



Advances in diagnosis of chronic liver diseases in pediatric patients

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Abstract

Background Chronic liver diseases (CLD) present important clinical problem in children with various age-dependent causes. Nonalcoholic fatty liver disease (NAFLD) with its increasing prevalence is a major problem with regard to its timely recognition and the need for long-term disease monitoring. At present, a perfect non-invasive method for the evaluation of liver fibrosis is not available.

Methods A non-systematic literature search was performed to summarize the current knowledge about transient elastography (TE) with controlled attenuation parameter (CAP) in children with CLD. Ovid MEDLINE, Ovid EMBASE, Google scholar, and The Cochrane Library databases were searched for relevant articles evaluating TE in the pediatric population.

Results Normal values of liver stiffness measurements (LSM) according to the age are given, as well as the advantages and disadvantages of the method. The utility of TE in specific liver disease in pediatric population is summarized.

Conclusions TE with CAP is a valuable non-invasive method for the liver-damage assessment. Clinical interpretation of TE results should be made in parallel with the assessment of the patient's demographics, disease etiology, and essential laboratory parameters.

Keywords Child · Liver disease · Liver stiffness · Pediatric · Transient elastography

Introduction

Chronic liver diseases (CLD) raise increasingly important clinical challenges in pediatric population with various age-dependent causes. Biliary atresia and inherited syndromes of intrahepatic cholestasis (e.g., choledochal cysts, Alagille syndrome, and inherited progressive cholestatic syndromes) are the main causes of CLD with consequent cirrhosis in children [1]. Aside from biliary atresia, genetic and metabolic diseases are frequent causes of CLD in the first years of life. Chronic viral hepatitis C and B, autoimmune hepatitis,

cystic fibrosis, Wilson's disease, and α 1-antitrypsin deficiency are typical CLD in older children. The most common cause of CLD in children is nonalcoholic fatty liver disease (NAFLD) with a pooled mean prevalence of 7.6% in children overall and of 34% in children with obesity [2]. NAFLD is suspected when abnormal serum aminotransferases and obesity are present, supported by hyperechoic liver appearance (i.e., the degree of fatty infiltration) on abdominal ultrasound, but only after other causes of liver disease have been excluded [3]. In 5–15% of pediatric patients with cirrhotic liver disease, it is not possible to determine the etiology [4]. Liver biopsy followed by histological analysis is currently considered the gold standard for the assessment of the degree of chronic liver damage. Due to sampling errors, interobserver and intraobserver variability [5], as well as possible complications of this invasive method, new reliable and non-invasive methods have been proposed. Biological markers of liver fibrosis such as routine biochemistry, FibroTest[®] score, pediatric NAFLD fibrosis index (PNFI), enhanced liver fibrosis test (ELF), and aspartate-to-platelet ratio index (APRI) are amongst the different options for diagnosing and following-up CLD. Novel non-invasive ultrasound-based method for the assessment of CLD is transient liver elastography.

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The aim of this study is to summarize the current knowledge about transient elastography (TE) with controlled attenuation parameter (CAP), and to identify studies that have reported about this non-invasive method in the initial assessment and follow-up of pediatric patients with various CLD.

Methods

Ovid MEDLINE, Ovid EMBASE, Google scholar, and The Cochrane Library databases were searched for relevant articles evaluating TE in pediatric population. Articles published from databases inceptions to the 1 of April 2018 were selected. In the PubMed advanced search, a combination of words “transient elastography” OR “liver stiffness” AND “child*” OR “pediatric” was used. No restrictions were applied to the search algorithm. Because of the diversity of CLD in children, small number of subjects and subjects belonging to various age groups enrolled in the studies, it was not possible to perform a systematic review with meta-analysis.

