

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Use of Transient Elastography in Children



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G&H How does transient elastography work, and how does it compare with liver biopsy for the assessment of fibrosis in children?

TM Transient elastography is a noninvasive tool that assesses the degree of fibrosis in the liver by measuring the stiffness of the liver. This tool has been validated in many adult liver diseases as well as several pediatric liver diseases. Determining normal stiffness of the liver has traditionally been challenging in children. Stiffness of the liver has been shown to increase with age and differs depending upon sex; males tend to have stiffer livers than females. In addition, correlating measurements of liver stiffness with histology can be difficult in pediatrics because liver biopsy, which has been considered the gold standard of assessment of fibrosis, is subject to sampling variation. Different parts of the same liver may yield different histologic patterns, not to mention that some diseases may be more focal or patchy, rather than homogeneous. Thus, the results of a liver biopsy can differ depending on whether the physician can capture the area of pathology.

An advantage of transient elastography over liver biopsy is that the former is likely to be more representative of the underlying features because it is based on 10 separate measurements. In addition, it is safer and less expensive than liver biopsy, especially if serial procedures are needed (eg, every 6 months or every year). Also, physicians usually try to avoid liver biopsy in children so that they are not subjected to general sedation, particularly for multiple procedures. Many studies examining the effects of an intervention on the progression of fibrosis have

shown a shift from serial biopsies to relying on the results of noninvasive transient elastography.

G&H When is transient elastography currently used in children?

TM Currently, there are no official guidelines for the use of transient elastography in children; its pediatric use has generally been extrapolated from its use in adults. However, children have different liver diseases depending on age. Infants tend to have genetic and cholestatic liver diseases, and as they grow older, the spectrum of diseases broadens.

The most common indication for liver transplantation in children is biliary atresia, which is likely the most rapidly progressive fibrotic state in the liver. A patient can progress from no fibrosis to frank cirrhosis within several months. In patients with biliary atresia, serial monitoring of the pace of progression is important for determining when to list for liver transplantation. Transient elastography can be used in this situation.

Transient elastography has also undergone study in patients with cystic fibrosis, a significant number of whom develop liver disease. In the past, it was not possible to predict which patients would develop liver disease. With the validation of transient elastography, it is possible to assess disease progression earlier, which can allow clinicians to be more aggressive with management and help prevent development of complications associated with portal hypertension. In addition, cystic fibrosis is associated with patchy disease of the liver, so liver biopsy may miss significant areas of fibrosis.

G&H Is transient elastography contraindicated in any pediatric patients?

TM There is no absolute contraindication to using transient elastography, although there has been less experience using it in infants. There may be challenges using transient elastography in children who have significant ascites and in those who are obese.

G&H Are there any disadvantages or limitations to using transient elastography in children?

TM It is necessary to have expertise and experience to use transient elastography in children. The appropriate equipment and probes are also needed; there are separate probes for children (S and M) and adults. It may be challenging to obtain the proper measurements, which have to be taken 10 times, especially in a young child who may be reluctant to lie still. Some debate exists regarding the reproducibility of the results. There are also some confounding factors; for example, inflammation by itself can increase the stiffness of the liver.

One of the scenarios in which physicians need to follow progression of pediatric fibrosis is in children who have undergone a Fontan procedure. These children were born with a single ventricle and develop hepatic congestion, which may lead to significant fibrosis over time. However, congestion in the liver can also increase liver stiffness. Thus, it may be challenging to determine whether the etiology of the liver stiffness is related to fibrosis or congestion.

G&H How does transient elastography compare with other methods for evaluating fibrosis in children?

TM Magnetic resonance elastography (MRE) is another noninvasive method for assessing the degree of fibrosis. MRE can be very accurate; however, it is much more expensive. In addition, some children need general sedation to undergo this procedure.

Other serum-based biochemical tools and/or biomarkers are also available to assess the degree of scarring of the liver and have been partially validated in children. This is an evolving field.

G&H What research has been performed on the use of transient elastography for assessing liver stiffness in children?

