FATTY LIVER DEGENERATION IN CHILDREN: ASSOCIATION WITH OBSTRUCTIVE SLEEP APNEA

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ABSTRACT

Fatty liver degeneration, also termed hepatic steatosis, is a condition in which lipids accumulate in the hepatocytes causing cellular dysfunction and eventually cell death. Hepatic steatosis is diagnosed histologically when liver fat exceeds more than 5% of the liver weight. In adults, fatty liver degeneration is typically associated with excessive alcohol intake as in alcoholic fatty liver disease or with sedentary lifestyle and high-calorie diet as in non-alcoholic fatty liver disease (NAFLD). With the rise of obesity in recent decades, fatty liver disease has become the leading cause of chronic liver disease, not only in adults but in children as well. Besides liver disease, obesity is associated with several conditions among which is obstructive sleep apnea.

The aim of this article is to review the pathogenesis of fatty liver degeneration focusing on NAFLD and its relationship with obstructive sleep apnea in children.

Keywords: *pediatric fatty liver, pathogenesis, obstructive sleep apnea*

INTRODUCTION

Fatty liver degeneration, also termed hepatic steatosis (HS), is defined as hepatic lipid accumulation affecting more than 5% of the total weight of the organ (1). Histologically, there are two forms of hepatic steatosis termed macrovesicular and microvesicular (2). Macrovesicular steatosis is characterized by one large vacuole containing triglycerides, which displaces the cell's nucleus to its periphery, whereas microvesicular steatosis is characterized by multiple miniscule lipid droplets in the hepatic cytoplasm, giving it foamy cytoplasm.

In adults, fatty liver degeneration is typically associated with excessive alcohol intake as in alcoholic fatty liver disease (AFLD) or with sedentary lifestyle and high-calorie diet as in primary non-alcoholic fatty liver disease (NAFLD) (3). Even though obesity is the leading cause of NAFLD in adults, the same correlation cannot be established for pediatric patients (4). In children fatty liver disease can also be caused by viral disease, inherent metabolic disease of lipid and carbohydrate metabolism, Wilson's disease, α1-antitrypsin deficiency, autoimmune disease, drugs, toxins, severe malnutrition or feeding disorders in which case NAFLD is termed secondary (5). NAFLD is an inclusive term used to describe a whole spectrum of diseases. Based on histology, NAFLD is further classified as non-alcoholic fatty liver (NAFL) or simple steatosis, non-alcoholic steatohepatitis (NASH) when inflammation is present, and NAFLD with fibrosis when periportal, portal or sinusoidal fibrosis is present (3).

EPIDEMIOLOGY

Because of its close association with obesity, NAFLD has become the most common chronic liver disease in both adults and children. Because the definitive diagnosis of NAFLD in children is reached by performing liver histology (1,3), the exact prevalence and incidence of the disease are unknown. According to a Schwimmer J et al. (6), who made a retrospective review of 742 children between 2 and 19 years of age who had an autopsy from 1993 to 2003, fatty liver was present in 13% of the subjects. After adjusting for age, gender, race and ethnicity, the authors estimated the prevalence to be 9.6%, the highest being for 15 to 19 years of age (17.3%) and obese children (38%).

A clear rise in prevalence meeting the rise of obesity during the last decade was elucidated by Welsch J. et al (7), who performed a cross-sectional retrospective study of the data from 12714 children between 12-19 years of age from the National Health and Examination Survey from 1988-1994 and 2007-2010. Using screening criteria for diagnosis of possible NAFLD (BMI > 85th percentile and alanine aminotransferase level >25.8 U/L for boys and >22.1 U/L for girls), the authors concluded that the prevalence of suspected NAFLD had risen twice over the investigated period, affecting half of the obese patient and 10.7% of all the patients included in the study.

Although the prognosis of pediatric NAFLD remains uncertain, given that it is by definition an early onset disease, it may represent an aggressive disease phenotype.

