

# Liver Biopsy in Children Under 5 Years Experience in a Colombian Pediatric Hospital

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## Abstract

**Objective:** The objective of this study was to evaluate the frequency and distribution of liver diseases justifying liver biopsies in Colombian pediatric patients.

**Methodology:** Liver biopsies performed at a pediatric hospital over a period of 5 years were assessed and then sorted according to age groups and diagnoses.

**Results:** A total of 182 histopathological studies of 168 patients (14 of whom had two procedures each.) were found: 53.6% were boys, and 46.4% were girls. Young infants were the age group which had the most biopsies, and cholestasis was the most frequent reason for these biopsies. Other diseases diagnosed included inflammatory processes (30.2%), abnormalities of the biliary tract (26.4%), tumor diseases (14.9%) and metabolic/storage disorders (9.3%). The remaining percentages were for rare entities and normal biopsies.

**Conclusion:** Liver biopsies are useful and practical for the diagnosis of pediatric liver disease when combined with clinical and laboratory data. In our study, inflammatory processes, abnormalities of the biliary tract and tumor diseases were the most frequently diagnosed categories.

## Keywords

Liver biopsy, pediatric liver disease, cholestasis.

## INTRODUCTION

Liver biopsies are of great importance for clinical practice because they allow assessment of the presence and severity of histopathological lesions in the liver. When added to the clinical, laboratory and imaging data, this is the basis for diagnosis, prognosis and monitoring of liver disease (1-4). This is especially valuable in pediatric medicine because of the very diverse etiologies of diseases that can manifest with similar clinical pictures. Histological findings frequently help establish definitive diagnoses (1, 5). Because there had been very few reports of about the incidence of liver disease in children in Colombia, this paper retrospectively evaluated the frequency and types of liver disease diagnosed with liver biopsies in a pediatric population

at the Fundación Hospital de la Misericordia in Bogotá, Colombia over a 5 year period.

## MATERIALS AND METHODS

This is a retrospective and descriptive study. Patients who had had liver biopsies from January 2006 to December 2010 in the Department of Pathology of the Fundación Hospital de la Misericordia were taken from the hospital's database. Two biopsies were excluded because there was no clinical information and resection specimens were not taken into account. Clinical and epidemiological data were evaluated and grouped according to pathological diagnoses into six categories:

1. Inflammatory processes

2. Abnormalities of the bile duct
3. Tumors
4. Metabolic / Disorders of deposit
5. normal biopsies or minimal changes not diagnostic
6. Other

The entities within each of these categories are shown in Table 1. Subsequently, these same diagnostic categories were evaluated by the following age groups: Newborns (under 1 month), infants (from 1 month to one year old), toddlers (one to two years old), preschoolers (two to six years old), elementary school age (six years to 12 years old) and adolescents (12 to 18 years old). Biopsies which had problem and imprecise diagnoses were reevaluated to determine if a new histological observation and/or updating of clinical or laboratory data could result in a better diagnosis. Data were analyzed with Microsoft Office Excel 2010 and analyzed with GraphPad StatMate 2.

**Table 1.** Entities included within each diagnostic category

Diagnostic category	Entities included
Inflammatory Processes	Neonatal hepatitis Acute hepatitis, Infectious hepatitis, chronic Hepatitis
Biliary tract abnormalities	Ductopenia Extrahepatic biliary tract atresia Congenital hepatic fibrosis Choledochal cyst
Tumors	Primary benign and malignant liver tumors Metastatic tumors or Lymphoproliferative disorders
Metabolic or storage disorders	Glycogenesis, lipidosis, $\alpha$ 1 antitrypsin deficiency, Niemann Pick disease, mucopolysaccharidosis
Normal/minimal alterations no diagnosis	No histological alterations, minimal histological alterations, unspecified histological alterations, and no diagnosis
Others	Alterations associated with parenteral nutrition, cystic fibrosis, reactive hepatitis, vascular alterations, steatosis, steatohepatitis, cholestasis, sample insufficient for diagnosis

## RESULTS

Between January 2006 and December 2010, 182 liver biopsies were taken from 168 patients at the Fundación Hospital de la Misericordia. Fourteen patients had two procedures each. In six cases, the second biopsy was taken to monitor chronic hepatitis, in four cases a second biopsy was taken because a conclusive diagnosis could not be established with the first sample. In one case, a second biopsy was taken to monitor a neuroblastoma which had metastasized to the liver, in another case a second biopsy

was taken to monitor an infiltrated atypical lymph node. In two cases, second biopsies were taken because the amounts of material sent in the first biopsy samples were inadequate for diagnosis.

