Liver Disease

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Non-alcoholic fatty liver disease: current concepts and management strategies

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Non-alcoholic fatty liver disease (NAFLD), the liver manifestation of the metabolic syndrome, is now considered to be the commonest liver problem in the western world. This apparent 'epidemic', coupled with an accumulating body of evidence that a significant proportion of patients with NAFLD can progress to cirrhosis, liver failure and hepatocellular carcinoma (HCC), has – perhaps not surprisingly – led to an exponential growth in clinical and basic studies investigating all aspects of this hitherto largely ignored disease. The result is a vast increase in understanding of the natural history, clinical features and pathophysiology of NAFLD over the last five years which has now begun to inform the development of rational management strategies.

Epidemiology

The reported prevalence of NAFLD is 10–51%, with studies differing in the type of population studied and the methods used for diagnosis. For unselected western populations, a consensus figure of 20–30% has emerged from several recent well conducted North American and European studies that have used ultrasound or magnetic resonance imaging to diagnose hepatic steatosis.[1,2] The prevalence is higher for patients with risk factors for NAFLD: for example, in obese individuals it has been reported as over 75%.[3] No large studies have examined the prevalence of NAFLD in patients with type 2 diabetes mellitus (T2DM). Importantly, a recent Italian study has demonstrated that the prevalence of NAFLD is the same in patients with normal liver blood tests as in patients with 'suspected' liver disease on the basis of a raised serum alanine aminotransferase (ALT), gamma-glutamyl transferase, hepatitis B surface antigen or HCV-RNA positivity.[1] Based on figures from selected case series, the prevalence of non-alcoholic steatohepatitis (NASH) in the general population of western countries is considered to be 2–3%.[4]

Natural history

In marked contrast to patients with alcoholic steatohepatitis, the short-term prognosis of patients with NAFLD is largely excellent. Information from large-scale, prospective studies examining the natural history of NAFLD is currently lacking, but the available data suggest their long-term prognosis depends critically on the histological stage of disease at presentation (Fig 1).[5] Patients with simple steatosis have a relatively benign 'liver' prognosis; their risk of developing clinical evidence of cirrhosis over 15–20 years is 1–2%. Patients with NASH and fibrosis can progress to cirrhosis, defined histologically or clinically, with the risk varying from 0% at five years to 12% over eight years.[6,7] NAFLD almost certainly accounts for the vast majority of cases of cryptogenic cirrhosis, with two studies reporting that the prevalence of obesity and diabetes in these patients is over 70%.

Once cirrhosis develops, patients are at high risk of developing hepatic decompensation and of dying from a liver-related cause, including HCC.[8,9] In a study of 27 patients with obesity-related cirrhosis, 33% died a 'liver' death and 25% developed HCC over a median 2.2 year follow-up.[8] The risk of HCC in NAFLD-related cirrhosis appears to be similar to the risk associated with alcohol and HCV-related cirrhosis, intermediate between cirrhosis due to autoimmune diseases and chronic hepatitis B infection.[10] This offers at least one plausible explanation for the recently reported associations between the risk of liver cancer, body mass index (BMI) and the presence of T2DM.[11,12]

Pathology

Hepatocellular steatosis is the hallmark of NAFLD; it is more commonly macrovesicular, with a single large fat droplet displacing the nucleus or with smaller well-defined intracytoplasmic droplets.[13] Until recently there was no widely accepted definition of what constitutes an 'abnormal' amount of steatosis or of the features required for a diagnosis of NASH. The National Institutes of Health NAFLD Clinical Research Network has recently published a validated histological scoring system that addresses the full spectrum of lesions of NAFLD. An NAFLD activity score is proposed for use in clinical trials.[14] Importantly, in common with other liver diseases, the histological lesions of NASH are unevenly distributed throughout the liver, with so-called 'sampling error' potentially resulting in substantial staging inaccuracies.[15]

