Non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent chronic liver disease that occurs in the setting of insulin resistance and increased adiposity. It is thought to be the hepatic manifestation of more widespread metabolic dysfunction. NAFLD is also associated with dyslipidaemia and increased risk of cardiovascular disease. A "multiple-hit" pathogenic model has been suggested to explain the progressive liver damage that occurs among children with NAFLD. The mainstay of NAFLD therapy is lifestyle interventions which aim to improve obesity. Effective pharmacological treatments are still under development. Bariatric surgery may have a role in treating morbid obesity. In this article, we briefly review the currently available knowledge on NAFLD.

Keywords Children; non-alcoholic fatty liver disease; non-alcoholic steatohepatitis; obesity

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease resulting from excessive fat accumulation in the liver. It is one of the most common causes of chronic liver disease and liver related morbidity and mortality worldwide, including developing economies. The term NAFLD is used to describe different degrees of fatty liver diseases ranging from simple fat accumulation in more than 5% of the hepatocytes (hepatic steatosis) to non-alcoholic steatohepatitis (NASH) with necro-inflammation and sometimes fibrosis and ultimately cirrhosis.

NAFLD is predominantly associated with excess adiposity, in particular central obesity, and occurs in the absence of significant alcohol intake. It can be found in lean individuals but typically they too have significant visceral adiposity or severe insulin resistance syndromes, such as lipodystrophy. NAFLD is thought to be a hepatic manifestation of more widespread underlying metabolic dysfunction and is strongly associated with a number of metabolic risk factors, including insulin resistance, dyslipidaemia, cardiovascular disease and most significantly, obesity.

The natural history of NAFLD in children is poorly understood because of its complex nature and limited prospective studies in children. Fifteen percent of children with NAFLD have significant fibrosis at diagnosis and disease in children appears to be more severe compared with adults. This review summarises current concepts of NAFLD, its epidemiology, aetiology, clinical features, diagnosis and management.

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Epidemiology

The precise incidence and prevalence of paediatric NAFLD is not known and it is variable depending on the method of detection. Most studies have used liver function tests or ultrasound for diagnosis, however liver biopsy remains the gold standard. In North American studies NAFLD prevalence ranges from 0.7% at age 2–4 years (confirmed at autopsy), to 29 % to 38% in obese children (by studies of high ALT and an autopsy study). The prevalence of NAFLD increased 2.7 fold from the late 1980s to the current era (2007–2010) and at a more rapid rate than childhood obesity, based on analysis of high ALT in serial National Health and Nutrition Examination Survey cohorts. Severe obesity (more than 95th centile for age and gender adjusted body mass index) is associated with more adverse clinical outcomes and greater risk of progression to NASH and cirrhosis.

Prevalence varies by race and ethnicity. It is highly prevalent in Hispanic children; white and Asian children have intermediate prevalence while in African-American children it is less common. NAFLD is more common in boys than girls. Prevalence is higher in obese compared with normal weight children. However, it can present in thin individuals with severe insulin resistance as occurs in lipodystrophy or in those with central obesity but a normal BMI. Several comorbidities like obstructive sleep apnoea, pre-diabetes, diabetes and panhypopituitarism have been associated with increased prevalence and/or severity of paediatric NAFLD.

Although NAFLD is generally related to a high calorie intake and sedentary life style, family clustering and heritability is observed in some children. Multiple genome-wide association studies have demonstrated the important impact of genetic polymorphism on disease severity and progression. Single nucleotide polymorphisms (SNPs) in genes involved in lipid metabolism (Lipin 1 [*LPIN1*], patatin-like phospholipase domain containing 3 [*PNPLA3*]), apolipoprotein C3 [*APOC3*], oxidative stress (superoxide dismutase 2 [*SOD2*]), insulin signalling (insulin receptor substrate [*IRS1*]) and fibrogenesis (Kruppel like factor 6 [*KLF6*]) have been associated with severity of liver damage in NAFLD patients.

Causes of NAFLD

The "multiple hit" hypothesis is the current theory used to explain NAFLD pathogenesis and progression. At disease onset, NAFLD is characterized by fat accumulation in the liver (steatosis) and insulin resistance, which is heavily influenced by a sedentary lifestyle, high calorie diets, genetic susceptibility and epigenetics.

Fat accumulation in the liver

Hepatic steatosis is caused by an imbalance between the delivery of fat in the liver and its utilisation. A high calorie diet, rich in fats and simple sugars, precipitates a rapid increase in post-prandial plasma glucose and insulin levels, increasing hepatic *de novo* lipogenesis, steatosis, insulin resistance and central obesity. These are associated with increased risk of NAFLD.

