



NAFLD in Children

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Abstract

Background: *Pediatric non alcoholic fatty liver disease (NAFLD) is an important cause of chronic liver disease in children in absence of significant alcohol consumption.*

Etiology of NAFLD is related to genetic predisposition, insulin resistance and obesity. In order to evaluate incidence, clinical and investigational profile of children with NAFLD the following study was conducted.

Methods: *The children (age 3 – 12 yrs) who attend pediatric gastroenterology OPD of PGIMER, Chandigarh from July 1993 to June 2003 with feature of NAFLD were admitted to pediatric gastroenterology ward of PGIMER, Chandigarh.*

Exclusion criteria was HBsAg, HIV positivity, low ceruloplasmin, high serum globulin, SMA/ANA positive etc.

The clinical profile (BMI / family history / daily physiological activity etc.), investigations (USG whole abdomen / blood sugar (F) / lipid profile / T3 T4 THS / FT4 / MR elastography / transient elastography / HBsAg / anti HIV / ceruloplasmin / LFT etc) were done.

Lifestyle modification (diet / exercise) was done. Regular follow up was done till resolution of fatty liver.

Results: *Fatty children were admitted in pediatric GE ward of PGIMER, Chandigarh from July 1993 to June 2003. Age was 3 – 12 yrs (mean 10 yrs) male was 30, female was 20. Overweight was 10 (BMI percentile 91 – 98) and obese was 40 (BMI percentile 98 – 99.6). twenty children were low birth weight (<2.5 kg at birth), 5 were large for date, 25 were normal AGA (appropriate for gestational age) at birth. Dietetic history shows consumption of >20% calories according to age. Small screen spending time (TV / mobile) was > 2 hours / day in 35 children (70%). Physical activity was less in 40 children (80%) cases. Blood sugar / lipid profile. LFT was normal in all 50 children. Nobody had NASH. Fatty liver was detected in all 50 children by USG.*

Conclusion: *NAFLD is an important cause of mortality / morbidity in children. Non invasive modality like USG whole abdomen / biometry / MR elastography / are more important in pediatric NAFLD rather than liver biopsy.*

Though life style modification is mainstay of treatment for pediatric NAFLD, promising therapeutic agent is needed for children.

Introduction

Non alcoholic fatty liver disease (NAFLD) is a growing problem in children in age 2 – 19 yrs.

Fatty liver is defined as 5% of hepatocytes containing macro vesicular fat.

Prevalence of NAFLD in children increases with age, ranging from 0.7% in 2 – 4 yrs age upto 17.3% in 15 – 19 yrs age. It differs significantly by race and ethnicity (Asian 10%, black 1%, Hispanic 11.8%, white 8.6%). The highest rate of fatty liver is seen in obese children (38%).⁽¹⁾

Knowledge of risk factors, pathophysiology, management and prognosis of pediatric Non alcoholic fatty liver disease (NAFLD) has evolved since it was first identified in 1983.⁽²⁾

The role of insulin resistance and obesity has been recognized as risk factor for fatty liver.⁽³⁾

NAFLD is defined as histologic evidence of hepatic steatosis (at least 5%) in absence of alcohol abuse, steatoglsic drugs, metabolic disease, viral hepatitis etc. Genetic predisposition and environmental triggers are involved in early NAFLD in children. Adults who have high incidence of complications have early onset of NAFLD in childhood.⁽⁴⁾

NAFLD is a spectrum of disease whose histology picture starts from simple fat deposition to ballon degeneration of hepatocytes / tubular inflammation / NASH, ultimately leading to fibrosis / cirrhosis. Young children with NASH shows typical periportal inflammation and fibrosis without ballooning.

Recently there is documented evidence of advanced NAFLD with fibrosis in first decade of life.⁽⁵⁾

Little is known about true incidence of pediatric NAFLD.⁽⁶⁾

Highest incidence is known among Hispanic children of mexican descent.⁽⁷⁾

Some study has shown that incidence of NAFLD is 8% in non obese and 34% in obese children.⁽⁸⁾

The NAFLD prevalence is higher in male children and adolescents and positively correlated with BMI.⁽⁹⁾

High prevalence of NAFLD is found in Hispanic and Asian ethnicity, impaired glucose intolerance, pre-diabetes, diabetes, panhypopituitaries, obstructive sleep apnea.⁽¹⁰⁾

Some study has shown that origin of NAFLD lies in perinatal period. High incidence of fatty liver is

assessed by MRI in neonates of obese mothers with gestational diabetes compared to neonates of normal wt non diabetic mothers.⁽¹¹⁾

