Childhood and Adolescent Nonalcoholic Fatty Liver Disease: Is It Different from Adults?

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Paediatric nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in childhood and adolescence. Although the condition is similar in many ways to NAFLD in adults, there are important differences in predisposition, presentation, differential diagnosis and potentially also in optimal management. Antenatal and early childhood exposures and the particular vulnerabilities to environmental influences in a growing child, present unique opportunities for intervention and modification of risk. The prevalence of significant fibrosis on biopsy in preadolescent children in the context of NAFLD should not be ignored, but the relevance of this fibrosis to long-term outcome is as yet unknown. The approach to children and adolescents with suspected NAFLD needs to include an assessment of risk factors in addition to exclusion of alternative or coexisting liver diseases. Liver biopsy is indicated for younger children and for those without clear predisposing factors leading to metabolic syndrome, also for those in whom significant fibrosis is suspected. The histology in children and adolescents differs from adults in whom type 2 NAFLD may be more prevalent, which is associated in turn with more significant fibrosis. Management in children and adolescents needs to focus on lifestyle intervention, which when weight loss is achieved, demonstrates excellent results in terms of resolution of disease. Appropriate intervention in childhood and adolescence may prove instrumental in avoiding the need for later transplantation while also decreasing all-cause mortality in these at-risk individuals. (J Clin Exp Hepatol 2019;9:716–722)

Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming the most common indication for liver transplantation in the Western world.[1] Paediatric NAFLD is thought to be as an early presentation of the adult condition and, in general, is thought not to frequently progress to decompensated end-stage liver disease or to hepatocellular carcinoma in childhood. That said, paediatric NAFLD presents both challenges and opportunities in terms of both diagnosis and management. Several important distinctions exist between adult and paediatric disease that need to be understood before we can effectively approach the management. It is not clear why some patients with NAFLD present during childhood with significant fibrosis often; it is possible that this is merely incidental, and the course of disease is still over 40–50 years before the end stage. The alternatives, however, are that paediatric NAFLD is a distinct disease with different susceptibilities and pathophysiology than the adult disease or that presenting in early life forebodes more significant or severe disease.[2] The question of the long-term outcome of those with paediatric-onset NAFLD is as yet unanswered.

In the first instance, early-life susceptibilities to the condition are most often identifiable in paediatric- versus adult-onset NAFLD. Preconception maternal obesity and gestational diabetes are recognised as important risk factors that need to be addressed at a societal and preventative level.[3] Early feeding practices, weaning and the exposure of children to the dangers of the high-sugar westernised diet particularly during a vulnerable stage of development are all relevant. The rapid physical and psychological changes that occur during adolescence during which insulin resistance peaks and body mass is laid down denote a critical period in which metabolism is regulated and may also be important in establishing or avoiding liver damage.

This review will approach paediatric NAFLD from the viewpoint of a comparison with adult disease and the different approach that may be taken in light of this distinction.

EPIDEMIOLOGY

NAFLD is thought to affect 10% of children younger than 18 years, as demonstrated by a post-mortem study of livers of children and young people who suffered unnatural death. Steatosis was found in 9% of children, with 3% having evidence of liver inflammation/fibrosis.[4] Epidemiological studies are less likely to use histological definitions of the disease, and the prevalence varies accordingly. When

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ultrasound is used to assess steatosis, prevalence varies from 1.8% in a normal population of children and young people to 60% of children and young people undergoing bariatric surgery to 80% of those in an obesity clinic.[5–7]

These figures are not far from adult prevalence and are closely linked to the prevalence of obesity. Severity of the disease in children does not necessarily associate directly with severity of obesity for example, and possibly, different prenatal and childhood exposures on a genetically susceptible individual may predispose to the early onset of disease. The degree of obesity in an individual does not correlate to severity of liver disease in that individual.[8] The concept that those with certain genetic susceptibilities should have a 'normal' body mass index (BMI), which may be less than the conventional 'normal', holds true for this condition.

