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Nonalcoholic Fatty Liver Disease (NAFLD)

Developed by Stephanie Rohn and Dr. Zachos for PedsCases.com.
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Introduction:

Hello everyone and thank you for tuning in to another PedsCases podcast. My name is Stephanie Rohn and I am a medical student at McMaster University. This podcast on nonalcoholic fatty liver disease (NAFLD) was made with guidance from Dr. Mary Zachos, a pediatric gastroenterologist at McMaster University in Ontario, Canada.

Objectives:

By the end of this podcast, listeners should be able to:

1. Define NAFLD and list risk factors for its development
2. Describe the pathophysiology and spectrum of disease of NAFLD
3. Build an approach to screening for NAFLD and what tests to perform for those deemed to be at high risk
4. Outline therapeutic interventions and preventative strategies

Case:

I will start this topic with a case that we will complete at the end of the episode. You are working at a family doctors office and go in to see a 13 year old boy named Marcus. He is coming in for his first appointment after being recently diagnosed with type two diabetes. He is feeling well, and has no symptomatic concerns to bring up at this visit. Physical exam is unremarkable besides a BMI of 27kg/m^2 (>99th percentile).

Given his obesity, what physical exam maneuvers and blood tests would you consider sending for Marcus to evaluate for comorbidities?

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Definition and epidemiology:

Nonalcoholic fatty liver disease is a chronic condition where there is an accumulation of excessive fat in the liver, also known as 'steatosis'. To be defined as NAFLD, the steatosis cannot be due to a secondary cause such as genetic/metabolic disorders, medication use, alcohol use or malnutrition[1]. An accepted cut-off for NAFLD is if the fatty infiltration involves >5% of the liver[1].

NAFLD is the most common liver disease in children in North America. It can be found in children as young as three years of age, but is much more likely to be present after 10 years old[2]. In North America it is thought to affect 22-29% of obese children[3]. It is more common in boys, and occurs more often in children of Caucasian, Hispanic or South Asian ancestry[2]. Pediatric NAFLD is believed to be more aggressive than NAFLD in adults, with more rapid progression to advanced stage disease[1].

Risk factors:

Obesity is thought to be the largest risk factor for the development of NAFLD. In Canada about 1 in 10 children are overweight, which has tripled in the last decade[2]. The risk is highest in those who have significant central adiposity, meaning their weight distribution is highest in their abdomen[2]. To diagnose obesity in children, body mass index is compared to age and sex specific averages. Those who are overweight fall in the 85th to <95th percentile BMI, and obesity is defined as a BMI at the 95th percentile or greater[4]. In children under 2 years of age, weight for length percentiles are used, with a cutoff of 98th percentile and above to be classified as overweight[4].

Other independent risk factors for the development of NAFLD include obstructive sleep apnea, type two diabetes, dyslipidemia and panhypopituitarism[1].

Pathophysiology and spectrum of disease:

NAFLD is an overarching term that includes a wider spectrum of disease relating to fatty infiltration. One subtype, non-alcoholic fatty liver (NAFL) refers to steatosis without significant inflammation or liver damage[5]. On its own, NAFL does not cause chronic liver disease however it can cause hepatomegaly (enlargement of the liver). NAFL can progress to NASH, or nonalcoholic

steatohepatitis. In this case, there is inflammation and injury to hepatocytes[5]. NAFLD can further be classified as NAFLD with fibrosis, or NAFLD with cirrhosis[1]. Essentially, these terms all denote different levels of fat-related changes in the liver, some of which can progress to end stage liver disease. Not everyone who develops NAFL will progress to NASH, but more research on the natural history of the disease is needed to identify concrete risk factors that predict the progression of disease[1].

Screening for NAFLD:

Screening tools for NAFLD are important because, like other chronic liver diseases, NAFLD is often asymptomatic. Screening allows for earlier detection and intervention before a child reaches end-stage disease, which is irreversible. NAFL, and even NASH, can be reversed before the development of advanced fibrosis.