Perinatal origin of NAFLD is proved in other study by the fact that infants of mother of high BMI and diabetes mellitus have increased incidence of hepatic steatosis.⁽¹²⁾

In a long term retrospective cohort study, 66 children were followed for 20 yrs to assess pediatric NAFLD progress and prognosis. In this study it has been shown that children with NAFLD had 14 times risk of prognosis to severe liver disease or death in comparison to children without NAFLD.⁽⁵⁾

Though hepato cellular carcinoma (HCC) is exceedingly rare in pediatric NAFLD, it has been reported in a 7 yrs old child with NAFLD.⁽¹³⁾

Pediatric NAFLD may have a rapid progress of liver disease (i.e. cirrhosis, end stage liver disease, HCC etc.). The need for liver transplant for end stage liver disease related to pediatric NAFLD is well known and it is increasing.⁽¹⁴⁾⁽¹⁵⁾

Pediatric NAFLD has association with multiple extra hepatic manifestation like hypertriglycerideamia, hypertension, premature atherosclerosis, obstructive sleep apnea, polycystic ovarian syndrome.⁽¹⁶⁾

Children with NAFLD are often asymptomatic Screening is often missed in at risk children of NAFLD.⁽¹⁷⁾

It is logical to screen for NAFLD in children at risk.⁽⁶⁾

Routine liver function test and abdominal ultrasound may lead to incidental findings of NAFLD in children.⁽⁴⁾

Certain risk factors (like BMI, insulin resistance, prediabetic or diabetic, dyslipidemia, obstructive sleep apnea, family history of fatty liver) should be considered whether to screen for NAFLD.⁽¹⁸⁾

Methods

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NAFLD were admitted to pediatric gastroenterology ward of PGIMER, Chandigarh.

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Lifestyle modification (diet / exercise) was done. Regular follow up was done till resolution of fatty liver.

Results

Fatty children were admitted in pediatric GE ward of PGIMER, Chandigarh from July 1993 to June 2003. Age was 3 – 12 yrs (mean 10 yrs) male was 30, female was 20. Overweight was 10 (BMI percentile 91 – 98) and obese was 40 (BMI percentile 98 – 99.6). Twenty children were low birth weight (<2.5 kg at birth), 5 were large for date, 25 were normal AGA (appropriate for gestational age) at birth. Dietetic history shows consumption of >20% calories according to age. Small screen spending time (TV / mobile) was > 2 hours / day in 35 children (70%). Physical activity was less in 40 children (80%) cases. Blood sugar / lipid profile. LFT was normal in all 50 children. Nobody had NASH. Fatty liver was detected in all 50 children by USG.

Discussion

NASPGHAN recommends screening for NAFLD between 9 and 11 yrs for all obese and overweight children with additional risk factors. The recommended screening test is alanine aminotransferase (ALT) using sex specific upper limits of values (Female 22 u/ht and male 26 u/ht). The guideline recommends USG as screening test because ALT has poor correlation with hepatic failure. Advanced hepatic failure has normal ALT.⁽⁶⁾

Before arriving at diagnosis of NAFLD, other cause of high ALT should be excluded (e.g. viral hepatitis, metabolic disease, Wilson disease, hepatotoxic medicines etc).⁽⁶⁾

High ALT, high globulin, high auto antibody titre may indicate autoimmune hepatitis which deserve liver biopsy. But liver biopsy for pediatric NAFLD is rarely needed because of serious inherent risk of liver biopsy. Because risk of liver biopsy should always be considered against potential benefit of confirmation of diagnosis.⁽¹⁹⁾

Severity of hepatic steatosis is assessed by MRI based technique like MR spectroscopy, proton density fat fraction.^{(20) (21) (22)}

Controlled attenuation parameter (CAP) or transient elastography (Fibroscan) is based on ratio frequency ultrasound signal to detect severity of hepatic steatosis and fibrosis. It is feasible in older children, operator independent and easily reproducible.⁽²³⁾

Some studies have shown that CAP can discriminate between different grades of hepatic steatosis / fibrosis with reasonable accuracy in comparison to liver biopsy.⁽²⁴⁾

Transient elastography and MR elastography have been proved to be accurate in adults but technique is still being validated in pediatric NAFLD with increasing results.⁽⁶⁾

Fibrosis biomarkers are yet to be validated in pediatric NAFLD.⁽²⁵⁾

Treatment modalities of pediatric NAFLD are broadly divided into lifestyle modification and pharmacotherapy. Bariatric surgery though not recommended in children may be considered when serious co-morbidities like diabetes mellitus, idiopathic intracranial hypertension, debilitating sleep apnea are present.⁽⁶⁾

The goal of treatment is to reduce disease burden, improve long term outcome, reduction in hepatocyte fat content, decrease hepatocyte inflammation, absence of fibrosis, reduction of transaminase.⁽¹⁴⁾

NASPGHAN recommends dietary restriction and use of fiber in diet for all obese children of NAFLD. Success of diet restriction and weight

loss alone is low. But lifestyle modification does work. Reduction in serum ALT / hepatic steatosis has been noted in children who lost 20% body weight in 12 months.⁽²⁶⁾

In our study lifestyle modification (diet / exercise) was done in all 50 children. They were followed up till resolution of fatty liver. Nobody had NASH / hepatic from fibrosis.