Results

Transient liver elastography

TE using the FibroScan[®] (Echosens, France) is an ultrasound-based assessment of liver stiffness measurements (LSM) and hence liver fibrosis [6]. LSM is evaluated by measuring the shear wave velocity, i.e., wave speed of propagation to a particular depth inside the liver [7]. The stiffer the tissue, the faster the shear wave is spread [8]. The probe of the FibroScan[®] is placed between the rib bones in proximity to the right lobe of the liver. The characteristics of currently available probes are given in Table 1.

To improve the test reliability, a minimum of ten valid readings (with at least of a 60% success rate and an

interquartile range of $\leq 30\%$ of the median value) has to be taken with the results shown in kilopascals (kPa) [7]. The median value of ten valid measurements is interpreted as representative. The number of valid measurements divided by the total number of measurements is defined as a success rate. LSM values range from 2.5 to 75 kPa; lower values suggest a more elastic liver [6].

FibroScan[®] can concomitantly determine LSM as an indicator for liver fibrosis, and controlled attenuation parameter (CAP), a marker of liver steatosis. CAP value is derived from the same region of liver as LSM and these two values are concomitantly displayed on the screen. CAP has been in the clinical practice since 2011, 10 years after the clinical application of LSM has been introduced [11]. FibroScan[®]'s M-probe presents values of CAP expressed in decibel per meter (dB/m) with range from 100 to 400 dB/m; higher values indicate a more pronounced steatosis [12].

First clinical data from TE were published in 2002 [13]. The method is well recognized in adult chronic hepatitis B and chronic hepatitis C patients. A very few studies are related to adult NAFLD patients and only a few to other CLD (i.e., primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, and liver transplant recipients) [13]. The accepted cut-off values in adults for cirrhosis are different for each CLD and range from 10.3 kPa in chronic hepatitis B to 17.3 kPa in chronic cholestatic diseases [14]. In studies conducted with adults, TE shows sensitivity and specificity values close to 90% in detecting advanced fibrosis [15]. Regarding reproducibility of TE, Fraquelli et al. [16] have demonstrated high intraobserver (98%) and interobserver (98%) agreement.

Transient elastography in children

The accuracy of TE in assessing liver fibrosis in children with CLD is documented only in few studies. De Ledingen et al. [17] suggested that LSM is feasible in children and is related to liver fibrosis as well as to clinical and biological

Table 1 Probes characteristics

| Variants | S probe | M probe | XL probe |
|------------------------------|--|-----------|---|
| Group of patients | Children Asthenic adults S1: Thorax circumference 45–75 cm S2: Thorax circumference < 45 cm | Standard | Obese patients (≥ 30 kg/m ²) |
| Transducer diameter | 5 mm | 7 mm | 10 mm |
| Frequency | 5 MHz | 3.5 MHz | 2.5 MHz |
| Measurement depth | S1: 15–40 mm S2: 20–50 mm | 25–65 mm | 35–75 mm |
| Quantitative liver parameter | LSM ^a | LSM + CAP | LSM + CAP |

LSM liver stiffness measurements, CAP controlled attenuation parameter. ^aS probe used in children is only applicable for LSM, but not for the CAP measurement [9, 10]

parameters. Engelman et al. [18] suggested to perform TE in small children under general anesthesia (GA) to maximize the success rate. On the other hand, Goldschmidt et al. [19] reported significantly increased liver stiffness under the GA. This may be well explained by an increased splanchnic blood flow due to the propofol use for induction of GA [20]. Engelman et al. [18] investigated the feasibility of TE in healthy children in three age groups (i.e. 0–5, 6–11, and 12–18 years), and the upper limits of LSM values were 5.96, 6.65, and 6.82 kPa, respectively. Different probes that were used in this study (S or M) introduce a severe bias [21]. Normal age-dependent LSM values were given in two recently performed studies by Lewindon et al. [22] and Tokuhara et al. [23] (Table 2). Tokuhara et al. [23] also found that CAP values are not age dependent. To determine normal values of LSM in children, more large-scale studies are to be conducted. The advantages and disadvantages of usage of TE in pediatric population are summarized in Table 3.

