

Review Article

Non Alcoholic Fatty Liver Disease- Is it a Rarity in Children of Bangladesh?

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Abstract:

Nonalcoholic fatty liver disease (NAFLD) is a disease of liver occurring due to excess accumulation of fat in the liver. For defining NAFLD, there must be evidence of hepatic steatosis (HS), either by imaging or by histology and lack of secondary causes of hepatic fat accumulation. Frequency of NAFLD is increasing worldwide. Overall prevalence of NAFLD in Bangladesh is 33.9%. Insulin resistance is the central factor for the pathogenesis of NAFLD. Most of the children are asymptomatic and are identified incidentally by elevated serum aminotransferases. The objectives of this review are to provide the pediatricians an overview of fatty liver disease in children regarding its etiology, patients' evaluation and management. This review also provides the approach to a child with fatty liver disease based on the best available evidence from electronic literature searches. Obese (BMI for age > 95th centile) and overweight children (BMI for age between 85th to 95th centile) having additional risk factors like insulin resistance should be routinely screened for NAFLD. Estimation of serum ALT and/ or ultrasonography are the recommended screening tests. Though the treatment of NAFLD includes dietary modifications, physical activities, drugs and surgery; diet and physical activities are the cornerstone of management of NAFLD.

Keywords: Bangladesh, Children, Nonalcoholic fatty liver disease (NAFLD), Non alcoholic steatohepatitis (NASH)

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a disease of liver occurring due to excess accumulation of fat in the liver. For defining NAFLD, there must be (1) hepatic steatosis (HS), evidenced by imaging or histology and (2) absence of secondary causes of fat accumulation in the liver.¹ In the majority of patients, NAFLD is commonly associated with metabolic co morbidities such as obesity, diabetes mellitus and dyslipidemia. Pediatric NAFLD is defined as chronic hepatic steatosis in under 18 children, which is not secondary to genetic/metabolic disorders, infections, use of steatogenic medications,

malnutrition, or alcohol consumption.² NAFLD can be categorized histologically into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL or hepatosteatosis means abnormal accumulation of fat in >5% of hepatocytes without inflammation. On the other hand non alcoholic steatohepatitis (NASH) means excess accumulation of fat in liver with hepatic inflammation. NASH may ultimately progress to hepatocellular necrosis, fibrosis and cirrhosis.³

Prevalence and Incidence

The prevalence of NAFLD varies by method of detection, which may include screening by alanine aminotransferase (ALT), imaging for steatosis, or confirmation by liver biopsy. It also varies from country to country. NAFLD prevalence ranges from 0.7% in young children of 2-4 years, to 29% -38% in obese children in North American studies.⁴ Moreover, the prevalence of NAFLD increased 2.7 fold from the

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late 1980s to the current era.⁵ The overall global prevalence of NAFLD diagnosed by imaging is around 25.2%.⁶ The highest prevalence of NAFLD is reported from the Middle East (31.8%) and South America (30.5%) whereas the lowest prevalence rate is reported from Africa (13.5%).⁷ The prevalence of NASH among NAFLD patients is estimated to be 59.1%.⁸ Using ultrasonography or estimation of serum ALT, the prevalence of NAFLD in children in general population is about 7% and up to 34% in obese children.⁹ Incidence of NAFLD from Asian countries detected by ultrasound was 12%.¹⁰ Overall prevalence of NAFLD in Bangladesh is 33.9%.¹¹

The followings are few risk factors for development of NAFLD¹²

Obesity, DM type 2, Dyslipidemia, Polycystic ovary syndrome, Psoriasis, Hypopituitarism Hypothyroidism, Hypogonadism, Obstructive sleep apnea, Pancreato-duodenal resection

Pathogenesis of NAFLD

The pathogenesis of NASH has not yet been entirely understood and the mechanisms leading to NASH appear to be multifactorial. It is also unknown why some patients have NAFL for many years, whereas others develop the progressive NASH, with or without fibrosis, within a couple of years. Genetic variation is one of the determinants to develop NASH.

