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Safety and Reliability Percutaneous Liver Biopsy Procedure in Children with Chronic Liver Diseases

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1. Introduction

Liver biopsy remains a golden standard in the evaluation of various liver diseases. It is one of the most specific test allowing to assess the severity of various liver diseases. Clinical evaluation may be inadequate as chronic liver diseases could be asymptomatic for a long period of time. The routinely used laboratory test may be irrelevant, as diffuse changes may possibly be present in the liver in spite of liver function test being within reference values. Percutaneous biopsy allows to obtain a tissue specimen suitable for pathological assessment. Liver biopsy is an important procedure in diagnosing liver diseases in infants and children as it often provides diagnostic information not possible to obtain by other methods. Therefore, liver biopsy is considered to be a golden standard in the diagnostics and follow-up of the patients with chronic diffuse hepatopathies. The role of the liver biopsy is to confirm the diagnosis of chronic hepatitis, assess the necroinflammatory activity (grading) and the severity of fibrosis (staging), confirm the presence of cirrhosis. Other hepatopathies may be excluded as well as associated diseases using this method [1].

The size of liver sample varies from 1 to 4 cm in length and 1.2 to 1.8 mm in diameter. Biopsy specimen represents 1/50,000 of the total mass of the liver, therefore the procedure carries the risk of sampling error. The specimen should be sufficient in length (2-2.5 cm) and number of portal spaces (at least 11). The fragmentation of the specimen should be avoided [2]. Liver assessment is also affected by an interpretative error and intraobserver variability of histological interpretation. Moreover, liver biopsy is an invasive procedure carrying the risk

of certain complications including pain, bleeding, pneumothorax, puncture of bile ducts or the gall bladder.

Repeating samples in different time intervals are useful in monitoring the efficacy of treatments. Many patients are, however, reluctant to experience repeated biopsies, which limits the ability to monitor disease progression and treatment effects. [3].

Due to the limitations of the procedure many non-invasive techniques were developed such as single serological markers, panels of different markers, imaging techniques and elastography [4]. None of the non-invasive methods is suitable and reliable enough to entirely substitute the liver biopsy. Non-invasive techniques are very helpful in the detection of severe lesions. However, results obtained from patients with intermediate lesions very often overlap between different categories of staging. Nevertheless non-invasive methods are useful in situations where contraindications to liver biopsy do not allow to perform the procedure.

Liver biopsy can be percutaneous, transjugular or laparoscopic. Percutaneous liver biopsy can be blind, ultrasound- guided or ultrasound assisted. Various approaches differ in the number of potential complications and require various equipment. Ultrasound guidance allows safer intercostal approach and may be useful in the evaluation of relative position of the liver, gall bladder, kidneys and lungs. The technique reduces the risk of hemothorax and pneumothorax and puncture of the gall bladder.

The aim of this study was to evaluate safety and reliability of the liver biopsy in children in relation to obtained results and potential complications.

2. Material and methods

Seventy five cases of percutaneous liver biopsies carried between 2005-2012 were analyzed. The biopsies were performed in children aged 4-17 years (mean 15.30 ± 2.35 years). Study group included 26 girls, 49 boys. Procedures were done due to chronic hepatitis C (CHC) – 44 cases, chronic hepatitis B (CHB) – 16 cases, autoimmune hepatitis (AIH) – 3 cases, hepatitis/hepatomegaly of unknown origin (HUO)– 12 cases, non-alcoholic fatty liver disease (NAFLD) – 2 cases. Number of the procedures performed in the following years has been presented in Figure 1.

Written informed consent was obtained from the parents and patients aged 16 years and over according to Polish law regulations. Before the procedure children were clinically evaluated and blood samples were taken for standard hematological and clinical chemistry analysis. Children with coagulopathies and thrombocytopenia below $80,000/\text{mm}^3$ were excluded from the procedure. All children underwent abdominal ultrasound performed the day before the procedure to exclude potential hemangiomas and malposition of the organs. All children were managed by Menghini procedure in sedation. Children aged less than 5 years received general anesthesia. 36 biopsies were ultrasound guided directly prior to the procedure (performed by the operator), 39 biopsies were blind. The ultrasound prior to the biopsy was performed to identify the intercostal space and to avoid accidental puncture of the gall

bladder, the lung, right kidney and large vessels. Immediately after the procedure ultrasound examination was performed searching for potential complications such as accidental puncture or bleeding. In the case of blind biopsied ultrasound examination was performed by radiologists in situations where complications were suspected basing on clinical symptoms. All patients were monitored 24 hours after the procedure in the department for vital signs, pain and other consequences.

