BSPGHAN
working for children with digestive and liver disorders
British Society of Paediatric Gastroenterology Hepatology and Nutrition

UK Fatty Liver Guideline

Background:

Non-Alcoholic Fatty Liver Disease (NAFLD) is defined as the presence of moderate to severe hepatic steatosis, confirmed by imaging or histology, in the absence of alternative aetiologies.

In association with the rising trend of obesity, NAFLD is now the most common chronic hepatopathy in children and adults [(1)].

Studies have shown that 38-83% of obese children may have a fatty liver (defined as ≥5% of hepatocytes containing macrovesicular fat) [(2-3)].

At primary school entry, 1 in 5 children is already overweight or obese and by the end of primary school, this figure increases to 1 in 3 [(4)].

NAFLD may progress to steatofibrosis, non-alcoholic steatohepatitis (NASH), cirrhosis, liver failure and hepatocellular carcinoma. It is now amongst the top three indications for liver transplantation in adults [(5)]. NAFLD may be suspected by either primary or secondary care physicians in children with non-specific symptoms, such as abdominal pain, through the detection of an echo-bright liver and / or elevated transaminases [(6)].

This guideline has been designed to aid practitioners in how to proceed when imaging studies identify hepatic steatosis (a bright, hyperechoic liver as compared to the spleen on ultrasound) or raised liver enzymes are detected in an overweight child [(7)].

Note not all children with NAFLD are obese [(7)]

Proposed assessment in primary/ secondary care:

1) Perform anthropometry

Plot height, weight, BMI [1], BMI Z score, and waist circumference on a centile chart [6,8-9]

https://www.rcpch.ac.uk/resources/growth-charts

https://www.rcpch.ac.uk/sites/default/files/2018-03/boys_and_girls_bmi_chart.pdf

Adult BMI parameters differ to those used in children and adolescents; BMI centile charts must be used for correct interpretation of results

2) History and examination:

- Elucidate symptoms: malaise, fatigue, abdominal pain
- Drug and alcohol history

Hepatotoxic drugs that may cause a fatty liver [1, 6-7]
Nifedipine
Diltiazem
Amiodarone
Corticosteroids
Oestrogens
Methotrexate
Valproate
L-asparaginase
Certain antipsychotics
Certain antidepressants
Zidovudine and HIV treatments
Ethanol, ecstasy, cocaine, solvents

- Nutritional history
- Assess for depression, anxiety and psychological stressors
- Family history of NAFLD, type 2 diabetes, cardiovascular disease, dyslipidaemia, metabolic disease and liver disease [5,7]
- Examination – document presence/ absence of:
    - Organomegaly
    - Peripheral stigmata of chronic liver disease
    - Evidence of insulin resistance (acanthosis nigricans)
    - Measure blood pressure and plot on centile chart

3) Imaging:

- Formal abdominal USS

To assess for steatosis, evidence of portal hypertension, and exclusion of other liver disease.

4) <u>Bloods:</u>

Assessment of co-morbidity [6,7]:

- Fasting serum glucose/ insulin.
    - HOMA-IR (fasting glucose x fasting insulin/ 22.5)
- HbA1c measurement
- Renal function tests
- Vitamin D level

Assessment of liver function and screening for other causes of raised transaminases/ steatosis [7-8]:

First Line Investigations	Second line investigations
• ALT, AST, ALP, GGT, Split bilirubin • FBC • Coagulation screen • Albumin • Fasting lipid profile	• If raised triglyceride level consider Lysosomal acid lipase
• Immunogloblins and complement levels • Autoimmune profile including ANCA • Anti-transglutaminase antibodies • Thyroid function tests • A1AT level and phenotype • Copper and caeruloplasmin	• Consider 24-hour urine copper collection, ophthalmic examination and/ or genetic testing for Wilson's disease
• Plasma free fatty acids, amino acids, organic acids, uric acid, acylcarnitines, and lactate	• If organomegaly/ raised uric acid/ raised lactate or a history of hypoglycaemia consider genetic testing for glycogen storage disease
• Hepatitis A, B, C and E serology	

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Without histological confirmation of NAFLD the diagnosis is one of exclusion. It is important to recognise that with the rising prevalence of obesity, the proportion of children with an underlying primary liver disease, and obesity +/- additional NAFLD increases- **It is important not to miss a treatable condition** [1, 10].

Optional investigations (if available in your centre)

- Non-invasive markers of fibrosis

To be referred for review at a national paediatric liver unit if:

- Age < 10 [1, 11]
- Evidence of alternative cause for steatosis detected through screening investigations
- Presence of metabolic syndrome, type 2 diabetes mellitus, and/ or hyperlipidaemia [1,7-8,11]
- Increased AST/ALT ratio (>1) and/or a raised AST/ ALT (≥80IU/L) *[1, 6-7]*
- Raised serum level of GGT *[6-7]*
- Child has panhypopituitarism [1,7,11]
- Raised non-invasive marker of fibrosis measurement [1,5, 8, 12-14]
- Presence of hepatomegaly
- Presence of splenomegaly [1, 11]
- Thrombocytopenia
- Jaundice
- Synthetic dysfunction (raised PT or low albumin level)

Management:

1. Education:

Patient information leaflets and guidance for NAFLD are available via the Children's Liver Disease Foundation at https://www.childliverdisease.org and the British Liver Trust at https://www.britishlivertrust.org.uk

Inform families that children with NAFLD are at risk of progressive liver disease and liver cancer [7-8, 15].