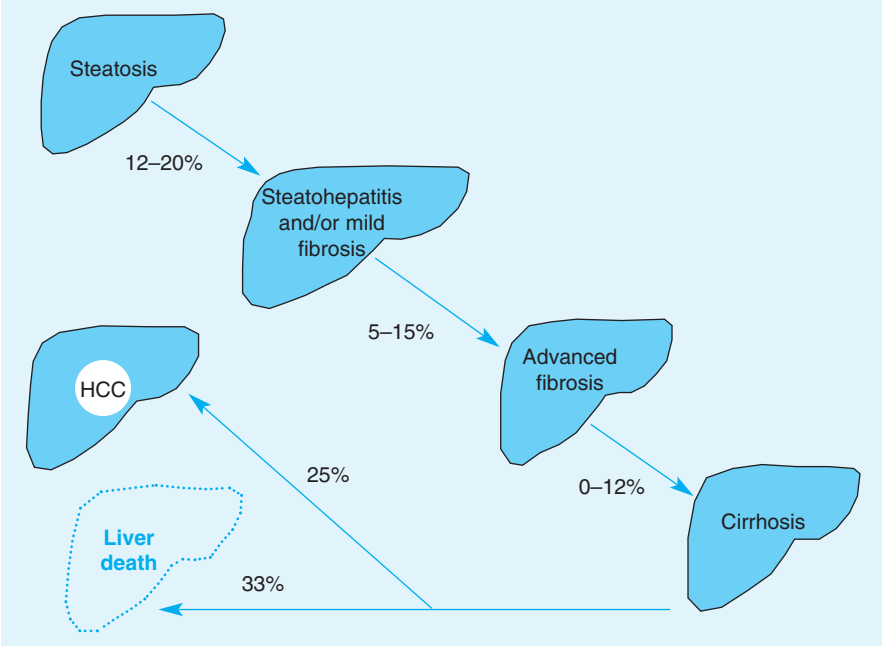

Fig 1. Natural history of non-alcoholic fatty liver disease. Follow-up ranged from 1 to 15 years in the different studies from which the data are drawn (advanced fibrosis = bridging fibrosis or cirrhosis; HCC = hepatocellular carcinoma).

Investigation of patients with suspected NAFLD

The key issue to consider when devising a protocol for the investigation of patients with suspected NAFLD is which (if any) patients warrant a liver biopsy. The first potential justification is that it helps to establish a diagnosis. In a patient presenting with abnormal liver function tests (LFTs), in association with the classical risk factors for NAFLD (obesity and T2DM) and an ultrasound consistent with steatosis, the diagnosis of NAFLD can be made with relative confidence without a liver biopsy after the other common causes of abnormal LFTs have been excluded. This is done by careful history taking (for alcohol intake and hepatotoxic drugs) and a standard liver 'screen', including serological markers for hepatitis B and C infection, autoantibodies, serum ferritin, caeruloplasmin and α-1 antitrypsin phenotype. It has been reported that more than two-thirds of patients presenting with unexplained abnormal liver blood tests will have NAFLD;[16] it seems likely to be even higher in patients with risk factors for NAFLD. In the absence of evidence to the contrary,[17] it appears reasonable to suggest that a weekly alcohol intake at or below currently recommended 'sensible' limits (21 units for men, 14 for women) is compatible with a diagnosis of NAFLD.

The main justification for performing a liver biopsy in patients with suspected NAFLD is that it will influence patient management in view of the different prognoses of the disease stages referred to above. For patients with simple steatosis, the commonly associated conditions should be sought and treated appropriately; in view of their largely benign prognosis, these patients should probably be discharged back to their primary care physician. In contrast, patients with NASH and fibrosis, with an increased propensity for disease progression, require long-term follow-up. Patients with advanced disease (bridging fibrosis or cirrhosis) should be entered into appropriate surveillance programmes for oesophageal varices and HCC. It is likely that in the next few years these more advanced patients will be candidates for a number of 'second-line' therapies currently being evaluated in large randomised clinical trials (RCTs).

Non-invasive markers of NAFLD stage

Given the large number of patients currently presenting with suspected NAFLD, it is impractical to perform a liver biopsy on them all. Currently available imaging modalities are incapable of differentiating patients with steatosis from those with NASH and fibrosis,[18] although in future newer imaging techniques, such as measurement of liver stiffness, may possess this capability.[19] Of more immediate utility, several studies have identified a number of independent clinical and laboratory predictors of advanced fibrosis in patients with NAFLD. Those currently considered to be the best predictors of advanced disease are:[20]

- older age (>45 years)
- increasing obesity (BMI >30 kg/m^2)
- diagnosis of T2DM (or raised fasting blood glucose), and
- aspartate aminotransferase/ALT ratio >1.

It would seem reasonable to restrict liver biopsy to patients with at least some, if not all, of these factors. There have been few studies of the ability of serum fibrosis markers to predict NAFLD stage, though promising results from studies in other liver diseases[21,22] suggest that they may be included in predictive algorithms for NAFLD staging in the not too distant future.

