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CASE REPORT

Liver cirrhosis secondary to nonalcoholic fatty liver disease in a 10-year-old child: a case report and review of the literature

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Abstract

Nonalcoholic fatty liver disease is a major cause of liver disease worldwide. In parallel with the increasing prevalence of obesity and other components of the metabolic syndrome, it is increasingly recognized in children and has become a worrying phenomenon. Although fibrosis is common in pediatric nonalcoholic steatohepatitis, rarely cirrhosis has been reported in this age group. In this paper, a child was reported with morbid obesity and type 2 diabetes, who developed liver cirrhosis from nonalcoholic steatohepatitis at the age of 10 years old, providing a review of the literature.

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INTRODUCTION

Childhood obesity epidemic is one of the most important public health problems in the world. It is an established risk factor for nonalcoholic fatty liver disease (NAFLD), a term which refers to chronic hepatic steatosis (lipid deposition in greater than 5% of hepatocytes), after other secondary causes of steatosis (such as viral hepatitis, autoimmune hepatitis, steatogenic medications, alcohol consumption, or inborn errors of metabolism) have been put aside[1].

NAFLD is the most common cause of liver disease in children and its prevalence continues to increase overtime. Its pathophysiology, natural history, and disease progression are still being clarified, but pediatric NAFLD may represent a more serious phenotype that will benefit from early identification and management, and careful medical monitoring[2]. A child with morbid obesity and type 2 diabetes was reported, who developed liver cirrhosis from nonalcoholic steatohepatitis at the age of 10 years old.

CASE REPORT

The patient was a full-term newborn, adequate or gestational age, exclusively breastfed up to 6 months, and developed obesity in her first year of life. At the age of 8 years, she went to the hospital vomiting and was diagnosed with type 2 diabetes (diabetic ketoacidosis was excluded, and at that time, HbA1c was 10.6%, and insulin 30.7UI/mL). Her follow-up was irregular, she missed a lot of medical appointments and had poor adherence to lifestyle and pharmacologic interventions. At 10 years old, she returned to an endocrinology appointment, her weight was 86.6kg, height 152cm (95th percentile by the WHO chart height for age), body mass index (BMI) 37.48 kg/m^2 (>99th percentile by the WHO chart BMI for age). Abdominal examination showed mild right upper quadrant tenderness and hepatosplenomegaly. She also had acanthosis nigricans in cervical, axillary and antecubital fossa.

The clinical history was negative for drug intake, parenteral exposure to blood products or illegal substances. She was nondysmorphic and had no clinical signs of genetic disorders. The family record was negative for liver disease. Laboratory studies revealed: glucose 288mg/dL, HbA1c 10.7%, albuminuria 61.5mg/L, aspartate aminotransferase (AST) 66U/L, alanine aminotransferase (ALT) 69U/L, gamma-glutamyl transpeptidase 79U/L, alkaline phosphatase 157U/L, total bilirubin 0.6mg/dL, lipase 45U/L, creatinine 0.4mg/dL, total cholesterol 147mg/dL, HDL 27mg/dL, triglycerides 246mg/dL, INR 1.13, prothrombin time (PT) 15.3 sec and PT activity 81%. Other causes of chronic liver disease were excluded.

An abdominal ultrasound showed a liver measuring 21cm at the level of the left lobe, with slightly serrated contours and blunt edges, with very high echogenicity, grade III/III; the right lobe measuring 18cm (Figure 1); nondilated biliary tract and normal gauge port vein (0.7cm); homogeneous spleen with 19cm; there was no ascites or adenomegaly. Liver

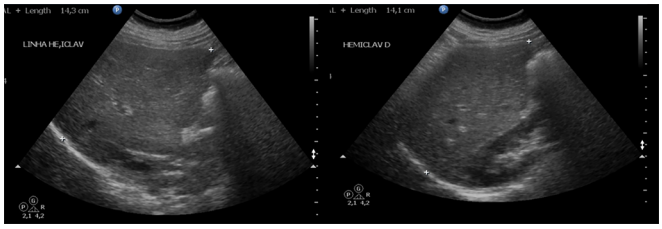


Figure 1. Abdominal ultrasound.

biopsy was performed, demonstrating a micronodular cirrhosis with thick septa and steatohepatitis with mild activity - NAS (NAFLD Activity Score) 5 (steatosis 3, lobular inflammation 1, ballooning 1) (Figure 2). Overnight polysomnography was compatible with obstructive respiratory disorder during sleep in moderate degree. Echocardiography was in the limits of normality for the age group. Videoesofagogastroduodenoscopy to rule out esophageal varices was normal.

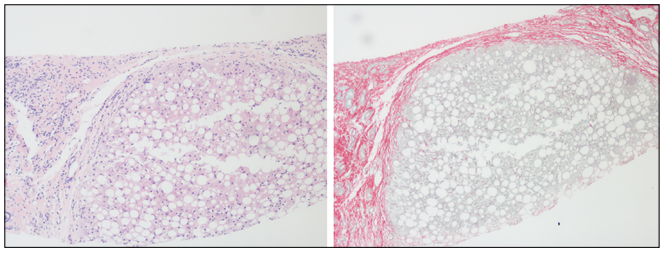


Figure 2. Pathology - liver biopsy.