TM Several studies have been performed in children. The FORCE study, which was sponsored by the National

Institutes of Health, examined children who had some of the most common cholestatic conditions, including biliary atresia, alpha-1 antitrypsin deficiency, and Alagille syndrome. The researchers found a correlation between liver stiffness and the development of any sign of portal hypertension. In addition, the findings correlated with biochemical values such as bilirubin, international normalized ratio, gamma-glutamyl transferase (GGT), GGT to platelet ratio, pediatric end-stage liver disease score, and spleen size. On the other hand, there was negative correlation with albumin and platelet count. Thus, the measurements had clinical significance.

A meta-analysis reviewed several studies that were performed on liver stiffness in children. The studies varied in several aspects, such as the number of patients and the types of conditions. Some of the studies were prospective, whereas others were retrospective. Some studies looked at various chronic liver conditions, whereas others focused on specific diseases such as biliary atresia, hepatitis C virus, and nonalcoholic fatty liver disease (the last of which is the most common chronic liver condition in children and adolescents). Liver stiffness measurements helped to identify which patients were more likely to progress and develop complications vs which patients would have a more benign process.

G&H What research has examined the use of transient elastography for evaluating stiffness of the spleen in children?

TM Assessment of the stiffness of the spleen has not been studied as frequently as liver stiffness. However, it has been shown that the spleen becomes congested and enlarged over time in patients who develop portal hypertension, and there is correlation between the degree of portal hypertension and splenic stiffness. Stiffness of the spleen has been studied in children with biliary atresia and has been shown to be associated with the risk of variceal bleed and significant esophageal varices. In addition, splenic stiffness has been studied in patients with Fontan physiology to differentiate whether the liver is enlarged because it is congested or because it is fibrotic. If a patient has liver fibrosis, there would be an increase in splenic stiffness as well. If the patient has hepatic congestion, the spleen would not be as stiff.

G&H Are there validated transient elastography cutoff values for liver stiffness and splenic stiffness in children?

TM Several studies have reported normal stiffness measurements for children, although these values vary based upon age and sex. However, other studies have not always

been able to reproduce the same results, leading to some concerns regarding the reliability and repeatability of transient elastography in children. Nevertheless, I think that most clinicians would accept transient elastography and consider it to be valid.

Transient elastography is very good at predicting extremes (ie, cirrhosis or no fibrosis). Thus, it would likely be better at differentiating between stages 0 and 1 fibrosis or between stages 3 and 4 fibrosis than between stages 2 and 3 fibrosis.

G&H How difficult is it to perform transient elastography in children?

TM It is important to have experience working with children and soothing them. Thus, the provider should be a professional who performs this procedure quite routinely; someone who does this test only once or twice a month may not be good at it from a technical standpoint. Transient elastography training takes between 2 and 4 hours. The person performing the test should also be able to understand how to interpret the results. One of the advantages of transient elastography is that findings are being given in real time.

G&H What do you foresee for the future of transient elastography in children?

TM There is a dire need for noninvasive markers of liver fibrosis. I can see patients undergoing transient elastography as part of their vital signs being checked in a hepatology clinic, similar to how blood pressure and weight are measured. Transient elastography is relatively quick; it can be done within 10 minutes and adds important information. It can help a clinician differentiate between patients who do not have fibrosis and those who have evidence of it. This latter group needs to be evaluated sooner and

screened for complications associated with portal hypertension. Perhaps these patients could also be offered interventions earlier in the course of their disease.

Disclosures

Dr Miloh has no relevant conflicts of interest to disclose.

Suggested Reading

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Sadly, Dr Miloh passed away in January 2022 at the age of 53. He made many contributions to the pediatric hepatology community and had an enormous impact on many patients and colleagues over the years. G&H sends condolences to his family and friends.

This column is based on an interview with Dr Miloh at the end of December 2021. It was reviewed in his place by Dr William F. Balistreri, Dorothy M. M. Kersten Professor of Pediatrics at University of Cincinnati College of Medicine.