

The Quality of the Fragment Obtained by Liver Biopsy for Staging Chronic Hepatitis

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Abstract

The aim of our paper was to assess the quality of the liver fragment obtained by liver biopsy for staging chronic hepatitis. **Material and method.** We analyzed retrospectively 250 echoassisted percutaneous liver biopsies (LB) concerning the length of the fragment and the mean number of portal spaces. We used Menghini modified needles 1.4 and 1.6 mm in diameter and the LBs were performed by the same senior hepatologist. **Results.** The indications for the LB were represented by: chronic hepatitis C in 69 % (172 cases), chronic hepatitis B in 17 % (43 cases), chronic hepatocytolysis in 10% (25 cases), primary billiary cirrhosis in 1.5% (4 cases), chronic B+C hepatitis in 3 cases, autoimmune chronic hepatitis in 2 cases and Wilson's disease in 1 case. From the 250 LBs, in 87% of cases (217 patients) the liver sample had 8-10 portal spaces ("good fragment") and in 69% of cases (173 patients) the liver sample had at least 11 portal spaces ("very good fragment"). In 13% of the cases (33 liver biopsies) the histological sample was suboptimal, less than 8 portal spaces. In 1.6% of the cases (4 biopsies), the liver sample was not adequate for the diagnosis (less than 4 portal spaces), so that we had to perform a second biopsy (in another session). In 88% cases (219 subjects), the length of the liver fragment obtained was longer than 2 cm and only in 12% of cases (31 patients) the fragment was smaller than 2 cm. The median length of the fragment obtained by LB in our department was 30.8 ± 8.7 mm, and the mean number of portal spaces was 14.9 ± 7.09 . **Conclusion.** In experienced hands, percutaneous liver biopsy can obtain "good" histological material in the vast majority of cases.

Key words

Chronic hepatitis - biopsy sample quality - liver biopsy

Introduction

Chronic hepatitis C is a worldwide public health problem. According to WHO data, there are approximately 170 million individuals infected with hepatitis C virus around the world (1), 9 million of them in Western Europe (2). It is estimated that in Romania approximately 5% of the population is anti HCV positive, so it is possible that 1 million people are infected with HCV. A study performed in 10 counties from Transylvania showed a higher prevalence of HCV infection in this area, i.e. 6.28% (3). Considering that 70% of the anti HCV positive individuals have active infection, with detectable viral load, we can estimate that in Romania approximately 700,000 individuals are viremic with HCV. Among the patients with chronic hepatitis C, approximately 80% are asymptomatic and 30-40% have persistently normal values of aminotransferases (4,5). Hence, the decision of treating the asymptomatic patients and the patients without hepatocytolysis, since the value of transaminases does not reflect at all the severity of the disease (2, 6).

A question arises: which patients with HCV infection should be treated, because it is quite clear that not all patients with detectable viral load have to be treated (7). Most current guidelines recommend that only those patients with chronic active liver disease, proven by means of liver biopsy (LB) with signs of histological activity, and, more important, with signs of fibrosis, should receive antiviral therapy (8).

The first problem that should be addressed is how adequate is liver biopsy (LB) for the staging of chronic hepatitis? In order to answer this question we performed a retrospective study regarding the diagnostic relevance of the specimens obtained by LB in our department.

Material and method

Our retrospective analysis of the length of the specimen and on the number of portal spaces obtained by percutaneous LB in the Department of Gastroenterology, Timișoara, extended to the last two years.

The LB was performed using Menghini modified needles 1.4 and 1.6 mm in diameter (Hepafix – Braun kits for LB), by the same senior hepatologist (I.S., 15 years experience and over 2,000 LBs performed). The maneuver was ultrasound-assisted in patients sedated with 3-5 mg Midazolam i.v. The liver specimen obtained by LB was visually inspected after the transfer into the recipient containing formaldehyde 10%. If the fragment was appreciated as insufficient (less than 1.5 cm), a second biopsy was performed in the same session.

The pathologist was asked to count the portal spaces present in the sample, in order to correlate the number of portal spaces with the length of the fragment and with the diameter of the Menghini needle (1.4 or 1.6 mm). We considered a sample as “good” if it had 8 up to 10 portal spaces and “very good” if it had at least 11 portal spaces. Also, we considered a fragment to be large enough for a good pathological diagnosis if, at visual inspection, it had a length of more than 2 cm.

Our study included 250 successive LBs performed mainly for chronic hepatitis C (68.8%) and B (17.2%) (Fig.1).

