

## Blind liver biopsy: a 17-year experience

Biopsia hepática a ciegas: experiencia de 17 años

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Recibido: 21/10/2020 - Aprobado: 24/12/2020

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### ABSTRACT

**Objectives:** Liver biopsy is the gold standard for assessing liver inflammation, necrosis and fibrosis. The aim of the study is to evaluate clinical indications and histopathological results of percutaneous liver biopsy. **Materials and methods:** A total of 516 children who underwent blind liver biopsy were evaluated retrospectively. **Results:** Blind liver biopsy was performed for chronic active hepatitis B in 50% of the cases (n=260), neonatal cholestasis in 14% (n=68), autoimmune hepatitis in 7.7% (n=40), Wilson disease in 7.3% (n=38), isolated elevation of the liver enzymes in 5% (n=26), chronic active hepatitis C in 4.2% (n=22), metabolic disease in 3.4% (n=17), malignancies in 2.2% (n=11) and the others in 3.4% (n=17). Major complications were observed in 0.19% of the cases (n=1) and minor complications such as pain at the biopsy site in 13.5% of the cases (n=70), hypotension and tachycardia in 1.9% (n=10). **Conclusions:** Blind liver biopsy is a safe method in diagnosing liver diseases in childhood.

**Keywords:** Biopsy; Liver; Pediatric; /complications (source: MeSH NLM).

### RESUMEN

**Objetivos:** La biopsia de hígado es el estándar de oro para evaluar la inflamación, necrosis y fibrosis del hígado. El objetivo del estudio es evaluar las indicaciones clínicas y los resultados histopatológicos de la biopsia hepática percutánea. **Materiales y métodos:** Se evaluó retrospectivamente a un total de 516 niños a los que se les realizó una biopsia hepática a ciegas. **Resultados:** Se realizó biopsia hepática a ciegas por hepatitis B crónica activa en el 50% de los casos (n = 260), colestasis neonatal en el 14% (n = 68), hepatitis autoinmune en el 7,7% (n = 40), enfermedad de Wilson en el 7,3%. % (n = 38), elevación aislada de las enzimas hepáticas en el 5% (n = 26), hepatitis C crónica activa en el 4,2% (n = 22), enfermedad metabólica en el 3,4% (n = 17), neoplasias en el 2,2% (n = 11) y los demás en un 3,4% (n = 17). Se observaron complicaciones mayores en el 0,19% de los casos (n = 1) y complicaciones menores como dolor en el sitio de la biopsia en el 13,5% de los casos (n = 70), hipotensión y taquicardia en el 1,9% (n = 10). **Conclusiones:** La biopsia hepática a ciegas es un método seguro en el diagnóstico de enfermedades hepáticas en la infancia.

**Palabras clave:** Biopsia; Hígado; Pediatría; /complicaciones (fuente: DeCS BIREME).

### INTRODUCTION

Percutaneous liver biopsy (PLB) plays an important role in the diagnosis of acute and chronic liver diseases, assessment of the liver damage, course of the disease and treatment response in childhood. This method is regarded as the gold standard in the assessment of the degree of liver inflammation, necrosis and fibrosis <sup>(1)</sup>. The liver biopsy needle first used by Paul Ehrlich <sup>(2)</sup> in 1883, leading to the development of the invasive method in clinical practice, indications and technical

approaches <sup>(3)</sup>. Two types of needles are used in liver biopsies: cutting needles (Tru-Cut, Vim-Silverman) and suction needles (Menghini, Klatzkin, Jamshidi) <sup>(4)</sup>. The Menghini technique has begun to be used in the late 1950s, was considered to be a simple, reliable and minimally invasive method in the histopathological evaluation of liver diseases <sup>(5)</sup>.

Percutaneous, transjugular, laparoscopic or ultrasonographic techniques can be used in liver biopsy <sup>(6,7)</sup>. It has not been proven that ultrasound-

guided PLBs were superior to blind percutaneous liver biopsies<sup>(8)</sup>. Blind liver biopsy is a minimally invasive procedure, but major complications such as bleeding, pneumothorax and bile leak or minor complications such as pain can be observed<sup>(6,7,9,10)</sup>.