Histological evaluation was performed using Ishak scoring system for grading and staging.

Categorical variables were compared using Fisher's exact test or chi-square test were appropriate. Result with p value <0.05 were considered statistically significant.

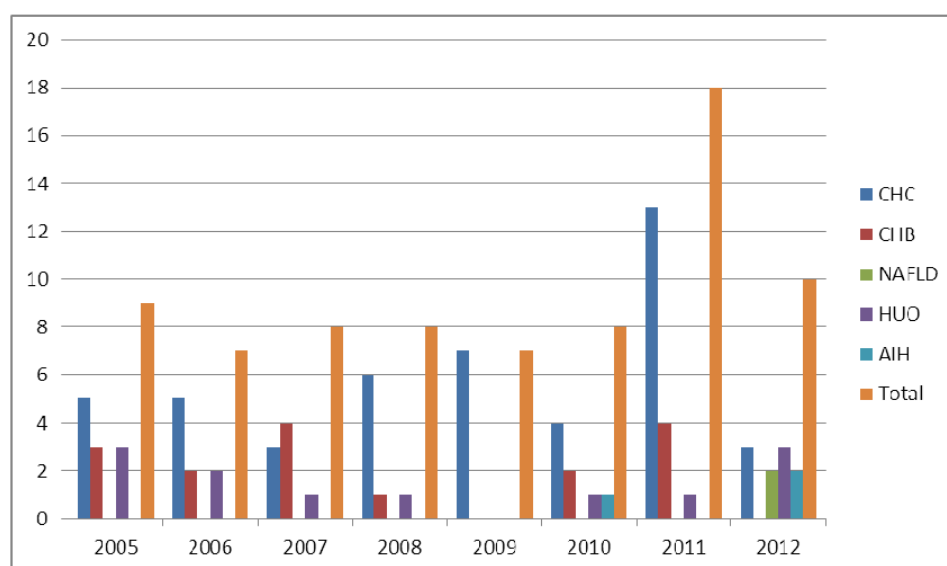


Figure 1. Number of liver biopsy performed in the Department of Infectious Diseases and Child Neurology due to various reasons in years 2005-2012 (until July) CHC- chronic hepatitis C, CHB – chronic hepatitis B, NAFLD – non-alcoholic fatty liver disease, HUO – hepatitis/hepatomegaly of unknown origin, AIH – autoimmune hepatitis

3. Results

Liver samples were obtained in all children. Adequate sample size was not obtained in the case of 5 children - 2 samples were too short and did not contain the adequate number of portal spaces, one sample was fragmented. Four inadequate samples resulted from the blind liver biopsy and 1 was obtained by the ultrasound guided procedure (p=0.21). No significant adverse events were observed. No clinical signs of hemorrhage, no cases of pneumothorax, puncture of the gallbladder nor severe infections were observed. Larger bile ducts were punctured in 4 cases – all undergoing blind procedure (p=0.07). 12 patients were complaining of pain in the right upper quadrant of the abdomen following the procedure that required more intensive analgesics – 3 undergoing ultrasound guided procedure, 9 having blind liver

biopsy done ($p=0.07$). Pain was mild to moderate and resolved after analgesics. There were no deaths following the procedure in both groups of children.

Results from pathological assessment were presented in Table 1. The majority of children underwent liver biopsy due to CHC. Remaining indications were CHB, AIH, NAFLD, HUO. In patients with viral hepatitis grading and staging assessed according to Ishak scoring system was usually mild to moderate. Nevertheless, severe lesions were also present in some patients. Figure 2 and Figure 3 show examples of inflammatory changes and portal fibrosis in various patients with CHC. In patients with AIH and NAFLD diagnosis was confirmed by pathological assessment. Ten of HUO patients gained diagnosis either of metabolic disorders or NAFLD thanks to pathological evaluation. Normal liver histology was described in 2 patients.