Pathogenesis of NAFLD

Understanding of the pathogenesis of NAFLD has increased dramatically over the past five years,[23,24] with studies in both humans and animal models of disease now providing the rationale for the development of treatment strategies. A detailed review of the pathogenesis of inflammation and fibrosis in NAFLD, outside the scope of this article, is available elsewhere.[23,24] A brief discussion of the important and recently emerging principles is pertinent to understand the basis for current and emerging therapies.

Inflammation

An increased supply of free fatty acids (FFA) to the liver, due to obesity and the

associated adipose tissue insulin resistance, appears to be the key factor for the development of inflammation. This extrahepatic insulin resistance may arise, at least in part, as a result of infiltration by macrophages of adipose tissue in obesity, releasing cytokines capable of impairing insulin signalling (TNFα, interleukin (IL)-6, IL-1β).[25] Once taken up by the liver, as well as being stored as triglyceride and oxidised, FFA activate the transcription factor NF-κB which functions as the 'master regulator' of pro-inflammatory cytokine, chemokine and adhesion molecule gene transcription.[26] The subsequent release of cytokines from hepatocytes, in particular TNFα, activates classical inflammatory cells including Kupffer cells;[27] these produce more cytokines capable of initiating hepatocyte injury by necrosis/apoptosis in conjunction with oxidative stress arising as a result of increased FFA oxidation. These cytokines also lead to hepatic insulin resistance, contributing to increased hepatic FFA oxidation and possibly to extrahepatic insulin resistance in muscle and adipose tissue.[27] Some evidence suggests that, as in alcoholic liver disease, gut-derived endotoxin my also play a role in Kupffer cell activation in NAFLD. Obesity and T2DM have long been associated with an increased frequency of bacterial overgrowth. The reduced production of the anti-inflammatory cytokine adiponectin by adipocytes in obesity may also contribute to the development of hepatic inflammation.[28]

Fibrosis

The mechanisms of inflammation and hepatocyte injury described above will lead to the activation of hepatic stellate cells (HSC) and deposition of scar tissue as part of the normal 'healing' response. In addition, an increasing body of evidence supports a role for non-necro-inflammatory mediators related to obesity and insulin resistance. HSC-activating, pro-fibrogenic roles have been demonstrated for leptin,[29] angiotensin II[30] and norepinephrine,[31] all of which are secreted by adipose tissue and are raised in the serum of obese patients. Furthermore, a direct fibrogenic role for insulin resistance-associated hyperglycaemia and hyperinsulinaemia has been suggested by studies showing that synthesis of the fibrogenic growth factor, connective tissue growth factor, by HSC is upregulated by glucose and insulin.[32] The reduced production of adiponectin associated with obesity may also contribute to the development of liver fibrosis since it appears to exert potent antifibrotic as well as anti-inflammatory effects.[33]

Management

To date, there are no published large RCTs of therapies for NAFLD on which to base definitive treatment recommendations. Encouraging results from pilot studies of several treatment modalities have been reported over the last few years and many are now being tested in large RCTs. Until results from these trials become available, it seems sensible to direct management strategies at the associated features of the metabolic syndrome: obesity, insulin resistance, dyslipidaemia and hypertension. These strategies will undoubtedly reduce mortality from cardiovascular disease and may also improve the underlying liver disease. It seems reasonable to advise patients to drink alcohol within currently recommended 'sensible' limits; the only study on this issue reported that 'light' to 'moderate' alcohol intake reduces the risk of steatosis and NASH in morbidly obese patients undergoing obesity surgery,[17] possibly by reducing insulin resistance and the risk of T2DM.[34]

The metabolic syndrome

Most patients with NAFLD will have some, if not all, features of the metabolic syndrome,[35] the most recent definition of which has abdominal obesity as the central feature (waist circumference for Caucasoids >94 cm in men, >80 cm in women, with ethnic-specific values for other groups), together with two or more of the following:

- hypertension (≥130/85 mmHg or on treatment)
- abnormal glucose tolerance (fasting blood glucose ≥5.6 mmol/l or known T2DM)
- hypertriglyceridaemia (>1.7 mmol/l or fibrate treated), and
- low high-density lipoprotein cholesterol (<0.9 mmol/l in men, <1.1 mmol/l in women).[36]

Patients with this syndrome have an increased risk of cardiovascular death[37] so require treatment regardless of the severity of any associated NAFLD. First-line management consists of

Key Points

Non-alcoholic fatty liver disease (NAFLD) is the liver manifestation of the metabolic syndrome and the commonest liver disorder in the western world

