Managing non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease is the most common cause of raised liver enzymes in the developed world.[1] It is a spectrum of disease, ranging from benign simple fatty liver disease (steatosis) to non-alcoholic steatohepatitis. Non-alcoholic fatty liver disease is associated with fibrosis and may eventually progress to cirrhosis.[2] It is histologically indistinguishable from alcohol-related liver disease and also accounts for a substantial number of cases that are misdiagnosed as cryptogenic cirrhosis.[3] It is an increasingly recognised form of liver disease and affects all age groups, including older people. We discuss the causes, clinical features, diagnosis, and management of non-alcoholic fatty liver disease and steatohepatitis.

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Non-alcoholic fatty liver disease affects 20% of the adult population, 2% of whom have the most serious form—non-alcoholic steatohepatitis,[2,4] and prevalence increases with age. Although no epidemiological studies have looked specifically at older people, one study noted that 46% of octogenarians admitted to hospital had the disease.[5] Many think that the incidence in the elderly population correlates with that seen in groups with other associated risk factors, but the prevalence is actually higher among older people because of increased prevalence of risk factors, patients living longer with the condition, and a considerable number of cases of burnt-out cryptogenic cirrhosis might actually be non-alcoholic steatohepatitis.

Ludwig and co-workers first described non-alcoholic steatohepatitis in 1980 at the Mayo Clinic.[6] It occurs worldwide and affects both sexes at all ages, but is more common in females.[7] According to one study, the condition affects approximately 50% of people who are morbidly obese, 20% of obese individuals, and a very small percentage of people with a low body-mass index.[8] It has also been reported in children, especially those who are obese.

The condition is poorly understood by health-care professionals and its causes are multifactorial. It is partly related to insulin resistance, but whether insulin resistance is a cause or a consequence is not clear. Metabolic syndrome, a culmination of adult-onset diabetes, abdominal obesity, hypertension, and hyperlipidaemia, is strongly associated with progression of non-alcoholic fatty liver disease. Hence, it is sometimes called the disease of the affluent. A two-hit theory[9] has been widely accepted: this theory suggests that the first hit is insulin resistance, leading to hepatic steatosis, and the second hit is oxidative stress in the presence of insulin resistance, culminating in steatohepatitis. Non-alcoholic fatty liver disease is classified as primary or secondary depending on its pathogenesis (box).[9]

Diagnosis

Non-alcoholic fatty liver disease is asymptomatic in the early stages, but can have a non-specific presentation such as fatigue and malaise. Occasionally right upper quadrant pain can be the initial manifestation of hepatomegaly, which is seen in approximately 75% of patients,[4] but features of severe liver disease are not very common. Cirrhosis occurs in later stages, especially in older age groups. Abnormal blood testing of liver markers in an asymptomatic individual can point to disease.

Alcohol is excluded as a cause of liver damage if the patient has an alcohol intake of less than 20 g (2 units) per day.[10]

Risk factors and indicators of non-alcoholic fatty liver disease[2]

- Age older than 45 years
- Body-mass index more than 30 kg/m^2
- Type-2 diabetes mellitus or elevated fasting glucose
- Raised alanine transaminase
- Raised aspartate transaminase

Non-alcoholic fatty liver disease is suspected in individuals with abnormal liver-function tests after exclusion of other causes of chronic liver disease. Other test results, such as for bilirubin and alkaline phosphatase, can be normal. Plasma ferritin and transferrin saturation may be increased. Both low-density-lipoprotein cholesterol and triglycerides may be raised. The treating physician should test for hepatitis B and C, anti-nuclear antibodies, anti-smooth muscle antibodies, caeruloplasmin, and alpha-1 antitrypsin to exclude other causes of liver disease.

An ultrasound scan, non-contrast CT, or MRI of the liver will show fatty infiltration. A CT scan has the added advantage of measuring the degree of fat, and can also demonstrate evidence of cirrhosis and varices if these are present.

The diagnosis of non-alcoholic fatty liver disease can be confirmed only by liver biopsy and, therefore, biopsy is the gold-standard test. At times, justifying a liver biopsy on an asymptomatic patient can be difficult. The risks of the procedure must be balanced against the benefits of additional information and its effect on treatment.

Prognosis

The natural history is commonly benign; although in 5–15% of cases, the disease may progress to fibrosis leading to cirrhosis, portal hypertension, and eventually decompensated liver disease.[2,4] The risk of hepatocellular carcinoma is increased in those in who have cirrhosis.