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Fat accumulation outside the liver

In addition, adipose tissue outside the liver secretes endotoxins, adipokines and pro-inflammatory cytokines that contribute to free fatty acid accumulation (FFA) and insulin resistance. Excessive FFA influx to the liver overwhelms the mitochondria leading to oxidative stress. The oxidative stress products diffuse into the extracellular space, influencing Kupffer cells and hepatic stellate cells thus inducing synthesis of proinflammatory and fibrogenic cytokines leading to liver inflammation and fibrosis.

The gut microbiota appear to be important

The gut–liver axis and gut microbiota play an important role in NAFLD progression. In NAFLD, an alteration in gut microbiota and enhanced gut permeability increase the exposure of the liver to endotoxins and other products of intestinal tissue injury which in turn activate innate immune responses contributing to further progression of NAFLD.

Recent research suggests a critical role of the Farnesoid X receptor (FXR) in carbohydrate and lipid metabolism, regulation of insulin sensitivity and NAFLD pathogenesis. FXR is a nuclear bile acid (BA) receptor highly expressed in tissues that participate in BA metabolism, such as liver, intestine, and kidneys. Gut microbiota can change the BA composition of the host, which can antagonize intestinal FXR and lead to metabolic dysfunction, including obesity and insulin resistance. BA can also influence NAFLD via activation of hepatic FXR and G protein-coupled receptor TGR5.

Clinical features and diagnosis

NAFLD is usually diagnosed incidentally when an obese child is found to have raised transaminases and/or a bright appearance of the liver on ultrasound scanning. Most children are asymptomatic but some complain of abdominal pain and fatigue. The most common physical signs include obesity (by body mass index-BMI), in particular central obesity (assessed by measuring waist circumference), acanthosis nigricans and hepatomegaly.

There is often a family history of obesity and/or type 2 diabetes mellitus. It is useful to ask about symptoms of obstructive sleep apnoea as this is associated with NAFLD progression. Female adolescents with NAFLD may have polycystic ovary syndrome (PCOS) and present with signs of hyper-androgynism-acne, hirsutism and irregular menstrual cycle.

NAFLD is a diagnosis of exclusion requiring the presence of hepatic steatosis and exclusion of other causes of hepatic steatosis besides NAFLD (Table 1).

Differential diagnosis for paediatric hepatic steatosis

Genetic/metabolic disorders
Nonalcoholic fatty liver disease
Wilson disease
Uncontrolled diabetes
Cystic fibrosis
α1 antitrypsin deficiency
Fatty acid oxidation and mitochondrial disorders
Citrin deficiency
Lipodystrophies
Lysosomal acid lipase deficiency
Familial combined hyperlipidaemia
Abeta-/hypobetalipoproteinemia
Glycogen storage disease
Medications
Corticosteroids
Methotrexate
Valproic acid
Amiodarone
Certain antipsychotics
Certain antidepressants
Vitamin A
Highly active antiretroviral therapy (HAART)
Total body irradiation in cancer therapy
Dietary causes
Protein-energy malnutrition (Kwashiorkor)
Rapid surgical weight loss
Parenteral nutrition
Alcohol abuse
Infections
Hepatitis C
Systemic
Celiac disease
Inflammatory bowel disease
Hypothalamic-pituitary disorders

Table 1

Laboratory tests and imaging studies

Laboratory tests

In paediatric NAFLD aminotransferases levels range from normal to mild or moderate elevation (usually $\times 2$–3 upper limit of normal). The degree of elevation does *not* correlate with the presence or severity of histological findings. However, an increased aspartate aminotransferase (AST): alanine aminotransferase (ALT) ratio of more than 1 is indicative of progressive liver fibrosis. High γ-glutamyl transpeptidase (GGT) also represents a risk factor for advanced fibrosis in NAFLD.

It is important to exclude other causes of liver disease especially those with a specific treatment (autoimmune hepatitis and Wilson's disease). Table 2 lists the usual investigations for any child with chronically raised transaminases. In young children or those who are not obese, further investigations to exclude metabolic diseases that cause fatty infiltration of the liver are required.

Children with NAFLD should have screening for dyslipidaemia (fasting lipid profile, triglycerides) and diabetes (fasting serum glucose, oral glucose tolerance test, glycosylated haemoglobin level-HbA1c). Homeostatic model assessment insulin resistance index (HOMA-IR) is a useful tool for evaluating insulin resistance in children with NAFLD in the specialist setting.

Various serum biomarkers such as the Enhanced Liver Fibrosis (ELF) test have been developed as non-invasive tools to identify NAFLD children with advanced fibrosis and at risk of progression to cirrhosis. This test measures hyaluronic acid, procollagen III amino terminal peptide and tissue inhibitor of metalloproteinase I.

Imaging studies

Ultrasound can identify moderate to significant steatosis (steatosis involving more than 30% of hepatocytes), however it cannot distinguish between the severity of the NAFLD spectrum.

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