Counsel that children with NAFLD are also at risk of hypertension, cardiovascular disease, type 2 diabetes and chronic kidney disease [6].

2. Lifestyle intervention is the first line of treatment for children with NAFLD [7-8]:

Lifestyle intervention with diet and increased physical activity induces weight loss and is associated with a significant improvement in both laboratory abnormalities and liver histology [16].

Weight loss ≥7% improves histological disease activity [17].

The highest rates of steatosis reduction, NASH resolution, and fibrosis regression occur in patients with weight losses ≥10% [18].

A low-glycaemic load diet and low-fat diet appear equally effective in decreasing hepatic fat content and transaminases. The limited evidence base inhibits the prescription of a specific dietary strategy [6,19].

Both aerobic and resistance exercise training at vigorous and moderate-to-vigorous intensities may reduce hepatic fat content in children and adolescents [19]

Recommendations:

- Children should be encouraged to exercise regularly
- Young people and their families should be given healthy eating guidance in accordance with the NHS Eatwell Guide and Public Health England advice
    - https://www.gov.uk/government/publications/the-eatwell-guide

- https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/618167/government_dietary_recommendations.pdf2016.
- https://www.nice.org.uk/guidance/cg189

3. **Children should be treated/ referred for management of co-morbidities where appropriate, for example:**
   - Insulin resistance and diabetes
   - Sleep apnoea
   - Depression and anxiety

Children with mental health disorders show poorer response to treatment

There is no currently strong scientific evidence to support the use of any medications to treat paediatric NAFLD [6, 19]

- Randomised controlled trials have failed to demonstrate significant improvement in biochemistry, steatosis or fibrosis from vitamin E [18, 21], metformin, or cysteamine. DHA supplementation improves liver steatosis on ultrasound and insulin sensitivity in children with NAFLD [8, 22], but polyunsaturated fatty acids have not been shown to improve histological outcomes [5].

4. **Bariatric surgery should be considered in select adolescents** [23]

- It can decrease the grade of steatosis, hepatic inflammation, and fibrosis in NASH.
- A Roux-en-Y gastric bypass is considered safe and effective.
- Uncomplicated NAFLD alone is not an indication for bariatric surgery.

Recommendation:

Adolescents may be referred to a National Paediatric Liver Unit to assess for hepatic fibrosis, and portal hypertension if they are:

- Morbidly obese (BMI > 40Kg/m2 or BMI 35-40Kg/m2 and other significant disease that could be improved with weight loss) with steatosis on USS

- Under 16 years of age (children aged 16-18 may be referred directly to adult hepatology services)

A young person may be considered for referral for bariatric services if they meet the criteria outlined in the National Institute for Health and Care Excellence (NICE) clinical guideline 189 [24] *and have failed to achieve clinically beneficial weight loss with previously organised behavioural / medical treatments.*

Follow-up to assess for liver disease progression:

- Children with evidence of cirrhosis – 3 monthly review; shared between a National Paediatric Liver Unit and local secondary or tertiary care.
- If evidence of hepatic fibrosis – 6 monthly follow up; shared between a National Paediatric Liver Unit and local secondary or tertiary care
- If no evidence of hepatic fibrosis: annual follow-up by a general paediatrician, with advisory service from National Paediatric Liver Service.

Achieving lifestyle change and weight loss is paramount to managing NAFLD. Studies have demonstrated that intensive, multi-disciplinary programmes, involving dietetic teams are more effective, and so frequency of follow-up for obesity may need to be higher to optimise outcomes [7]

<u>At each follow up clinic perform:</u>

- Full anthropometry; height, weight, BMI/ BMI Z score, and waist circumference
- BP measurement
- ALT, AST, ALP, GGT, split bilirubin
- Albumin
- FBC
- Clotting screen
- Lipid profile
- Urea, Creatinine and Urinalysis to assess for proteinuria

<u>Annual tests:</u>

- Fasting glucose, insulin, and HbA1C measurement
- AFP: in children with evidence of cirrhosis

- Non-invasive markers of fibrosis if available
- USS to assess for signs of liver disease progression.

Role of the National Paediatric Liver Units:

1. Exclude alternative diagnoses
2. Perform liver biopsy to:
    a. confirm histological diagnosis
    b. assess for NASH/ fibrosis/ cirrhosis

> Fibrosis stage independently, and regardless of presence or severity of other histological features is the most relevant liver biopsy feature; associated with overall- and liver-related mortality/liver transplantation or liver-related events [25]

3. Monitor for disease progression and development of fibrosis using non-invasive markers of fibrosis:
    a. Paediatric NAFLD fibrosis score (PNFS) [12]
    b. Paediatric NAFLD fibrosis index (PNFI) +/- ELF [13-14]
    c. Acoustic radiation force impact (ARFI)
    d. Transient elastography

4. Recruitment of children to trials in NAFLD
    a. European Paediatric NAFLD Registry (EU-PNAFLD)
    b. Using Nuclear Magnetic Resonance (NMR) Spectroscopy to understand hepatic lipid metabolism in paediatric NAFLD
    c. Role of Sarcopenia in Paediatric Non-Alcoholic Fatty Liver Disease

5. Monitor children on a variceal banding programme if evidence of portal hypertension

6. Monitor children with cirrhosis for timing for liver transplantation

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