PATHOGENESIS

Currently, the pathogenesis of NAFLD is defined by multifactorial interaction, leading to hepatic triglyceride accumulation, termed the "multiple hit" hypothesis (8). At disease onset, genetic susceptibility, epigenetic mechanisms, sedentary lifestyle and hypercaloric diets lead to increased delivery of carbohydrates and free fatty acids (FFAs) to the organism. Under the effect of insulin, carbohydrates are used to form acetyl-coenzyme A, which is used in lipogenesis in the liver with the resulting FFAs transported to the adipose tissue for storage. In the adipocytes, insulin causes inhibition of lipolysis and induces esterification of FFAs to triacylglycerol (TAG), which is stored in the adipocytes.

Over time, insulin resistance (IR) ensues by lipid accumulation interfering with insulin receptor phosphorylation which leads to unsuppressed lipolysis in the adipocytes and release of FFAs to the liver. Hepatocytes also experience IR, which leads to reduced suppression of gluconeogenesis but preserved stimulation of lipogenesis. The accumulated lipids in the hepatocytes are mainly in the form of TAG, which can be considered a protective mechanism because TAG is not hepatotoxic unlike FFAs. When lipid efflux exceeds the ability of the liver for triglyceride storage, FFAs exhibit their lipotoxicity, which predisposes the hepatic cells to "secondary hits" such as pro-inflammatory cytokines, oxidative stress, and mitochondrial dysfunction (9,10).

Relationship Between Obstructive Sleep Apnea and NAFLD in Childhood

An example of "secondary hit", which induces a more severe form of NAFLD, is obstructive sleep apnea (OSA). Patients with OSA experience episodes of recurrent upper-airway obstruction during sleep, leading to hypoxia alternating with normoxia (chronic intermittent hypoxia - CIH), resembling the pathophysiology of ischemia/reperfusion injury. The condition is associated with all manifestations of metabolic syndrome, including obesity and NASH. The direct association of CIH and NASH was documented by Savransky et al. (11) using mice on high-cholesterol, high-fat diet for 6 months and simultaneously exposing them to CIH which resulted in raised ALT and AST levels, inflammatory infiltration and fibrosis of the liver, and significant increases in levels of pro-inflammatory cytokines IL-1β, IL-6, and MIP-2 in liver tissue, whereas control animals on the same diet exhibited liver steatosis without any evidence of inflammation. Murine models on regular diet exposed to different CIH have shown that both severe CIH with an inspired oxygen nadir of 5% and moderate CIH with an inspired oxygen nadir of 10% lead to lipid peroxidation in the liver, and the levels of lipid peroxidation are related to the severity of hypoxia (12).

The link between OSA and NAFLD has been recognized not only in adults (13) but in children as well (14,15). The prevalence of NAFLD in pediatric patients suffering from OSA was described by Kheirandish-Gozal et al. (16), who studied 518 consecutive snoring children 4 to 17 years of age who were being evaluated for habitual snoring and suspected OSA. Among the 142 overweight/obese children, 46 had elevated LFT levels (32.4%); of these children, 42 had OSA (91.3%). In contrast, OSA was present in only 71.8% of Ob children without elevated LFT level ($p < 0.01$).

Regarding treatment, in 2018, Sundaran et al. (17) studied 9 pediatric patients with biopsy proven NAFLD before and after treatment with continuous positive airway pressure (CPAP) including laboratory testing and F(2)-isoprostanes – a marker of oxidative stress, compared to a control group. The authors reported that at baseline the target group had severe OSA, metabolic syndrome, elevated aminotransferases and high F(2)-isoprostanes. After treatment duration of 89 ± 62 days with adherence of 296 minutes/night and 73% of nights prescribed, the treatment group showed improvement not only in obstructive sleep apnea/hypoxia severity but also in alanine aminotransferase level, metabolic syndrome markers and F(2)-isoprostanes. Unfortunately, the sample size of the study was a limiting factor to reaching statistical significance.

CONCLUSION

The emerging global obesity epidemic has made pediatric NAFLD one of the most common chronic liver diseases in childhood, with estimates of 9.6% of children being affected. Because NAFLD is part of the spectrum of obesity related diseases, care should be taken to consider co-existing conditions which may be associated with NAFLD progression such as OSA. Based on the current evidence that the risk of NAFLD is higher in habitually snoring obese children and that CPAP therapy is associated with improvement in surrogate markers for disease severity, obese children with OSA may benefit from coordinated treatment and evaluation of ENT specialists and gastroenterologists.

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