APRI and FIB-4 - a simple predictor of fibrosis in NAFLD/NASH at the primary care level - A case report

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Abstract

The importance of simple investigations like platelets, AST (Aspartate aminotransferase) and ALT (Alanine aminotransferase) when managing patients with NAFLD (non-alcoholic fatty liver disease) and NASH (non-alcoholic steatohepatitis) in primary care should not be overlooked, as this would predict the progression to fibrosis and cirrhosis. A better control of diabetes, metabolic syndrome and the reduction of bodyweight at an early stage when the APRI (AST to Platelet ratio index) and/or FIB-4 score is significant, would have delayed/aborted the progression to fibrosis and cirrhosis is highlighted by this case report. Physicians in primary care should be aware of the significance of low platelet count and high AST (a 'red flag') in a case of NAFLD and NASH, and should provide intense control of diabetes, obesity and metabolic syndrome followed by a referral to a gastroenterologist/hepatologist at an early stage.

Key words: Primary Care, General Practice, NASH, NAFLD, FIB-4, APRI, Red flag, low platelet, cirrhosis, primary prevention

Introduction

The incidence of NAFLD and NASH are rising globally [1] secondary to the increasing prevalence of obesity, metabolic syndrome and diabetes. A significant proportion of patients with NAFLD will progress to fibrosis and cirrhosis requiring liver transplantation [2].

Even though abdominal ultrasound (USG) has a good sensitivity and specificity for diagnosis, [3] a Fibroscan or Magnetic resonance (MR) elastography is required for the quantitative assessment of fibrosis and cirrhosis in a patient with NAFLD [4]. These investigations are expensive and may not be available in many of the health care services. Primary care physicians should be aware of the simple clinical predictors for fibrosis and cirrhosis in a patient with NASH as they are the first point of contact. A low platelet count and high AST resulting in significant APRI (AST to Platelet Ratio Index) [5] and FIB-4 (Fibrosis-4) [6] score in a patient with NAFLD should raise the alarm, and effective management of diabetes, metabolic syndrome and obesity should be provided at this stage to delay/prevent the progression to fibrosis and cirrhosis. A referral to the gastroenterologist/hepatologist should also be made at this stage for further management.

Case Report

A 42 year old gentleman presented to the health centre with a one month history of abdominal distension and a one week history of bilateral leg swelling. He had no history of decreased urine output, facial swelling, breathlessness on exertion, paroxysmal nocturnal dyspnoea, orthopnea, chest pain or palpitation. His appetite was normal. However, he had a recent weight gain of six kilograms over a period of one month. There was no history of hematemesis or bleeding per rectum. He has been a known diabetic for the past eight years with no history of hypertension. He does not smoke or consume alcohol. There was no history of intake of hepatotoxic drugs. He was also diagnosed as having NASH (based on history, examination, LFT, USG and blood investigations that ruled out aetiology for other chronic liver diseases) two years ago with no proper follow up or monitoring.

On physical examination he was found to be overweight (Weight 91 kg, BMI 29, Waist circumference 111 cm). His vitals were normal. He had bilateral parotid gland enlargement. There was also mild bilateral pitting pedal edema. There was no other evidence of chronic liver disease like spider nevi, palmar erythema, gynecomastia, testicular enlargement, Dupytren's contracture etc. There was no evidence of hepatic encephalopathy. Abdomen was slightly distended with mild free fluid as evidenced by shifting dullness. Liver and spleen were not palpable. Cardiovascular and respiratory system examination were normal.

Laboratory investigations done a month ago revealed Haemoglobin 12 g/dL (normal 13-17 g/dL), white cell count 2.9 x 10^3 /micro L (normal 4-10^3 /micro L), Platelet count 49 x 10^9/L (normal 150 to 400 x10^9/L). Peripheral smear revealed normocytic normochromic anaemia with mild anisocytosis, few ovalocytes and elliptocytes and occasional schistocytes, WBC count was reduced showing mild neutropenia and lymphopenia with few atypical lymphocytes. Marked thrombocytopenia was a striking feature.

