Fatty liver disease

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Abstract

It is now widely accepted that fatty liver disease is one of the commonest causes of cirrhosis and liver cell cancer (even in the absence of cirrhosis), in its own right as well as being an important cofactor for the progression of other diseases e.g. viral hepatitis. While much work has been done on developing non-invasive techniques for assessing liver disease, the liver biopsy remains the benchmark against which these tests have to be validated as well as providing information that cannot be obtained in any other way. This review describes the histological features that alcoholic and non-alcoholic liver disease have in common (e.g. fatty change, ballooning and Mallory–Denk bodies) as well as identifying those that are more characteristic of each of them (e.g. nuclear vacuolation in non-alcoholic fatty liver disease and a florid fatty liver hepatitis in alcoholic fatty liver disease). Recent developments in the assessment of the degree of fatty change are described.

Introduction

Fat accumulation in the liver can be divided, histologically, into large droplet and small droplet fatty change. This review will deal with the former, which is much commoner. Large droplet fatty change is characterised by triglyceride accumulation within the cytoplasm of hepatocytes, with total liver fat accumulation exceeding 5–10% of liver weight.[1] Fatty liver is classically separated aetiologically into non-alcoholic fatty liver disease (NAFLD) and alcohol related liver disease although there are overlapping pathogenic and pathological features.

Abbreviations: (ALP), alkaline phosphatase; (ALT), aminotransferase; (AST), aspartate aminotransferase; (CK), cytokeratin; (GGT), gamma-glutamyltransferase; (HCV), hepatitis C virus; (H&E), haematoxylin and eosin stain; (NAFLD), non-alcoholic fatty liver disease; (NAS), NAFLD Activity Score; (NASH), non-alcoholic steatohepatitis; (NASH CRN), Nonalcoholic Steatohepatitis Clinical Research Network; (PT), prothrombin time; (US), ultrasonography.

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Epidemiology

Excessive alcohol consumption, viral hepatitis and the metabolic syndromes related to obesity are the leading causes of cirrhosis and primary liver cancer in Europe.[2] Liver cirrhosis is responsible for 170,000 deaths in Europe each year (albeit with large inter-country variation).[2] In the UK and Ireland liver cirrhosis associated mortality has increased over the last ten years.[2] Clearly, fatty liver disease is a significant cause of liver related death in these populations.

Linking aetiology with the burden of liver disease, a recent systematic review of European liver disease data by Blachier et al. noted that more than 50% of European adults are overweight or obese and that alongside this the prevalence rate of NAFLD in Europe varies from 2% to 44%. In regards to specific diseases, the study found that 42.6%–69.5% (46.2% in a UK study) of people with type 2 diabetes were affected by NAFLD.[2] Blachier et al. also noted that the presence of NAFLD carries an increased risk of overall mortality and specifically cardiovascular and liver disease related death.[2] However this review does not separate simple fatty liver disease from non-alcoholic steatohepatitis (NASH) and importantly a Swedish study found that reduced survival was specifically associated with NASH and not simple fatty change.[3]

Europe is the heaviest drinking region in the world, in terms of the prevalence of excessive alcohol consumption, with over 20% of the European population aged ≥15 years reporting heavy episodic drinking. Blachier et al found that alcohol is the main cause of liver disease in Europe and the strongest risk factor for liver cirrhosis.[2] In the UK approximately 14,700 hospital admissions each year are attributable to alcohol related liver disease.[4] The UK standardised mortality ratio from alcohol related liver diseases is 12.5 and 6.1 per 100,000 in men and women respectively[2] and accounts for a tenth of all deaths of those aged 40–50 years.[4] The exact prevalence of alcoholic hepatitis in the UK is unknown but histological features are present in 20% of heavy drinkers undergoing liver biopsy.[4] The burden of liver disease attributable to the harmful use of alcohol is significant compared to other aetiologies and is also associated with considerable general health, social and economic issues.[2]

Non-alcoholic fatty liver disease

NAFLD is defined as the accumulation of liver fat exceeding 5% of hepatocytes in the absence of significant alcohol intake (significant alcohol intake being defined as 20 g/10 g per day for men/women respectively) or other specific aetiology.[5] NAFLD is considered the hepatic manifestation of metabolic syndrome, which encompasses insulin resistance or diabetes, visceral obesity, dyslipidaemia and hypertension. NAFLD is likely to account for up to 90% of all cases of deranged liver function tests after other aetiologies (viral, alcohol, inherited and drugs) are excluded.[1] NAFLD therapy focuses on the treatment of the underlying risk factors and metabolic syndrome.[1]

The pathogenesis of NAFLD is not fully understood however the current theory is of a two-hit hypothesis. The first hit, simple fatty change, sensitises the liver to the induction of inflammation by a combination of second hits that may lead to steatohepatitis. What is still unclear is why some individuals develop simple fatty change only and others progress to steatohepatitis. Research has

so far highlighted insulin resistance and increased levels of free fatty acids, TNF-α, oxidative stress, and apoptosis as potentially key cellular events (review: Levene and Goldin[6]).

