MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

Section Editor: Naim Alkhouri, MD

Overview of Metabolic Dysfunction-Associated Steatohepatitis in Children

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G&H What is the current prevalence of metabolic dysfunction-associated steatohepatitis in children?

RK Overall, approximately 1 in 6 children have a diagnosis that fits within the umbrella of metabolic dysfunction-associated steatotic liver disease (MASLD). Zooming in, approximately 5% to 7% of children have metabolic dysfunction-associated steatohepatitis (MASH), which is on the more severe spectrum of the MASLD umbrella. These children have an inflammatory and/or fibrotic component within the definition of MASLD, which necessitates the presence of steatosis, or hepatic lipid accumulation.

G&H What is the typical clinical presentation of MASH in children?

RK Although the disease has long-term consequences on individuals, there are not many overt clinical symptoms. As the definition states, there is a background of metabolic dysfunction, so the key elements may include any or all of hypertension, high cholesterol, and a body mass index (BMI) that is greater than the 95th percentile. However, outside of being overweight and/or obese or having acanthosis, which is a marker of insulin resistance, not many symptoms are produced by having MASH until it is very advanced. Then, patients develop symptoms that are consistent with chronic liver disease such as jaundice or the propensity to bleed more than usual or for longer; the dysfunction of the liver is so severe that patients do not produce enough clotting factors. However, those signs are typically not present in children or adolescents because there is not enough time during childhood or adolescence to develop signs at that level; those are features of very advanced chronic liver disease.

G&H What are the main risk factors for MASH in the pediatric setting?

RK The main risk factor is having a weight that is disproportionately high for the age and sex of the child. Although BMI is an imperfect measure, it is used clinically because it is the easiest and best tool currently available to identify children who are overweight or obese. Cutoffs have been established by the American Academy of Pediatrics for definitions of obesity and/or overweight, and these are used as screening tools.

Another risk factor involves ethnic or racial ancestry. Pediatric MASH is highest among Hispanic children, followed by Asian children. Genetic polymorphisms associated with MASH are known to be of higher prevalence within the Hispanic population. Therefore, there is a higher prevalence of MASH within the Hispanic pediatric and adolescent populations. Similarly, having a family history of MASH is also a risk factor.

The overall prevalence of MASLD and MASH has been increasing in children over time, as documented within multiple publications, including a relatively recent one from Southern California. Using a large database from Kaiser Permanente, researchers from the University of California, San Diego showed that there was an almost doubling of the incidence of MASLD from 36 to 58 per 100,000 from 2009 to 2018. Thus, the environment is

also a risk factor for MASH and is potentially modifiable because during that time period the same geography containing the same demographics was potentially exposed to changing paradigms of nutrition and environmental influences.

G&H Are there differences between pediatric and adult MASH in terms of pathophysiology or histology?

RK As mentioned earlier, MASH is the advanced form of MASLD so seeing it be identified in adolescents or children, just by sheer definition, means that their disease is somehow more aggressive. In contrast, other children or adolescents with the same BMI, height, and sex do not have the same amount of inflammation and/or fibrosis develop. This tells us that those who have MASH and/or advanced fibrosis and inflammation in their livers were likely at higher risk. MASH is faster-moving for individuals with an underlying genetic predisposition or exposure to more environmental toxins than others, as some combination of risk factors has made them present earlier with more aggressive disease. As to the question of how MASH is different in adults vs children, I am more worried about the individuals who are presenting early with the same environmental exposures. These individuals are having more advanced disease within a few years of exposure as a child compared with having similar scarring, fibrosis, inflammation, and steatosis developing over 3 to 4 decades.

Another difference is at the histologic level on biopsy. The pattern of inflammation in children appears to be distinct from adult inflammatory distribution. In some publications, investigators divided nonalcoholic steatohepatitis (NASH; the former name for MASH) into type 1 (adult) and type 2 (pediatric) NASH. This is not completely understood, but there appears to be a slight difference in terms of inflammatory cells and where they attack within the liver, which can be seen on liver biopsy and potentially could be a distinguishing feature as well.

