The Progression and Natural History of Pediatric Nonalcoholic Fatty Liver Disease

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KEYWORDS

• Children • Adolescents • Nonalcoholic steatohepatitis • Obesity • Epidemiology • Morbidity • Mortality • Outcomes

KEY POINTS

- Evidence suggests nonalcoholic fatty liver disease (NAFLD) may begin in the perinatal period in children of diabetic mothers.
- Pediatric NAFLD is typically diagnosed between 10 and 13 years of age.
- At diagnosis, among children with NAFLD, 25% to 50% of children have nonalcoholic steatohepatitis and 10% to 25% have advanced fibrosis.
- Cardiovascular derangement in the form of left ventricular dysfunction and increased left ventricular strain and mass is observed in adolescents with NAFLD, raising concern for premature cardiovascular morbidity and mortality.
- Obesity in childhood is a known risk factor for hepatocellular carcinoma in adulthood.

INTRODUCTION

The question of interest this review addresses is: What is the progression and natural history of nonalcoholic fatty liver disease (NAFLD) in children? The natural history of pediatric NAFLD is a complex topic, in that there is a paucity of longitudinal data in children with NAFLD. Understanding the natural history is also challenging because

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it is difficult to properly date the onset of disease. Currently, there is insight about the range of disease severity at the time of biopsy diagnosis. With respect to progression over time, however, the data are lacking. One cannot assume that the time point of clinical diagnosis equals the starting point. In fact, for most children with NAFLD, disease onset is unknown. Thus, a better understanding of the severity range, variability, and associations of pediatric NAFLD is important, as children may represent different time points on a history continuum.

In order to answer the broad question of the natural history of NAFLD in children, this article is divided into the following series of subquestions to better address the comprehensive clinical phenotype:

1. When does NAFLD start in children?
2. What is the histologic starting point and severity?
3. What is the associated morbidity?
4. What is the longitudinal hepatic outcome?

When Does Nonalcoholic Fatty Liver Disease Start in Children?

Some data suggest that NAFLD begins in utero. Two studies have used neonatal magnetic resonance spectroscopy (MRS) to assess steatosis in infants born to mothers with gestational diabetes. Hepatic fat fraction (HFF) at 1 to 3 weeks of age was performed in neonates born to normal weight mothers (n = 13) and was compared with those born to obese mothers with gestational diabetes (n = 12). In this study, neonates born to obese mothers with gestational diabetes had a mean HFF that was 68% greater than infants born to normal weight mothers.[1] In a study by Modi and colleagues,[2] 105 mother/neonate dyads were studied to determine if maternal body mass index (BMI) influenced neonatal HFF. Their key finding was that maternal BMI at conception was associated with neonatal HFF. Similarly, the presence and severity of fetal hepatic steatosis were assessed in 33 stillborn babies of diabetic mothers compared with 48 stillborn babies of mothers without diabetes.[3] The diabetic mothers were more likely to be obese compared with controls (61% vs 33%). There was a substantially higher rate of hepatic steatosis in neonates born to mothers with diabetes (79%) versus controls (17%). It is not known, however, if the steatosis identified in the neonatal period progresses to the NAFLD that is typically diagnosed in adolescence.

There is evidence that postnatal factors may also have an effect in pediatric NAFLD. Breast-feeding, for example, has also been postulated to be protective for NAFLD. In a study of 191 Italian children with biopsy-proven NAFLD, hepatic steatosis, inflammation, hepatocyte ballooning, and fibrosis were worse in children who were not breast-fed compared with breast-fed children.[4]

If NAFLD begins in utero, at birth, or soon after, one would expect a meaningful prevalence of NAFLD in very young children. However, in the Study of Child and Adolescent Liver Epidemiology (SCALE), this was not the case in the younger age group, whereby the prevalence of NAFLD for a 10-year period 1993 to 2003 was 0.7% in children aged 2 to 4 years.[5] As opposed to a general population-based study, there may be unique populations of young children with higher rates of NAFLD. In a study of obese preschool-aged children in Chicago, elevated alanine aminotransferase (ALT) was reported in 26% of obese children aged 2 to 5 years.[6] In a study of Hispanic children in Houston with most of the children being obese, ALT greater than 35 U/L was reported in 15% of 4 to 5 year olds.[7] Several gaps remain. In the 2 studies of ALT in preschool children, it is not known how many actually had NAFLD. Also, this population does not typically have symptoms and is well below the age at