Although it has been suggested in recent years that the use of ultrasound-guided liver biopsies as proposed, have the lower risks such as hemorrhage, hematoma due to injuries of hepatic artery or portal vein and rupture of gall bladder, there is no sufficient studies suggesting that mortality or morbidity were reduced by ultrasound-guided liver biopsies<sup>(9)</sup>.

As it is a safe procedure with low risk of complications in both adults and children, increasing numbers of liver biopsies have been observed in recent years<sup>(11)</sup>. In this study, we evaluated the indications, histopathological results and biopsy related complications of blind PLB in children.

## MATERIALS AND METHODS

A total of 516 children (1 month to 18 years of age) who underwent liver biopsy at division of pediatric gastroenterology between January 1999 and January 2016 were evaluated retrospectively. The demographic features of the cases, indications for liver biopsy and histopathological results of the tissue specimens were obtained from medical records (Table 1). Only the cases who underwent blind PLB were included in our study. Laparoscopic or ultrasound-guided biopsies were excluded. The patients who have severe coagulopathy, sepsis and acidosis had biopsy after the biochemical and clinical improvement.

Liver biopsy was done to the patients who had positive HBV serological markers or HCV-RNA, autoantibody positivity, suspected metabolic diseases primarily low ceruloplasmin level, unexplained elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for three months or more, hepatosplenomegaly and cholestasis.

Blind PLB was performed by an experienced hepatologist by using the disposable Hepafix-Menghini liver biopsy set (Hepafix®, B.Braun Melsungen, Germany) in all cases after 8-hours of fasting. As the diameter of the needle (1.2 mm-1.4 mm/14 G-18 G) varies according to the age of the patient, a 16 G needle was used most commonly. Before the procedure, every patient was placed in back-lying position and right arm was raised and extended behind the head and over the left shoulder. The biopsy area was identified by caudal percussion over the right hemithorax between the anterior and midaxillary lines, at the intercostal space where dullness is maximal at the end of maximal

expiration. 2% lidocaine solution was used as local anesthesia and intravenous midazolam (0,1-0,2 mg/kg) for short-term sedation. Patients were placed in the lateral right position after biopsy and cold compression was applied to the biopsy area.

Biopsy specimens were placed in 10% formaldehyde solutions and sent to the department of pathology. Measurement of dry copper in liver was done. Vital functions and parameters (baseline blood pressure, heart rate and hematocrit) were evaluated every 15 minutes during the first 2 hours and every 30 minutes during the following 2 hours and then every 60 minutes during the last 2 hours after initial biopsy in all of the cases. Pain at the biopsy site was assessed as minor complication whereas hypotension and hemoglobin level <2 mg/dl as major complications. The patients were followed up 24 hours after biopsy and discharged according to clinical well-being.

## RESULTS

The age of 516 patients ranged from 1 month to 18 years (mean age:  $6.23 \pm 2.3$  years), and male:female ratio was 1.24. Among 50% of the patients who had elevated liver enzymes, positive HbsAg, HbeAg and HBV-DNA, 200 had liver biopsy (histological activity index (HAI):  $6.3 \pm 1.2$ ) and regarded as chronic active hepatitis B and were treated with lamivudine, interferon alpha-2a or 2b. Sixty cases were followed because their liver enzymes were slightly high and HAI was below 5.

Among 68 cases (13.1%) with neonatal cholestasis, histopathologic examination of 36 cases revealed enlargement with mononuclear inflammatory cell infiltration and swelling of hepatocytes (giant cell hepatitis) in the portal areas and regarded as neonatal hepatitis. Cytomegalovirus infection was detected in 28 of these cases. As the number of bile ducts increased and the number of portal ducts decreased (less than 4%, in each area) in 4 cases, then they were diagnosed as intrahepatic bile duct hypoplasia.