SUSCEPTIBILITY

The effects of the intrauterine environment in terms of priming may be more relevant to paediatric patients in terms of developing NAFLD.[9] Both small-for-gestational-age and large-for-gestational-age infants are over-represented in those who develop NAFLD during childhood and adolescence.[10] Intrahepatic lipid content investigated using magnetic resonance imaging (MRI) is higher in infants of mothers who were obese and those with type 2 diabetes than in those born to normal-weight mothers.[11,12] Interestingly, intrahepatic fat content was more closely related to maternal BMI than to birthweight.[12] In a post-mortem study of stillborn infants, those born to mothers with gestational debates had a prevalence of 78.8% steatosis versus those stillborn infants of mothers who were not diabetic.[13] Deposition of subcutaneous fat does not occur until the third trimester; it is conceivable that there is hepatic storage of excess substrate in the foetal liver, in addition to in utero *de-novo* lipogenesis in response to a high transplacental glucose supply.[9] Insulin does not cross the placenta, but it is thought to increase placental inflammation, altering the transfer of nutrients to the foetus. In addition, increased fatty acids signal placental toll-like receptor 4 expression; again, this pro-inflammatory response may increase foetal nutrient transport.[14]

Placental insufficiency has also been associated with a higher inflammatory milieu and increased metabolic risk.[15] There is a clear relationship between maternal obesity and BMI in childhood.[16,17] It is thus likely that the consequent complications of obesity, including NAFLD, will follow this increased risk.[18]

The link between antenatal and early postnatal exposure and NAFLD is complex and multifactorial. In part, the possibility is that the microbiome may be involved in establishing susceptibility to poor metabolic health. Infants with decreased micro biome diversity at the age of 6 months are at a greater risk of obesity by the age of 7 years than controls.[19] It is known that immune tolerance is promoted by gut microbiota; this is also decreased in offspring of obese women.

Breastfeeding, which has shown to be protective against NAFLD in some studies (although the confounding principles of socioeconomic influences on this observation are difficult to be unpicked), may act in part at least via the microbiome, although the confounding issue of socioeconomic influence. Breastfeeding promotes colonisation of the intestinal microbiome, providing oligosaccharides as prebiotics.[18]

Animal studies can elucidate further the antenatal risk to the foetus and the compounding influence of early-life exposure. In mice, a study reported the influence of the high-fat diet (HFD) in dams and in pups versus controls. The HFD in dams led to fatty liver in offspring; this was seen to a greater extent when the pups were also fed HFD but also seen in normal-fed chow-fed pups. HFDs both before and after pregnancy lead to cumulative risk.[20] Both DNA methylation alteration[21] and a decrease of diversity in the microbiome are possible mediators of this effect. Another mouse model of maternal obesity demonstrated higher oxidative stress and impairment of innate immunity in pups after an in utero HFD. At 12 months, the pups showed steatohepatitis and fibrosis with an increased number of inflammatory and fibrogenic mediators.[22]

A similar experiment in rats demonstrated a sex prediction in that male offspring of high-fat dams demonstrated more injury than females, possibly due to the different growth trajectory expected in male versus female pups.[23]

Nonhuman primates fed with a HFD before breeding, which was then normalised during pregnancy, demonstrated that effects on offspring can be modified. An increased liver triglyceride content with increased expression of lipogenic genes in liver tissue and increased activation of inflammatory gene expression was demonstrated in these animals.[24]

GENETICS

In terms of genetic susceptibility, findings in children largely mirror those in adults with the minor allele of PNPLA3 (rs738409) widely reported as a susceptibility factor,[25,26] and frequency varies according to ethnicity of the patients affected. Other genetic variants such as TM6SF2 rs58542926[27,28] and GCKR[29] are implicated in susceptibility, but there have been few widespread paediatric genome wide association study (GWAS), and there was only one study on biopsy-proven NAFLD in children.[30] In this study, 234 Hispanic boys were investigated for genetic variations, predisposing them to NAFLD. In addition to PNPA3 and TMSF6, the authors found that novel variants in trafficking protein particle complex 9 (TRAPPC9) were associated with the NAFLD activity score (NAS), and a

single-nucleotide polymorphism in a region close to actin-related protein 5 was associated with fibrosis.

Clearly, genetic variation plays some part but is not in itself sufficient to explain propensity to disease. Given that even within the obese population, genetic susceptibility only comprises part of the risk, much focus has been given to dietary components and whether specific diets convey risk.

