Transient elastography for liver fibrosis in children with chronic liver disease

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Abstract
Liver fibrosis results from chronic hepatocyte inflammation. Underlying cause may differ in each case. Liver fibrosis can progress to cirrhosis. Liver biopsy is the gold standard to diagnose and prognosticate such children. Non-invasive modalities for liver fibrosis assessment are now available. It can be done by transient elastography (TE). Normal values for median liver stiffness are available in children. I retrospectively studied children with chronic liver disease. Median liver stiffness was measured and analysed with clinically important factors like splenomegaly, varices and stage of fibrosis on histopathology reports.

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Introduction

Chronic liver disease (CLD) is associated with long standing irreversible change in the hepatic structure due to specified aetiology. Metabolic liver disease and autoimmune hepatitis are common causes of underlying CLD in children. Liver biopsy is the gold standard investigation for diagnosis**.** Being invasive it has its own limitations. It needs indoor or day care admission. Non-invasive assessment can be a reasonable alternative. This can be done by transient elastography (TE) in the Out Patient Department (OPD). TE is the technique used by the fibroscan machine. It is based on controlled transient shear wave generation with specific frequency and amplitude.

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The returning wave's velocity is converted into liver stiffness measurement (LSM). LSM is expressed in Kpa. TE uses $E=3pVs^2$, based on Hooke's formula where E=Young's modulus; P=mass density; Vs=velocity of shear wave[1,2]. TE calculates LSM in a specific cylindrical measured tissue volume in the area of interest depending upon the probe[1,2]. Three probes are available; S1, S2 and M. LSM is the measure of liver fibrosis[3]. Liver steatosis is measured by a different non-invasive modality in terms of controlled attenuation parameter[3]. I did not calculate the controlled attenuation parameter values in my series.

Method

I retrospectively studied 41 patients with CLD. Twenty boys and 21 girls were included. The most common cause of underlying CLD was neonatal cholestasis which was about 24% (n=10) in my series. Neonatal cholestasis syndrome included biliary atresia, neonatal hepatitis and paucity of bile ducts. Liver biopsy data were available in 11 of 41 patients. The stage of fibrosis in the histopathology report was noted. Upper GI endoscopy report, where available, was analysed. Endoscopy was done in almost all patients after informed consent to note presence or absence of varices. Median liver stiffness was calculated in all patients with the help of the Fibroscan Machine@402 model Echo-sense Europe. All manufacture recommendations were followed.

TE was performed by a single experienced technician. All children were kept fasting for 3 hours prior to the procedure. No sedation was used. For very young children, to reduce agitation and crying, sucrose dipped gauze for non-nutritive sucking was used. None of the patients had ascites. TE was done in a dorsal decubitus position with the right arm in maximum abduction using the right lobe of the liver in intercostal space. Only M probe was used. Ten shots within 5 minutes were taken. The median liver stiffness measured by shots was calculated as LSM in K pa. As an indicator of variability IQR i.e. ratio of inter-quartile range of liver stiffness to median value (IQR/M) was calculated. IQR/M >0.3 readings were discarded. Fibroscan values were taken at 4 different points in each case i.e. highest possible inter-costal space in anterior axillary line, highest possible inter costal

space in mid-clavicular line and one intercostal space below /above the mentioned positions.

Three probes, S1 probe for chest circumference <45cm, S2 probe for 45-75cm and M probe for >75cm chest circumference were recommended by the manufacturer. I used M probe in all the cases. Few studies[4] noted no difference in LSM value between S and M probe. Fibroscan S probe (5 MHz; diameter 5cm)[4] is better in children <2 years and XL probe (2.5 MHz; diameter 10mm)[5] in children with very thick adipose tissue but in my centre they were not available. In all 41 children LSM could be calculated with nil failure rates. Youngest patient we did was 6 months of age. Oldest child was 16 years of age.

Ethical issues: As it was a retrospective study, no ethical clearance was obtained and informed consent was not feasible. The study was carried out in my own clinic on an outpatient basis. This is a private set up, not attached to any institution and hence confidentiality of data is secure.