Box : Causes and contributing factors

Primary disease

- Obesity
- Glucose intolerance
- Hypertension,
- Hypertriglyceridaemia,
- Low concentrations of high-density-lipoprotein cholesterol

Secondary disease

- Drugs—corticosteroids, tamoxifen, diltiazem, aspirin, highly active antiretroviral therapy, valproate, amiodarone, methotrexate,
- Total parental nutrition
- Hepatitis C
- HIV
- Metabolic disorders—hypobetalipoproteinaemia, lipodystrophy, hypopituitarism, hypothalamic obesity, Weber-Christian syndrome, acute fatty liver of pregnancy, Reyes syndrome, Wilson's disease, Zellweger's syndrome, mitochondriopathies
- Ogranic solvents
- Mushroom toxins
- Rapid weight loss
- Intestinal bypass surgery
- Starvation

Management

No treatment has been proven to be curative. Eliminating or modifying an offending agent should be tried at first. Management is primarily aimed at reducing the patient's weight and increasing exercise.[11]

The role of insulin sensitising agents, such as metformin[12] and

Key points

- Non-alcoholic fatty liver disease is asymptomatic in most cases
- Obesity, diabetes mellitus, hypertension, and hyperlipidaemia are frequently associated features
- Raised alanine transaminase is the most common abnormality
- Liver biopsy is rarely needed
- Long-term prognosis is generally benign
- Graduated weight loss is the best available treatment

thiazolidinediones,[13] is debatable. These drugs may improve liver biochemistry, but their effect on fibrosis is not known. Neither ursodeoxycholic acid nor antioxidants (eg, vitamin E13) are beneficial.[14] Further trials are needed to assess the efficacy of other agents.

Correcting cholesterol, triglycerides and controlling diabetes is appropriate in most patients. The management of these areas has been shown to significantly ameliorate liver function in patients with non-alcoholic fatty liver disease.[8] Liver transplantation is appropriate for patients with end-stage liver disease, but disease can recur in the grafted organ.[4]

No data regarding the aggressive treatment of the condition in elderly people are available, but the use of bariatric surgery, aggressive exercise programmes, and liver transplantation may be limited in this age group. For example, transplantation for any liver disease in people aged 60 or older is associated with a much poorer outcome than in younger age groups. However, this does not mean that these options cannot be used in older people—in fact, a transplant is the only option for patients with complicated, end-stage disease.

Lifestyle modifications (if appropriate), weight loss, correction of dyslipidaemia, and achieving optimum blood-glucose concentrations in diabetic patients are beneficial. Treatment of hepatoma or liver transplantation may not be appropriate in the presence of significant comorbidity or, to a lesser extent, the patient's age. In these situations, each patient needs to be assessed on an individual basis and discussion with the local liver unit is essential.

Conclusion

Non-alcoholic fatty liver disease is a common condition related to insulin resistance, obesity, and glucose intolerance. The course is generally benign, but the public-health burden may be considerable. The disease can progress from fatty liver disease to steatohepatitis, and then eventually to cirrhosis with associated complications including portal hypertension, hepatic failure, variceal bleed, and hepatoma.[8] Both hospital doctors and general practitioners should be aware of this condition. Further research into disease pathogenesis will help to identify the patients at greatest risk of progressive disease.

We have no conflict of interest.

References

1. Ekstedt M, Franzén LE Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006, **44**: 865–73
2. Collier, Jane. Non-alcoholic fatty liver disease. *Medicine* 2007; **35**: 86–88
3. Caldwell SH, Crespo DM. The spectrum expanded: cryptogenic cirrhosis and the natural history of non-alcoholic fatty liver disease. *J Hepatol 2004*; **40**: 578–84
4. Burke A, Lucey M. Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and orthotopic liver transplantation. *Am J Transplant* 2004; **4**: 686–93
5. Adams L, Lindor K. Non-alcoholic fatty liver disease. *Ann Epidemiol* 2007; **17**; 863–69
6. Ludwig J, Viggiano TR, McGill DB, et al. Non-alcoholic steato-hepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; **55**: 434–38
7. Agarwal N, Sharma BC. Insulin resistance and clinical aspects of non-alcoholic steatohepatitis (NASH). *Hepatol Res* 2005; **33**: 92–96
8. McAvoy NC, Lockman A, Hayes PC. Non-alcoholic fatty liver disease (NAFLD): an overview. *J R Coll Physicians Edin* 2007; **37**: 9–17
9. Day CP, James OFW. Steato-hepatitis: a tale of two hits? *Gastroenterology* 1998; **114**: 842–45
10. Neuschwander-Tetri BA, Caldwell SH. Non-alcoholic steato-hepatitis: a summary of an AASLD single topic conference. *Hepatology* 2003; **37**: 1202–19
11. Ueno T, Sugawara H Sujaku K, et al. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol* 1997; **27**: 103–07
12. Marchesini G, Brizi M, Bianchi G, et al. Metformin in non-alcoholic hepatitis. *Lancet* 2001; **358**: 893–94
13. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, et al. Interim results of a pilot study demonstrating the early effects of the PPAR-gamma ligand rosiglitazone on insulin sensitivity, aminotransferases, hepatic steatosis and body weight in patients with non-alcoholic steatohepatitis. *J Hepatol* 2003; **38**: 434–40
14. Yakaryilmaz F, Guliter S, Ozenirler S, Akyol G. Vitamin E treatment for patients with non-alcoholic steatohepatitis: Results of a pilot study. *J Hepatol* 2003; **38**(suppl 2): 203