

Fatty liver disease in children

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NAFLD/NASH is now recognised as an increasing clinical problem in children and adolescents. Risk factors include obesity, insulin resistance, and hypertriglyceridaemia. Drug hepatotoxicity and genetic or metabolic diseases that can cause hepatic steatosis must be excluded. Affected children are usually asymptomatic although a few may complain of malaise, fatigue, or vague recurrent abdominal pain. Liver biopsy is the gold standard for diagnosis, and is important in determining disease severity and prognosis. The natural history of childhood NASH may be progressive liver disease for a significant minority. Long term follow up studies in this population are still lacking. The mainstay of treatment is weight reduction. The use of pharmacological therapy, though promising, ideally needs further evaluation in well designed randomised controlled studies in children.

diagnosis of “non-alcoholic” fatty liver disease can be made confidently. In children, this is less of a diagnostic problem, although alcohol consumption is an increasing feature of adolescent culture and cannot be totally excluded in adolescent NAFLD. Consumption of more than 14 units of alcohol per week is considered the level at which fat in the liver should be attributed to the alcohol intake. However, in children an underlying metabolic liver disease should always be kept in mind.

The stereotype of the typical adult patient with NAFLD was a middle aged, massively obese woman.^{1–8} However, NAFLD has been recognised to occur in men and patients who may not be extremely obese,⁹ although most adult patients with NAFLD are critically above the ideal weight (that is, weigh 110–130% of ideal weight or body mass index (BMI) > 25 kg/m²) and may not have non-insulin dependent diabetes mellitus (NIDDM).^{5–9–10}

NAFLD in children was first reported in the early 1980s.¹¹ Since then, a number of case series have been described,^{12–15} with the following clinical characteristics: occurrence in young children, a male predominance; serum ALT raised more than serum AST, hypertriglyceridaemia as the typical blood lipid abnormality, and non-specific symptoms; and vague abdominal pain often being the reason for clinical assessment. Cirrhosis complicating childhood NAFLD^{13–15} has been encountered, and seen in children as young as 9 years.¹³

Most of the series of children with NAFLD involve some degree of selection bias: either a referral bias, or the child having required a liver biopsy because of persistently raised serum aminotransferases. An important question is the prevalence of NAFLD in the general paediatric population. A study of 810 schoolchildren from northern Japan showed an overall 2.6% prevalence of fatty liver by ultrasound, with a strong correlation to indices of obesity such as body mass index.¹⁶ In obese children screened for raised serum aminotransferases, this prevalence has been found to be between 10% and 25%,^{17–19} with male predominance.

In the UK, 9% of boys and 13% of girls aged 5–16 years are obese, characterised as an epidemic by the press,²⁰ and associated with a diet containing more salt and refined sugar and a lifestyle including less exercise. In this environment it is not surprising that NAFLD/NASH,

Fatty liver disease is increasingly recognised in children in the absence of identifiable inborn errors of metabolism. Usually the abnormality of liver tests is discovered while investigating for abdominal pain, or liver function tests get reported from an incidental biochemical profile and subsequent ultrasound scan of the liver, suggesting fatty change, and leading to a diagnosis of fatty liver disease. In adults fatty liver with abnormal liver enzymes is commonly seen with alcohol abuse. The term non-alcoholic steatohepatitis (NASH) was first coined in 1980 by a pathologist at the Mayo Clinic to describe a clinicopathological condition in which the liver histology was consistent with alcoholic hepatitis, but in whom alcohol use was denied.¹ NASH may be considered part of a larger spectrum of non-alcoholic fatty liver disorders (NAFLD) that extends from simple steatosis through steatohepatitis (NASH) to forms of cryptogenic cirrhosis in which the steatosis may be inconspicuous.^{2–3}

Over the past two decades, NASH has been recognised as a clinically significant condition which is both prevalent and has potentially serious sequelae.^{4–5} It has been shown to progress to cirrhosis, and there is an increasing body of evidence that some cases of cryptogenic cirrhosis requiring liver transplantation could have been the result of NASH.⁶ Recent reports have also described hepatocellular carcinoma arising in patients with NASH associated cirrhosis.⁷