NAFLD can progress to cirrhosis and hepatocellular cancer

Older age, glucose intolerance, increasing body mass index and an aspartate aminotransferase/alanine aminotransferase ratio greater than one predicts the presence of advanced fibrosis

Inflammation in NAFLD results from the activation of NF-κB by an increased supply of free fatty acids to the liver

Cytokines secreted by adipose tissue (adipocytokines) may contribute to the development of liver fibrosis in obesity

Treating the components of the associated metabolic syndrome is the main therapeutic strategy in NAFLD

Metformin and gastric banding surgery have been shown to improve liver histology in patients with NAFLD

KEY WORDS: fatty liver, hyperlipidaemia, metabolic syndrome, obesity, steatosis, type 2 diabetes mellitus

lifestyle intervention, with weight loss, increased exercise and smoking cessation as the primary goals. If the individual components of the syndrome persist, they should be treated according to conventional guidelines, since large RCTs have shown that treatment of T2DM, hypertension and dyslipidaemia results in significant mortality reduction.

Direct evidence from large RCTs is largely lacking but, based on the pathogenic mechanisms discussed above, there are good reasons to believe that treatment strategies directed at components of the metabolic syndrome may have beneficial effects on the liver in patients with NAFLD. Indeed, the evidence is probably already sufficient for the choice of therapy for hypertension, T2DM and dyslipidaemia to be influenced by the severity of any coexisting NAFLD and the perceived or established beneficial hepatic effects of the different treatment modalities.

Associated obesity

There is a sound theoretical basis for believing that strategies aimed at achieving and maintaining weight reduction in patients with NAFLD will improve hepatic histology since this will reduce hepatic FFA supply and the levels of profibrotic adipocytokines while increasing the production of the anti-inflammatory, antifibrotic adipocytokine, adiponectin.

Diet and exercise. Most studies using diet to achieve weight loss relied on simple calorie restriction with none examining specific diets. This may be an area for future study since both the saturated fat content of the diet and the fibre intake are known to influence insulin resistance and a diet high in saturated fat appears to be a risk factor for NASH in obese individuals.[38] The value of exercise in achieving and maintaining weight loss is now well established. The only controlled study of weight loss that has achieved an improvement in histology in treated patients (only steatosis was significant) combined three months of increased exercise with moderate calorie restriction.[39]

Pharmacological agents. Encouraging results have been reported from pilot studies of the pancreatic and gastric lipase inhibitor orlistat[40] and the centrally acting appetite suppressant sibutramine in patients with NASH. Data from currently ongoing large RCTs are awaited with interest.

Surgery. Three surgical procedures are currently used for the treatment of obesity. The first, biliopancreatic diversion, appears to be associated with a significant risk of liver failure and worsening fibrosis; it should be avoided in patients with NAFLD.[41] Much better results have been reported for gastric bypass and gastric banding surgery. Dixon *et al*[42] recently reported the effect of adjustable gastric banding, surgery on 36 patients with NASH. This procedure, which acts by inducing satiety and restricting food intake without affecting intestinal absorption, led to a decrease in BMI from 47 kg/m^2 to 34 kg/m^2 in 26 months and a significant improvement in steatosis, necroinflammation and fibrosis.

Associated diabetes mellitus/insulin resistance

Reports that insulin resistance is a universal finding in patients with NASH, coupled with the fact that it is undoubtedly a key mechanism of both inflammation and fibrosis,[43] have led to several pilot studies of metformin and other insulin-sensitising agents in NAFLD patients with and without diabetes. There is, as yet, no direct evidence that the use of insulin or sulphonylureas has any adverse effect on the liver of diabetic patients, but the putative role of insulin in the pathogenesis of fibrosis in NAFLD suggests that these agents should be avoided if glycaemic control can be achieved by other means.

Metformin. Initial pilot studies of metformin in diabetic and non-diabetic patients with NAFLD were contradictory in terms of sustained improvements in liver biochemistry, but the largest study performed so far been more encouraging. In an open label, randomised trial, non-diabetic NAFLD patients were treated with either metformin (2 g/day, n = 55) or vitamin E (800 IU/day, n = 28) for 12 months or by a prescriptive, weight-reducing diet (n = 27). Metformin treatment was associated with higher rates of aminotransferase normalisation and a significant decrease in liver fat ($p = 0.0004$), necroinflammation and fibrosis ($p = 0.012$ for both).[44]

Thiazolidinediones, a new class of antidiabetic drugs that act as agonists for peroxisome proliferator activated receptor γ (PPARγ), improve insulin sensitivity, at least in part, via antisteatotic effects in liver and muscle, which may in turn result from an increase in adiponectin secretion by adipocytes. This latter effect may also account for the antifibrotic effects of thiazolidinediones in animal models of fibrosis.[45] Pilot studies of the second-generation thiazolidinediones, pioglitazone and rosiglitazone, showed improvements in insulin sensitivity and liver biochemistry and histology.[46,47] Several on-going large RCTs were based on these findings.

