middle aged Americans have NAFLD. However, older adults are likely to have more severe biochemical, hematologic and histologic changes.¹ The prevalence in the elderly falls in extreme decades of life, thought to be due to decreased survival or decreased fatty changes in advanced nonalcoholic steatohepatitis (NASH).^{1,3,4}

NAFLD encompasses a spectrum of histologic lesions. They are classified in the following categories: 1) Nonalcoholic Fatty Liver (NAFL), also known as benign steatosis; 2) Nonalcoholic Steatohepatitis (NASH), which is hepatic steatosis with inflammation and necrosis with or without fibrosis; 3) Fibrosis and 4) Cirrhosis. Steatosis is the "ballooning" of hepatic cells, which change shape resulting in swelling of nuclei and displacement to the edge of these cells. NAFLD is the most common cause of cryptogenic cirrhosis, which is cirrhosis that cannot be explained by chronic viral hepatitis, alcohol abuse, toxin exposure, autoimmune disease, congenital causes, vascular outflow obstruction, or biliary tract disease.^{1,3,4}

Risk factors for NAFLD include metabolic syndrome, insulin resistance, diabetes, obesity, dyslipidemia (especially hypertriglyceridemia and low high-density lipoprotein), and hypertension. Age is also an independent risk factor for severe fibrosis in NAFLD (Odds ratio 5.6 in those aged 45 or older).² The exact pathogenesis of NAFLD is unclear and likely multifactorial. Pathogenesis is thought to be due to increased visceral adipose tissue, which leads to insulin resistance, development of pro-inflammatory markers, and increased serum free fatty acids. The combination of these factors ultimately result in liver injury. Most patients with NAFLD are asymptomatic and typically incidentally diagnosed. Patients

can present with fatigue, daytime sleepiness, vague right upper quadrant pain, hepatomegaly, normal or high alanine aminotransferase (ALT), and obesity and features of diabetes. The most common cause of death in NAFLD patients is cardiovascular disease due to an increased association with atherosclerosis. Mortality is dependent on the presence and extent of fibrosis, and NASH is considered an independent risk factor for cardiovascular disease. Malignancy and cirrhosis are the second and third most common causes of death in patients with NAFLD. Prognosis is better if NAFLD is detected earlier.¹⁻⁴

Nonalcoholic Steatohepatitis (NASH) affects 3-5% of the general population and up to 12% in older patients and diabetics.⁴ Twenty percent of patients with NASH will progress to cirrhosis. The prevalence of NASH is higher in elderly patients with NAFLD. Unfortunately, the diagnosis of NASH is often delayed until cirrhosis develops. The diagnosis of cirrhosis due to NAFLD can be delayed by almost a decade in the absence of symptoms.⁵ Liver function tests may be normal, and ultrasound may be unreliable as the percentage of steatosis decreases in advanced NASH. Definitive diagnosis of NASH is with liver biopsy.^{3,4,6-8} Liver biopsy is usually safe in the elderly but often overlooked and may help with treatment plan and prognostication.²

There are several non-invasive ways to assess for NASH. The NAFLD Fibrosis Score incorporates age, BMI, hyperglycemia, platelets, albumin, AST/ALT ratio, and has 75% sensitivity and 58% specificity. ALT can also be used, but it is normal in 30 to 60% of patients with biopsy-confirmed NASH. Ultrasound can assess for increased echo texture (increased brightness) but has only 67% sensitivity and 77% specificity for steatosis. Ultrasound is inaccurate when steatosis is less than 30%. MRI Elastography (with and without contrast) is more sensitive in detecting fatty infiltration of the liver. A Fibrosis serum panel, such as FIBROspect II, can be used to differentiate between absent and mild liver disease (Metavir F0-1) from significant liver fibrosis (Metavir F2-4). Metavir stage 0 indicates absence of fibrosis, while stage 4 indicates cirrhosis. Sensitivity of the fibrosis serum panel is 73-95%, specificity 66-74%, and accuracy 73-90%.^{3,6-9}

There are no specific therapeutic guidelines for treatment of NAFLD in adults ages 65 and older. Management should be tailored to the individual geriatric patient. For patients with hepatic encephalopathy, Rifaxamin and lactulose can be used. Lactulose can help improve cognition and quality of life in patients with hepatic encephalopathy; however, it does not prevent progression of hepatic encephalopathy or improve survival.² Lifestyle changes, such as weight loss (for overweight and obese patients), exercise, and dietary changes can be effective.¹ Weight loss of 10% is associated with biochemical and histological improvement.^{1,2} However, lifestyle changes may be difficult in elderly patients who often have physical limitations and inadequate oral intake. Vaccination for Hepatitis A and B is recommended for patients with no serologic evidence of immunity. Glucose and lipid control should be optimized. Statins may possibly delay progression from NAFLD to NASH, and alcohol and

hepatotoxins should be avoided. There is variable data on efficacy of Vitamin E and insulin sensitizers in patients with biopsy-confirmed NASH. Vitamin E may improve histologic features in patients with NASH who do not have diabetes or cirrhosis but may be associated with possible increase risk of cardiovascular mortality and prostate cancer.⁴ Pioglitazone may improve biomarkers, steatosis and inflammation in patients with NASH but may increase cardiovascular risk. Metformin has shown no benefit for histologic improvement in non-diabetic patients with NAFLD.^{1,3,5,7}

Conclusion

Nonalcoholic fatty liver disease (NAFLD) is common in the elderly, in whom it has a more severe course due to worse intrahepatic and extrahepatic manifestations.^{1,2} Geriatric patients with NAFLD are at increased risk for developing Nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma, and cardiovascular and metabolic complications.¹ Since liver function tests can be normal in NASH,⁴ the diagnosis of NASH is usually delayed until cirrhosis is already present. In patients with metabolic syndrome presenting with altered mental status, clinicians should consider the possibility of undiagnosed NASH in the differential diagnosis, and order an ammonia level as part of the workup. Non-invasive tests are available to help the clinician make a diagnosis.

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