A multidisciplinary weight reduction program with psychologist, nutritionist, physician, nurse and physiotherapist included hypocaloric diet with 1,000kcal/day, exercise and pharmacologic treatment - topiramate 100mg, fluoxetine 10mg, metformin 850mg 3 times daily and enalapril 5mg (for albuminuria). A weight loss of 12.3% was achieved and the patient reached 75.9kg in the second month of treatment. At that time, compared to the previous ultrasound, there was also a reduction in hepatomegaly (left lobe went from 21cm to 15.2cm and right lobe from 18cm to 16.4cm); HbA1c was 5.7%; ALT 2 U/L; AST was 30U/L.

DISCUSSION

It is estimated that about 25% of the world population has NAFLD. Although most cases occur in adults, it is now the leading chronic liver disease in children worldwide[3,4]. Estimating the prevalence of NAFLD in children is difficult mostly due to variations in study designs, reference methods and thresholds for detection. In the US, it varies from 7.6% in the general population, 34.2% in studies based in pediatric obesity clinics, and can reach up to 76% of NAFLD in studies evaluating severely obese pediatric population undergoing bariatric surgery[2,5]. Moreover, nonalcoholic steatohepatitis (NASH), which is a more severe phenotype of NAFLD defined by the histologic findings of inflammation, with or without ballooning injury to

hepatocytes and fibrosis, is the fastest-growing indication for liver transplant among young US adults[2,6].

NAFLD results from the combination of environmental influences and predisposition of genetic variants. Risk factors include obesity, diabetes, hyperlipidemia and panhypopituitarism. There are many studies exploring its association with other factors, such as intestinal microbiome, epigenetics, and dietary risk determinants, like fructose and added sugars[1,7]. The natural history of this comorbidity in children is not well-described. It seems to be asymptomatic in most pediatric population, but symptoms, when present, include abdominal discomfort, fatigue and irritability. The patient from the present study showed acanthosis nigricans, which is a frequent sign, reflecting the association between NAFLD and insulin resistance.

In rare cases, children can have rapid progression of the disease, leading to cirrhosis and life-threatening complications[1]. Sharma et al. (2014)[8] reported a case of liver cirrhosis secondary to NAFLD in a 12-year-old girl of Middle Eastern origin with a BMI of 52kg/m^2, diabetes, severe obstructive sleep apnea and central hypoventilation. Molleston et al. (2002)[9] described a case of a 10-year-old Hispanic boy with a BMI of 32kg/m^2, showing fatigue and elevated aminotransferases, with a liver biopsy consistent with cirrhosis. The same authors also reported a case of a 13-year-old boy that gained more the 30kg and developed diabetes mellitus after resection of a large craniopharyngioma, with postoperative hypopituitarism and diabetes insipidus. At age 14, he developed variceal bleeding, mild encephalopathy and ascites, with liver histology consistent with cirrhosis[9].

Screening laboratory test with ALT is recommended in children from 9 years old if obese (BMI ≥95th percentile) or if overweight (BMI ≥85th percentile and <94th percentile) with additional risk factors. Screening is also advised in younger patients with severe obesity; with a family history of NAFLD; or with hypopituitarism. It is recommended to use the upper limit of normal of 22U/L for girls and 26U/L for boys. In case of normal results, ALT should be repeated every 2 to 3 years if risk factors persist, or earlier if clinical worsening. Ultrasound is not recommended as a screening test for NAFLD in the pediatric population[2].

Once chronic elevation of ALT is detected, it is important to exclude other causes of hepatic injury. Magnetic resonance based methods can detect and quantify hepatic steatosis in children and are more accurate than ultrasonography. Liver biopsy remains the current standard to diagnose NAFLD and to ascertain its severity[2].

Weight management focusing in lifestyle modifications is the established treatment for NAFLD. It is often recommended to avoid sugar-sweetened beverages, consumption of balanced diets, daily moderate-to-high-intensity physical activity, reduced screen time (no more than 2 hours per day), and family engagement[10]. Patients should be counseled to avoid alcohol consumption and must be immunized against hepatitis A and B.

No medication or supplement is currently recommended for routine treatment of pediatric NAFLD. Pharmacologic therapies studied include metformin, cysteamine bitartrate, ursodeoxycholic acid, probiotic supplements, and omega-3 supplements, with variable and inconclusive results[11]. Treatment with vitamin E appears to improve some histologic features of NAFLD in children, but the evidence is limited; there may be long-term adverse effects, and its clinical impact has not yet been established[11]. In adults who suffer from diabetes mellitus and NASH, pioglitazone and liraglutide improve fibrosis, inflammation and steatosis, but these drugs are not approved to be used in the pediatric population.

Weight loss surgery is a potential treatment that may be considered for several obese adolescent patients without response to nonsurgical treatment, but there are few data evaluating improvement of NASH after bariatric surgery in this population. Besides, follow-up of children and adolescents with bariatric surgery will demonstrate clinical outcomes into adulthood[12,13].

Although changes in ALT do not necessarily correlate with disease severity, it should be evaluated in association with the patient's clinical history and physical examination to monitor treatment. ALT normalization, or its reduction of more than 50%, are used as parameters of NAFLD improvement in clinical trials. Particularly in children with advanced stages of NAFLD in previous biopsies or with clinical worsening, a new biopsy should be considered.

In the pediatric population, NAFLD is an underdiagnosed and undertreated disease. Future researches should focus on innovative pharmacological approaches, development of strategies for comorbidity treatment and promotion of adherence to lifestyle modifications. This case report demonstrates rapid development of cirrhosis in an obese diabetic child, emphasizing the importance of careful monitoring of children with risk factors, since NASH may not be an indolent process in this population; progression to cirrhosis, although rare, can happen and implicates a worse prognosis.

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