Of the studies reviewed, 163 biopsies (89.6%) were performed in the hospital. Of these, 148 (90.8%) were wedge biopsies and 15 (9.2%) were percutaneous biopsies. Nineteen cases were material sent for review for second opinions (10.4%).

### Distribution by gender and age group

Of the 168 patients evaluated, 90 (53.6%) were boys and 78 (46.4%) were girls. Neither this difference ( $p = 0.15$ ) nor differences between age groups within each gender (data not shown) were significant.

The largest number of biopsies were taken from infants ( $n = 81$ , 44.5%), followed in decreasing order by elementary schoolchildren ( $n = 31$ , 17%), preschoolers ( $n = 29$ , 15.9%) toddlers ( $n = 19$ , 10.4%), adolescents ( $n = 17$ , 9.4%) and newborns ( $n = 5$ , 2.8%).

### Indications for biopsy

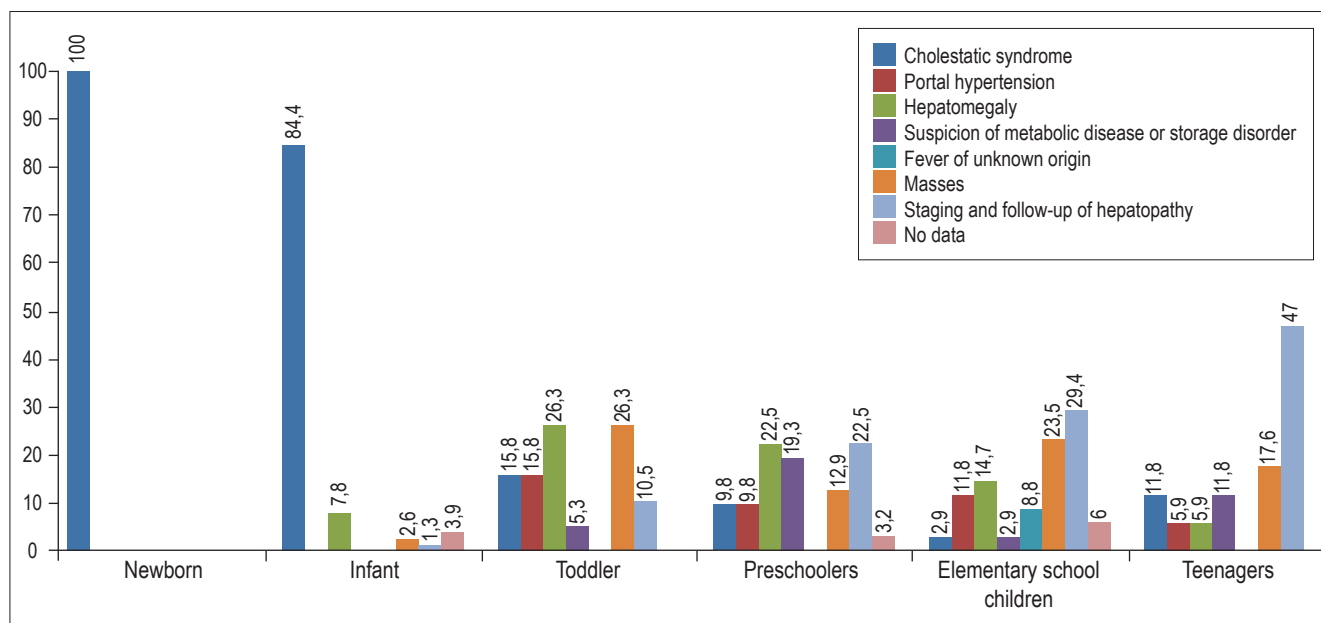
Overall, the most common for performing liver biopsy indication was the study of cholestatic jaundice ( $n = 79$ , 43.4% of cases), followed by staging or monitoring of chronic liver disease ( $n = 28$ , 15.4%), hepatomegaly studies ( $n = 24$ , 13.2%), hepatic masses ( $n = 22$ , 12.1%), portal hypertension ( $n = 11$ , 6%), suspicion of storage disorder ( $n = 10$ , 5.6%) and fever of unknown origin ( $n = 3$ , 1.6%). The records did not show the reason for biopsies for five patients (2.7%).