Bilirubin was slightly raised - total bilirubin 35 micromol/L (normal 3.4 to 20.5 micromol/L), direct bilirubin 11.3 micromol/L (normal 0 to 8.6 micromol/L); Alanine aminotransferase was 26 U/L (normal 0-40 U/L) and AST 37 U/L (normal 0-37 U/L); Gamma glutamyl transferase was normal; Alkaline phosphatase was slightly raised; Albumin was slightly low at 34g/L (normal 35-50 g/L); HbA1c was 6.2%; Urinary Albumin-Creatinine ratio was normal; Hepatitis B and C serology were negative; Cholesterol was 3.38 mmol/L, LDL 1.92, HDL 1.19, TG 0.61. The calculated APRI score was 2.041, FIB-4 score was 6.22. An APRI score of >0.702 and FIB score of >1.19 is considered significant [9].

A review of the past investigations (via Electronic Medical Record) was done as part of diabetes and NASH workup which showed hepatomegaly with mild to moderate fatty infiltration with no coarse architecture of the liver, spleen and portal vein were normal and there was no ascites on USG (dated 3 years ago). His previous laboratory values dated 3 years ago showed a low platelet count (109 x 10^9/L), normal Hb and white cell count, and liver function tests showing mild elevation of liver enzymes (ALT 55 U/L, AST 52 U/L) and HBA1C of 8%. The calculated APRI score was 1.289 and FIB 4 score was 2.51. An APRI score of >0.702 and FIB score of >1.19 is considered significant [9].

Based on the present and past medical history and investigations, a provisional diagnosis of chronic liver disease with portal hypertension was made. As evident from clinical and biochemical parameters he was overweight and had metabolic syndrome. His diabetes, though controlled presently, was poorly controlled three years ago when the diagnosis of non-alcoholic fatty liver disease was first made.

Patient was asked to do further lab investigations like thyroid function test, serum calcium, ESR, a full LFT, Hepatitis B and C serology, alphafeto protein, ferritin, alpha 1 antitrypsin, autoantibodies (to rule out autoimmune hepatitis) and stool for occult blood. An ultrasound of the abdomen was also requested. An appointment with the Family Physician was booked after two weeks. However, the patient was admitted in the emergency department of the tertiary care hospital within a few days as he developed increasing abdominal distension and bilateral leg swelling. He was later followed up by the Internal Medicine and Gastroenterology departments in the next few months.

A repeat lab investigation showed Hb of 11.4 gm/dl, WBC 2.4 x 10^3/micro L, Platelet of 56 x 10^9/L (a picture of pancytopenia predominantly affecting the platelet series). A repeat liver function test showed total bilirubin of 32 micromol/L, direct bilirubin 10.4 micromol/L, albumin 33 g/L, ALT 23 U/L, AST 42 U/L, ALP 163 (normal 40-150 U/L). The APRI score was 2.027, FIB-4 score was 6.57. As mentioned previously both these scores are significant [9].

Hepatitis B and C hepatitis were ruled out, as well as other causes of Chronic Liver Disease (autoimmune hepatitis, alpha1 antitrypsin deficiency, Wilson's disease etc) with appropriate blood tests. Serum alphafeto protein was slightly raised (12 IU/ml. Normal 0-6 IU/ml). Ferritin and Serum protein electrophoresis were normal. PT was high at 20.3 seconds (normal 9.4 - 12.5 seconds) with an INR of 1.7. APPT was normal. An USG showed a liver size of 13.2 cm, coarse echotexture with irregular border, splenomegaly and minimal ascites-features consistent with Cirrhosis and Portal Hypertension. A therapeutic abdominal paracentesis done in the ED showed normal cytology, ascitic fluid albumin 5.6 gm/L with a SAAG (serum albumin to ascitic fluid albumin gradient) value of 28.4 gm/L which is consistent with portal HTN. MRI revealed a nodular liver with fibrotic changes and regenerating nodules, splenomegaly and no significant ascites, a picture consistent with Cirrhosis and portal hypertension. An upper GI endoscopy was also done which showed generalised gastritis and 2-3 small lower esophageal varices with no bleeding. Currently the patient is stable with Furosemide 40 mg, Carvedilol 6.25 mg, Spironolactone 50mg, Metformin 1g, Sitagliptin 100 mg and Rosuvastatin 10 mg.