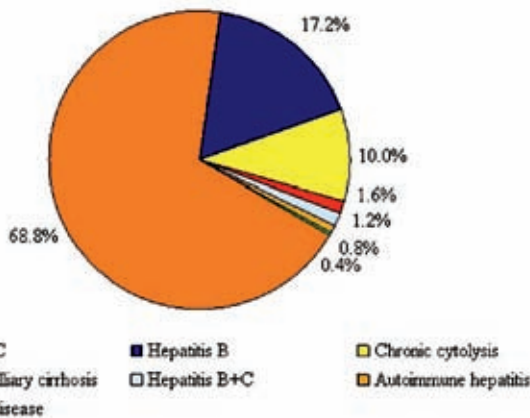


Fig.1 The etiology of liver diseases for which liver biopsy was performed.

To study the correlation between the diameter of the needle used for LB and the number of portal spaces and between the macroscopic dimension of the fragment and the number of portal spaces we used Pearson’s correlation coefficient, calculated using Microsoft Office Excel 2003.

Results

During the mentioned period, 250 LBs were performed by the same senior hepatologist. During the procedure, there were no major complications. Only some of the patients presented post-biopsy pain. From those LB, in 217 (86.8%) cases the liver sample had 8-10 portal spaces and only in 173 cases (69.2%) the liver sample had at least 11 portal spaces. In 13.2% of the cases (33 liver biopsies) the histological sample was suboptimal, less than 8 portal spaces. In 1.6% of the cases (4 biopsies), the liver sample was not enough for the diagnosis (less than 4 portal spaces),

so that we had to perform a second biopsy later on (in another session) (Fig. 2).

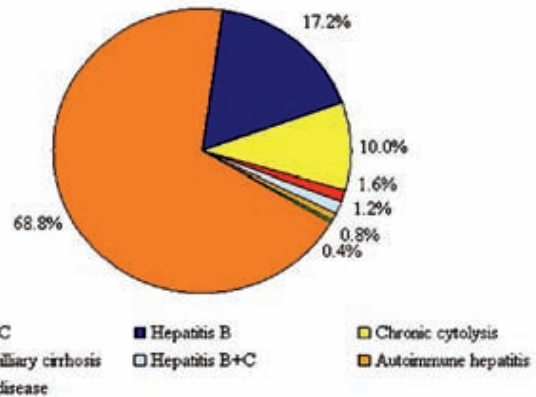


Fig.2 Number of portal spaces (PS) obtained by LB.

From the 250 LBs performed, in 219 (87.6%) cases the length of the histological fragment was more than 2 cm; only in 31 (12.4%) LBs the fragment was smaller than 2 cm. In 2 cases (0.8%), after visual inspection the fragment was considered too small and we repeated the LB in the same session. The median length of the fragment obtained was 3.08 +/- 0.87 cm, and the mean number of portal spaces was 14.9 +/- 7.09.

The correlation coefficient (Pearson) between the diameter of the needle used for the LB and the number of portal spaces was r = 0.0366 (no correlation). The correlation coefficient between the macroscopic dimension of the fragment and the number of portal spaces was 0.179 (not significant correlation).

Discussion

Liver biopsy is currently considered to be the “gold standard” for the diagnosis of chronic liver disease. Some relevant aspects should be discussed regarding this issue. The specimen obtained by LB represents roughly 1/50,000 of the liver and it is a known fact that fibrosis is unevenly distributed through the liver. Another problem is how relevant is the fragment obtained by LB regarding its dimension and the number of portal tracts. A liver specimen is considered to be adequate for pathological examination if it is longer than 25 mm, and if it includes more than 8 portal tracts (9) or more than 11 portal tracts in the opinion of other authors (10).

The question is how to manage to obtain liver samples large enough for an accurate pathological examination. A multicentric study performed in France showed that the median length of the fragment obtained by LB was 15 mm (11). Another French study (11) showed that from 323 LBs analyzed, 49 (15.2%) were considered as uninterpretable by the pathologist. In this study the median length of the fragment was 19±8 mm. A study performed on 1,257 LB (11), showed that in 132 cases (10.5%), the fragments were considered uninterpretable by the pathologist. From these,

in 64 cases after a second opinion, the biopsy could be interpreted, but in 64 cases, the LB had to be repeated, the initial fragment being smaller than 10 mm.