Histopathological examination of 10 patients with acolic gaita revealed interlobular bile duct proliferation, bile plugs, edema and fibrosis in portal areas. 6 of these cases with biliary atresia had Kasai operation, 2 had liver transplantation and 2 lost to follow-up. Three patients with preliminary diagnosis of familial progressive intrahepatic cholestasis (PFIC) had intracanalicular cholestasis, pseudoglandular formation, portal and perivenular fibrosis. Because mutation analysis could not be done in these cases, they were diagnosed as Byler disease and PFIC -3 according to clinical and laboratory findings. One case with peripheral pulmonary stenosis, butterfly vertebrae and broad forehead was diagnosed as Alagille syndrome.

Among 32 patients with isolated aminotransferases elevation 15 of them were evaluated as nonspecific hepatitis because of nonspecific findings such as portal mononuclear infiltration, steatosis, focal hepatocyte necrosis, lobular inflammation, lobular macrophage and lymphocyte in liver biopsy specimens.

Eight patients who had enlargement of portal areas with mononuclear inflammatory cell infiltration and swelling in hepatocytes (giant cell hepatitis) regarded as neonatal hepatitis.

Four patients with negative autoantibodies and elevated liver enzymes had mild lymphoplasmacytic

portal inflammation and piecemeal necrosis were regarded as autoimmune hepatitis (OIH).

A case who had infection was evaluated as hemophagocytosis due to infection because of mononuclear inflammatory cell infiltration and erythrophagocytosis in the portal areas. Another one with direct hyperbilirubinemia who had melanin-like pigment accumulation especially around the central vein diagnosed as Dubin-Johnson syndrome.

Twenty-six patients (5%) with solid, hematological malignancy or hematologic diseases and concurrent anti-HCV and HCV-RNA positivity, had a mean HAI

**Table 1.** Indications of liver biopsy and histopathological diagnosis of the patients.

Indications	Number of patients N (%)	Histopathological diagnosis	Number of patients N
HBV-DNA positivity	260 (50%)	Chronic active hepatitis B	260
Neonatal cholestasis	68 (13.1%)	Neonatal hepatitis	36
		Extrahepatic biliary atresia	10
		Nonspecific	7
		Cirrhosis	5
		Byler disease	4
		PFIC-3	3
		Alagille syndrome	1
		Niemann-pick disease	2
Autoimmune hepatitis	40 (7.7%)	Autoimmune hepatitis	40
Wilson's disease	38 (7.3%)	Wilson's disease	38
Isolated liver enzyme Elevation	32 (6.2%)	Nonspecific	15
		Neonatal hepatitis	8
		Autoimmune hepatitis	4
		Cirrhosis	2
		Hemophagocytic syndrome	1
		Dubin-Johnson syndrome	1
HCV-RNA positivity	26 (5%)	Chronic active hepatitis C	26
Metabolic diseases	22 (4.2%)	Glycogen storage disease	5
		Galactosemia	4
		Tyrosinemia	2
		Niemann-pick disease	2
		Alpha-1 antitrypsin deficiency	1
Malignancies	11 (2.1%)	Hepatocellular carcinoma	3
		Lymphoma	4
		Neuroblastoma	3
		Hepatoma	1
Others	19 (3.6%)	Cirrhosis	10
		Congenital hepatic fibrosis	3
		Cystic fibrosis	3
		Sclerosing cholangitis	2
		Budd-Chiari	1

of  $6.5 \pm 2.2$  and fibrosis rate of 2-3 and were given ribavirin and interferon alfa-2a or 2b treatment.

Among 22 patients (4.2%) with preliminary diagnosis of metabolic diseases, 5 patients with hepatomegaly, hypoglycemia, hypertriglyceridemia had hydropic degeneration, glycogenous inclusions in hepatocytes and positive diastase-sensitive periodic acid-Schiff (PAS) regarded as having glycogen storage disease (GSD). As two of these patients had also fibrosis in addition to hydropic degeneration in hepatocytes and the other two had progression to cirrhosis, then enzymatic analysis were done and GSD type 3 and 4 were detected. Severe hypoglycemia, hypertriglyceridemia and doll like face were present in the other three cases who had GSD type 1.