Fats accumulate in adipose tissue and inappropriately in liver and muscle as free fatty acid and triglycerides. Insulin resistance promotes gluconeogenesis, glycogenolysis, and FFA release from adipose tissue. Unregulated FFA uptake by hepatocytes increase triglyceride synthesis and impairs FFA oxidation, resulting in increased hepatocyte lipid. Progression of fatty liver to NASH may be due to genetic factors causing an increased susceptibility of hepatocytes to oxidative stress. There have been multiple hypotheses describing the pathogenesis of NASH, such as the “two hits,” “three hits,” and “multiple hits” hypotheses.^{3,8,13}

The “two hits” hypothesis was originally proposed in 1998 in which insulin resistance is the primary and main factor for dysregulation of fat metabolism.¹⁴ Insulin resistance leads to aberrant lipid accumulation in the liver as the first hit. First hit is followed by a second hit driven by inflammatory cytokine induced mitochondrial dysfunction and oxidative stress leading to hepatocyte death and inflammation.¹⁵ In

the healthy liver, replication of existing mature hepatocytes replace the dead hepatocytes and maintain normal liver function.

In NASH, however, the replication of mature hepatocytes are inhibited and accompanied by expansion of a progenitor cell population. The abnormal expansion of progenitor cells contribute to more unfavorable outcomes such as hepatic stellate cells activation and liver fibrosis. Thus, a “third hit,” which induces NASH pathogenesis.¹⁶ More recently, a number of different inflammatory mediators released from adipose tissue and the liver/gut axis have been implicated in NASH pathogenesis. Thus, a “multiple hits” hypothesis involving organ-organ interactions in NASH pathogenesis take place. Gut-derived endotoxins due to increased gut permeability and gut dysbiosis, adipokines secreted from adipose tissue, are also crucial for NASH.^{13,14}

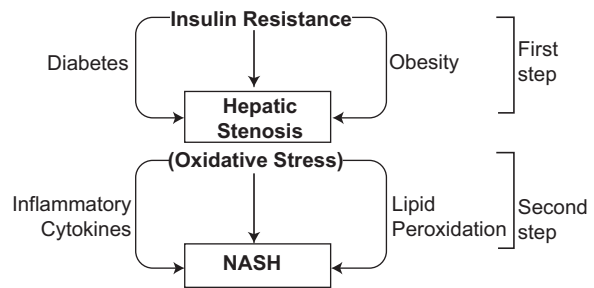


Fig.-1: Pathogenesis of NAFLD and NASH: Two-hit hypothesis

Presentation of NAFLD

Children often have a positive family history for the metabolic syndrome. NAFLD commonly presents after the age of 10 years. Most of the children are asymptomatic and identified incidentally by elevated serum aminotransferases.¹⁵ The most commonly reported symptoms in children are abdominal pain and fatigue. Abdominal pain is due to stretching of liver capsule.

In childhood, NAFLD presenting with overt jaundice and signs of end-stage liver disease are very rare.¹⁶ The majority are overweight (gender-and age-specific BMI for age > 85th percentile) or obese (BMI for age > 95th percentile). Acanthosis nigricans is common.¹⁷ It is a brown to black, poorly defined, velvety hyperpigmentation of skin, found on the back of neck, joint, groin, armpit, intertriginous area or body fold in about one third to half of the patients. Presence of acanthosis nigricans indicates insulin resistance.

Increased waist circumference is associated with progression to NASH. Obese children may have hypertension. Hepatomegaly may also be present. Patient may present with features of advanced liver disease.

Abnormal liver functions are found in 7-11% of patients.¹⁸

Whom to screen?

Obese (BMI for age > 95th centile) and overweight (BMI for age between 85th to 95th centile) children having additional risk factors like insulin resistance, DM, hyperlipidaemia, family history of NAFLD, central adiposity and sleep apnoea. Screening should be started after the age of 9 years. When initial screening tests are negative, repeat screening should be done every 2 years if risk factors still persist.^{2,19}

Screening for NAFLD

NAFLD is often asymptomatic. NAFLD is frequently identified incidentally by liver function tests and abdominal imagings such as ultrasound, MRI or computed tomography (CT), done for other indications. Screening for NAFLD is appropriate because early detection and treatment can prevent and reverse the liver damage, if treatment can be initiated early in the course of disease, especially before advanced fibrosis has developed.