The tool recommended for screening is measuring the levels of alanine aminotransferase or ALT, an enzyme produced by the liver that is elevated in instances of liver damage[1]. This is an inexpensive test that is minimally invasive. An elevation in ALT to 2 times the sex-specific upper limit of the normal range has a 88% sensitivity level, meaning 88% of those with NAFLD who are tested will have an ALT level at this range[1]. If the ALT is 80U/L or higher, the child is more likely to have progressed to NASH[1]. For those with elevations above the upper limit of normal but below 80 U/L, the ALT should be repeated in 2-3 months to confirm elevation[1]. At that point a referral to a pediatric gastroenterologist is warranted for a full diagnostic evaluation. An alternate screening tool that has been used is an abdominal ultrasound, but it has a low sensitivity and specificity in children who have less than one third of hepatocytes with steatosis[1].

Currently, screening is recommended for all obese children starting around age 9-11, as well as overweight children who have additional risk factors mentioned earlier such as dyslipidemia or type two diabetes[1]. If ALT does not meet the screening criteria, you can repeat this test every 2-3 years, or earlier if clinical risk factors become more severe (for instance, the child develops type 2 diabetes)[1].

Making the diagnosis:

As mentioned, most patients with NAFLD are asymptomatic. However, a minority of children can present with non-specific findings like abdominal discomfort, fatigue, or right upper quadrant pain[6]. The disease very rarely progresses to decompensated cirrhosis during childhood, so one would not usually expect to see a child with NAFLD who has signs of end-stage liver disease like jaundice or cutaneous stigmata[6]. On history and physical examination it is important to also identify symptoms of comorbidities like diabetes, hypertension, obstructive sleep apnea, and hypothyroidism which can all worsen fatty infiltration[6]. In addition, ruling out potentially causative medications is important such as certain antipsychotics, corticosteroids, methotrexate and valproic acid, as well as alcohol use[1].

It is very important to not assume an elevated ALT in an overweight or obese child is attributed to NAFLD, and it remains a diagnosis of exclusion as it has a 26% specificity for NAFLD[1]. A full evaluation must be done for those with ALT>80 or ALT>2x the upper limit of normal for >3 months. These include screening labs for other comorbidities, including a CBC with differential, other liver enzymes (AST, GGT, ALP), synthetic liver function tests (INR, total and direct bilirubin, albumin), hemoglobin a1c and fasting lipid panels[1]. Then one should test for other specific causes of liver disease. This includes viral hepatitis serologies, celiac disease, hypothyroidism, autoimmune liver disease markers, and markers for genetic liver diseases such as Wilsons disease or alpha one antitrypsin deficiency[6]. An abdominal ultrasound can help rule out hepatic or biliary anatomic abnormalities. If there is no other evident etiologies of liver disease then a diagnosis of NAFLD can be made, as again it is a diagnosis of exclusion[6].

To assess the extent of steatosis or the presence of NASH or fibrosis, one can consider a liver biopsy. It has more utility when performed in kids with an ALT equal to or above 80 U/L as there is a higher likelihood of NASH[1]. Liver biopsies are considered safe in children with a low risk of complications, allow for the ability to diagnose other liver diseases like autoimmune hepatitis, and help identify those who need more intensive treatment. However, this is ultimately a shared decision with the family[1].

Therapeutic interventions and preventative strategies:

It is important to intervene with children who have NAFLD as there is an increased mortality due to cirrhosis, cardiovascular disease, and hepatocellular carcinoma[6]. There is also an increased prevalence of chronic kidney disease,

therefore some providers perform yearly renal function tests such as creatinine, BUN, and a urine albumin to creatinine ratio[6].

All children should be provided counselling on lifestyle interventions if they are overweight or obese. These interventions can also be proposed as preventative strategies for children who have risk factors but who have an ALT within normal range. Therapies that can be offered include changes towards a healthier diet, increased physical activity, and having less than two hours per day of screen time[7]. Making small goals, such as a goal of avoiding sugary beverages, with your patients can help to make these changes less intimidating and more sustainable over time. It is also important to screen children for psychiatric comorbidities which may be contributing to maladaptive habits[7]. A multi-disciplinary weight management clinic or involvement of other services, such as a dietician, social worker, or a psychiatrist, can help tailor treatment to an individual child's needs.

