Diagnosing Pediatric NAFLD

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Abstract

NAFLD; Non alcoholic fatty liver disease is accumulation of excessive fat in liver. It progress to inflammation and cirrhosis. Ethnic differences and clinical heterogeneity regarding NAFLD is well known. More children are getting diagnosed. Multiple factors are involved in pathology of NAFLD. This review focuses on diagnosis of NAFLD children based on available guidelines and literature. Clinical approach to NAFLD is suggested.

Key words:

NAFLD: Non alcoholic fatty liver disease; ALT: Alanine Transaminase; Steatosis Index; Fibrosis Index; Liver biopsy; USFLI SCORE: ultrasonographic fatty liver indicator; MRI – PDFF: Magnetic Resonance Imaging - Proton density fat fraction

Non alcoholic fatty liver disease (NAFLD) is accumulation of excessive fat in liver. It progress to inflammation and cirrhosis. Ethnic differences and clinical heterogeneity regarding NAFLD is well known. More children are getting diagnosed. Multiple factors are involved in pathology of NAFLD. This review focuses on diagnosis of NAFLD children based on available guidelines and literature. Clinical approach to NAFLD is suggested.

Is it NAFLD?

Non alcoholic fatty liver is rare in children less than 3 years. In Children between 3-10 years other causes of fatty liver should be ruled out prior considering diagnosis of NAFLD. Children above 10 years with central adiposity, elevated body mass index; clinical signs of insulin resistance, positive family history of co-morbid metabolic pathology is the classical setting for diagnosis of NAFLD. Sedentary life styles do contribute to the diagnosis .Obvious liver failure, conjugated jaundice, large hepatosplenomegaly rarely presents as NAFLD [1].

Metabolic diseases [1] like ornithine transcarbamylase deficiency can present as micro-vesicular steatosis. Citrin deficiency, hepatic form of glycogenosis, hereditary, fructose intolerance, congenital disorder or glycosylation, cholesterol ester-storage disease should be suspected in differential diagnosis. The non-classical presentation in clinical signs and atypical age group would help in diagnosis. Children with abetalipoproteinemia and hypobetalipoproteinemia can develop abnormal accumulation of fat in liver. Other differential diagnoses are cystic fibrosis, celiac disease and mal-nutrition which can present as fatty liver or hepatic steatosis. Endocrinopathies [1] like hypothyroidism and hypothalamic diseases are suspected with associated clinical signs and symptoms. Genetic disorders like Down's syndrome and turner syndrome have non alcoholic fatty liver as frequent co morbidity. Auto immune hepatitis can present in conjugation with steato-hepatitis. HIV infected children can have steatosis. Drugs [1] like Long term steroids, methotrexate, tetracycline, aminodarone, nucleoside analogues, aspirin, antiretroviral drugs are few of important drugs causing fatty liver. Diagnosis of NAFLD needs

through clinical evaluation, ruling out co-morbid clinical conditions and appropriate drug history.

Secondary NAFLD is suspected in non-obese children with elevated ALT (>2 x upper limit) which is persistent for 6 months even after life style intervention [2]. Secondary NAFLD sometimes is called as Lean NAFLD. Lipodystrophy and alternative diagnosis due to genetic and congenital conditions should be ruled out. Monogenic causes of chronic liver disease like fatty acid oxidation defects, peroxisomal disorder, lysosomal storage disease should be considered in non over-weight and very young children as per AASLD guideline [3]. NASPGHAN guideline gives strength – 1, level of evidence – A for recommending to exclude alternative etiologies for evaluating hepatic steatosis [4].

Clinical diagnosis of NAFLD:

Most children with hepatic steatosis are asymptomatic. There may be non-specific abdominal pain, malaise or fatigue. Mild hepatomegaly can be appreciated .Acanthosis nigricans, raised waist circumference are accompanying clinical signs in some cases with NAFLD [5,6,7] .Waist circumference and waist to height ratio provide an estimate for adiposity. Clinical history of obstructive sleep apnea should raise suspicion of lean NAFLD [8].

Biochemical investigations:

The best screening test recommended by NASPGHAN for diagnosis NAFLD is ALT (strength – 1, evidence – B) but it has limitation [4]. ALT can be elevated in many hepatic disorders. Persistent elevated ALT for more than 3 months twice the upper limit of normal should direct one to investigate for NAFLD or other causes (strength – 1, level C) .Furthermore if ALT > 80 U/l the likelyhood of significant liver disease is higher. (strength -2, evidence C). Normal ALT does not exclude liver steatosis or its progression to cirrhosis as per ESPGHAN guideline [5]. The AST: ALT ratio > 1; directs towards increasing fibrosis [9].