Indications for taking biopsies differed according to age group as shown in Figure 1.

### Diagnostic categories for all cases

Histopathological findings were grouped by diagnostic categories for all cases and for each age group. In all cases, the most frequently diagnosed category was inflammatory processes with 55 cases (30.2%). This was followed by biliary tract abnormalities in 48 cases (26.4%), tumors with 27 cases (14.9%), and metabolic disorders/storage disorders with 17 cases (9.3%). "Other" occupied fifth place and included a variety of rare entities and cases of insufficient biopsy material. There were a total of 20 cases (11%) in this category. Finally, the category of normal or minimally altered biopsies had 15 cases (8.2%).

Twenty-three (41.8%) out of the 55 cases of inflammatory processes were chronic hepatitis, twenty-three (41.8%) were neonatal hepatitis and nine (16.4%) were either suggestive



**Figure 1.** Indications for liver biopsy: percentage by age group

of inflammatory changes or confirmed infectious processes. Of the latter, one case of Histoplasmosis was confirmed, two patients tested positive for hepatitis A, and three tested positive cytomegalovirus. It was not possible to establish the infectious agent for the remaining three cases.

Nineteen (39.6%) of the 48 cases of biliary tract abnormalities were extrahepatic biliary atresia, eighteen were ductopenia (37.5%), seven were choledochal cysts (14.6%), and four were congenital hepatic fibrosis (8.3%).

Of the 27 cases of tumors, 17 (63%) were primary liver tumors. Of these, 13 (76.5%) were malignant and 4 (23.5%) were benign. Among the malignancies were six cases of hepatoblastoma, six cases of hepatocellular carcinoma and one sarcoma. There were two cases of benign nodular regenerative hyperplasia and two cases of hemangioendothelioma. Two tumors which had metastasized were found: one neuroblastoma and one malignant mixed germ cell tumor. We also included eight cases of lymphoproliferative disorder with liver involvement in this category.

The “other” category’s twenty cases included five patients with cholestasis (25%), three with changes associated with parenteral nutrition (15%), three with steatosis and/or steatohepatitis (15%), and two with reactive hepatitis (10%). It also included three biopsies (15%) with minor vascular alterations (portal hypertension and obstruction of the hepatic vein), one case of cystic fibrosis of the pancreas (5%) and three biopsies (15%) that were considered insufficient for diagnosis or of poor quality.

In 17 patients a diagnosis of metabolic disease or storage disorder was established and correlated with other labora-

tory examinations. Eleven (64.7%) of these disorders were glycogen storage disorders. We also found one case each of lipodosis, alpha-1-antitrypsin deficiency, Niemann Pick disease and mucopolysaccharidosis. A definitive diagnosis was not established for the other two cases.

The final category contained 15 biopsies that were normal and/or had only minimal changes. Four of these patients had extrahepatic portal hypertension. Two patients had liver mass studies: one had been treated for neuroblastoma and another had previously been diagnosed with chronic hepatitis.

### Diagnostic categories by age group

**Newborns:** Three of the five newborns (60%) had biliary tract abnormalities: two cases of extrahepatic biliary atresia and one case of ductopenia. There was one case (20%) of an inflammatory process, neonatal hepatitis, and one (20%) case that was in the “other” category as the result of a non-specific diagnosis of cholestasis.

**Infants:** Among the 81 cases in this population, there were 36 cases (44.4%) of biliary tract abnormalities diagnosed, 27 inflammatory processes (33.3%), ten cases in the “other” category (12.4%), three normal biopsies or biopsies with nonspecific changes (3.7%), three tumors (3.7%) and two metabolic disorders and/or deposit disorders (2.5%).