G&H What are the preferred diagnostic tests for MASH evaluation in children?

RK Most programs have guidelines to start evaluation at the primary care level of children with an elevated BMI for age and sex and other risk factors for MASH. The first screening test that is commonly used is serum alanine aminotransferase (ALT), which is widely available and a fairly standard biochemistry test. It is used as a screening tool initially if patients have more than 2 to 3 times the upper limit of normal for ALT, which is 26 IU/L for adolescent males and 22 IU/L for adolescent females. The most recent guidelines from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, for which I was part of the writing group, used a cutoff of 80 IU/L for ALT measured at 2 disparate time points in the setting of elevated BMI. That is the point wherein referral to a pediatric gastroenterologist is recommended for further workup of the child. This would include imaging to establish further structure of the liver, gallbladder, and so forth to make sure there are no gallstones or tumors. Providers should also make sure not to assume that any child has MASH or MASLD just because they are overweight and should look for other chronic liver diseases that are inherited and/or acquired from the environment, such as hepatitis B or C. Also, providers should make sure they are not missing underlying autoimmune hepatitis, which can be triggered in a child, despite them more than likely having MASH because of elevated ALT 2 to 3 times the upper limit of normal in the right setting and phenotype with obesity. After serologic tests and imaging, the final diagnosis is made on liver biopsy if the program decides to include it as part of their tools for pediatric MASH.

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G&H How often is liver biopsy used in the pediatric setting for MASH?

RK I think liver biopsy is an important tool that has to be used in the right context. The clinical algorithm that my colleagues and I follow at Children's Hospital Los Angeles waits for a specific period of time after counseling has been given, lifestyle management has been addressed, and providers have ruled out other chronic liver diseases. Liver biopsy is used as a tool to decide whether to offer further treatment modalities. The treatment landscape continues to change and will evolve further, but includes vitamin E or weight loss options beyond lifestyle modifications such as bariatric surgery and/or the new medications for

obesity and diabetes that have been approved by the US Food and Drug Administration (FDA), the glucagon-like peptide-1 (GLP-1) receptor agonist category of medications. Children's Hospital Los Angeles has elected to formally have a liver biopsy pathway, and a significant majority of our patients who end up undergoing liver biopsy through this pathway are diagnosed with MASH. Waiting to offer interventions that go beyond lifestyle modifications only once we have a pathologic diagnosis of the severe form of the disease (MASH) makes us more confident in our recommendations.

G&H How effective are nutritional interventions for managing children with MASH?

RK Nutritional interventions work. When we started putting together clinics that were multidisciplinary to address this disease in the early 2000s, I was part of a publication at Cincinnati Children's Hospital where we monitored the outcomes of lifestyle interventions very carefully. We, as well as other groups, showed that a well-structured multidisciplinary program with frequent clinic visits and touch points from dietitians, nurse practitioners, physicians, exercise physiologists, and psychologists can lead to weight loss as well as improvements in liver-specific outcome measures such as ALT. However, the issue is maintenance of said improvements over a sustained period of time without that frequent multidisciplinary intervention.

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When intervention is not done on a consistent basis, and sometimes even when consistent intervention is available, children and adolescents drop out of those programs. Our publication noted a retention rate of only 47%, which is not too different from what has been reported in the literature for weight management programs. With more directed interventions—including bariatric surgical procedures such as sleeve gastrectomy, which is currently the most popular one in adolescence and I would say even on the adult side, and the newly approved GLP-1 receptor agonist medications for patients over 12 years of age—more sustained improvements can be seen.

G&H Have medications been studied for the treatment of pediatric MASH?

