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Transient elastography in the evaluation of patients with nonalcoholic steatohepatitis

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Abstract

The aim of the study was to determine the role of noninvasive evaluation by transient elastography in patients diagnosed with nonalcoholic steatohepatitis (NASH), and to establish the need for further investigations, especially liver biopsy

Material and method: Transient elastography was performed in 226 out-patients previously diagnosed with NASH.

Results: The liver stiffness was ≤5.9 kPa in 36.2% of patients (correlated with F=0), 6-6.8 kPa in 21% patients (correlated with F=1), and ≥ 6.9kPa (corresponding to F=2-3-4) in 42.7% patients

Conclusions: The moderate and severe fibrosis found in 42.7% of the patients included in this study required further investigations (liver biopsy) in order to have a precise quantification of the lesion.

Key words: nonalcoholic steatohepatitis, transient elastography, noninvasive evaluation

Rezumat

Scopul acestui studiu a fost de a determina rolul evaluării neinvazive prin elastografie impulsionala la pacienții diagnosticați cu steatohepatită nonalcolică şi de a determina necesitatea investigațiilor suplimentare, in special biopsia hepatică

Material şi metodă: Elastografia impulsionala a fost efectuată la 226 de pacienți internați cu diagnosticul de steatohepatită nonalcolică

Rezultate: Duritatea hepatică a fost ≤5.9 kPa la 36,2% dintre pacienți (valoare corelată cu F=0),), 6-6.8 kPa la 21% dintre pacienți (valoare corelată cu F=1) şi ≥ 6.9kPa (valoare corelată cu F=2-3-4) la 42.7% pacienți.

Concluzii: Fibroza moderată şi severă decelată la 42,7% dintre pacienții incluşi în acest studiu necesită investigații suplimentare (biopsie hepatică) pentru a putea cuantifica cu precizie această leziune.

Cuvinte cheie: steatohepatita nonalcoolică, elastografia impulsională, evaluare neinvazivă

Introduction

Nonalcoholic steatohepatitis is the association between steatosis, inflammation, and fibrosis that appears in persons that do not consume alcohol.

The prevalence of this disease has increased lately due to occidental life style. Based on statistics performed in the Outpatient Department of our Clinic, from 614 consultations performed during a 6 month period, 36 patients (5.8%) had NASH [1].

The main causes for NASH are: obesity, diabetes, dislipidemia, especially high levels of triglycerides, jejuno-ileal by-pass performed in cases of morbid obesity, prolonged total intravenous nutrition as well as some drugs such as amiodarone, diltiazem, tamoxifen. Obesity is a major problem worldwide, in USA up to 25% of the population being obese and NASH has nowadays spread to 20-30% in adults and 10% in children. A body mass index (BMI) greater than 30 kg/m^2 predisposes to NASH

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and the frequency of this disease is directly correlated to the severity of obesity [2, 3].

Most of the patients have no symptoms when presenting to the doctor. Only few have fatigue and pain in the right hypochondrium. These patients are evaluated by means of serological tests, noninvasive evaluation by ultrasonography (US) and transient elastography (TE), as well as invasive tests, such as liver biopsy.

The aim of our paper was to determine the role of noninvasive evaluation using TE in patients diagnosed with NASH, having in mind the fact that we do not perform the liver biopsy in all patients with this diagnosis [4, 5].

Material and method

We evaluated 226 patients with NASH, from our Outpatient Department, by using TE, during May 2007-February 2009. The inclusion criteria were abnormal serological tests (hepatocytolytic syndrome, with or without dislipidemia or hyperglycemia), and liver steatosis (different grades of hyperechogenicity detected by US examination of the liver) (fig 1).



Fig 1. Ultrasonographic aspect of the liver steatosis, comparing with the right kidney (RD)

We excluded other causes for chronic liver disease (viral: negative HBs Ag and anti HCV antibodies; negative anamnesis for alcohol abuse; negative markers for autoimmune hepatitis, primary billiary cirrhosis, etc). Four experienced physicians (3 of them with more than 800 evaluations each and the 4th with an experience of more than 300 cases) performed transient elastography (using FibroScan, Echosens, Paris, France) to all patients (fig 2). Liver stiffness (LS) measurements were performed according to the classical methodology [6], on patients lying in dorsal decubitus with the right arm in maximal abduction. The right lobe of the liver was aimed at, through the intercostal spaces. The tip of the probe transducer was covered with coupling gel and placed on the skin, between the ribs, at the level of the right lobe of the liver. The operator, assisted by ultrasound time-motion and A-mode images provided by the system, located a portion of the liver free of large vascular structures that was at least 6 cm thick. Once the measurement area was located, the operator pressed the probe button to begin an acquisition. Ten successful acquisitions were performed in each patient.

The success rate (SR) was calculated as the ratio of the number of successful acquisitions over the total number of acquisitions. In each patient 10 valid measurements were performed, after which a median value of the LS was obtained, measured in kPa. Only in patients in which LS measurements had a SR of at least 60%, with IQR<30%, the measurements were considered reliable (IQR = interquartile range, it is the difference between the 75th percentile and the 25th percentile, essentially the range of the middle 50% of the data).



