Case Studies – Individuals

Non-alcoholic liver disease in an HGV driver

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Case history

A 43-year-old obese (BMI 38 kg/m²) heavy goods vehicle (HGV) driver with Type 2 diabetes recently visited the practice nurse during an annual diabetes assessment. His recent HbA_{1c} was 9.5% (DCCT) (80.3 mmol IFCC). His main complaint was an increasing feeling of fatigue. He has a strong family history of diabetes mellitus and premature death from cardiovascular disease. He currently takes Metformin 2.5 g/day. His sulphonylurea was stopped six months ago due to recurrent hypoglycaemic events. On routine blood tests, the abnormal findings were an isolated elevation in alanine aminotransferase (ALT) of 84 U/L and aspartate aminotransferase (AST) of 76 U/L. His albumin levels were 38 g/L, his platelet count was $315 \times 10^9/L$ and clotting studies were within normal limits. The case was brought to the Ealing multi-disciplinary group meeting to discuss the challenging issues.

Ways to think of the problem

What is the cause of the abnormalities in liver function in this patient?

Liver function tests (LFTs) describe a set of biochemical tests that commonly include alkaline phosphatase (ALP), ALT, AST and bilirubin. LFTs may also include prothrombin time, albumin and gamma-glutamyl transferase (GGT). The most sensitive way to monitor liver function, however, is by measuring its synthetic function – worsening synthetic function is reflected by a raised bilirubin, low albumin or a prolonged prothrombin time. LFTs are often routinely measured and hence abnormalities may be detected in asymptomatic patients.

After exclusion of viral hepatitis and alcohol-related liver disease, non-alcoholic fatty liver disease (NAFLD)

is the most common cause of chronically abnormal LFTs. In the United Kingdom, liver disease is the only major cause of death still increasing year on year with alcohol causing 50% of cases of liver cirrhosis. NAFLD, which affects approximately 20–30% of the UK population, describes a spectrum of histological characteristics beginning with simple steatosis, in turn leading to steatohepatitis, fibrosis and ultimately cirrhosis. Steatohepatitis in patients with no history of excess alcohol is termed non-alcoholic steatohepatitis (NASH). It is important to note that only 20% of patients with NAFLD have NASH, and that only 20% of patients with NASH progress to cirrhosis over 10 years. Nonetheless, because 80% of obese patients and 70% of patients with Type 2 diabetes have NAFLD, the incidence of cirrhosis from NASH is rising rapidly, and this condition is expected to become the leading reason for liver transplants in the next decade.

Serum ALT has commonly been used as a screening test for NAFLD; the degree of enzyme elevation is not marked. However, there are limitations to this test with regards to sensitivity and specificity, and there is no clear correlation between degree of enzyme elevation and the extent of hepatic damage. Therefore, LFTs can be normal in patients with NAFLD and even in patients with cirrhosis.¹

What investigations are necessary to make a diagnosis of NAFLD?

The exclusion of other causes of liver disease is a prerequisite in making the diagnosis of NAFLD. A careful history of alcohol intake, as well as a drug history (including over the counter and herbal remedies) and a family history of liver disease are vital. Although secondary causes of steatosis do exist (see Table 1), NAFLD should be suspected in the obese patient who has features of metabolic syndrome, in the absence of an alcohol history (i.e. <21 units/week

Table 1 Common secondary causes of fatty liver seen in primary care

Excessive alcohol
Hepatitis C (genotype 3)
Starvation
Medication (amiodarone, tamoxifen, methotrexate, corticosteroids)

for men and < 14 units/week for women). Although symptoms can include malaise, fatigue and right upper quadrant or diffuse abdominal discomfort, most patients, including some with advanced fibrosis, are asymptomatic.

In the absence of advanced disease, physical examination may be normal, with the most common abnormality being hepatomegaly. All patients presenting with deranged LFTs should undergo a non-invasive liver screen consisting of:

- hepatitis B & C serology;
- liver autoantibodies (anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, anti-liver–kidney microsomal antibody);
- serum electrophoresis;
- ferritin and transferrin saturation;
- α 1-antitrypsin; and
- in those aged under 40, copper studies.

Although there are no specific diagnostic blood tests for NAFLD, it is relatively common for patients with steatohepatitis, due to alcohol or NAFLD, to have elevated immunoglobulin (Ig)A levels.