Future research is needed to identify specific diets which are beneficial for either healing or reversing disease progress.^{(27) (28) (29)}

Pioglitazone Peroxisome, a proliferator activated receptor (PPAR) to against that boosts insulin sensitivity has shown to reduce hepatic steatosis, transaminase, inflammation of NASH in adult NAFLD.⁽³⁰⁾

Pioglitazone is not recommended in pediatric NAFLD because some of side effects of pioglitazone include weight gain, cardiac failure, bladder cancer.⁽³¹⁾

Metformin increases insulin sensitivity in children and is recommended for diabetic children. But tonic trial (treatment of NAFLD in children) fails to establish superiority of metformin over placebo in improving NAFLD histology.⁽³²⁾

Oxidative stress and reactive oxygen species can accelerate hepatic fibrosis in fatty liver.⁽³³⁾

Tonic trial has shown that NAFLD score is significantly reduced with 800 IU Vitamin E daily with resolution of NASH in 58% cases.⁽³²⁾

However normalization of ALT and improvement of hepatic fibrosis have not been significant with antioxidant therapy.⁽³⁴⁾

NASPGHAN does not recommend vitamin E treatment for pediatric NAFLD/NASH.⁽⁶⁾

Omega 3 fatty acids [e.g. Docosahexaenic acid (DHA) and eicosapentaenic acid (EPA)] helps improving liver histology in NAFLD patients by promoting fatty acid oxidation and inhibiting denovo lipogenesis.

A randomized controlled trial of DHA (250 and 500 mg/day) for 6 months in NAFLD children (biopsy proven) showed significant reduction of hepatic steatosis as shown by USG in comparison to placebo.⁽³⁷⁾

USG cannot accurately predict hepatic steatosis because it is operator dependent and subjective to sonologist. Recent randomized controlled trial of DHA in obese and overweight children with NAFLD (ALT \geq 30u/lit and USG evidence of hepatic steatosis) has demonstrated no effect on hepatic steatosis, ALT, insulin resistance.⁽³⁸⁾

There is potential risk of prostate cancer in long term vitamin E therapy.^{(35) (36)}

DHA is a safe viable choice for pediatric NAFLD though its efficacy in improving liver histology is controversial.

Gut microbiota plays a big role in energy metabolism, obesity and obesity related complications like NAFLD.

Lactobacilli Rhamnosus GG (12 billion colony – forming units/day) (ends to significant improvement in ALT compared to placebo independent of changes in BMI.⁽³⁹⁾

Four month trial with VSL#3 has shown significant reduction of hepatic steatosis (as determined by USG) in comparison to placebo.⁽⁴⁰⁾

A randomized placebo controlled trial of probiotic for 12 weeks has shown improvement of ALT / Lipid profile in obese children.⁽⁴¹⁾

Statin, glucagon like peptide-I agonists, angiotensin receptor have shown good results in adult NAFLD but there is no data in children.

Obeticholic acid (OCA) is a synthetic analogue of chenodeoxycholic acid and a potent activator of farnesoid X receptor which exists in liver and modulates bile acid, lipid, glucose metabolism. OCA has shown significant reduction in hepatic fibrosis in adult NAFLD. But its use in pediatric NAFLD has not yet been validated.⁽⁴²⁾

Elafibrinor, an insulin sensitizer is both PPAR and PPARY against a dose of 120 mg for 52 who should significant resolution of NASH in adults compared to placebo but not in cirrhosis. But its role in pediatric NAFLD is yet to be proved.⁽⁴³⁾

Conclusion

Pediatric NAFLD is an important cause of mortality and morbidity in children and adolescents.

Effective screening will ensure early treatment, reduce social burden of this epidemic.

Though liver biopsy is gold standard for NAFLD and staging fibrosis, imaging modalities and non invasive biomarkers are being validated.

Though life style modification (i.e. diet and exercise) is mainstay of treatment, research is going on to get an effective therapeutic agent.

Conflict of interest – Nil

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