In our study, probably because all biopsies were performed by a senior hepatologist, the results were better. The median length of the fragment obtained was 30.8 ± 0.87 mm versus 15 or 19 ± 8 mm in the French study (11), and the mean number of portal spaces was 14.9 ± 7.09 . But, maybe, most important is the number of uninterpretable histological specimens. The two mentioned studies found that between 10.5 and 15.2% (11) of LBs were histologically uninterpretable (too small fragments). In our study, only in 1.6% of the cases (4 biopsies from 250), the liver sample was not adequate for the diagnosis, so we had to perform a second biopsy later. It is very important to make a critical evaluation of the size of liver specimen immediately after LB. If, visually, the fragment is not long enough, a new biopsy should be performed in the same session (thus reducing the discomfort and stress for the patient). Using this strategy, the number of biopsy results returned from the Department of Pathology as "histologically uninterpretable" has been reduced.

Concerning the number of portal spaces, we consider that the mean number of portal spaces ($14.9 + 7.09$) obtained in our study is a good one. That means that the median number of portal spaces is higher than the number of portal spaces required for a "very good" biopsy (>11 portal spaces). We found no correlation between the macroscopic dimension of the fragment and the number of portal spaces. Thus, obtaining a good liver specimen is not a guarantee for having enough histological material. We also found no correlation between the diameter of the needle used for the LB and the number of portal spaces. Consecutively, we might use for LB a needle of 1.4 or 1.6 mm in size with the same results.

Another problem when evaluating the LB results is the interobserver and intraobserver concordance when interpreting a sample. The interobserver evaluation of a LB in chronic hepatitis C showed that discordance can occur: regarding the Knodell score, concordance for assessing fibrosis was 0.78, and for necroinflammatory activity 0.48. If the Metavir score was used, the concordance when assessing fibrosis was 0.80, and it was 0.56 when assessing the necroinflammatory activity (11).

One must also consider that LB can be associated with side effects, some mild (pain - 20%, vagal reactions 1-3%), but some severe (arterio-venous fistula, hemoperitoneum, hematoma of the liver, hemobilia, biliary peritonitis, etc). The risk of death is 1-3/10.000 cases. In more than 2,000 LB, we had only two major complications: hemoperitoneum (treated conservatively) and arterio-venous fistula with a large intrahepatic hematoma (surgically treated).

Considering all these facts, in 2006, a question arises: how relevant is LB for the staging of chronic hepatitis, even if it is still considered the "gold standard" for the evaluation of liver disease.

There is a large consensus that suggests that the non-invasive evaluation of chronic liver disease could be used

to complete or even replace LB. The FibroTest-ActiTest is already currently used in France and the FibroScan (liver elastography) was recently introduced to select the patients that require treatment.

The noninvasive tests for the assessment of CH were evaluated in several studies in the last years, aiming at replacing LB. After 2000, the noninvasive predictive histological tests were evaluated more often, especially in chronic C hepatitis (13), and more recently in chronic B hepatitis (14) and in NASH (15-17). Validated FT-AT are being used (Biopredictive, Paris, France; Fibro-SURE LabCorp, Burlington, NC), that provide an accurate measurement of bridging fibrosis and/or moderate necroinflammatory activity with AUROC (Area Under Receiver-Operating Characteristic Curve) predictive value between 0.70 and 0.80 when compared with LB (18).

Another noninvasive method of assessing liver fibrosis is transient elastography. This technique enables the assessment of the liver's stiffness and it is performed by a device called FibroScan. Transient elastography is painless, rapid (takes a few minutes), and easy to perform at the bedside or in the outpatient clinic. The results are immediately available and are independent from the operator. The diagnostic performances of elastography remain to be evaluated, but in the last 1-2 years, many papers showed the value of this noninvasive test as compared to LB (12, 19-22) and some showed a slight superiority of FibroScan vs. FibroTest (21, 22).

In some studies the FibroScan has a positive predictive value of 97% for the diagnosis of fibrosis (11), and when the values of the parenchymal stiffness are high, it can predict the presence of esophageal varices. FibroScan is a very interesting alternative for the repetitive evaluation of fibrosis during interferon therapy.

Castera et al (21) suggest that only ALT should be used for the evaluation of the necroinflammatory activity in patients with chronic hepatitis C, and FibroTest combined with FibroScan should be used for the evaluation of fibrosis. If the two non-invasive test show concordant results, then LB could be avoided. If the two noninvasive tests have discordant results, LB should be performed.

This is the reason why LB is still the most used method for the assessment of the severity of the liver lesions in chronic hepatopathies, several guidelines recommending it as compulsory for deciding the treatment (9,23,24). Probably this would be correct for centers where the percentage of uninterpretable liver specimens is less than 10 or 5%. If the uninterpretable histological fragments are 15% or more, the non-invasive markers of fibrosis would probably give the same results as the liver biopsy. We hope that in the next years most guidelines will recommend these modalities of investigation. The viral load (in viral B and C chronic hepatitis) and the non invasive markers of fibrosis will be the criteria of evaluation for antiviral treatment.