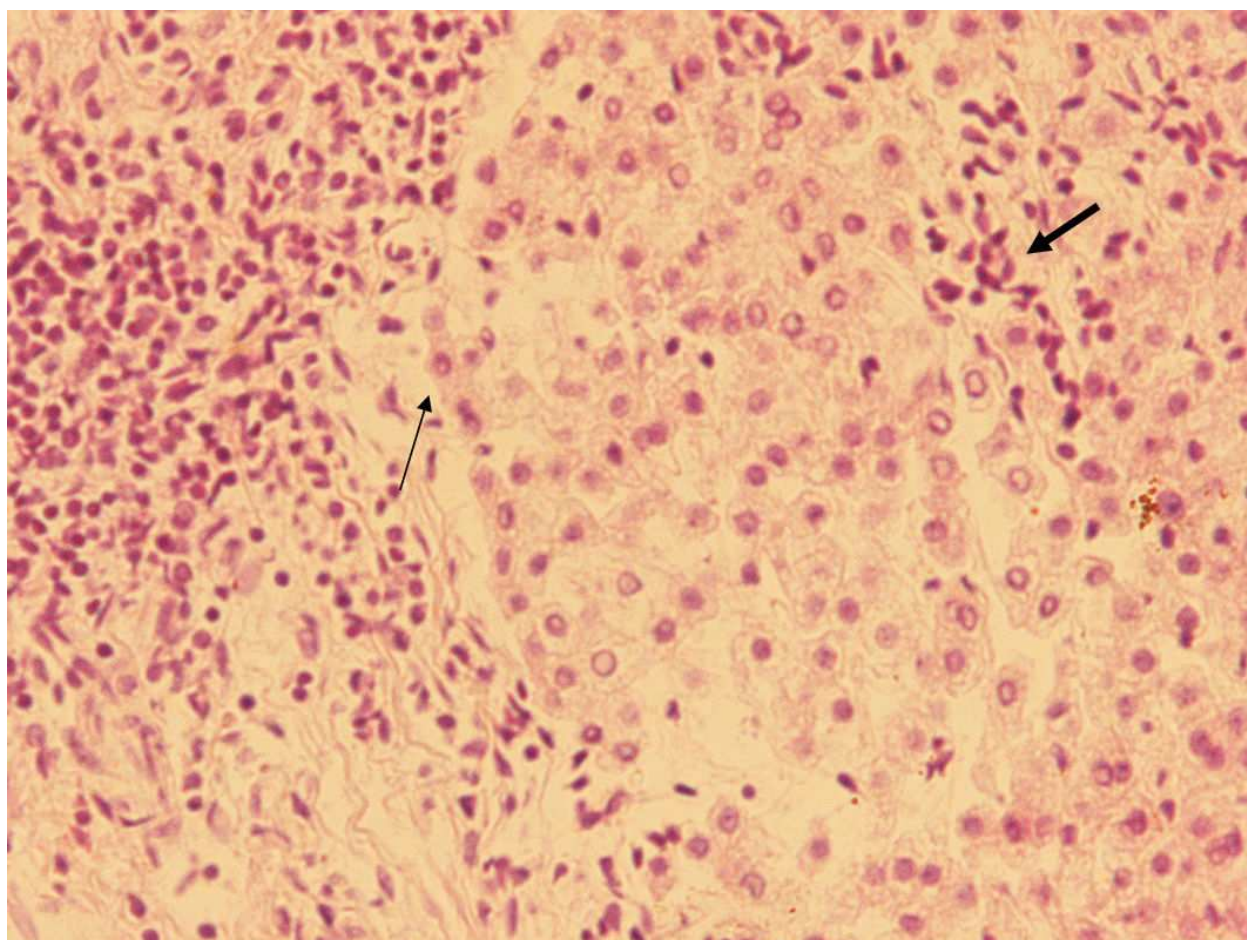


Figure 2. Liver biopsy specimen of the patient with CHC where inflammatory infiltrates cross lamina basalis of the lobuli (thin arrows) and intralobular focus of inflammatory infiltrate (thick arrow). Staining: hematoxylin+eosine. Magnification 40x

Fifteen children with viral hepatitis underwent repeated procedures allowing to assess the progression of lesions in time. In 9 of them the progression of lesions was described, 6 had similar results in both biopsies.

| Indication for the biopsy | Result | Number of children |
|---------------------------|------------------------------|--------------------|
| CHC - 44 | Grading | |
| | 1 | 23 |
| | 2 | 11 |
| | 3 | 5 |
| | 4 | 5 |
| | Staging | |
| | 0 | 1 |
| | 1 | 19 |
| | 2 | 17 |
| | 3 | 5 |
| | 4 | 2 |
| CHB - 16 | Grading | |
| | 1 | 3 |
| | 2 | 8 |
| | 3 | 3 |
| | 4 | 2 |
| | Staging | |
| | 1 | 3 |
| | 2 | 7 |
| NAFLD - 2 | Steatosis | 1 |
| | Steatohepatitis | 1 |
| HUO - 12 | Metabolic disorders | 3 |
| | Nonalcoholic steatohepatitis | 6 |
| | Wilson disease | 1 |
| | Normal liver histology | 2 |
| AIH - 3 | Autoimmune hepatitis | 3 |