Serum uric acid is important investigation in considering diagnosis of NAFLD. Higher serum uric acid is noted with hepatic steatosis in children [10]. The risk of developing NAFLD increases with increase in GGT levels [11]. High GGT in NAFLD is associated with liver fibrosis [12]. One of the best independent predictive risk factor for diagnosis NAFLD in obese children is fasting serum insulin > 18.9 u/ml [13]. Insulin resistance and high serum triglyceride are additional risk factor for NAFLD [5]. HOMA – IR provides an estimate for insulin resistance. It has its limitation in metabolic conditions.[14] The 4.9 cut-off value for HOMA-IR is associated with severe steatosis in obese children with a 100% negative predictive value and a 33% positive predictive value in studies.[14]

Other non invasive biomarkers are studied in children with NAFLD [15]. More validation studies are required as per AASLD and NASPGHAN and ESPGHAN guidelines. In atypical lean or secondary [2] NAFLD cases; other causes for hepatic steatosis should be ruled out viz Hbsag, GGT, IgA, IgA TTG(Tissue transglutaminase), serum CPK, serum ceruloplasmin, autoimmune markers. Sr.TSH should be done to rule out hypothyroidism. Lipid profile would rule out co-morbid dyslipidemia. Mean ALT of child over follow up of 96 weeks and percentage of change of ALT from base line to 96 weeks are noted to be significant predictors of NAFLD.ALT > 60 at baseline and mean ALT < 62-77 U/lt over time predicted improvement in NA5H [16]. NICE guideline considered using enhanced liver fibrosis test (ELF) in children diagnosed with NAFLD. ELF score > 10.50 suggest advance liver fibrosis and early referral to specialist. If ELF < 10.51, children should be retested every 2 years [17]. During follow up HOMA – IR might help to identify patient at risk of fibrosis progression.

Genetic signature of NAFLD:

PNPLA3 single nucleotide polymorphic is associated with portal pattern of steatosis, inflammation and fibrosis [18]. Another study identified that PNPLA3 , TM6SF2T alleles have more than threefold higher risk of NAFLD than

non carriers [19]. The mutated PNPLA3I 148M variant attached to surface of lipid droplets reduces the cleavage of triglyceride leading to lipid retention in hepatocyte and hepatic steatosis [20]. The genetic risk score based on combination of variants and clinical risk factors improves prediction of NAFLD in obese children by 5.2% as compared to clinical factor alone [21].

Metabolic signature of NAFLD:

The lipid lipoprotein profile in NAFLD is characterised by increased extremely large to small VLDL. Triglyceride remnant cholesterol and saturated fatty acid concentrates of glycoprotein acetyls are also increased which suggest chronic inflammation [22]. Saturated fatty acids, palmitic acid, myristic acid in saliva are increased in paediatric obesity related liver disease. Higher level of salivary pyroglutamic acid is suggested biomarker of increasing severity of NAFLD [23]. Steroid metabolities are also altered in non-syndromic childhood obesity. Urine 5 alpha reductase, 21 hydroxylase activity are increased while 11beta HSD1 activity, DHEA is reduced in NAFLD. These findings reflected lesser hepatic recycling of cortisone to cortisol which is compensated by increased adrenal cortisol leading to higher gluco-corticoid metabolites and lower mineralo-corticoid metabolites [24]. It is also called as steroid metabolic signature of liver disease in childhood obesity.

Microbiome signature of NAFLD:

NAFLD children have altered intestinal flora. The proportion of actinomycetes is lower and proportion of thermus is higher in NAFLD group at level of phylum. At the level of genus the proportion of bacteroids and bifidobacterium in NAFLD children is lower while the proportion of prevotella is higher. This is supposed to alter lipid metabolic pathway leading to NAFLD [25].

Intestinal dysbiosis is also confirmed in analysis of fecal microbiomes of children with NAFLD. NAFLD children have lower diversity of microbiome in the gut. High prevotella is associated with fibrosis. Genes involved in flagellar assembly are enriched in patient with fibrosis [26]. Small intestinal bacterial over growth also affects insulin level and NAFLD [27].

Genetic, metabolic & microbiome signature of NAFLD are newer approaches to study and diagnose NAFLD. The need for studies across different ethnicity is must for further validation.

Newer biomarkers of NAFLD:

NAFLD liver fat score ,fatty liver index and hepatic steatosis index need further validation confirmatiory studies.4 Combined paediatric NAFLD fibrosis index and enhanced liver fibrosis score are proposed to be accurate in children with NAFLD [4,5]. ESPGHAN, NASPGHAN, AASLD recommends more studies to confirm the role of biomarkers in children with NAFLD. NICE guideline considers ELF test for NAFLD liver fibrosis. A Brief overview of clinically significant test is described here with.