Discussion

Non-alcoholic fatty liver disease (NAFLD) has a high prevalence globally due to its close relation with type 2 diabetes, obesity and metabolic syndrome [1, 2]. The prevalence of NAFLD is approximately 32% worldwide [10]. NAFLD is a spectrum of liver disease ranging from fatty liver to steatohepatitis, fibrosis and cirrhosis [11]. Liver fibrosis is associated with an increased risk of complications such as cirrhosis, hepatic failure (necessitating liver transplantation), hepatocellular carcinoma and even death. NAFLD is also closely associated with CVD which is the most common cause of mortality in these patients [12].

Abdominal ultrasonography is the most common imaging method for the assessment of NAFLD with a relatively high sensitivity and specificity. It is safe, low cost and accessible. However, the limitations of USG include operator variability and technical difficulty in assessing the liver due to abdominal obesity with which NAFLD is closely associated [13].

Fibroscan and MR elastography is a non-invasive and easy to use modality that can assess hepatic fat and liver stiffness with high accuracy. However, its use is limited due to the relatively high cost, non-availability in all health care services and technical difficulty in obese patients [4].

Liver biopsy, considered the gold standard for assessment and quantification of liver fibrosis, has its limitations due to the invasiveness of the procedure, potential for bleeding, sepsis and damage to the surrounding structures in addition to the fact that only a small volume of liver is assessed which cannot reflect the fibrotic changes in the entire liver. Another limitation is the fact that different parts of the liver may be at different stages of fibrosis and the biopsied sample may not reflect the true stage of fibrosis [14, 15].

On the other hand, a simple blood test that includes AST, ALT and platelets, from which useful parameters like APRI score [5] and FIB-4 score [6] are derived, can predict progression to fibrosis and cirrhosis at an early stage of NAFLD/NASH, thereby allowing early recognition of patients of NAFLD/NASH who are at a risk of fibrosis. Effective treatment of these patients (better control of Diabetes, Metabolic syndrome and Obesity) including lifestyle modification with particular emphasis on diet, exercise and weight loss, and early referral to a gastroenterologist/hepatologist will delay or abort the progression to severe fibrosis and cirrhosis with its potential complications [2].

Several studies have revealed a fairly good sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) for both APRI and FIB-4 [11, 15, 16, 17]. Sensitivity, specificity, PPV, NPV and DA of APRI at the 0.702 cut-off showed 84.1, 88.2, 66.1, 95.3 and 87.3% and FIB-4 at the 1.19 cut-off showed 97.7, 72.7, 49.4, 99.2 and 78% respectively [9].

APRI and FIB-4 can be calculated using the following formula [7, 8].

$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST ULN (upper limit of normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

$$\text{FIB} - 4 = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{ALT\ (U/L)}}$$

As evident from the review of past investigations, the low platelet count (109 x 10^9 /L, dated 3 years ago) with raised AST and ALT (52 U/L and 55 U/L respectively dated 3 years ago) with an APRI score of 1.28 and a FIB-4 score of 2.51, at a time when the USG showed only a moderate degree of fatty infiltration of the liver with no fibrosis should have alarmed the primary care physician that the patient was progressing to significant fibrosis and cirrhosis. A better control of his diabetes (HBA1C 8% dated 3 years ago), metabolic syndrome and reduction of bodyweight at that stage would have prevented/delayed the development of fibrosis and cirrhosis of liver. Additionally, the patient should have been referred to the gastroenterologist/ hepatologist at that stage when the APRI and FIB-score was significant for better assessment and management of NAFLD/NASH.

Conclusion

This case highlights the importance of simple blood investigations like platelet count and liver enzymes in a patient with NAFLD, particularly in a primary care setting where there is no access to a fibroscan and MR elastography. A low platelet count and high liver enzymes should not be overlooked as this is a predictor for fibrosis and cirrhosis. An intense medical treatment of diabetes, metabolic syndrome and obesity with particular emphasis on diet, exercise and optimization of weight, should be provided at this stage in the hope of delaying/aborting significant fibrosis and cirrhosis. A significant APRI and/or FIB-4 score should also prompt the primary care physician to refer the patient to a gastroenterologist/hepatologist.

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