Associated lipid abnormalities

Hypertriglyceridaemia is present in 20–80% of patients with NAFLD. As with weight loss and insulin sensitisers, there is good scientific rationale supporting the use of fibrates (the conventional triglyceride-lowering agents) in patients with NAFLD. Fibrates are agonists for PPARα receptors, transcription factors that upregulate the transcription of genes encoding a variety of proteins that would be expected to reduce the hepatic concentration of FFA. Unfortunately, in the only controlled study with histological follow-up, one year of clofibrate therapy had no effect on liver biochemistry or histology.[48]

There is no rationale for the use of statins in NAFLD, but they should be prescribed for the 'conventional' indications which include T2DM regardless of cholesterol concentration. Importantly, there is no evidence that patients with NAFLD are more likely to suffer from statin-induced idiosyncratic hepatotoxicity than patients with normal livers.[49]

Associated hypertension

No studies have specifically examined the effect of different antihypertensive agents on the livers of hypertensive patients with NAFLD. Recent evidence that angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors are antifibrotic in animal models of hepatic fibrosis[50] suggests they are worth examining in clinical trials. Supportive pilot data have recently been reported.[51]

Liver-directed therapies

Based on an increased understanding of mechanisms of progressive disease, investigators have recently begun to examine therapies for patients with NASH not directed at components of the metabolic syndrome.

Antioxidants. Several pilot studies of agents whose potential beneficial effects may be related to their anti-oxidant effects have been encouraging. These include probucol,[52] betaine[53] and vitamin E (α-tocopherol).[54] However, a recent RCT of vitamins E and C combined in patients with NASH found no difference in the proportion of patients with an improvement in their fibrosis score between the drug and placebo groups.[55]

Anticytokine therapy. Beneficial effects of anticytokine (TNFα) strategies have been reported in animal models of NASH. The first pilot study in humans has recently reported an improvement in aminotransferase levels.[56] Given the emerging importance of pro-inflammatory cytokines in both liver pathology and insulin resistance in obesity, it seems likely that cytokines and their regulatory molecules, including NF-κB, will become major therapeutic targets in both NAFLD and T2DM in the near future.[24,57]

Ursodeoxycholic acid. A recent, large, placebo-controlled RCT in patients with NASH has shown no benefit of ursodeoxycholic acid, 13–15 mg/kg/day, on histology after two years' treatment.[58]

Liver transplantation

Patients with NAFLD who progress to decompensated cirrhosis or develop HCC are candidates for liver transplantation. Unsurprisingly, steatosis recurs in the majority of patients by four years, with 50% developing recurrent NASH and fibrosis. Cases of recurrent cirrhosis have also been reported.[59,60] Risk factors for recurrence are:

- the presence of insulin resistance/T2DM pre- and post-transplantation
- weight gain post-transplantation
- cumulative steroid dose.[58]

These factors clearly suggest several strategies aimed at reducing the frequency of disease recurrence in a group of patients who seem likely to contribute increasing numbers to transplant programmes in the future.

Conclusions

At present there is no established therapy for NAFLD based on evidence from large RCTs. Treatment for all patients, whatever the severity of their disease, should therefore be directed at the associated features of the metabolic syndrome; this will reduce morbidity and mortality and may also be beneficial to the liver. Patients with risk factors for advanced NAFLD should probably undergo liver biopsy to determine their disease stage. Those with advanced fibrotic disease should be followed up and entered into surveillance programmes for varices and HCC. While awaiting the results of large RCTs based on several encouraging pilot studies, consideration should be given to offering gastric banding surgery to morbidly obese patients with progressive NAFLD and metformin to less obese patients with more than simple steatosis.

The recent elucidation of the mechanisms linking hepatic lipid overload to inflammation, fibrosis and insulin resistance[24] suggests a variety of novel targets worth testing in animal models of NAFLD, and hopefully subsequently in pilot studies in humans.

An overall management strategy for patients presenting with suspected NAFLD is suggested in Fig 2.