Two patients with cholestasis, hepatosplenomegaly and positive urine-reducing substances test had cholestasis, steatosis and bile duct proliferation in liver histopathology. When galactose 1-phosphate uridyl transferase enzyme levels were detected low, galactosemia was diagnosed. One of them who admitted with ascites died in spite of appropriate treatment. In four cases with hepatosplenomegaly and bicytopenia, acid phosphatase was detected high. Histopathological examination of liver biopsy revealed Gaucher cells and low beta-glucocerebrosidase enzyme levels confirming the diagnosis of Gaucher disease. All of the cases were given glucocerebrosidase at a dose of 60 IU/kg /dose every two weeks.

Four cases with macrovesicular steatosis in liver biopsy were unexplained. Two cases were diagnosed as tyrosinemia due to high urinary succinyl acetoacetate, cholestasis, micro and macro steatosis and pseudo-asiner formation of cells. These patients were lost to follow-up.

Two cases with jaundice and ascites diagnosed as Niemann-Pick type C due to foam cells in bone marrow and liver and enzyme analysis. Two cases without neurological involvement were Niemann-Pick type B are still being followed, but two with Niemann-Pick type C lost to follow-up.

Alpha-1 antitrypsin deficiency was determined in a 3-month-old infant who had 30 mg/dl serum alpha 1 antitrypsin level and PAS positive eosinophilic cytoplasmic granules in liver biopsy.

Ten patients with jaundice and hepatosplenomegaly had nodular formation, hepatocellular hyperplasia, abnormal hepatocytes with enlarged nuclei, thickening of hepatocytes membranes. These patients had cirrhosis, but no etiology was determined. Liver biopsy of two cases with cystic fibrosis revealed steatosis, accumulation of eosinophilic substance in the

interlobular bile ducts and fibrosis. Two patients with ulcerative colitis in whom elevation of liver enzymes was observed during follow-up had liver biopsy which revealed onion-skin fibrosis in interlobular and septal bile ducts and pleomorphic infiltration composed of lymphocytes, neutrophils, plasma cells and eosinophils.

A case who admitted with abdominal distention and pain, vomiting, ascites had hepatic vein thrombosis and hepatocyte necrosis, marked central congestion and endothelium thickening in the central venules in liver biopsy. The case was diagnosed as Budd-Chiari syndrome and died during liver transplantation.

Three cases who admitted with upper gastrointestinal bleeding, splenomegaly had congenital hepatic fibrosis due to the findings such as enlarged, irregular, fibrotic portal areas and increased, abnormal bile ducts in liver biopsy.

Eleven cases (2.2%) had malignancies: 3 hepatocellular carcinoma, 3 lymphoma, 3 neuroblastoma, and 1 hepatoma. 3 cases with hepatomegaly, HbsAg positivity and liver masses had cells with atypical nuclei scattered among round normal hepatocytes in liver biopsy. These patients with hepatocellular carcinoma died while awaiting liver transplantation. 3 cases with hepatomegaly diagnosed as lymphoma due to diffuse atypical lymphoid infiltration in the liver biopsy. Hepatoma was determined in a case with small undifferentiated cells between hepatocytes.

Major complication (0.19%) was observed only in a 3-month-old case with neonatal hepatitis who had hemorrhage controlled with blood transfusion. Hypotension and tachycardia developed in 1.9% (n=10), pain at the biopsy site in 13.5% (n=70). No mortality was observed in our study.

## DISCUSSION

Despite the advances in serological tests, liver biopsy is still the most important diagnostic method for the differential diagnosis of liver diseases and biliary diseases. It is the gold standard in determining the inflammation, necrosis and fibrosis in the liver<sup>(1,10)</sup>. PLB can be performed via ultrasound-guided or blind method.