Table 2 LSM and CAP values in healthy children

| Studies | Number of cases | Mean LSM, kPa (\pm SD) or (5th–95th) | Mean CAP, dB/m (5th–95th) |
|---------------------------------------|-----------------|---|---------------------------|
| Lewindon et al. [22] ^a (y) | | | |
| < 2 | 8 | 3.5 \pm 0.5 | |
| 3–5 | 21 | 3.8 \pm 0.3 | |
| 6–11 | 51 | 4.1 \pm 0.2 | |
| 12–18 | 43 | 4.5 \pm 0.2 | |
| Tokuhara et al. [23] ^b (y) | | | |
| 1–5 | 20 | 3.4 (2.3–4.6) | 180 (104–240) |
| 6–11 | 46 | 3.8 (2.5–6.1) | 181 (112–240) |
| 12–18 | 57 | 4.1 (3.3–7.9) | 190 (111–288) |

LSM liver stiffness measurements, CAP controlled attenuation parameter. ^aObesity was not excluding criteria. ^bOverweight or obese patients were excluded

Table 3 Advantages and disadvantages of TE in children

| Advantages | Disadvantages and explanations |
|-----------------------------|--|
| Non-invasive method | Age: narrow intercostal spaces in small children, non-compliance, sedation often needed for younger than two years [22] |
| Easy to perform | Probe choice: the probe must be small enough to fit between the ribs; LSM tends to decrease with increasing probe size |
| Instantaneous results | Obesity: because visceral fat attenuates the transmission of the shear wave into the liver, in addition to limited penetration of the wave, the applicability and accuracy of LSM in obese patients are low |
| High reproducibility | Ascites: penetration up to 65 mm; waves do not travel through liquids |
| Inexpensive | Food: 2-h fast is currently recommended [12] |
| Quantificational accuracy | Chronic hepatitis, 5 \times upper normal limit of ALT, extrahepatic cholestasis, congestive heart failure: Intrahepatic deposits (including inflammatory cells) and blood congestion may increase liver stiffness [24] due to increased intracellular pressure |
| Applicable during follow-up | |

De Lendingen et al. [17] performed a study in a cohort of 116 pediatric patients with various CLD to examine the feasibility and accuracy of TE. This is the first study considering TE in pediatric population, currently a highly dynamic research area. Most of the studies were conducted in pediatric patients with various liver diseases. The main results and conclusions from the most relevant articles are summarized in Table 4. More detailed data from the studies considering usage of TE in CLD in children are given in Supplement.

Transient elastography with controlled attenuating parameter in children

To date, only two studies described about usefulness of CAP in the determination of the liver steatosis in children. To diagnose steatosis in pediatric patients, optimal threshold is > 225 dB/m, shown by Desai et al [9]. Taking into account the heterogeneity of a group of pediatric patients with various liver diseases, no consistent thresholds between grades of steatosis can be pointed out. Cho et al. [10] compared CAP values in obese children, those with liver disease and healthy ones, and reported significantly higher CAP values (285 ± 60 dB/m) in children with obesity than in the other two groups (i.e., control group 179 ± 41 dB/m; liver disease group 202 ± 62 dB/m). These results suggest association between childhood obesity and liver steatosis defined by CAP values.

Discussion

TE is feasible, non-invasive, preferable, simple, and efficient method for an assessment of a liver damage. LSM and CAP values must be interpreted with caution and take into account medical history, physical examination, laboratory