One of the difficulties in defining NASH has been in determining the minimal dose of alcohol use in the setting of hepatic steatosis before a

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FFA, free fatty acids; NAFLD, non-alcoholic fatty liver disorders; NASH, non-alcoholic steatohepatitis; NIDDM, non-insulin dependent diabetes mellitus; VLDL, very low density lipoproteins

Table 1 Differential diagnosis of steatosis**General/nutritional**

Acute systemic disease
 Acute starvation
 Protein calorie malnutrition
 Total parenteral nutrition
 Inflammatory bowel disease
 Coeliac disease
 Mauriac syndrome

Infections

Hepatitis C

Metabolic

Cystic fibrosis
 Wilson's disease
 α antitrypsin deficiency
 Galactosaemia
 Fructosaemia
 Cholesterol ester storage (Wolman) disease
 Glycogen storage disease
 Mitochondrial and peroxisomal defects of fatty acid oxidation
 Lipodystrophies
 Abetalipoproteinaemia
 Weber-Christian disease
 Schwachman syndrome

Drug toxicity

Amiodarone
 Methotrexate
 Prednisolone
 L-asparaginase, methotrexate
 Vitamin A
 Valproate
 Tamoxifen
 Zidovudine and anti-HIV treatments

Ethanol
 Ecstasy

once rare in our practice, is becoming common, with 26 patients diagnosed in the past two years.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

Laboratory investigations show mild to moderate increase of serum aminotransferases (usually less than four times normal). The ratio of alanine aminotransferase (ALT) to aspartate aminotransferase (AST) is higher than in alcoholic hepatitis where AST levels usually exceed ALT levels. Gamma-glutamyl transpeptidase and alkaline phosphatase can be mildly raised, but bilirubin, albumin, and prothrombin time are usually normal unless the disease is advanced. AST > ALT may be a marker of fibrosis or progressive disease.

Various radiological modalities (ultrasonography, computerised tomography, magnetic resonance imaging, and radio-nucleotide scans) have been used to evaluate hepatic steatosis. Unfortunately none of these are helpful to differentiate simple hepatic steatosis from NASH, unless in instances where established cirrhosis is present.

Liver biopsy is the gold standard for the diagnosis of NAFLD/NASH for the following important reasons:

- To confirm diagnosis and establish severity of fibrosis and presence of cirrhosis
- To exclude other co-existing conditions that can result in hepatic steatosis.

The histological diagnosis of steatohepatitis relies on a constellation of lesions that include steatosis (mainly macrosteatosis, occasionally microsteatosis), ballooning of hepatocytes, perisinusoidal fibrosis, and a mixed lobular inflammatory infiltrate.²¹

The presence of microvesicular steatosis (which is indicative of defective β oxidation of fatty acids) alone should alert one to the possible diagnosis of inherited mitochondrial disorders, fatty acid oxidation defects, urea cycle disorders, and valproate hepatotoxicity, rather than NAFLD. A "bright liver" on ultrasound examination, which may be indistinguishable from NAFLD, can be seen in these conditions, a scenario where liver biopsy is of particular diagnostic value.

Chronic liver conditions, which can result in hepatic steatosis and must be differentiated from NAFLD/NASH, include Wilson's disease, chronic hepatitis C infection, cystic fibrosis, and α_1 antitrypsin deficiency. These have specific treatment modalities and separate prognostic implications. Table 1 gives the differential diagnosis of steatosis.

NATURAL HISTORY/PROGNOSIS

The natural history of NAFLD has been shown to vary according to the histological type.^{3,5} Patients with steatosis without inflammation appear to have a benign clinical course without histological progression. In contrast, patients with NASH have been noted to progress to cirrhosis. Matteoni and colleagues have proposed four stages of NAFLD based on natural history and risk of progressive disease.⁵ From their retrospective analysis of 132 patients, 98 of whom had complete 10 year follow up data, cirrhosis developed in 21% of histological grade 3 and 28% of grade 4 patients respectively.