DIETARY INTAKE

Many studies have drawn associations between the intake of fructose, saturated fat and decreased fibre intake, polyunsaturated fats and the development of NAFLD.[31] Children have a particularly high consumption of fructose containing sweetened beverages up to 300 kcal/day.[32] In addition, children have the highest intake of ultraprocessed food at 33% (32.1–35%) versus that of adults at 29.6% (28.5–30.7%).[33] Both have been linked to poor metabolic health including NAFLD. Indeed, the consumption of a Western diet was strongly associated with NAFLD in both Australian[34] and Chinese adolescents.[35] A review of children with biopsy-proven NAFLD compared with obese controls in the UK did not reveal any major dietary differences between the two groups; however, the NAFLD group tended to be lighter and more active in general.[36] It is difficult to conclude that inclusion or exclusion of one or more components of the diet may make a difference to the development and progression of NAFLD in children.

DIAGNOSIS

The diagnosis of NAFLD in children brings challenges. Although significant alcohol consumption particularly in children younger than 14 years is unlikely to play a major contribution to liver injury, many other liver diseases of childhood may present with steatosis with or without inflammation and fibrosis. Given that 30% of the paediatric population worldwide is overweight or obese,[37] in those presenting with Wilson disease or other hepatitis C, the presence of overweight and obesity equates to the population norm. Thus, the presence of overweight or obesity does not mean that a child with steatosis does not have an alternative diagnosis to NAFLD! The workup for fatty liver, usually found incidentally when a child has blood tests for another reason and goes on to have an ultrasound scan because of abnormal liver function tests (LFTs), should be comprehensive.[38] In addition to screening for associated features of metabolic syndrome such as fasting lipid levels, hypertension, HbA1C, homeostatic model of assessment of insulin resistance (HOMA-IR) and impaired glucose tolerance, children should undergo a workup for alternate liver conditions. This should include, but is not limited to, infectious hepatitis, Wilson disease, inborn errors of metabolism (fatty acid oxidation disorders and mitochondrial disease), coeliac disease, alpha-1 antitrypsin deficiency and abnormalities of lipid metabolism (for example, hypobetalipoproteinaemia). There are several other conditions that may be investigated based on clinical suspicion and are summarised in Table 1. In addition, a full family, feeding and medication history should be taken. Parenteral nutrition and medications such as steroids, antipsychotics and antidepressants may all predispose to weight gain and steatosis.

Although the definition of NAFLD is a histological one, noninvasive methods to detect and stage the disease are now common in clinical practice.[39] The most useful is

Table 1 Differential Diagnosis of Fatty Liver in Children and Young People.

Differential diagnosis	Diagnosis
Wilson disease	Low ceruloplasmin, high urinary or tissue copper, mutational analysis
Alpha-1 antitrypsin deficiency	Phenotype / Genotype
Drugs—steroids, amiodarone, alcohol, methotrexate, MDMA (ecstasy), L-asparaginase, vitamin E, valproate, tamoxifen, antiretrovirals	History
Cystic fibrosis–associated liver disease	History/sweat test or mutational analysis
Malnutrition	History
Coeliac disease	Tissue transglutaminase/IgA, HLA typing, jejunal biopsy
Hepatitis C	HCV antibody status
Parenteral nutrition–associated liver disease	History
Mitochondrial disease/fatty acid oxidase deficiency	Lactate, acylcarnitines, respiratory chain enzymes, mutational analysis
Metabolic disease: lysosomal acid lipase deficiency (cholesterol ester storage disease)	White cell enzymes, mutational analysis
Galactosaemia	Gal-1-PUT
Fructosaemia	Enzymology
Glycogen storage disease	White cell enzymes, mutational analysis
Peroxisomal disorders	Very long-chain fatty acids, mutational analysis
Mauriac syndrome	History of type 1 diabetes
Hypobetalipoproteinaemia/ abetalipoproteinaemia	Low lipid levels, reduced/absent Apo1B, mutational analysis
Lipodystrophies	Mutational analysis
Shwachman syndrome	Pancreatic insufficiency/ mutational analysis

MDMA, 3,4-methylenedioxymethamphetamine; HLA, human leucocyte antigen; HCV, hepatitis C virus; Gal-1-PUT, galactose-1-phosphate uridyltransferase; Apo1B, apolipoprotein B.

the ultrasound that can detect >30% steatosis, which is probably the level at which it is most clinically significant. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamytransferase (GGT) levels may reveal liver inflammation at a point in time but will not reliably differentiate those with and without fibrotic disease, which is the main determinant of the outcome.