Table 4 Studies examining TE in various CLD in children

| Studies | Etiology | Number of patients | Age (y) | Gold standard | LSM (kPa) |
|---------------------------|--------------------------------------|--------------------|---------|--------------------------------|---|
| Fitzpatrick et al. [25] | Various CLD | 104 | 6–18 | Liver biopsy ($n = 104$) | Cut-off for severe fibrosis = 7.5 ^a Cut-off for cirrhosis = 14.1 |
| Lee et al. [26] | Various CLD | 128 | 0–27 | Liver biopsy ($n = 128$) | Cut-off for advanced fibrosis = 8.6 ^b |
| Behairy et al. [27] | Various CLD | 90 | 4–16 | Liver biopsy ($n = 90$) | Cut-off for severe fibrosis = 8.25 ^c Cut-off for cirrhosis = 29.5 |
| Breton et al. [28] | Various CLD with portal hypertension | 72 | 4–18 | Liver biopsy ($n = 14$) | Median = 26.5 |
| Nobili et al. [29] | NASH | 52 | 11–16 | Liver biopsy ($n = 52$) | Cut-off for advanced fibrosis = 10.2 ^d |
| Shin et al. [30] | Biliary atresia | 47 | 9–180 d | Liver biopsy ($n = 46$) | Cut-off for severe fibrosis = 9.6 ^d Cut-off for cirrhosis = 18.2 |
| Chongsrisawat et al. [31] | Biliary atresia | 73 | 3–14 | Upper gastroscopy ($n = 39$) | Cut-off for esophageal/gastric varices = 12.7 |

CLD chronic liver disease, TE transient elastography, LSM liver stiffness measurements, NASH nonalcoholic steatohepatitis, NAFLD nonalcoholic fatty liver disease. ^aAccording to METAVIR score: F3=severe fibrosis; F4=cirrhosis. ^bAccording to METAVIR score: F3 or F4=advanced fibrosis. ^cAccording to Ishak score: \geq F3=severe fibrosis; F6=cirrhosis. ^dAccording to Brunt's scoring system: \geq 3=advanced fibrosis

tests, and imaging methods to diagnose liver fibrosis/steatosis. The reference intervals for LSM across a range of age groups need to be established. A few prospective recent studies evaluated the correlation of TE with liver fibrosis in larger cohorts of patients with various liver diseases [10, 17, 25–27].

According to the currently published literature (Table 4, Supplement), there is no consensus about the cut-off values for various stages of liver fibrosis. Due to the variable pathophysiology of CLD, Behairy et al. [26] emphasized the need for disease-specific cut-off values of LSM to predict different stages of fibrosis in children.

The chief challenge in pediatric populations remains the timely recognition of the severe liver diseases. Different disorders may have similar initial clinical presentation, often resulting in late recognition of the underlying disease. CLD in pediatric population accounts for significant morbidity and mortality, yet it still remains under-expected, under-recognized, under-studied, and consequently often under-managed.

Finally, it should be emphasized that the growing incidence of NAFLD in both adult and pediatric population makes this field of investigation mandatory. Early non-invasive differentiation between simple steatosis and non-alcoholic steatohepatitis (NASH) in patients with NAFLD should be a cornerstone in the prevention of advanced liver disease. Three non-invasive approaches have been employed to determine the severity of fibrosis in children with NAFLD: the pediatric NAFLD fibrosis index (PNFI), the enhanced liver fibrosis (ELF) test, and TE [40]. Nobili et al. [28] compared the TE values with histologic fibrosis stages in pediatric patients with NASH and concluded that

TE had an excellent diagnostic accuracy (Table 4). TE and CAP are viable alternatives to ultrasonography, both in initial assessment and during the follow-up of patients with NAFLD, as suggested by Mikolasevic et al. [12]. Its ability to exclude patients with advanced fibrosis may be used to identify low-risk NAFLD patients for whom liver biopsy is not required, thus reducing the risk of complications and the financial costs. Even if NAFLD is more common in adult patients with type 1 diabetes mellitus, a recent study advocates against the systematic screening for NAFLD in pediatric patients with type 1 diabetes mellitus [41].