Results

The most common cause of underlying CLD was follow up patients of neonatal cholestasis syndrome viz. 10. There was a case of chronic hepatitis B and hepatitis C. Autoimmune hepatitis constituted about 12% of total studied cases. Out of 41 only 4 cases were of metabolic liver disease. Wilson's disease was not included in this subgroup. Total number of Wilson disease patients was 8. They were analysed separately. I could not find the cause of chronic hepatitis in 8 patients, labelling them as cryptogenic chronic hepatitis. I could do liver biopsy in 11 patients of the total cohort of 41. Stage 3 liver fibrosis was noted in 5 cases. The remaining 6 patients had stage 2 liver fibrosis.

Nineteen (46%) children scanned with fibroscan had median liver stiffness measurement >10kpa. The remaining 22 of 41 had LSM <10Kpa. Forty nine percent had splenomegaly. Five children in the series had gastro-oesophageal varices. None of children with CLD had portal hypertensive gastropathy or isolated gastric varices.

About 80% of patients who had stage 3 fibrosis on liver biopsy had median liver stiffness of >10kpa with sensitivity of 80% and specificity of 83%, negative predictive value of 83.3% and specificity of 83%. Using Chi-square statistics with Yate's correction (Fisher exact) p value was 0.135 so that the association was not statistically significant as depicted in table 1. Small sample size may be the cause.

Table 1: ***Liver fibrosis stage on histopathology - Liver stiffness measurement on fibroscan***

Stage of liver Fibrosis	LSM≤10	LSM>10	Total
2	5	1	6
3	1	4	5
Grand total	6	5	11

Twice the number of patients who had splenomegaly on clinical examination had median liver stiffness >10 K pa (n=14) as compared to patients with splenomegaly but without liver stiffness of >10 K pa (n= 7). Splenomegaly in patients with chronic liver disease was an important variable to predict increased median liver stiffness. This correlation was statistically significant (p= 0.0182, with Chi-square statistic with Yate's correction (Fisher exact) significant $p<0.05$; sensitivity 66.67%; specificity 75%, negative predictive value 68.18%; positive predictive value of 73.68% as depicted in Table 2. I could not establish statistically significant relationship or dependency between presence of varices and median liver stiffness >10kpa.

Table 2: ***Clinical splenomegaly and liver stiffness measurement correlation***

Clinical criteria	LSM≤10	LSM>10	Grand total	Comments
No splenomegaly	15	5	20	Positive predictive value =73.7%
Splenomegaly	7	14	21	Negative predictive value = 68.2%
Grand total	22	19	41	Sensitivity=66.7% Specificity=75%

I did calculate the average median LSM or A(LSM) for specific diseases. A(LSM) for autoimmune hepatitis was 16.28Kpa. Neonatal cholestasis syndrome had A(LSM) of 16.08Kpa. For non-syndromic paucity of bile ducts we noted A(LSM) OF 17.65Kpa. In Wilson disease A(LSM) was 14.11Kpa. Chronic hepatitis B and chronic hepatitis C had A(LSM) of 4.2Kpa and 8.4Kpa. Cryptogenic chronic hepatitis had A(LSM) of 12.71Kpa. Duration of chronicity in each case was different.

Discussion

Importance of non–invasive assessment of liver fibrosis in children is the need of the hour. Serological and radiological tests are options available. Ultrasound based fibroscan, using

principle of TE to assess liver fibrosis in children, is now easily available.

Proposed normal value of LSM in Indian children is 4.9Kpa[6]. The mean LSM in healthy non obese individual is 4.68Kpa[7]. In a few studies age and sex variations were noted. Adolescent boys may have higher TE value compared to adolescent girls[6]. Median LSM increases with age. For 1 to 5 years LSM values are: 3.4Kpa; 6 to 11 years: 3.8Kpa; 12 to 18 years: 4 Kpa[8]. LSM values are higher in obese group[9]. Childhood obesity is associated with increased hepatic fat deposition which correlates with increased LSM value in subgroup[4]. Sedative drugs or anaesthesia significantly increases liver stiffness in children[8]. One needs to understand these parameters while analysing LSM values. This may lead to miscalculation. Post-prandial status affects liver stiffness measurement[9,10]. It is preferable to be in fasting state prior measuring LSM. Children with poor inter costal space distance; food intake and agitated state (excessive crying with motion-artefacts) may give us wrong LSM values. The largest possible probe should be used to avoid overestimation of fibrosis.