The indications of liver biopsy include acute hepatitis of unknown etiology, elevated liver enzymes of unknown cause, chronic hepatitis B, C, and D infections requiring treatment, neonatal cholestasis, Wilson's disease, autoimmune liver disease, unexplained portal hypertension, fatty liver disease, hemochromatosis, hepatosplenomegaly, focal lesions and masses in the liver<sup>(12)</sup>. We evaluated the indications and histopathologic examinations of our cases who

underwent liver biopsy in light of literature review in this study.

Chronic hepatitis B had complications such as hepatic failure, fulminant hepatitis, cirrhosis and hepatocellular carcinoma. Liver biopsy is recommended before initiation of treatment<sup>(13)</sup>. 200 cases with positive HBV-DNA, HbsAg, and HBeAg, and elevated liver enzymes had high HAI. 60 cases had HAI lower than 5. No cases of cirrhosis were detected. Also, 25 cases with hepatitis C had liver biopsy before treatment and all cases were given ribavirin and interferon alpha-2a or 2b. Besides grading of inflammation and fibrosis by liver biopsy before treatment, excluding cirrhosis is also very important.

The most common cause of neonatal cholestasis is idiopathic neonatal hepatitis and biliary atresia. As the etiology remains unknown in most of the cases with neonatal hepatitis, it can be sporadic or familial, due to metabolic or viral agents. Liver biopsy is very important in the diagnosis besides virological and genetic tests for syndromes. Increased extramedullary hematopoiesis, inflammation and marked cholestasis are observed in liver biopsy. Syndromic biliary hypoplasia (Alagille syndrome) is characterized by chronic cholestasis, hypoplasia of the biliary tract, congenital malformations such as posterior embryotoxin, butterfly vertebrae, and peripheral pulmonary stenosis<sup>(14)</sup>. Intrahepatic biliary hypoplasia may also occur without developmental anomalies or genetic disorders. Early cholestasis and progressive liver disease can develop at an early stage in nonsyndromic biliary hypoplasia<sup>(15)</sup>. 6 cases had nonsyndromic and only one syndromic biliary hypoplasia in our study. No mutation analysis could be performed.

Liver biopsy is the most important method for the diagnosis of biliary atresia<sup>(1,7,9)</sup> and should be performed as soon as possible confirming the diagnosis and referring the patients for the Kasai operation. Liver transplantation was recommended in 4 of our 10 cases and was performed in two. 6 of the cases had Kasai operation.

Autoimmune hepatitis (OIH) is chronic, progressive, inflammatory liver disease characterized by the presence of various serum autoantibodies (ANA, ASMA, Anti-LKM-1), high gamma globulin levels and periportal or portal mononuclear cell infiltration (piecemeal necrosis) in histopathological examination<sup>(16-20)</sup>. In these cases, liver biopsy is crucial in determining the inflammation and fibrosis in the liver and demonstrating the presence of cirrhosis in addition to the diagnostic criteria defined by the Autoimmune Hepatitis Group for the diagnosis of OIH<sup>(21)</sup>.

Wilson's disease is an autosomal recessive disorder of copper metabolism, which if not properly treated, may progress to cirrhosis<sup>(22)</sup>. The low level of serum

ceruloplasmin as well as the copper level above 250 mcg / gram in the dry liver tissue is very important in the diagnosis of Wilson's disease. In our cases, the dry liver copper level was  $253.14 \pm 108.42 \mu\text{g} / \text{g}$  and had morphologic variation ranging from mild fatty change to acute hepatitis, chronic hepatitis and cirrhosis depending on the degree of accumulation in the liver biopsy.

Liver biopsy can help determining liver enzyme elevations that can not be explained by history, physical examination, biochemical, serological and imaging methods. Iorio et al.<sup>(22)</sup> performed liver biopsy to 425 patients and observed that 12 of 18 patients with isolated liver enzyme elevation had no pathology other than inflammation. In 3 of the 7 patients with isolated liver enzyme elevation diagnosed as glycogen storage disease in the study of Bugeac et al.<sup>(23)</sup> Akbulut et al.<sup>(3)</sup> reported OIH in 1 case, nonspecific changes in 9 and no pathology in 3 among 13 patients with isolated liver enzyme elevation who underwent liver biopsy. In our study, 15 of 32 patients (6.2%) with isolated liver enzyme elevation had nonspecific hepatitis in histopathological examination. Two patients had cirrhosis, eight had neonatal hepatitis and four OIH.

