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SUMMER SCHOOL: PEDIATRIC HEPATOLOGY

Non-alcoholic fatty liver disease in children

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Summary Non-alcoholic fatty liver disease is increasingly prevalent in children, together with obesity. Transaminases, tests for insulin resistance, ultrasonography and MRI are variably used as surrogates markers of steatosis. Other liver diseases, such as Wilson disease, should be excluded. A liver biopsy is performed in selected cases: young children, familial history of severe disease, inconclusive tests for other pathologies, suspected advanced fibrosis, hypertransaminasemia despite weight loss and in clinical trials. Weight reduction, and changes in lifestyle, are the front-line treatment. Drug therapy is under evaluation.

Non-alcoholic fatty liver disease (NAFLD) is a condition, ranging from a simple liver steatosis to steatohepatitis (NASH), that may progress to cirrhosis and end-stage liver disease. NAFLD is now believed to be the liver presentation of the metabolic syndrome (MS), and is related to a cluster of risk factors such as obesity, insulin resistance, diabetes mellitus and dyslipidemia.

Epidemiology

Obesity and MS have recently become more common in children and adolescents, and that resulted in a higher prevalence of NAFLD. Epidemiological data show that NAFLD may affect up to 10% of children, is more frequent in boys, and increases with age. The liver biopsy remains the gold standard for diagnosis, but is not routinely feasible, therefore the true prevalence of NAFLD is unknown. Hence, most epidemiological studies use surrogate markers for the diagnosis, such as serum aminotransferases (ALT/AST) or ultrasound (US) findings. A recent population-based prevalence study in the USA, within the National Health and Nutrition Examination Survey 1999—2004 (NHANES), showed a prevalence of high ALT in 8% of adolescents not known to present a liver disease.

Pathophysiology

Over a decade ago, Day et al. proposed the ''two hits'' theory, to explain the progression from simple steatosis to NASH and cirrhosis (Fig. 1). The ''first hit'' is a peripheral insulin resistance, leading to the accumulation of fat in the hepatocytes, together with an increase in lipid peroxidation. Hyperinsulinemia and insulin resistance accompanying obesity, lead to liver steatosis, possibly by increasing the absolute FFA uptake in the liver, the esterification of hepatic FFAs to form triglycerides (TG), the FFA synthesis from cytosolic substrates, the decreased apolipoprotein B-100 synthesis, with a subsequent decreased export of FFAs and TG, a diminished hepatic triglyceride and FFA export, and an increased beta-oxidation of mitochondrial long-chain fatty acids.

Another potentially important factor in insulin resistance is adiponectin, as it protects hepatocytes from TG

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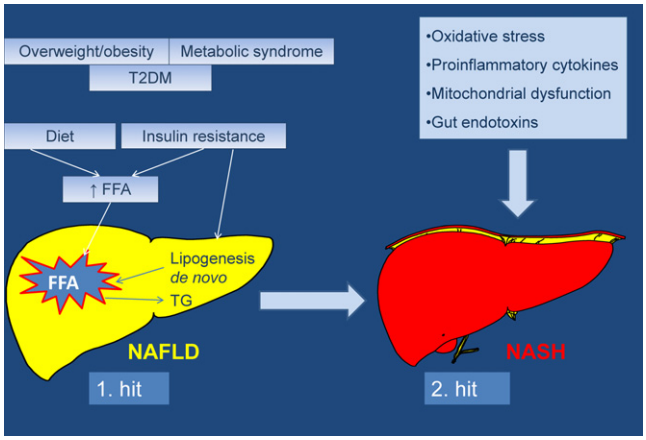

Figure 1 Two hits theory explaining liver steatosis and progression to liver cirrhosis.

accumulation, possibly by increasing the β-oxidation of FFAs or decreasing de novo their production in the hepatocytes. The *adiponectin* gene plays an important role in the activation of the peroxisome proliferator-activated receptor (PPAR)-γ. The deficiency of PPAR-γ in adipocytes leads to elevated levels of serum FFAs and TG, and subsequent steatosis. The adiponectin modulates the inflammatory response from the endothelial cell, through inhibition of the nuclear factor (NF)-κB and blockage of the release of tumor necrosis factor alpha (TNF-α). TNFα interferes with insulin transport and signaling, and might be involved in NAFLD-associated insulin resistance. TNF-α induces hepatocellular necrosis, but also promotes liver regeneration. As TNF-α serum concentrations are higher in NASH, it is thought to play a role in the progression of liver disease to steatohepatitis.