LSM >10.6Kpa is associated with significant fibrosis on histopathology[4]. LSM>15.05Kpa is correlated with severe fibrosis with good sensitivity and specificity in study by Jain, *et al*[6]. De Ledinghen V, *et al*[11] proposed 10.2Kpa as cut off for significant fibrosis. Fitz Patrick, *et al*[12] showed 6.9Kpa for significant and LSM value more than 7.5Kpa for severe fibrosis. Nobili, *et al*[13] showed LSM >7.4Kpa and LSM >10.2Kpa to be associated with significant and severe fibrosis respectively. The variation in cut off value in different studies is possibly due to heterogeneity in underlying cause and severity. LSM >15.15Kpa is helpful to differentiate cirrhotic from non-cirrhotic patients with sensitivity of 85% and specificity of 91% in specific biliary atresia cohort[14]. In our case series, we noted >10Kpa was associated with stage 3 fibrosis. Specific sub cohort analysis of LSM values for example in biliary atresia, hepatitis B, hepatitis C, NASH, auto immune hepatitis etc. may refine the value of LSM for cut off discrimination in future studies.

In published Indian study[6] median liver stiffness measurement of more than 10.6Kpa was associated with significant fibrosis while some studies in children[12,13] suggested different cut off >7.4Kpa or 6.9Kpa. My case series noted median liver stiffness of more than 10Kpa cut off for stage 3 liver fibrosis but this association was not statistically significant. Poor sample size might be the overruling parameter. Variation in cut off value in different studies was due to heterogeneity in underlying aetiology of chronic liver disease and duration.

I did study the aetiological variation in median liver stiffness value. Average median lived stiffness for neonatal cholestasis related chronic liver disease was 16.08kpa, similarly for autoimmune hepatitis, Wilson's disease, cryptogenic chronic liver disease; average median liver stiffness were 16.3kpa, 14.1kpa, 12.7kpa respectively. These values were considerably higher than our proposed cut off value 10Kpa. Thus disease specific and duration optimised median liver stiffness cut off should be considered in future studies. Even specific genetic mutations; where possible need to be studied and should be correlated with liver fibrosis on histopathology and fibroscan.

Variceal bleeding is a known complication of portal hypertension in childhood CLD. 31.5Kpa cut off value in biliary atresia patients to differentiate bleeding group and non-bleeding group was proposed in children with chronic liver disease[15]. My case series could not establish a statistically significant relationship between median liver stiffness and presence or absence of gastro-oesophageal varices. None of my children had variceal bleeding. Hence I could not differentiate the bleeding and non-bleeding groups.

Splenomegaly in CLD can be due to aetiology itself or complication of chronic liver disease i.e. portal hypertension. I did not measures splenic–stiffness. Earlier study[16] concluded that variceal bleeding did not occur with splenic stiffness measures <60Kpa. I did not study splenic stiffness. Clinically palpable spleen in chronic liver disease was associated with increased median liver stiffness in my case series. ($p = 0.018$, $p < 0.05$). This association was statistically significant. I propose non-invasive fibro-scan to assess liver fibrosis in all patients with chronic liver disease who have splenomegaly.

Main limitation of my case series was limited number of patients in whom we could do liver biopsies. That could be the reason that I could not establish a statistically significant relationship between stage of liver fibrosis and median liver stiffness. The proposed cut off of LSM >10Kpa was noted to be associated with stage 3 fibrosis on liver biopsy. Another limitation; I did not have follow up liver stiffness measurement values in our series after specified duration. Hence progression of liver fibrosis with time and it's correlation with prior results could not be done.

Disease and duration specific median liver stiffness charts are needed to avoid heterogeneous cut off values in future. Chronic liver disease with

splenomegaly should be considered as the valid indication for doing transient elastography to assess liver fibrosis in children.

Conclusions

Fibroscan can be used as a non-invasive radiological method to assess liver fibrosis in children.

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