Several studies have identified independent risk factors for hepatic fibrosis in patients with NAFLD to be age, obesity, and NIDDM.^{10,21} In one study, age >45 years, AST/ALT ratio >1, and the presence of obesity or diabetes was associated

Table 2 Investigations of suspected NAFLD/NASH

1. Basic profile—full blood count, liver function tests, urea and electrolytes, INR
2. Serum lactate, pyruvate, urate
3. Serum copper, caeruloplasmin, 24 hour urinary copper
4. HBV, HCV serology
5. CF alleles, (sweat test if symptoms suggest CF or heterozygous genetic result)
6. α_1 antitrypsin phenotype
7. Plasma fatty acids and acyl carnitine profile
8. Urinary steroid metabolites
9. Abnormal glucose tolerance test (GTT)
 Basal >7.0 mmol/l
 2 hour peak after 75 g (1 g/kg) glucose >7.8 mmol/l
10. Hyperinsulinism on GTT (85% of subjects)
 Basal >50
 At 30–120 min >100
11. Specific tests as suggested by history and examination
12. Liver biopsy
13. Investigations specific to rare metabolic conditions and as indicated by other results including liver biopsy

with a 50% risk of hepatic fibrosis.¹⁰ Similarly, another study showed that patients <50 years, with a body mass index <28 kg/m², normal serum triglycerides, and ALT <2× raised, did not develop septal fibrosis on liver biopsy.²² Information from such studies would be useful in guiding clinicians as to the need to perform a liver biopsy in patients with NAFLD. Unfortunately, there are no comparable studies evaluating such risk factors in children. In their absence in obese children without features to suggest rare metabolic conditions, we have undertaken preliminary investigations to exclude commoner causes of fatty liver (table 2) and arranged counselling to try to achieve weight loss. If no progress in improving the ultrasonographic or biochemical evidence of liver disease has been achieved in 3–6 months a liver biopsy and tertiary investigations for rare causes of liver dysfunction are performed in all cases. Patients who are not obese warrant liver biopsy investigation once the preliminary tests have excluded alternative specific diagnoses. Other indications for liver biopsy are splenomegaly, ambiguous diagnosis (particularly possibly Wilson's disease), and to determine the prognosis.

PATHOGENESIS OF NASH

The two hit hypothesis for the pathogenesis of NASH was first proposed in 1998.²² Accumulation of fat ("first hit") within the liver, would predispose it to the "second hit" which then leads to hepatocyte injury, inflammation, and fibrosis. The two main pathways of hepatocellular injury are considered to be oxidative stress induced lipid peroxidation and cytokine mediated injury.

Lipid peroxidation and NASH

Pessayre and colleagues,²³ in their experimental mouse model, have shown that excess fat deposition in liver is associated with lipid peroxidation; the degree of this peroxidation is directly related to the severity of steatosis. The end products of lipid peroxidation, 4-hydroxynonal and malondialdehyde, covalently bind to hepatic proteins, and act as potent agents for neutrophil chemotaxis and stimulating pro-inflammatory cytokines. Malondialdehyde also activates hepatic stellate cells to produce collagen, leading to fibrosis.

Cytokines and NASH

Cytokines are also attractive candidates for the "second hit" in the pathogenesis of NASH. Firstly, they are capable of producing all the classical histological features of NASH, including hepatocyte death/apoptosis (TNF- α), neutrophil chemotaxis (IL-8), and hepatic stellate cell activation (TNF- α , TGF- β).²⁴ Secondly, there is evidence both in humans and animal models that endotoxin mediated cytokine release is important in the occurrence of hepatic steatohepatitis,^{25–26} and that the use of antimicrobial therapy may be able to prevent or reverse its development. It has also been shown that patients with NASH have an increased expression of TNF- α mRNA in both their livers and adipose tissue compared to obese controls; this over-expression correlated with histological severity.²⁷

Free fatty acids and NASH

The same author that proposed the two hit model for the pathogenesis of NASH has recently suggested a modification of that model with greater emphasis on the potentially central role of free fatty acids (FFA).²⁸ Knowledge of the major processes of lipid metabolism within the liver makes it easier to understand how this may occur. After absorption from the intestine, fat is carried to adipose tissue for storage in the form of triglycerides. It is released as free fatty acids when the body is deprived of food or under the effect of certain hormones/drugs (such as adrenaline, corticosteroids). Free fatty acids are carried to the liver bound to albumin.