Clinical presentation and biochemistry

Clinically the majority of patients with NAFLD are asymptomatic and when symptoms are present they are often non-specific.[1] Serum liver enzymes may be within normal limits in 78% of patients with NALFD[1] but when serum liver enzyme abnormalities are present the elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are usually mild or no greater than four times the upper limit of normal.[1] The AST/ALT ratio is usually less than one although this may increase with the development of cirrhosis. Serum alkaline phosphatase (ALP) is sometimes mildly elevated but it is rarely the only abnormal liver function test in NAFLD. Serum gamma-glutamyltransferase (GGT) is frequently elevated and has been associated with increased mortality. GGT levels above 96.5 U/L have been associated with advanced fibrosis (83% sensitivity, 69% specificity).[1] Elevated ferritin levels have been reported in 50% of patients with NASH.[1]

There is currently no single biomarker that can diagnose NAFLD or ascertain disease severity but recent work has proposed caspase-generated cytokeratin (CK)-18 fragments. CK-18 fragments are formed in the final steps of hepatocyte apoptosis. Immunohistochemistry has confirmed the presence of CK-18 fragments in liver biopsies of patients with NASH but the marker was rarely seen in liver biopsies of patients with simple fatty change or normal livers.[7] Further work has shown that this increased tissue expression translates to increased serum levels.[8]

Diagnosis

The diagnosis of NAFLD needs confirmation of hepatic fatty change by either imaging studies or liver biopsy along with the clinical exclusion of excess alcohol consumption.[1] Ultrasonography (US) is the most commonly used imaging modality and can detect hepatomegaly, diffuse increases in echogenicity of the liver parenchyma and vascular blunting that suggest fatty liver. Transient elastography is a US based modality that measures liver stiffness and shows good correlation with biopsy diagnoses of moderate and severe fibrosis/cirrhosis. However US based imaging (including fibroscan) loses sensitivity in the obese and where fatty change is mild (less than 30%) and imaging cannot be used to differentiate between the histological subtypes and stage of NAFLD.[1]

Therefore when staging the severity of NAFLD the liver biopsy remains the gold standard.[1] Liver biopsy is not without limitations. It is an invasive procedure with complications including pain (<3% risk of severe pain), bleeding (<0.5% risk of significant haemorrhage) and death (<0.1% risk).[9] Liver biopsy also represents only a very small proportion of the liver (1/50,000 of the total mass of the liver) and is therefore prone to sampling error.[1]

Histology

Histological features of NAFLD range from simple fatty change to NASH. Twenty percent of patients with NASH will go on to develop cirrhosis[1] and therefore diagnosis of NASH is important to the clinician caring for the patient as it may signal the need for more aggressive management. It is important to note that not only is NASH associated with an increased risk of liver cancer in cirrhotics but that these tumours may arise in non-cirrhotic patients.[10] Additionally, liver biopsy may exclude other liver diseases such as drug-induced liver injury, haemochromatosis and autoimmune hepatitis.[1] There has been considerable debate about whether iron overload is associated with more severe NAFLD but a consensus has developed that it is.[11]

On liver biopsy NAFLD changes are predominantly parenchymal and fat accumulation occurs in a zone 3/perivenular location.[1] Of note the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) describe a pattern of zone 1 fatty change and portal inflammation with infrequent balloon cells that is predominantly seen in children and is associated with fibrotically progressive NAFLD.[12,13]

Fatty change is usually macrovesicular although, recently, mesovesicular fatty change has also been described. The latter is characterised by a centrally placed nucleus and multiple medium sized droplets of fat (Figure 1 compares (a) mesovesicular fat with (b) macrovesicular fat). It needs to be emphasised that in true microvesicular fatty change, as seen in fatty liver of pregnancy, individual fat droplets cannot be easily resolved. Recent attempts to improve the assessment of the severity of fat in liver biopsies using image analysis with or without Oil-Red O staining

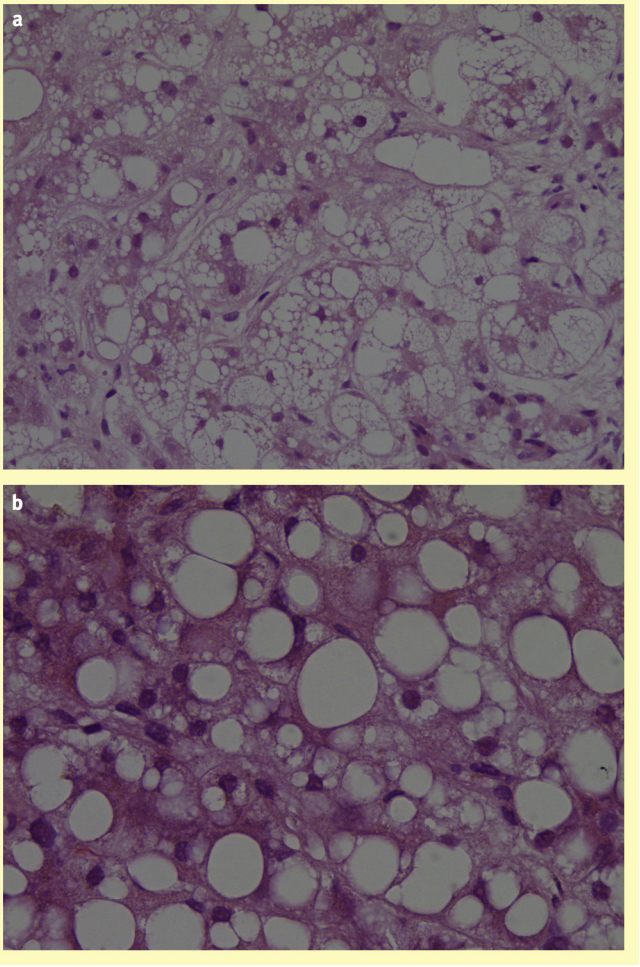

Figure 1 (**a**) Mesovesicular steatosis, (**b**) Macrovesicular steatosis for comparison, H&E ×200 magnification.