Screening tests

There is no single screening test for NAFLD. Cheap and available recommended screening test is estimation of serum ALT.^{2,20} In the United States upper limits of normal serum ALT level in children are 22 mg/dL for girls and 26 mg/dL for boys.² Twice normal ALT in overweight and obese children age 10 years or older has a sensitivity of 88% and a specificity of 26%.^{1,21} About more than fifty percent of children with NASH do not have elevated serum ALT and AST levels, even in more advanced disease.²⁰ While normal AST and ALT levels do not exclude advanced liver disease in paediatric NAFLD, when elevated they raise a high level of clinical suspicion, particularly in overweight or obese patients with a family history of NAFLD. That is why it is a good screening test.^{18,21}

Abdominal ultrasonography is the most commonly used screening test for NAFLD. Relatively low cost, wide availability, safety and high acceptability makes it a good screening tool.²² It is an effective tool for

identifying pure hepatic steatosis and mild NASH in children and has led to a great increase in findings of NAFLD in recent years. In NAFLD, the liver usually enlarged and appears "bright," or echogenic, due to fat accumulation within the parenchyma. It is difficult to quantify the true extent of steatosis and its sensitivity diminishes significantly in cases where hepatic fat accumulation remains below 30%, in individuals who are severely obese (BMI for age >95th centile) and in children with severe NASH. USG is not able to differentiate between simple steatosis and steatohepatitis or exclude fibrosis reliably. The diagnostic efficacy of abdominal ultrasound is also greatly dependent upon operator proficiency and lacks standard methods of interpretation for paediatric NAFLD.²²

Magnetic Resonance Imaging (MRI) and CT scanning exhibit high sensitivity and specificity for paediatric NAFLD. These tests can identify the extent of steatosis and fibrosis. They can differentiate simple steatosis from NASH. However, the relatively high cost, need for sedation in young children and high radiation exposure in CT scan limit the use of this modality.²³

Investigations of NAFLD

The following investigations are to be done for confirming the diagnosis and for exclusion of differential diagnosis.

1. Liver function tests: ALT, AST, Prothrombin time. Liver function tests are to be done to see the extent and progression of liver disease.
2. Biochemical tests: Fasting blood sugar, fasting lipid profile and fasting insulin level. Fasting blood sugar usually remains normal but fasting insulin level and serum triglyceride level are usually high.
3. Calculation of Homostatic Model Assessment for Insulin Resistance (HOMA-IR)²⁴

$$\text{HOMA-IR} = \frac{\text{Fasting serum insulin (microunit/L)} \times \text{Fasting blood sugar (nmol/L)}}{22.5}$$

It is a method of assessing insulin resistance. High HOMA-IR indicates insulin resistance and low value value indicates insulin sensitivity. 22.5 is a constant.

4. Ultrasonography of hepatobiliary system
5. Magnetic Resonance Imaging: unlike abdominal ultrasound, MRI exhibits high sensitivity and

specificity for paediatric NAFLD and is able to differentiate, even in severely obese patients, between simple steatosis and NASH^{17, 20}. It is also able to quantify the distribution and severity of even mild steatosis and fibrosis throughout the entire liver and with moderate to strong correlation with histological grading in children and adults. However, due to high cost and need of sedation in young children widespread use of MRI in clinical practice is prohibited and, as such, it remains primarily a research tool. It also unable to assess the extent of inflammation or cirrhosis in the liver parenchyma but rather identifies the consequences of chronic liver disease, such as hepatosplenomegaly and portal hypertension.

Computerized Tomography (CT) offers greater sensitivity than abdominal ultrasound in detecting the presence and extent of hepatic fat accumulation in NAFLD but the high radiation exposure prohibits its routine use in young children. Furthermore, it is also unable to detect mild steatosis and small changes in fat content. Any child having high serum ALT should be screened for other liver diseases. These include viral hepatitis, Wilson disease, autoimmune hepatitis, celiac disease, etc.

6. Serum biomarkers- Several biomarkers are associated with NAFLD. These biomarkers are cytokeatin 18 (CK-18) fragments, apolipoprotein A1, hyaluronic acid, C-reactive protein, fibroblast growth factor-21, interleukin 1 receptor antagonist, adiponectin, and TNF.²⁵

Elevated serum CK-18 fragments is a marker of NASH. Plasma CK-18 levels are markedly elevated in patients with NASH, in compared with simple steatosis, and are able to predict NASH accurately. CK-18 is a potential marker of NASH if once the diagnosis of NAFLD had been made, as hepatocyte apoptosis may occur in conditions other than NAFLD. Though it has significant clinical potential, CK-18 is not readily available and a standard cut-off value not established yet.