After entering the hepatocytes they are either oxidised to produce energy or resynthesised and transported back to the adipose tissue bound to very low density lipoproteins (VLDL). Fatty acids are also synthesised by hepatocytes when there is dietary excess of carbohydrates. Conditions leading to excess fatty acid load in hepatocytes (obesity, acute starvation), increased fatty acid synthesis by the hepatocytes (high dextrose parenteral nutrition, dietary excess of carbohydrate, or diabetes), impaired binding of triglycerides to VLDL (hypo or abetalipoproteinemia), or decreased β oxidation of fatty acids in mitochondria will all lead to hepatic steatosis. There is also growing evidence implicating FFA in the production of oxidative stress within hepatocytes. Increased fatty acid β oxidation and peroxisomal fatty acid oxidation can both lead to increased generation of reactive oxygen species and subsequent lipid peroxidation. In the fasting state, patients with NAFLD have increased plasma levels of β -OH butyrate.²⁹

Hepatic insulin resistance and NASH

The association between the severity of insulin resistance and the risk of NASH can be explained by peripheral insulin resistance increasing the supply of FFA to the liver and by hepatic insulin resistance favouring the development of oxidative stress. The increased supply of FFA to the liver leads to steatosis and may also contribute to the hepatic insulin resistance observed in humans with NAFLD, who have shown impaired insulin mediated suppression of hepatic glucose production compared with controls.^{29–30} This development of insulin resistance with increasing hepatic steatosis may be a mechanism whereby the liver protects itself from continuing enlargement in the face of continuing excessive substrate supply at the expense of impaired glucose tolerance. Supporting a central role for hepatic insulin resistance in NASH is a recent report that an agent which primarily improves hepatic insulin sensitivity, metformin, was associated with a fall in transaminase levels in patients with NASH.³¹

Inherited factors for NASH

The association of type 2 diabetes, hyperlipidaemia, hyperuricaemia, and hypertension, manifestations of the metabolic syndrome or syndrome X with NASH, and with a worse prognosis for NASH, suggests a constitutional predisposition. Certain individuals may be genetically prone to develop NASH, while others are resistant in the same dietary and lifestyle environment despite obesity. Family history and racial differences also suggest genetic predisposition in certain individuals.^{30–32} These associations may imply that NASH/NAFLD patients have increased risk of the cardiovascular complications of hyperlipidaemia and insulin resistance in adult life and of liver diseases such as alcoholic liver disease or "cryptogenic" liver disease, even if they manage to control obesity during childhood. Certainly, those found to have hyperlipidaemia should be referred to a specialist clinic for follow up.

Other factors

Although obesity and insulin resistance are associated with the development of NASH, the majority of such obese, insulin resistant individuals develop steatosis, while only a minority develop NASH. A postmortem study of 351 non-drinking individuals reported that 60% of obese patients with NIDDM had steatosis; only 15% had NASH.³³ This suggests that it is likely that some other environmental or genetic factors are required for the progression of NASH. Studies in leptin deficient ob/ob mice which have profound insulin resistance have dramatic hepatic steatosis without steatohepatitis or fibrosis, suggesting that leptin may in fact have a role in promoting hepatic fibrogenesis, directly by an autocrine effect on hepatic stellate cells and indirectly by up-regulating