Metabolic diseases should be considered in differential diagnosis of hepatosplenomegaly in childhood. Biochemical, molecular and enzymatic tests made diagnosis of metabolic diseases easier. In the diagnosis of GSD, diastase-sensitive PAS positivity is important for demonstration of glycogen<sup>(24)</sup>. 5 of 22 cases (4.2%) diagnosed as GSD in this study.

Alpha-1 antitrypsin deficiency is the most common cause of genetic liver diseases in children, resulting in defective A1AT accumulation in the liver cell endoplasmic reticulum, leading to liver damage. It can cause neonatal cholestasis and chronic liver disease in children. As no specific treatment exists for the disease, it is the most important genetic disorder leading to liver transplantation<sup>(25)</sup>. Only one case was diagnosed as alpha-1 antitrypsin deficiency in our study. Since the family did not accept the liver transplantation, the child was lost while awaiting for the cadaver liver.

Although the rate of liver involvement in patients with cystic fibrosis is unknown, it has been reported to be 20-50% in different studies<sup>(26)</sup>. Only 3 of our cases with cystic fibrosis showed liver involvement.

Involvement of the liver and bile ducts has been reported in inflammatory bowel diseases as well as joint, eye, and skin involvement<sup>(27)</sup>. We detected sclerosing cholangitis in two cases with ulcerative colitis by liver biopsy.

Budd-Chiari syndrome (BCS), one of the rare causes of liver disease, is caused by obstruction of the hepatic

venous outflow and can be seen in a wide clinical spectrum ranging from fulminant hepatic insufficiency to chronic liver disease <sup>(28)</sup>. A 13-year-old girl who admitted to our department with abdominal distention diagnosed as hepatic vein thrombosis and Budd-Chiari syndrome due to factor V Leiden mutation was lost during liver transplantation.

Although liver biopsy is accepted as a safe method, some complications can develop. It has been reported that the Menghini needle causes fewer complications than the Tru-Cut needle <sup>(11)</sup> and the complication rate was 2.4% and the mortality rate 0.25% in PLB. Major complications such as hemorrhage, intrahepatic hematoma, hemobilia, gall bladder and colon perforation, as well as minor complications such as pain at biopsy site and vasovagal reaction can be seen in blind PLB. Minor complication rate is 4-5% and major complication rate is between 0.13-5.4%, while mortality rate is between 0.009-0.11% <sup>(7,9)</sup>. It is known that 62% of the complications are seen in the first two hours, 82% in the first 10 hours and 96% in the first 24 hours <sup>(9)</sup>. El-Shabrawi *et al.* <sup>(29)</sup> reported minor complication rate as 17.5% and no major complication. Although Younossi *et al.* <sup>(30)</sup> reported a complication rate of 4% with blind percutaneous needle biopsy and 2% with the ultrasound-guided liver biopsy, Scheimann *et al.* <sup>(6)</sup> observed no difference in terms of complications between ultrasound-guided and blind biopsy in children. Only in a 3-month-old infant out of 516 cases had hemorrhage in our study. Hypotension and tachycardia due to vasovagal reaction 2 hours after biopsy developed in 1.9% (n=10) and pain at the biopsy site probably due to the retraction of the capsule in 13.5% (n=70) compatible with the literature. No case was lost after biopsy. Since our data show similarities with the literature, we can explain this by using blind percutaneous liver biopsy is a reliable method.

In conclusion, blind liver biopsy is a reliable method for diagnosis, staging, grading of liver diseases and evaluating the efficacy of various medical treatments with a very low complication rate. But it can be performed successfully with experience and basic skill. For this reason, liver biopsy which supports diagnosis and treatment in patients with suspected liver disease can be performed safely by experienced gastroenterologists.

**Declared conflict of interest of all authors:** None.

**Funding:** None.

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