7. Transient elastography (TE) is a non-invasive technique of assessing hepatic steatosis. It is painless and user friendly. Cirrhosis can be identified easily. It can detect liver stiffness and steatosis from the same region of interest. TE has limited value in ascites, obesity, and narrow intercostal space, in heart failure and in acute

and chronic hepatitis.²⁶

8. Liver biopsy is to be done to confirm the diagnosis and to differentiate NASH from hepatosteatois. Indications of liver biopsy are serum aminotransferase >2.5 times upper limit of normal, AST/ALT >1, inhomogenous liver parenchyma on ultrasonography and who were treated empirically but failed to resolve laboratory abnormalities. Histologically NASH is of two types- Type 1(adult type) and Type 2 (Paediatric type). Macrovesicular steatosis, lobular inflammation, balloon degeneration of hepatocyte with Mallory hyaline and perisinusoidal fibrosis but absence of intraportal inflammation are the histological features of Type 1 NASH. In type 2 NASH typical histological pictures are greater degree of macrovesicular steatosis, intraportal inflammation and fibrosis. Ballooning degeneration and perisinusoidal fibrosis is not a feature of type 2 NASH.²⁷

Treatment of NAFLD

Treatment should be given to all children with NAFLD. Goals of treatment are to regression of NAFLD, resolution of NASH, prevention of liver related morbidity-mortality and improvement of cardio metabolic co morbidities.¹ Regression of NAFLD can be identified on the basis of decrease in steatosis, inflammation, and/or fibrosis. As liver biopsy is an invasive procedure, decrease in ALT is often used as a marker of improvement of histology. Principles of treatment in NAFLD include dietary modification, physical activity, drugs and surgery.²

Dietary modifications include decrease calorie, fat, fructose and alcohol intake. Low calorie diet can mobilize liver fat and may reduce cardiovascular risk. Ten percent reduction in calorie intake may result in improvement of hepatosteatois and insulin resistance.² Taking food of low glycaemic index is preferable. Intake of refined sugar, glucose and fructose may induce increased insulin production, thus promoting FFA synthesis and liver fat accumulation. Sugar sweetened beverage should be avoided. Intake of saturated fatty acid with low poly unsaturated fatty acid may aggravate NAFLD. Caloric restriction is the main therapy. Snacking between meals is to be avoided. There is debate about the benefit of intermittent fasting. Mediterranean diets high in fish oil and PUFA with low carbohydrate are beneficial.^{28, 1}

Physical activities are encouraged but rapid weight reduction is not recommended. Slow weight reduction is preferable. Sustained exercise for 20 minutes on 3 days in a week may significantly be effective. One hour daily exercise is more effective in improvement of insulin resistance, reduction of liver fat accumulation and lowering of serum aminotransferase level. Screen time activities should be limited to <2 hours/day.^{29, 30}

Drugs are used for preventing or reversing hepatic steatosis, inflammation, and fibrosis, reducing body weight, improving hyperinsulinaemia and treating hyperlipidaemia.³¹ Common drugs are

- Metformin
- Thiazolidinedione- pioglitazone, rosiglitazone
- Antioxidant- vit E
- Ursodeoxycholic acid
- Obetocholic acid
- Omega 3 fatty acid
- Nicotinic acid
- Orlistat
- Statin
- Probiotics- still under trial to be used in NASH
- Angiotensin II receptor blockers

Uses of these drugs are not universally accepted but their beneficial effects have been found in different studies. Efficacy of any intervention should be assessed after 6 months. If ineffective, additional therapeutic options are to be considered.

Metformin- It is a drug that reduces insulin resistance and hyperglycemia. It acts by increasing glucose uptake in peripheral tissues, decreasing FFA release from adipose tissue resulting in decrease uptake of FFA by the liver and decreasing appetite. Five hundred mg twice daily for 24 weeks was found to be effective in several studies. NASPGHAN and AASLD do not recommend the use of this drug in NAFLD children because of limited safety data³²

Thiazolidinedione- Pioglitazone and rosiglitazone are the drugs of this group. They are peroxisome proliferator activated receptor gamma (PPAR γ) agonist and act by increasing FFA uptake by adipocytes and thus transporting triglyceride from liver and muscle to adipose tissue. It also increases insulin sensitivity. Side effect of this drug is cardiotoxicity, obesity and fracture. It is recommended in adults but not in children.³³