To monitor for improvement in steatosis, a decrease in ALT is an acceptable marker. Liver biopsies would be the gold standard, but more research is needed to develop an appropriate frequency and timing to weigh the risks and benefits of the procedure[1]. Other goals for patients are to decrease central adiposity, reduce high blood pressure, improve dyslipidemia and manage diabetes. Weight loss goals should be attainable and safe, such as a rate of 1-4lbs per month[6].

A number of medications have been trialed for use in pediatric NAFLD, such as metformin (an oral antihyperglycemic) or vitamin E. However, to date no medications or supplements have been proven to benefit a majority of patients with NAFLD[6]. In those with a BMI of 35 or greater who are having trouble with lifestyle interventions, bariatric surgery can be discussed as an adjunct to help improve weight loss. This can help control serious comorbidities like severe sleep apnea, however there is insufficient data on whether it helps reverse NASH or fibrotic changes[1].

Guidelines recommend following children with NAFLD on a yearly basis, however when providing initial counselling on lifestyle changes more frequent visits are associated with better outcomes[7]. It is also very important to prevent further damage to the liver. This includes counselling adolescents on alcohol intake and smoking risks, vaccinating against hepatitis A and B, and avoiding or closely monitoring the initiation of known hepatoxic medications[1].

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Case wrap up:

Marcus presents with two risk factors for the development of NAFLD – type two diabetes, and a BMI that is greater than 95th percentile for his sex and age range. When a child is diagnosed with type two diabetes, it is recommended to commence yearly screening of their ALT to monitor for NAFLD[8]. It is also important to screen for other comorbidities such as hypothyroidism and dyslipidemia. Marcus had his ALT measured and it came back as 55 U/L, which is greater than 2x the upper limit of normal for boys. A repeat value again in 3 months showed an ALT of 60 U/L. Marcus was referred to a pediatric gastroenterologist who performed various tests for other liver diseases, which all came back as negative. His family declined to have a liver biopsy performed.

You have a long, non-judgmental discussion about the implications of NAFLD and how healthy lifestyle interventions can reduce the risk of further progression. Together you make the goals of going for walks and playing basketball about four times a week, as well as reducing the amount of time spent playing video games. You refer Marcus to a dietician to help him learn more about how to make healthy choices. His family will be involved in these goals, and will join Marcus in planning meals and going for walks. You plan to meet Marcus and his parents again in a few months to evaluate their progress and create new goals, as well as measure a repeat ALT value.

Key points and conclusion:

Let's summarize the key take-aways:

1. Nonalcoholic fatty liver disease is a chronic liver condition related to the accumulation of excess fat in the liver. This term includes a spectrum of disease severity, from simple fatty deposition to associated inflammation and fibrotic changes.
2. NAFLD is the most common liver disease affecting children, and incidence is on the rise. It is most likely to present in children who are overweight or obese, or who have other relevant comorbidities like type two diabetes and dyslipidemia.
3. Alanine aminotransferase is an enzyme useful for screening for NAFLD. Levels consistently above 2x the upper limit of normal, or above 80U/L, should prompt referral to a pediatric gastroenterologist.
4. It is important to screen for other causes of liver disease before diagnosing someone with NAFLD, such as viral hepatitis or autoimmune hepatitis.

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5. Finally, lifestyle interventions such as healthy diet changes, exercise, and reducing screen time are the most important therapies available to help treat NAFLD. Goals set with patients should be small and attainable, and follow-up is important to mark progress.

To conclude, it is important for physicians to screen children at risk for NAFLD and intervene in a timely manner to prevent irreversible liver damage. I hope this podcast served as an effective overview of NAFLD, and inspires you to read more about this topic. Thank you to Dr. Zachos for her guidance on this topic, and thank you for tuning in to listen!

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