REVIEW ARTICLE

NASH IN CHILDREN – A SHORT REVIEW

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) describes a hepatic disorder with the typical characteristics of an alcoholic liver disease without alcohol consumption. NAFLD is the most common metabolic paediatric liver disease. Prevalence of NAFLD is high in the Western hemisphere. Most of the data on paedriatic NAFLD originates from the West. Most of the patients with NAFLD are asymptomatic, and the disease is detected incidentally. The natural history of pediatric nonalcoholic steatohepatitis (NASH) has yet to be defined, but most of the biopsies in this age group demonstrate some degree of fibrosis. Distinct histological patterns of NASH have been identified in the pediatric population. While the optimal treatment of pediatric NAFLD has yet to be determined, lifestyle modification through diet and exercise should be attempted.

Key Words: *Nonalcoholic fatty liver disease (NAFLD), Nonalcoholic steatohepatitis (NASH), Cirrhosis, children.*

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) describes a hepatic disorder with the typical characteristics of an alcoholic liver disease without alcohol consumption. It encompasses simple steatosis to Non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. NAFLD is the most common metabolic paediatric liver disease. It is becoming an increasingly prevalent in the pediatric population in direct correlation with the emergence of childhood obesity as a significant pediatric health problem.

The term NASH is kept reserved to describe the progressive forms of NAFLD with degenerative changes and fibrosis. Histologically, NASH resembles alcohol-induced liver disease in the absence of alcohol abuse.

Prevalence of NAFLD is high in the Western hemisphere. Most of the data on paedriatic NAFLD are also from the USA, Italy, Japan and China with the prevalence varying considerably between 10-77%. Limited data is available on the prevalence of NAFLD in children from rest of the Asia, Africa and South America.

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Childhood obesity is no longer confined to Western society. It has become a global epidemic and continues to be a rapidly growing problem. An estimated 22 million of the world's children under the age of 5 years are overweight. Whereas an estimated 0.7% children in Africa show features of undernutrition, over 3% of them are overweight. Although in the fast developing countries of Asia, figures for childhood obesity are rising from the mid-1980s, to date little is known about this specific problem in the developing world and also about how changes of lifestyle and nutritional habits in recent years have affected development and growth in children and adolescents. Besides it is also not known whether the complications rate is similar to that in Europe and North America.

Risk Factors

Central obesity (BMI> or=30), diabetes mellitus, dyslipidemia and hypertension are strongly associated with NAFLD.[1] Subjects with visceral fat adiposity appear to be at risk for fatty liver because of their ability to transport free fatty acids directly into the portal vein for conversion to triglycerides within the liver. A stronger relationship of serum ALT to visceral adiposity than BMI is demonstrated.[2] The severity of sonographic steatosis is positively correlated with BMI, raised ALT, insulin resistance and hypertryglyceridaemia.[3] BMI > 26.3 is the only independent predictor of fibrosis.[4]

Incidence and Prevalence

Type 1 and type 2 NASH are distinct subtypes of pediatric NAFLD. The NASH types differ significantly ($P < .001$) by race and ethnicity. Type 1 NASH is more common in white children, whereas type 2 NASH is more common in children of Asia and Native America, and Hispanic ethnicity.[5] Boys are significantly ($P < .01$) more likely to have type 2 NASH and less likely to have type 1 NASH than girls.[5] In obese individuals, Hispanic ethnicity and male gender appear to increase the risk.[6]

Clinical Manifestation

Most patients with NAFLD are asymptomatic, and the disease is detected incidentally. Some patients complains of fatigue, malaise, and vague right upper abdominal discomfort. The most common signs are hepatomegaly and laboratory abnormalities, which include a 2-4-fold elevation of serum aminotransferase levels, while other liver function test results are usually normal unless advanced liver disease is present. Most are obese, many have diabetes mellitus, hypercholesterolemia, or hypertriglyceridemia.[7]