Radiological techniques such as magnetic resonance spectroscopy (MRS) and MRI proton density fat fraction will differentiate different grades of intrahepatic lipid, and MR elastography is a useful measure of liver stiffness—a proxy for fibrosis.[40,41] MRI is expensive and cumbersome and, however, not suited for day-to-day clinical practice, although it can be a useful research tool.

Transient elastography is well validated in paediatric and adult studies to detect fibrosis in NAFLD.[41,42] The relatively new controlled attenuation parameter measurement may also prove useful in quantifying steatosis in a longitudinal manner, but use in children has not been adequately validated as yet.[43]

Acoustic radiation force imaging and other types of shear wave elastography (aside from transient elastography (TE)) are other emerging methods of detection and quantification of fibrosis.[44] They have not yet been extensively validated in paediatric patients with NAFLD, although encouraging reports are emerging.[45]

Such is the enormity of the prevalence of NAFLD in the population, the question of who and when to refer to the paediatric hepatologist is a difficult one. In general, in those with a fatty liver on ultrasound, NAFLD is a diagnosis of exclusion. In the absence of the typical phenotype, other conditions must be suspected first. Even in those with other features of metabolic syndrome and a relevant family history of NAFLD, other or coexisting disease should be suspected. Severity of disease is not easy to elucidate in primary care. Several algorithms have been developed in large adult cohorts to differentiate significantly fibrotic disease. Unfortunately, most are not applicable to children, given that they include age, BMI (adult reference) or markers of collagen turnover. For example, it is well established that FIB4 is unreliable in those younger than 35 years;[46] the fatty liver index uses the BMI, the absolute number of which is not applicable to children (rather needs BMI z-score or centile).[47] The enhanced liver fibrosis (ELF) score uses P3NP as a variable, which is an age- and sex-dependent marker of collagen turnover.

The paediatric NAFLD score is the only paediatric-specific algorithm but still has not been validated outside of a Caucasian Italian population.[48]

Thus, as per both European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines, we first need to be cautious about making a positive diagnosis of NAFLD, considering relevant differential diagnosis.[49,50]

Histological diagnosis is ideal, although only rarely practical. Assessing severity of disease is focused on detection and staging of fibrosis. Until the time that appropriate serum biomarkers or algorithms are available and validated, the noninvasive determination of degree of fibrosis will be still limited to larger centres that have transient elastography or other imaging techniques for fibrosis readily available.

HISTOLOGY

Typical 'paediatric' NAFLD differs histologically from that in adults.[51] This pattern, found predominantly in children and young people, has been labelled 'type 2 NAFLD' and is periportal in distribution versus the largely pericentral disease in adults. In various series, the prevalence of type 2 histology differs.[51,52] Often, children may have a mixed type 1 and type 2 pattern. In type 1 NAFLD, steatosis, inflammation and fibrosis are mainly lobular, surrounding the central vein. In type 2, steatosis, inflammation and fibrosis are preferentially periportal. Ballooning, one of the classical histological features of NAFLD, is less common in children with type 2 disease.

The NAS was developed by a collaboration of pathologists using material from adults and children with NAFLD through the non -alcoholic steatohepatitis (NASH) clinical research network.[53] It is the most commonly used scoring system in the literature and is based on a score of 0–3 for steatosis, 0–2 for ballooning and 0–3 for lobular inflammation. Fibrosis is scored separately from 0 to 4. The diagnosis of nonalcoholic steatohepatitis from a research perspective is based on a NAS of 5 or more. A score of 2 or less is not NASH and 3 or 4 is borderline. Children tend to score lower on the NAS because of less lobular inflammation and ballooning. The presence of NASH was previously thought to be the most important prognostic factor in determining the outcome in patients with NAFLD. It is now recognised, however, that the presence of fibrosis is a more reliable predictor of the outcome, not least as the degree of inflammation in a biopsy may change over days to weeks.[54]

The presence of type 2 disease is associated with more advanced fibrosis and progressive disease.[55] Steatosis may be macrovesicular or microvesicular or both. The presence of microvesicular steatosis should prompt the possibility of mitochondrial disorders or other inborn errors of metabolism, although the prevalence of microvascular steatosis in adult-onset NAFLD is reported and associated with greater severity of disease.