Table 1. Histological assessment of the liver biopsy specimens performed in 75 children. CHC- chronic hepatitis C, CHB – chronic hepatitis B, NAFLD – non-alcoholic fatty liver disease, HUO – hepatitis/hepatomegaly of unknown origin, AIH – autoimmune hepatitis

4. Discussion

Studies describing the safety of liver biopsy performed on larger cohorts of patients seem to prove that the procedure results in more complications in children than in adults [5]. Nevertheless, Lebensztejn et al. described the group of 250 pediatric patients undergoing blind procedure with serious complications as internal hemorrhage and puncture of the gallbladder occurring in 3 children [6].

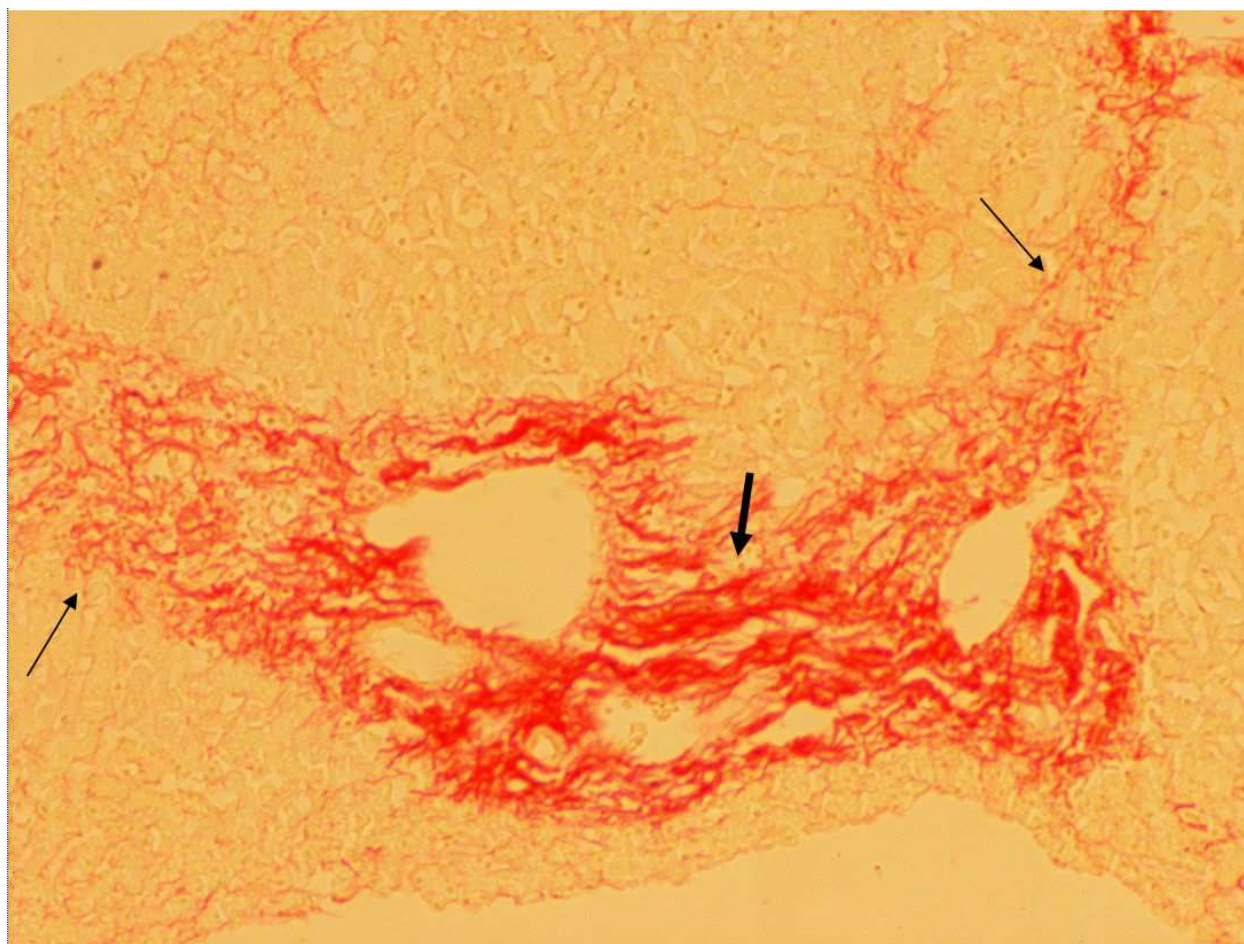


Figure 3. Sirius red staining of the liver specimen of CHC patient with present fibrosis in dilated portal space (thick arrow) and porto-portal bridging. Magnification 40x.

Number of biopsies in the current study was lower, however even the number of mild complications was relatively low. Moreover, no serious adverse events were noted among children from the study group. Noted complications included puncture of larger bile ducts and pain after the procedure. Although the results were not statistically significant, both problems were more frequent in children undergoing blind liver biopsy. Ultrasound assistance during the whole procedure was found to reduce the number of potential consequences [7]. Thus, ultrasound guidance even performed right before and after the biopsy makes the whole procedure safer. Since the majority of complications occur within first hours after the liver biopsy all children were monitored for 24 hours after the procedure as inpatients. Although hospitalization increases the costs of the procedure, monitoring enables quick response to encountered complications and prompt treatment, if necessary. Another issue is general anesthesia performed in small children in order to obtain liver sample. Although costly, general anesthesia decreases fear, pain and enables to perform the procedure in safe circumstances, reducing the risk of hemorrhage caused by lack of cooperation from the patient side.

The majority of children underwent the liver biopsy due to chronic viral hepatitis – mostly CHC. Histological assessment was not necessary to establish diagnosis since it is usually based on blood tests. However, information regarding grading and staging was essential for treatment decisions since the length of treatment may vary depending on the severity of lesions. In patients with CHB decisions regarding the initiation of the treatment may depend on the presence of lesions in the liver tissue [8]. In both types of chronic viral hepatitis patient with liver cirrhosis requires different approach than the child with mild lesions in the liver. In children with AIH the diagnosis was confirmed