Among the cases of biliary abnormalities there were 17 cases of extrahepatic biliary tract atresia (47.2%), 16 cases of ductopenia (44.4%), two cases of choledochal cysts (5.6%) and one case of congenital hepatic fibrosis (2.8%).

The vast majority of inflammatory processes, twenty-two out of twenty-seven cases (81.5%), were neonatal hepatitis. Of the ten patients in the “other” category, there were three patients with alterations associated with parenteral nutrition, four patients with cholestasis, two cases of biopsy samples which were not satisfactory for diagnosis, and one case of reactive hepatitis secondary to shock. Two cases of metabolic disease, one case of Niemann Pick disease, and one case of glycogen storage disorder were diagnosed. Two primary tumors, one hepatoblastoma and one heman-gioendothelioma were found, and one case of neuroblas-toma that had metastasized was found.

**Toddlers:** There were 19 toddlers of whom seven (36.8%) were diagnosed with tumors, four were diagnosed with inflammatory processes (21.1), three with biliary tract abnormalities (15.8%), and two with metabolic or storage disorders (10.5%). There were two patients in the “other” category (10.5%), and one normal biopsy (5.3%).

Among the seven tumors were four cases (57.1%) of hepatoblastoma, one malignant mixed germ cell testicular tumor that had metastasized (14.3%) and two cases of lymphoproliferative disease (28.6%). The four cases of inflam-matory processes included two cases of acute hepatitis, one of which was due to histoplasmosis, and two cases of chronic hepatitis. Bile duct abnormalities included two cases of congenital hepatic fibrosis and one choledochal cyst. Two cases of metabolic or deposit disorders were diagnosed: one case of  $\alpha$ 1 antitrypsin deficiency and one case of glycogenesis. The “other” category included a case of non-alcoholic steatohepatitis and a fibrosis scar in a patient with a history of hepatoblastoma.

**Preschoolers:** Of the 29 cases in this population, ten were diagnosed with metabolic or storage disorders (34.6%, five with biliary tract abnormalities (17.2%), five with tumors (17.2%), and five with inflammatory processes (17.2%). There were two in the “other” category (6.9%) and two normal biopsies (6.9%).

Seven of the 10 cases (70%) of metabolic diseases were glycogenesis, one case of lipidosis (10%) was found, and two cases (20%) could not be diagnosed definitively. There were three cases with biliary abnormalities: one choledochal cyst, one case of congenital hepatic fibrosis and one case of ductopenia. The five cases of chronic inflammatory hepatitis included two cases of autoimmune hepatitis, one case of hepatitis B due to vertical transmission, one case due to cavernous transformation of the portal vein (CTPV) and one case for which the etiology could not be established. The five cases of tumors included two cases of nodular regenerative hyperplasia, one hepatoblastoma, one hemangioendothelioma and one case of Langerhans

cell histiocytosis (LCH). The “other” category included one case of extrahepatic portal hypertension and one case of steatosis.

**Elementary School Children:** Of the 31 cases in this population, eleven cases of inflammatory processes were diagnosed (35.5%), nine tumors (29%), two metabolic or storage disorders (6.5%), and one biliary tract abnormality (3.2%). Five biopsies (16.1%) were normal or had nonspecific changes, and there were three cases in the “other” category (9.7%).