The reason that children demonstrate relatively greater prevalence of type 2 disease is not entirely clear. It may be speculated that it could be linked to the development of zonation in the liver lobule.[56,57] Enzymes involved in the Krebs cycle are found mostly in zone 1 in the periportal region. Hepatocytes responsible for detoxification and metabolism due to the

p450 mechanism are preferentially located in zone 3 (perivenular). It is possible that the differential function along the lobule may predispose children to susceptibility to injury at different stages of development.[56,57]

NATURAL HISTORY AND TREATMENT

A handful of case series have reported on the long-term follow-up of children with NAFLD including the need for liver transplantation at an early age, although it is rare.[58–60] The difficulty with assessment of severe paediatric fatty liver disease is the concern that an alternative undiagnosed metabolic disease may be present, particularly in the case of 'lean NAFLD'.[38] In adults, it is thought to take approximately 7 years to progress one fibrosis stage.[60] A study analysed paired liver biopsies from 122 children who were in the placebo group in two randomised clinical trials for NAFLD (lifestyle advice only for either 52 or 96 weeks). During the trial period, the fibrosis stage progressed in 23% and improved in 34%. Younger children with more serve fibrosis at the time of biopsy may progress more readily, and it is likely that in these selected children, the effects of genetic variants on susceptibility may outweigh environmental factors.

Lifestyle change resulting in weight loss is an effective way of reversing or stabilising disease. A small number of trials in children have demonstrated the results. In an Italian study of 84 children, a weight loss average of 4 kg over a 12-month period resulted in an improvement in ALT and ultrasound features of steatosis.[61] There was a drop-out weight of 30%. Another paediatric study of intensive lifestyle intervention in North America achieved improvement in the BMI z-score with a decrease of 0.1 unit ($p < 0.05$) from baseline to one year and a decrease in ALT in 69% of the follow-up cohort. There was a 53% drop-out rate however.[62]

These results are reflected in the literature regarding adults with NAFLD; a meta-analysis of studies showed that achieving a weight loss of 5% or more resulted in improvement in steatosis, whereas a ≥7% weight loss resulted in improvement in steatohepatitis, and in those with ≥10% weight loss, all features of NAFLD were reversed or stabilised.[63] In a prospective study in adults, these outcomes were confirmed.[64] There was a high drop-out rate however, and only 50% successfully achieved a 7% weight loss or more. Of note, in 94% of those who achieved a ≥5% weight loss, fibrosis stabilised or reversed.

The success of weight loss alone on the outcome of patients with NAFLD is remarkable, yet the barriers to achieve this for all patients have not yet been adequately addressed. It is known that the coexistence of major depressive disorder, for example, is a major factor in the failure of lifestyle treatment of NAFLD. Willingness to engage in the programme and readiness to change are naturally crucial. The window of opportunity for many may be during childhood and early adolescence as the likelihood of overweight children becoming overweight adults is >80%.

There is a burgeoning industry in developing drugs and compounds to treat NAFLD, given the inability of many to lose weight. In children, neither the TONIC trial (comparing metformin, vitamin E and placebo)[65] nor the CYnCH trial (comparing cysteamine bitartrate and placebo)[66] reached their primary outcome measure. The use of vitamin E in improving some parameters of histology (ballooning) demonstrated statistical significance.

Newer, more targeted compounds such as FXR agonists, antifibrotic drugs and certain inflammation inhibitors show some promise in preclinical and early clinical trial, but use in children have not yet been studied.

Bariatric surgery has been clearly shown to reverse the disease;[6,67] it is not clear whether this effect is via decreased intake/appetite control or via other disruption of metabolic pathways by banding or by bypassing the stomach.

The opportunities to use intensive lifestyle change and maintenance of the lifestyle change through family education, counselling and an individualised approach are stark. Undoubtedly, deprivation and easy availability of ultraprocessed inexpensive foodstuffs is impossible to tackle at an individual level, and we need to exert our challenge at a societal level.

Paediatric NAFLD is a prevalent condition world-wide. Though it shares many features with adult – onset disease, paediatric NAFLD has important differences. In particular early life influences and susceptibilities and an approach to diagnosis and management need to be considered. There is a real opportunity to reverse the course of the disease in childhood and paediatricians should be aware and ready to act.

CONFLICTS OF INTEREST

The authors have none to declare.

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