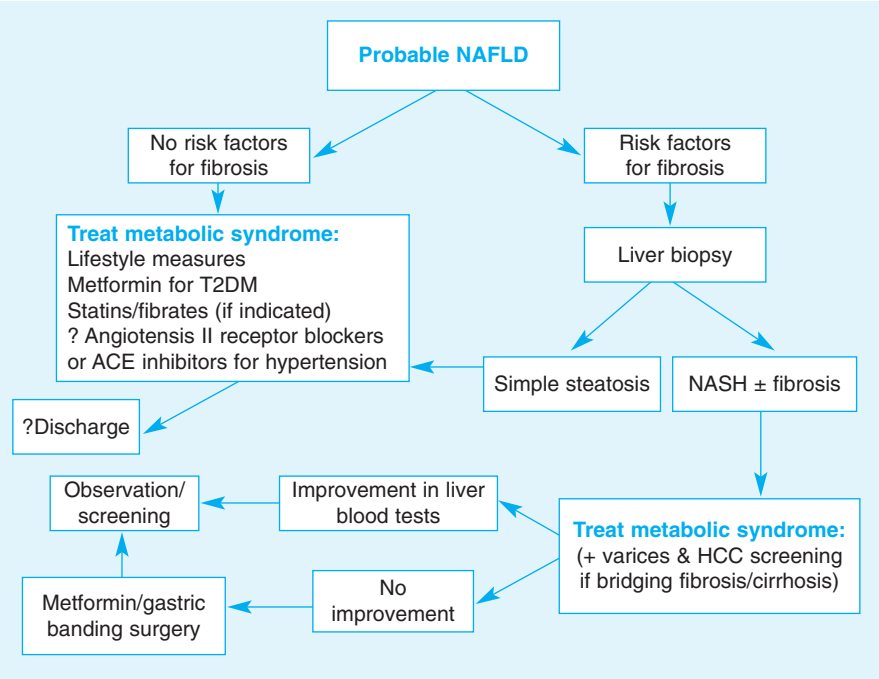

Fig 2. Management strategy for patients presenting with suspected non-alcoholic fatty liver disease (NAFLD). They are assumed to have had alternative causes of abnormal liver blood tests excluded by history (for alcohol excess and hepatotoxic drugs) and serology (for autoimmune disease and viral hepatitis), with steatosis detected on abdominal ultrasound (ACE = angiotensin converting enzyme, HCC = hepatocellular carcinoma, NASH = non-alcoholic steatohepatitis, T2DM = type 2 diabetes mellitus).

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Autoimmune hepatitis

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Autoimmune hepatitis (AIH) is a chronic inflammatory disorder of the liver associated with hypergammaglobulinaemia and the occurrence of autoantibodies.[1,2] It was the first liver disease in which controlled trials proved both the efficacy of a therapeutic intervention (corticosteroids) and that timely diagnosis and adequate therapy can change a dismal prognosis into a normal life expectancy in the vast majority of patients.[3] AIH describes a complex disease entity with a wide range of clinical presentations.

The prevalence of AIH is estimated as one in 5,000–10,000.[4] It can manifest at any age between very early childhood and the 80s and, like many other autoimmune diseases, is more common in women (3:1). AIH often presents subclinically[5] leading to delayed diagnosis, which explains why about a quarter of patients already show cirrhosis at presentation.[6] Up to one-third of patients may present with an acute disease, some even with fulminant hepatic failure. Delay in diagnosis and initiating treatment in such patients can be fatal.

Diagnosis

A diagnosis of AIH should be considered in any patient with elevated liver enzymes. The clinical picture only occasionally provides important clues to the diagnosis. The typical patient has subacute disease, presenting with lethargy and often jaundice without a risk factor for viral hepatitis. Other clinical symptoms may include arthralgia and slight, right upper quadrant pain.

With the possible exception of

Table 1. Criteria for the diagnosis of autoimmune hepatitis (AIH).

Criteria	
Major	Hypergammaglobulinaemia (with a preferential increase of IgG) Demonstration of autoantibodies (ANA, SMA, SLA/LP, LKM) Absence of viral hepatitis Portal hepatitis (with lymphoplasmacellular infiltrates) on histology
Minor*	Personal or family history of other autoimmune disease History of a spontaneously fluctuating course Arthralgia Presence of HLA-DR3 or DR4

* additional features may give further support to the diagnosis.
ANA = antinuclear antibody; IgG = immunoglobulin G; LKM = liver-kidney microsomal antigen; SLA/LP = soluble liver antigen; SMA = smooth muscle antigen.