Vitamin E- oxidative damage is the main mechanism in NAFLD. Oxidation of FFA produces free radicals. Normally liver have got counter protective mechanisms against oxidative stress, but over production of free radicals cannot be combated. Antioxidants protect liver from oxidative injury. Dose is 400 to 1200 mg daily for 4 to 10 months. There is extensive controversy about using this drug. Though it is beneficial in NAFLD, further evidences are needed before its routine recommendation.³⁴

Ursodeoxycholic acid- It is a synthetic bile acid that protects hepatocytes and has got antioxidant property. Ursodeoxycholic acid in combination with Vit E was found to be effective in improving liver functions. Further studies are needed before its recommendation to use in NASH.^{35, 36}

Omega 3 fatty acid- It is not recommended in NAFLD or NASH in children but can be used in treating hyperlipidaemia in NAFLD. It has got anti-inflammatory, antithrombotic, antiarrhythmic, hypolipidaemic and vasodilator properties.³⁵

Orlistat- Human intestine does not absorb orlistat. It is approved by FDA for children after 12 years of age for treating paediatric obesity. It is enteric lipase inhibitor. It inhibits the pancreatic and gastric lipase, thus reducing fat absorption in intestine. It is effective in weight reduction and reduction of FFA. Many clinical trials have been conducted with this drug and were found beneficial but still its use in NAFLD in children is controversial. Moreover it has got gastrointestinal side effects including diarrhoea, fecal incontinence and oily stool.³⁶

Statin- By inhibiting HMG-CoA reductase enzyme, statins block the synthesis of cholesterol in the liver. Most of the circulating cholesterol comes from internal synthesis rather than from diet. When the liver can no longer produces cholesterol, levels of cholesterol in the blood will fall. Common statins are atorvastatin and simvastatin. American Association for Study of Liver Disease recommends use of statin in adult but its use in children is controversial.³⁵

Angiotensin II receptor blockers (Telmisartan, Losartan)- are angiotensin II type 1 (AT1) receptor blocker. Telmisartan have an agonistic effect on peroxisome proliferator-activated receptor (PPAR)- α in addition to the effect of angiotensin II blockade. Telmisartan blocks the first hit by modulating PPAR- α activity and thereby increasing insulin sensitivity,

which decreases hepatic fat accumulation. Telmisartan, by blocking angiotensin II receptor, inhibits hepatic stellate cell activation and thus suppresses hepatic fibrogenesis. Telmisartan is also effective in reducing blood pressure. These drugs are still not recommended in children.³⁵

Surgery- Bariatric surgery is indicated in severely obese adolescent children with BMI of 35 kg/m² or more having NASH in whom dietary modifications, physical activities and drugs fail to improve the condition. Surgical procedures include gastric banding, gastrectomy, biliopancreatic diversion and roux-en-Y gastric bypass. Aims of these procedures are to promote satiety and delay gastric emptying.³⁵

Follow up: the child should be followed up clinically and by investigations. Frequency of follow up schedule depends upon the severity of NAFLD.

Clinical: Body weight, BMI for age, waist circumference, acanthosis nigricans, blood pressure and hepatomegaly should be monitored.

Laboratory: The following laboratory tests should be done periodically to observe improvement of the condition

- Liver function- ALT
- USG of liver to see fat content
- Fasting lipid profile
- Fasting blood sugar
- Fasting serum insulin
- HOMA- IR
- Liver biopsy is needed in some cases.

Conclusion

Nonalcoholic fatty liver disease in children was thought an uncommon disease previously. Now a day, it is found more prevalent than other form of liver disease. Pediatric NAFLD is defined as chronic hepatic steatosis in under 18 children, which is not secondary to genetic/metabolic disorders, infections, use of steatogenic medications, malnutrition, or alcohol consumption. NAFLD is strongly associated with obesity. Insulin resistance is the primary and most important factor for developing NAFLD. Most patients with NAFLD have no symptoms caused by the liver disease, although many patients may progress to cirrhosis. Screening for NAFLD should be performed in all children with obesity (BMI for age e⁹⁵th percentile), and for those who are overweight

(BMI for age e⁸⁵th percentile) having additional risk factors. Screening should consist of measurement of serum ALT with or without ultrasonography. Most, but not all, children with NAFLD have mild elevations of ALT. A provisional diagnosis of NAFLD can be made by excluding other causes of liver disease. Dietary modification and physical activity are the main modality of treatment for NAFLD. Medications have limited role in the routine treatment of NAFLD in children.

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