Biliary atresia is an idiopathic congenital obliterative cholangiopathy which rapidly progresses to liver cirrhosis. Patients with severe fibrosis or cirrhosis established preoperatively have worse survival rate after Kasai portoenterostomy [42–44]. Therefore, TE as a non-invasive method for the assessment of liver fibrosis, done before surgery and liver biopsy, could be used in outcomes prediction, suggesting more effective treatment options [29]. Liver fibrosis can be progressive even after portoenterostomy, including portal hypertension and esophageal varices, as life-threatening complications. To date, three studies evaluated TE as a useful screening method for the preendoscopic detection of varices in postoperative patients with biliary atresia [30–32]. Hahn et al. [33] investigated the role of TE in long-term follow-up of biliary atresia patients after the Kasai operation.

Cystic fibrosis (CF) is a genetic disorder that affects function of exocrine glands causing severe damage to multiple organ systems. Late clinical presentation of advanced liver disease at puberty remarkably contributes to the fact that it is the third most common cause of death in patients with CF [45]. TE has been evaluated for cystic

fibrosis-associated liver disease in several studies [17, 27, 34, 36, 37, 46–48]. Malbrunot-Wagner et al. [34] investigated the correlation between TE values and the esophageal varices presentation in patients with CF and concluded that TE can indicate the need for esophagogastroduodenoscopy. Witters et al. [36] showed that TE could contribute to the early detection of cystic fibrosis-associated liver disease, allowing timely treatment with ursodeoxycholic acid. Recent study has found that liver stiffness > 6.8 kPa had a specificity of 91.7% and sensitivity of 91.5% in predicting liver disease in patients with CF [35]. Aqul et al. [37] found significant increase of LSM in correlation with the presence and severity of liver disease in patients with CF.

Wilson's disease (WD) is a rare inherited disorder of copper metabolism that is characterized by excessive deposition of copper in the liver, brain, and other tissues. WD presents with liver disease more often in children than in adults with cirrhosis as the most common initial presentation. Study by Karlas et al. [38] reported cut-off value of 6.1 kPa for cirrhosis detection in WD patients. Stefanescu et al. [49] found a decrease in liver stiffness in pediatric patients with WD during treatment for increasing urinary copper excretion.

Gastroesophageal varices are late and life-threatening consequences of portal hypertension due to various CLD. Although only one study evaluated the feasibility and applicability of spleen stiffness measurement by TE as a new non-invasive marker for assessment of portal hypertension in children [50], the need for non-invasive prediction of complication related to portal hypertension is indisputable. The proposed preliminary cut-off value of spleen stiffness for variceal bleeding is 60 kPa [50].

The use of TE as a predictor of liver histopathology in children with intestinal failure [51] and for diagnosis of liver allograft fibrosis in pediatric liver transplant recipients [39, 52] has also been assessed.

The main problem is that the majority of these studies are conducted on CLD patients with various underlying causes. Other limitations are a relatively small sample size of participants in each of the study, participants of different ages, and different methodology of each study. Therefore, the systematic review and meta-analysis were not possible to perform. This is, to date, the first non-systematic review upon TE in pediatric population.

Conclusions

TE as a non-invasive, easy repeating, bedside method is simple assistant in making the diagnosis and during the follow-up of CLD. LSM and CAP are not only helpful tools in the initial assessment, but are also important for the evaluation of disease progression as well as for the further management

guidance. Correct disease-specific classification of fibrosis is still under discussion. Clinical interpretation of TE results should be made in line with the assessment of patient demographics, disease etiology, and essential laboratory parameters. An algorithm using a combination of serum biomarkers with LSM and CAP for timely recognition and precise evaluation of liver fibrosis/steatosis in specific CLD has yet to be developed. Prospective validation studies, including randomized controlled trials and meta-analysis, are needed to assess the impact of TE with CAP in larger cohorts of pediatric patients. A perfect non-invasive method for the evaluation of liver fibrosis does not exist. In the near future, a consensus on the use of non-invasive methods could limit the indications of the pediatric liver biopsy, ultimately benefiting the pediatric patients.

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Compliance with ethical standards

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Conflict of interest None.

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