Ultrasound is useful in confirming steatosis, assessing for evidence of macronodular cirrhosis and excluding biliary tract disease. Unfortunately, it cannot distinguish among simple fatty liver, NASH and fibrosis. Both computed tomography (CT) and magnetic resonance imaging (MRI) are more sensitive for the quantification of steatosis, but still cannot distinguish between the various stages in the NAFLD spectrum. Liver biopsy is the gold standard diagnostic investigation, and is the only accurate assessment tool that determines the extent of fibrosis in NASH and informs long-term prognosis. However, safety and cost limitations mean that liver biopsy is not a practical option in all patients. In larger secondary care centres throughout London, liver elastography (Fibroscan®) can now be used to detect fibrosis in NASH with a relatively high degree of sensitivity and specificity. However, the rate of measurement failure increases in patients with higher BMIs, and it is less accurate at determining the severity of fibrosis.

For the primary care setting, the NAFLD fibrosis scoring system (www.naflscore.com) has been developed using non-invasive blood parameters and

been validated to allow risk stratification in terms of likely fibrosis severity.² This score can be readily calculated by entering the patient's age, BMI, AST, ALT, platelets, albumin and the presence of diabetes or impaired fasting glucose into the online calculator – a recent large prospective UK study of primary care patients with NAFLD demonstrates that one half of these patients have a low fibrosis score, which has been shown to exclude advanced fibrosis with high accuracy and suggests these patients can be managed safely in a primary care setting.^{2,3}

What are the current therapies for NAFLD?

Weight reduction is the mainstay of treatment for NAFLD. Co-existing components of metabolic syndrome such as hypertension, hyperglycaemia and dyslipidaemia should be screened for and treated appropriately. If conventional weight loss programmes involving caloric restriction and increased physical activity do not work, the patient should be considered for bariatric surgery.

Further treatment options can be considered in a secondary care setting. The strong relationship between insulin resistance and NAFLD suggests that medicines traditionally reserved for patients with Type 2 diabetes may be beneficial in NAFLD. Trials involving thiazolidinediones have shown improvement in ALT and hepatic steatosis, even in those without overt diabetes, with pioglitazone also showing an improvement in the stage of fibrosis. Large, randomised controlled trials are lacking, but initial evidence supports the use of pioglitazone in the management of NAFLD. Metformin decreases hepatic lipogenesis, steatosis and inflammation. Although human studies involving metformin have mostly shown improvement in LFTs in NAFLD patients, these studies have been too small to assess improvement in histology.

Is it safe to use statins in this patient?

Patients with NAFLD may safely receive statins, and serious statin-induced liver injury is rare in clinical practice. This rare side effect is clearly outweighed by

the benefits in this cohort of patients with a high incidence of cardiovascular disease. All statins can cause an elevation in aminotransferases with an increased incidence at higher therapeutic doses; however, there is no evidence that mild ALT increases long-term hepatotoxicity. If an isolated transaminase increase of one to three times the upper limit is found, the statin can be continued. If there is an increase above this level or the patient exhibits signs or symptoms of hepatic dysfunction, other causes of liver disease should be excluded and consideration should be given to reducing the dose or discontinuing the statin.

How will you improve his glycaemic control?

This patient is obese and advice regarding lifestyle modifications and weight loss should be given. If an oral glucose-lowering drug is required, an SGLT2 inhibitor (e.g., Dapagliflozin) or a gliptin (e.g., Sitagliptin) would be helpful. Pioglitazone is also safe for use in patients with NAFLD, but higher doses may be associated with fluid retention, fractures and an increase risk of developing bladder carcinoma. A GLP-1 analogue (e.g., Byetta or Liraglutide) is also indicated according to NICE guidance. Because of the patient's occupation as an HGV driver, insulin therapy will be reserved as a last resort.

Which patients should be referred to secondary care for further assessment and management?

All patients with symptoms and signs of chronic liver disease warrant referral, as do those with evidence of synthetic hepatic dysfunction (raised bilirubin, low albumin or prolonged prothrombin time). Platelets are a sensitive marker for portal hypertension and a chronic thrombocytopaenia in the presence of deranged LFTs indicates the need for further investigation and referred to a specialist.

Where additional aetiologies beyond NASH are suspected as a cause for deranged LFTs, patients should

be referred for assessment of compound liver disease. Patients whose deranged LFTs are not responding to lifestyle and cardiovascular risk factor controls as described above, should be referred to a specialist. Finally, patients at risk of significant fibrosis as determined by the NAFLD fibrosis score should be further assessed by the local gastroenterology or hepatology service. The NAFLD score for this patient is -1.089 , which puts him in the low-risk category (see www.naflscore.com). In addition, his platelet, albumin and clotting studies were normal – therefore, he does not currently need to be referred to a specialist.

The patient we describe in our case history was informed that he has non-alcoholic fatty liver disease. In addition, he was given lifestyle and dietary advice. The long term plan was to monitor his liver function tests annually. To improve his glycaemic control, he was prescribed dapagliflozin; three months later, his HbA_{1c} had improved from 9.5% to 8.3% DCCT (67 mmol/mol IFCC) and his weight had dropped by 3 kg.

REFERENCES

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