PNFI [28] paediatric NAFLD fibrosis index using age, waist circumference and triglycride can be use in place of liver biopsy to rule in liver fibrosis. PNFI > 9 has positive predictive value of 98.5%. Enhanced liver fibrosis (ELF) test [29] is proposed for screening progressive fibrosis. It uses hyaluronic acid, aminoterminal propeptide type III collagen (PIINP) and tissue inhibitor of metalloprotienase (TIMP – 1). Combination of PNFI & ELF [30] is also used to predict presence of fibrosis. PNFI < 3.47 rule out liver fibrosis. PNFI > 9 can rule in liver fibrosis. If PNFI is 3.47 to 8.99 then ELF score is used. ELF < 8.49 can rule out fibrosis.

Paediatric study for validation for fibrosis - 4 (FIB – 4) is noted to be insensitive [31]. AST / ALT ratio, APRI, NFS have poor accuracy. BARD score is not evaluated for detecting mild – moderate fibrosis .It has also poor accuracy. ELF test is the test with high accuracy buts its costly and needs kit from manufactures which make it difficult to access. PNFI and PNES are complex with poor- moderate accuracy [32].

Low neuregulin 4 level, adipokine in NAFLD is considered to be diagnostic. Elevated neuregulin 4 is associated with decreased risk of

NAFLD [33]. Another adipokine chemerin is noted be a suitable biomarker of liver steatosis [34]. Leptin / adiponectin ratio is also raised in children with NAFLD [35]. Hepatokines are produced by liver regulating glucose and lipid metabolism like FGF – 21 is significantly noted to be higher in NAFLD [36].

Liver biopsy:

As per AASLD guideline liver biopsy should be done in children suspected NAFLD in whom diagnosis is unclear and there is the possibility of multiple diagnosis or before starting hepatotoxic medical therapy. While NASPGHAN guideline considered Liver biopsy in patient with increased risk of NASH and /or advanced fibrosis, ALT > 80 U/lt, splenomegaly and AST / ALT > 1, panhypopituitarism, type 2 DM (strength I, evidence B). ESPGHAN guidline accepted the indication to do liver biopsy as follow: to exclude other treatable diseases, in case of clinically advanced disease, before pharmacological / surgical treatment, as a part of intervention protocol or clinical research trial, < 10 years of age, family h/o severe NAFLD.

Histopathology of liver biopsy in children particularly prepubertal boys show more steatosis less ballooning and more portal based inflammation and fibrosis, commonly described as type II NASH [32]. The diagnosis of NAFLD is established when an atleast 5% of hepatocytes present with micro or macro-vesicular steatosis [37]. Two widely accepted and validation methods for scoring and staging the pathologic lesion of NAFLD are NASHCRN proposed score (NAFLD activity score) [38] and score by the European fatty liver inhibition of progression (SAF score) [39] Paediatric NAFLD histological scores strongly correlate with presence of NASH [40].

Imaging for NAFLD:

Ultrasonography (USG): It is the first line imaging modality for diagnosis of NAFLD. Ultrasound for fatty liver is safe, inexpensive test, but plain ultrasound cannot quantify steatosis or fibrosis. It is useful to rule out other pathologies, but it has poor specificity as per NASPGHAN and ESPGHAN guideline. NICE guideline uses USG for screening purpose. Increased brightness of the liver compared to adjacent right kidney or spleen indicates hepatic steatosis [41]. USG score more than or equal to 2 by saverymuttu [42] score, has high pool specificity of 96% and sensitivity of 52%. The mean sensitivity [43] of USG for steatosis identification range from 73-90%. Controlled attenuation parameter (CAP) is used to assess presence of hepatic steatosis by using shear wave propagation. It is used in transient elastography; fibroscan CAP value > 24 1 dB/m) suggest steatosis [44]. CAP value estimation has limitation in obese [44] children. Liver stiffness measurement by fibro-scan > 5.5 Kpa is useful to diagnose hepatic fibrosis. [45] More validation studies are needed.

Magnetic Resonance Imaging (MRI) : It is not cost effective but can help in diagnosing steatosis and fibrosis .Proton density fat fraction(PDFF) by MRI is an objective test for quantification of liver steatosis [46]. MRI – PDFF allows fat mapping of entire liver. HMR spectroscopy measures concentration of lipids in small area of interest in liver [47]. More paediatric specific research is indicated.

Newer tests like non invasive semi quantitative ultrasonography fatty liver indicator are studied in paediatric NAFLD. USFLI SCORE more than 2 is diagnostic of NAFLD [48]. USFLI score >6 has positive predicative value of 71% sensitivity of 75% and specificity of 63% for predicting hepatitis in children with NAFLD. [49]

Field of artificial intelligence integrating radiologic bio-images with genomic data and its correlation with liver biopsy would improve diagnosing NAFLD in future.

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