The oxidative stress in the 'two hits' theory seems to explain the progression to liver fibrosis. Reactive oxygen species (ROS) can induce hepatocellular injury, by inhibition of mitochondrial respiratory chain enzymes, inactivation of glyceraldehyde-3-phosphate dehydrogenase and inactivation of membrane sodium channels. ROS further cause lipid peroxidation, cytokine production, and induce Fas ligand, that might contribute to the hepatocellular injury and fibrosis.

The role of genetic factors in NAFLD is possible, as there is an association with polymorphisms e.g. on the *IL-6* (*174G/C*) and *TNF-α* genes.

Diagnosis

Experts of the Hepatology Committee of ESPGHAN agreed recently on a position statement for the diagnostic approach to NAFLD in childhood, describing the role of different tests including the liver biopsy [1].

NAFLD is rare in children aged less than 10 years, and usually presents with overweight/obesity, acanthosis nigricans, sometimes abdominal pain, fatigue, or hepatomegaly.

The diagnosis of NAFLD needs the recognition of fatty liver, and the exclusion of other causes of steatosis. The diagnosis of steatosis is histological, but the liver biopsy is an invasive procedure usually not initially performed. Thus, surrogate markers are commonly used, such as transaminases and imaging techniques (US, CT, MRI). None of these have proven to be reliable, and the sensitivity and specificity are undetermined. A mild to moderate hypertransaminasemia, often seen in NAFLD, has a low sensitivity and is not correlated to the histological severity. Other biochemical findings are hypertriglyceridemia, elevated fasting insulin levels with normal fasting glucose, and HOMA-IR and QUICKI indices consistent with insulin resistance. The sensitivity of ultrasound in NAFLD ranges from 60 to 94%, with a specificity from 84 to 100%, but it has not been evaluated in children. Computed tomography is more specific but is not used for screening of fatty liver in obese children. Magnetic resonance imaging (MRI) and 1H-MRS have the greatest accuracy to determine hepatic fat content, but are used rarely due to high costs. The Fibroscan® uses transient elastography to evaluate the fibrosis. It correlates well with liver fibrosis, on histology, in few studies in both adults and children.

Differential diagnosis of NAFLD should be based first on clinical features, then on noninvasive tests, and finally liver biopsy. Other causes of chronic liver disease including hepatitis B and C, Wilson disease, alpha-1-antitrypsin deficiency, autoimmune hepatitis, cystic fibrosis and drug toxicity should be excluded. Alcohol abuse must always be questioned. Especially in young children (less than 3 years), a detailed diagnosis for metabolic causes of fatty infiltrations in the liver should be performed. In some metabolic diseases, overweight or obesity are frequent (Table 1).

The liver biopsy is the only way to assess the histological severity of the disease (degree of steatosis, inflammation, and fibrosis or cirrhosis), and to differentiate between simple steatosis and NASH. Furthermore, it is necessary to exclude other causes of liver disease. NAFLD is histologically defined as macrovesicular steatosis in > 5% of hepatocytes. Type 1 NASH is found commonly in adults, with inflammatory changes (ballooning degeneration of hepatocytes, or focal hepatocyte dropout, with a polymorphonuclear infiltration) and fibrosis, mostly severe in the perivenular zone. Type 2 NASH is predominantly described in children, with mononuclear periportal inflammation and fibrosis. The NASH Clinical Research Network proposed a histological scoring system that comprises the evaluation of steatosis (0—3), lobular inflammation (0—2), hepatocellular ballooning (0—2) and fibrosis (0—4). NAS ≥ 5 correlates with the diagnosis of NASH, whilst NAS < 3 is defined as 'not NASH'. As this system is typically developed for adult 'type 1' NASH, the interobserver agreement for paediatric NASH is weaker [2].

The demonstration of the fat infiltration in the liver is based on histology. There are controversies about the timing of the liver biopsy. Most experts use criteria defined by Roberts et al. in children with NAFLD: young age (< 10 years), family history of severe NAFLD, presence of hepatosplenomegaly, abnormal laboratory results (high and persistent hypertransaminasemia, severe insulin resistance, presence of non organ-specific autoantibodies), inconclusive results for other pathologies including Wilson disease, transaminases significantly increased despite weight reduction, suspected advanced liver disease, and clinical trials.

Liver biopsy cannot be used as a screening test, therefore, there is a need for simple, non-invasive tests, that can determinate the histological severity and monitor disease progression. Several reports showed that serum markers