Pathogenesis

The exact pathophysiology of NAFLD remains unclear, although the interplay of insulin resistance, oxidative stress, and release of proinflammatory cytokines are implicated in the process. The 'two hit' hypothesis constitutes the currently prevailing theory for the development of NAFLD and nonalcoholic steatohepatitis. The first hit is fat accumulation in the hepatocytes. This is believed to be caused by insulin resistance by means of increased lipolysis and increased delivery of free fatty acids to the liver. The second step includes endotoxins, cytokines and environmental toxins causing oxidative stress and lipid peroxidation contributing to the development of necroinflammation and fibrosis.

Histology

The major histologic features of NAFLD resemble those of alcohol-induced liver disease and include steatosis (fatty liver), steatohepatitis (fatty liver plus parenchymal inflammation with or without accompanying focal necrosis), and variable degrees of fibrosis (including cirrhosis). However, significant histological differences exist between adult and paediatric NAFLD.[8] Two distinct histological patterns of NASH have been identified in the pediatric population, and discrete clinical and demographic features are observed in children with these two patterns. Type 1 is characterized by steatosis, ballooning degeneration, and perisinusoidal fibrosis; type 2 is characterized by steatosis, portal inflammation, and portal fibrosis.[5] In cases of advanced fibrosis, the pattern is generally that of type 2 NASH.[5] The propensity for NASH to develop in obese, insulin-resistant pubertal boys of Hispanic ethnicity or a non-Hispanic white race may provide clues to the pathogenesis of NAFLD in children.

In contrast to morbidly obese adults, lobular inflammation, significant ballooning, and perisinusoidal fibrosis are rare, whereas portal inflammation and portal fibrosis were more prevalent, even in those who did not meet criteria for NASH. These findings support use of a modified scoring system for pediatric NASH. Presence of the metabolic syndrome in morbidly obese adolescents does not distinguish NASH from steatosis alone.[9]

Diagnosis

NAFLD should be considered in obese children which have abnormal liver enzymes, hepatomegaly, or bright liver on ultrasound and present with features of metabolic syndrome. Liver biopsy can provide critical diagnostic and staging information.

Although associated with childhood obesity other liver diseases causing fatty liver and/or abnormal liver tests, notably Wilson disease and chronic viral hepatitis, need to be excluded. Associated genetic or endocrine disorders need to be identified.

Other noninvasive methods used in NAFLD include:

- Liver stiffness measurement: Transient elastography which is an accurate and reproducible methodology to identify pediatric subjects without fibrosis or significant fibrosis, or with advanced fibrosis.[10]
- Serum type III procollagen (PCIII) level is an early and sensitive indicator of NAFLD and is correlated with the disease progress.[11] Increasing aspartate aminotransferase AST level and gamma-glutamyltransferase level are associated independently with increasing severity of NASH.[12]

Natural History

The natural history of pediatric NASH has yet to be defined, but most of the biopsies in this age group demonstrate some degree of fibrosis. In addition, cirrhosis can be observed in children as young as 10 years.[13,14]

Treatment

There is no consensus on the treatment of pediatric nonalcoholic fatty liver disease (NAFLD). While the optimal treatment of pediatric NAFLD has yet to be determined, lifestyle modification through diet and exercise should be attempted in children diagnosed with NAFLD. Where possible, a team approach, including a dietician and psychologist, should be utilized, as adolescents do better in a supportive atmosphere. Current front-runners are vitamin E and metformin. Metformin do not appear more effective as compared lifestyle intervention in ameliorating levels of aminotransferases, steatosis, and liver histology in these children with NAFLD.[15] Daily oral vitamin E administration normalized the serum aminotransferase and alkaline phosphatase levels in children with NASH.[14] The roles of drugs that alter appetite and bariatric surgery for adolescents with NAFLD have not yet been determined.

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CONFLICT OF INTEREST
Authors declare no conflict of interest