by the detection of specific inflammatory cells in the liver tissue. Although the number of NAFLD was small, the procedure distinguished between simple steatosis and steatohepatitis. Patients who underwent the procedure due to HUU benefited from diagnosis in 10/12 children. Metabolic disorders were detected in 3 patients and steatosis was detected in 6 children, 1 child was found to have Wilson's disease. Normal liver histology found in the specimens from the following 2 children with HUU raises questions regarding indications to the liver biopsy. The decision concerning the procedure was always carefully made basing on clinical and laboratory findings. Obtained results may be a consequence of the limitations of the procedure regarding sample size and sample error related to the site of the biopsy. Diffuse liver diseases are hardly ever evenly distributed in the organ.

Another problem with pathological assessment is an intraobserver variety. Except for skillful operator, an experienced pathologist is essential for proper evaluation of the samples. However, differences in the assessment between to various pathologists are difficult to avoid even with the use of validated scoring systems.

In recent years many non-invasive methods of liver assessment were developed. Imaging techniques allow to describe steatosis, focal changes, malformations, inflammatory processes of bile ducts and advanced fibrosis. Mild changes are, however, still difficult to detect. Elastography has been developed to evaluate liver stiffness being a useful tool to assess liver fibrosis [9]. Fibrosis is also evaluated by different serological markers and panels of direct and indirect markers or combination of both. Various cut-offs of the markers to detect advanced fibrosis and cirrhosis were validated in numerous studies [4]. Nevertheless, problem with intermediate stages of fibrosis still exist, since in such cases serological markers overlap.

Attempts to completely replace the biopsy with other non-invasive methods are not effective as the collection of adequate liver sample and proper histological evaluation allows to determine the extent of the liver damage and helps to establish the diagnosis.

5. Conclusions

Percutaneous liver biopsy is safe even in small children. Although severe complications are rare, patients require frequent monitoring. Ultrasound guidance seem to reduce the number of complications. Remaining a golden standard, the liver biopsy has certain limitations and drawbacks that influence the results.

Acknowledgements

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Abbreviations

AIH – autoimmune hepatitis, CHB – chronic hepatitis B, CHC – chronic hepatitis C, NAFLD – non-alcoholic fatty liver disease, HUO – hepatitis/hepatomegaly of unknown origin,

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