RK Two studies have been done systematically under the auspices of the National Institutes of Health NASH Clinical Research Network. One was for vitamin E in patients with biopsy-proven MASH. The other was a negative study for cysteamine, a glutathione precursor that increases potential antioxidant effects. GLP-1 receptor agonists have not been studied in the MASH setting for children as of yet. These medications have been studied in adults for the treatment of MASH and in children and adolescents over 12 years of age for obesity, and are currently approved by the FDA for the indication of obesity, not MASH.

G&H What should be the role of bariatric surgery in the treatment of pediatric patients with MASH and obesity?

RK Guidelines from the American Society for Metabolic and Bariatric Surgery and the American Academy of Pediatrics Task Force consider bariatric surgery an option for improved outcomes in adolescents who have MASH in the setting of obesity. Bariatric surgery has been shown to be safe. Very closely monitored, multicenter studies have been conducted through the National Institutes of Health. Strong data have shown positive outcomes with bariatric surgery for weight loss, including improvements in cardiac, lipid, and cholesterol outcomes. These studies have demonstrated that bariatric surgery should be part of the tool kit for advanced severe MASLD such as MASH for the right patient at the right time.

Looking at specific procedures of bariatric surgery, there does not appear to be discernible differences in terms of outcomes in adolescents who underwent Roux-en-Y gastric bypass or sleeve gastrectomy. However, in the past decade, if not longer, sleeve gastrectomy has become the procedure of choice, likely because there are surgical elements that are less invasive compared with Roux-en-Y gastric bypass. Recovery time may be shorter postoperatively, although there might not be a large difference in experienced hands. Most importantly, sleeve gastrectomy does not involve manipulating most of the small or large intestine. It is a more limited-scope procedure in terms of invasiveness, which probably makes it more attractive to the individuals undergoing surgery and their families.

G&H What is the economic impact of MASH in children?

RK The economic impact is definitely in the billions of dollars, although it depends on how this is studied.

Nevertheless, pediatric MASH has a significant impact on the present situation as well as on the future; these children and adolescents are going to need surgery and/or medication for life. As mentioned earlier, the incidence of MASH is increasing in children likely because of our changing environment. If we want to prevent or reduce the economic impact of this disease through interventions such as bariatric surgery and/or medications as well as the impact on the individuals themselves, resources should be spent on reversing the environmental impact, starting with schools, grocery stores, and even our kitchens. That is a broader discussion, not for pediatric gastroenterologists alone or maybe even not pediatricians alone, but for the community to have as to what can be done at a societal level to reverse the changes in our environment that are making susceptible individuals, such as children of Hispanic descent, develop MASH in childhood.

G&H What are the future directions involving MASH in children?

RK Better noninvasive testing modalities are needed to screen and identify children who are at risk for MASH. There is aggressive damage occurring inside the liver that we sometimes do not find until it is too late. The screening tool typically used, ALT, is not very accurate, especially over time. When measured in a single individual over time, there is going to be vacillation in the level of ALT. A better biomarker is needed. Under the leadership of Dr Rachel Schenker, our group recently published a paper on the potential biomarker dihydroxyacetone phosphate (DHAP). When combined with ALT, DHAP was found to have a much better sensitivity and specificity than ALT alone. However, this was a small early study, and DHAP needs to be validated in larger cohorts.

Additionally, we need an intervention that is specific and proven to change long-term outcomes for children that is less invasive than bariatric surgery. Bariatric surgery works, as discussed, but it is not reversible for the most part. We should study how bariatric surgery works, unpack it such that we could hone in on the factors that are helping the liver disease resolve after the procedure, and then package that for the children who are at highest risk for MASH and/or who are presenting with MASH in childhood or adolescence. We could provide that as an antifibrotic or anti-inflammatory intervention, or both, and prevent these children and adolescents from becoming young adults who need liver transplantation. Research from Dr Naim Alkhouri several years ago found that NASH, as the disease was known at the time, was the fastest-growing indication for liver transplantation in young adults.

Disclosures

Dr Kohli was a consultant to AstraZeneca in the past.

Suggested Reading

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