Table 3 A care pathway for NAFLD/NASH

1. Diagnosis and investigation—see text and tables
2. Liver biopsy if diagnosis/prognosis unclear
3. Counselling for weight loss, dietary improvement, and increased exercise—aim for close to 500 g/week weight loss
4. Referral to hyperlipidaemia/hypertension/diabetic clinic if necessary
5. Follow up with ultrasound at 6 months
6. Liver biopsy if not performed already if condition persists
7. Referral to specialist liver clinic if not already made
8. Referral to specialist feeding/obesity clinic if no progress with weight
9. Trial of pharmacological management in specialist centre if progressive liver disease

the production of TGF- β from sinusoidal endothelial cells and Kupffer cells.³⁴

TREATMENT

Treatment of obesity, NIDDM, and hyperlipidaemia would seem to be a logical first step in view of their close association with the development of NASH. Studies have shown that steatosis and steatohepatitis may resolve with weight reduction.^{35–36} However, patients with more rapid and drastic weight loss were found to have developed slightly more portal inflammation and fibrosis despite a more pronounced reduction of fatty change.³⁷ Similar findings of biochemical improvement following weight reduction have been seen in obese children;^{13–17} however in general, histological response has not been assessed in these paediatric studies. Currently, weight loss of no more than 500 g/week is recommended.

A number of pharmacological agents have been shown to be promising in the treatment of NASH. These include lipid lowering agents (clofibrate and gemfibrozil),³⁸ ursodeoxycholic acid,^{39–40} antioxidants (vitamin E, N-acetylcysteine),^{41–43} and drugs that improve insulin sensitivity.^{30–43} However, most of these are open label, uncontrolled studies. There is therefore a need to perform well controlled randomised clinical trials that have adequate duration of follow up and are analysed on an intention to treat basis with clinically relevant end points.

An initial management strategy for an obese child with persistently raised aminotransferases from NAFLD would be an attempt at gradual weight loss using a combination of diet and exercise. Blood glucose control and serum lipids should be evaluated and managed accordingly. If liver enzyme abnormalities persist, especially if 10% weight loss has been achieved, then liver biopsy should be considered. In patients with simple steatosis, no further treatment in addition to weight reduction and metabolic control of NIDDM and hyperlipidaemia has been recommended. However, patients with steatohepatitis, and particularly those with fibrosis on liver biopsy have a worse prognosis. They should be monitored closely, with a greater effort on metabolic control, and be offered enrolment in well controlled clinical trials evaluating the potential benefit of the above promising medications. For patients with cirrhotic stage NASH and decompensated disease, liver transplantation is a potentially life saving therapeutic alternative; however reoccurrence after transplantation is possible. Table 3 shows a care pathway for management.

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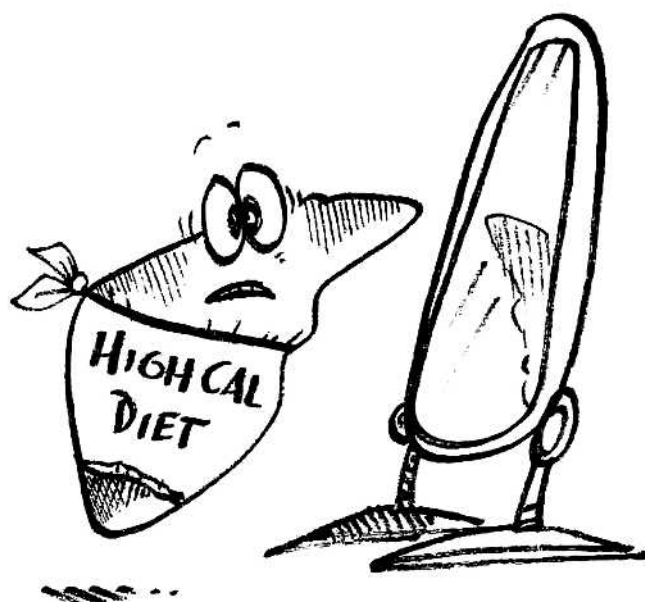
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DOES THIS MAKE ME LOOK FATTY?