Fig 2. Fibroscan device

We calculated the mean value of LS for the whole group. For a statistical study of quantitative variables, the mean and standard variation were calculated. T-test was performed to compare the mean value of LS patients with NASH to the one in normal subjects, previously obtained in another study [7]. The statistical analysis was performed using Microsoft Excel program.

Results

From 226 patients, in 13 cases we could not obtain 10 valid measurements, thus a failure rate of 5.7%. The study was carried out based on the remaining 213 patients (94.3%). Regarding the sex distribution, there were 62 women (27.4%) and 164 men (72.6%). The mean age was 44.3±3 years.

The mean value of LS in patients with NASH was 7.1±1.2kPa, statistically significant higher than in normal individuals (4.8±1.3 kPa, $p<0.0001$), as proven in an anterior study from our group [7]. We obtained the following values for LS in the 213 patients with valid measurements: ≤5.9 kPa in 77 patients (36.2%), 6-6.8 kPa in 45 patients (21%), and ≥ 6.9kPa in the rest of 91 patients (42.7%).

Discussions

NASH is an important disease that affects the medium aged adults, prevailing in men, and represents 6.5% of all the cases with liver diseases that were investigated by using transient elastography in our department [7].

Ultrasonography is preferable for screening in asymptomatic patients with high levels of liver enzymes and suspicion for NASH. A typical fatty liver image shows different grades of hyperechogenicity of the liver together with posterior attenuation.

Resuming the published data regarding the value of US for the diagnosis of steatosis, we can conclude that: by using multiple criteria to diagnose steatosis, the positive predictive value can be as high as 94%, in high-prevalence populations [8]; the performance tends to improve with the severity of steatosis [9]; US can not predict the presence of fibrosis and inflammation in patients with NASH [10]. Also, US examination is an operator-dependent method, it does not offer quantitative information regarding the severity of fat infiltration of the liver and the sensibility of the method decreases below 40% in patients with morbid obesity [4, 11].

Other techniques such as computer tomography and magnetic resonance imaging better estimate the grade of steatosis by quantifying the fat inside the liver, but these are highly expensive methods and are not currently used in the evaluation of patients with NASH.

Liver biopsy is a precise method that allows the exact staging of the patient with NASH, able to quantify the inflammation and fibrosis, but it is not used routinely for NASH. In most cases the result from the liver biopsy does not influence the therapy.

A rather recent technique is transient elastography (FibroScan) that measures liver stiffness and estimates the severity of fibrosis. Encouraging results were obtained in studies performed initially in patients with chronic viral C hepatitis [12], but also in other chronic hepatopathies, like NASH, haemochromatosis, PBC [4, 13, 14], in which specificity and sensibility of FibroScan were similar to those obtained with FibroTest or other fibrosis markers.

In cases with NASH, steatosis can interfere with liver stiffness. A study performed by Lupsor and coworkers demonstrated that steatosis ($p=0.025$) and inflammation ($p=0.039$) influence the liver stiffness [15].

One other problem concerning the use of transient elastography in patients with NASH is the impossibility to obtain valid measurements in obese patients, as is often the case in NASH. We showed in a previous study that in patients with BMI≥30kg/m^2 we failed to obtain valid measurements in 17.1% patients, the failure rate reaching 45% in patients with BMI≥40 kg/m^2 [16].

A solution to overcome this inconvenient is to use serological non-invasive tests: SteatoTest and NashTest. The SteatoTest, intended for the diagnosis of steatosis, includes the six components of the ActiTest plus BMI, glucose, triglycerides and cholesterol adjusted for age and gender [17]. The NashTest is a slight variation of the SteatoTest and ActiTest, intended for the differential diagnosis of steatosis vs. NASH. AUC for the diagnosis of NASH in the training and validation groups were both 0.79 [18]. With the two groups pooled together, the sensitivity and specificity were 33% and 94% respectively. For borderline NASH, the sensitivity improved to 88%, but specificity dropped to 50%.

Since several studies proved that values of LS< 6kPa are characteristic for normal liver [7, 19], and cut-off values proposed for significant fibrosis (F≥2) were: 6.8 kPa [20], 7.1 kPa [12] to 8.8 kPa [21] in chronic C hepatitis; 7 kPa in chronic B hepatitis [22]; 7.3 kPa in cholestatic hepatopathies [14], we considered that NASH patients with LS<6kPa had no fibrosis, and those with LS≥6.9 kPa had at least moderate fibrosis.

The result of our personal study was that an important number of patients with NASH (42.7%) had moderate and severe fibrosis according to transient elastography evaluation. In these cases the liver biopsy might be considered useful in order to have a clearer view of the morphology of the liver lesions.

In **conclusion** TE is a noninvasive method capable for quantifying the liver fibrosis in patients with NASH. In future, it remains questionable if this method will be able to differentiate fibrosis from steatosis, in order to evaluate the evolution of fibrosis during therapy.

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