Conclusion

In our study concerning percutaneous liver biopsy

performed in 250 cases, suboptimal samples (less than 8 portal spaces) were obtained in 13.2% of the cases. In only 1.6% of the cases, the fragment was uninterpretable by the pathologist. In good hands (experienced centers), percutaneous liver biopsy is an adequate method for evaluating viral chronic hepatitis, but for the general practice (where the percentage of uninterpretable samples is higher than 10 or 15%), non-invasive markers of fibrosis can be taken into consideration for the staging of the liver diseases.

Conflicts of interest

None to declare.

References

1. Anonymous. Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board. Antwerp, Belgium. *J Viral Hepat* 1999; 6: 35-47
2. Moreno-Otero R. Therapeutic modalities in hepatitis C: challenges and development. *J Viral Hepat* 2005; 12: 10-19
3. Molnar GB, Cocian S, Jebeleanu L, Popa S, Feder A. Evaluarea seroepidemiologică a infecției cu virusul hepatitic C la populația din 10 județe ale României. *Rev Rom Boli Infect* 2005;8:3-7.
4. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1998; 47: 1-39
5. Anonymous. Management of hepatitis C. NIH Consensus Statement. *Hepatology* 1997; 15: 1-41
6. Conry-Cantilena C, VanRaden M, Gibble J et al. Routes of infection, viremia and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med* 1996; 334: 1691-1696
7. Heathcote J, Main J. Treatment of hepatitis C. *J Viral Hepat* 2005; 12, 223-235
8. National Institute of Health Consensus Development Conference Statement: Management of Hepatitis C. *Hepatology* 2002; 36: S3-S20
9. Grant A, Neuberger F. Guidelines on the use of liver biopsy in clinical practice. *The British Society of Gastroenterology. Gut* 1999; 45 (Suppl.4): 1-11
10. Guido M, Rugge M: Liver biopsy sampling in chronic viral hepatitis. *Semin Liver Dis* 2004; 24: 89-97
11. Beaugrand M. [FibroScan: instructions for use]. *Gastroenterol Clin Biol* 2006;30:513- 514
12. Sporea I, Șirli R, Cornianu M et al. How relevant is the liver biopsy with Menghini modified type needles for the diagnosis of chronic hepatitis? *J Gastrointestin Liver Dis* 2006; 15 (Suppl. 1): 100
13. Gebo KA, Herlong HF, Torbenson MS et al. Role of liver biopsy in management of chronic hepatitis C: a systematic review. *Hepatology* 2002; 36: S161-S172
14. Poynard T, Zoulim F, Ratziu V et al. Longitudinal assessment of histology surrogate markers (FibroTest-ActiTest) during lamivudine therapy in patients with chronic hepatitis B infection. *Am J Gastroenterol* 2005; 100: 1970-1980
15. Laine F, Bendavid C, Moirand R et al. Prediction of liver fibrosis in patients with feature of metabolic syndrome regardless of alcohol consumption. *Hepatology* 2004; 39: 1639-1646
16. Ratziu V, le Calvez S, Imbert-Bismut F et al. Diagnostic value of biochemical markers (FibroTest) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. *Hepatology* 2003; 38: 729A
17. Rosenberg WM, Voelker M, Thiel R et al. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology* 2004; 127: 1704-1713
18. Poynard T, McHutchison J, Manns M, Myers RP, Albrecht J. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa-2b and ribavirin. *Hepatology* 2003; 38: 481-492
19. Sandrin L, Fourquet B, Hasquenoph JM et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003; 23: 1705-1713
20. Foucher J, Vergniol J, Castera L et al. Fibrosis evaluation in chronic liver diseases: comparison of FibroScan with liver biopsy, FibroTest, Forns score, APRI, hyaluronan, prothrombin time and AST/ALT ratio. 40-th Annual Meeting of the EASL, Paris, 2004 (abstract)
21. Castera L, Vergniol J, Foucher J et al: Prospective comparison of transient elastography, Fibrotest, APRI and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; 128: 343-350
22. Colletta C, Smime C, Fabris C et al. Value of two noninvasive methods to detect progression of fibrosis among HCV carriers with normal aminotransferases. *Hepatology* 2005; 42: 838-845
23. European Association for the Study of the Liver. Consensus statement. EASL: International consensus Conference on hepatitis C. *J Hepatol* 1999; 26 (Suppl.): 2S-10S
24. Bacon BR. All hepatitis C patients should be offered liver biopsy and treatment. *AGA Perspectives* 2005; 4: 4-12