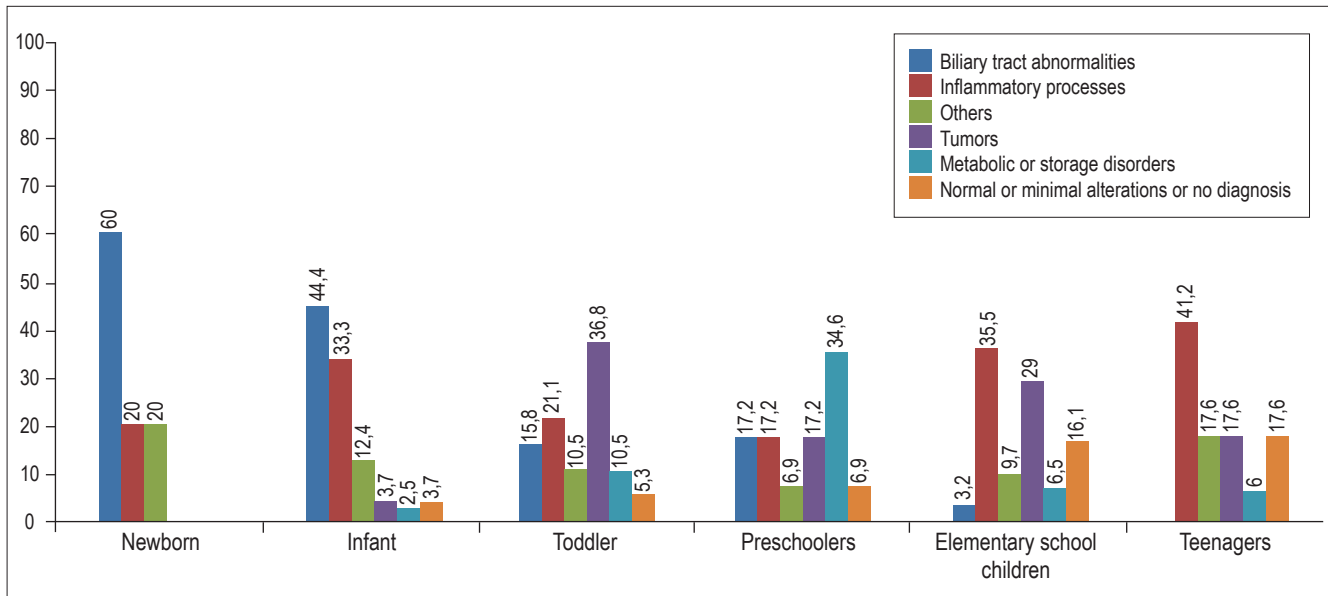
Among the eleven cases of inflammatory processes, there were six (54.5%) cases of autoimmune hepatitis, one case of infectious hepatitis A, and four patients whose etiologies could not be established. The nine cases of tumors included five (55.6%) with hepatocellular carcinoma, three (33.3%) with lymphoproliferative disease and one case of embryonal sarcoma (11.1%). Only two cases of metabolic disease were found: both were glycogenesis. There was one case of choledochal cysts. The “other” category included a case of cystic fibrosis of the pancreas, one case of reactive hepatitis and one case of steatosis.

**Teenagers:** Of the 17 cases of this population, seven cases of inflammatory processes were diagnosed (41.2%), three tumors (17.6%), and one case of metabolic or storage disorder (6%). The “other” category included three cases (17.6%), and there were three cases that had normal biopsies or biopsies without specific changes (17.6%).

All of the seven cases of inflammatory processes were chronic hepatitis (100%), six of these had autoimmune etiologies (85.7%) and one was hepatitis B (14.3%). Among the three tumor cases were one case of hepatocellular carcinoma (HCC) and two cases of lymphoproliferative disease with liver involvement. We found only one case of metabolic disease and no biliary tract abnormalities. The “other” category included two cases with minor vascular alterations and one case with insufficient diagnostic material. Figure 2 summarizes the diagnoses according to age groups.

## DISCUSSION

This study describes the experience of five years of liver biopsies performed at a level three pediatric hospital. The 182 samples included in the study are two percent of the surgical specimens evaluated in the institution during this period (182/11,038). No statistically significant differences were found to discriminate patients by gender or age group. Unlike most published series in which percutaneous biopsies are preferred (6-8). Our hospital prefers wedge biopsies (90.8%). This is the technique for which our sur-



**Figure 2.** Diagnostic categories: percentage by age group

geons have better training, and it is they who take most biopsy samples since we have limitations in our interventional radiology program. Importantly, whatever technique was used, in our hospital all procedures are done under general anesthesia regardless of patient age. Only one patient in the study had both wedge and puncture biopsies, but the latter was obtained during surgery as the result of an intraoperative decision made by the prosector who wanted to compare the data provided by each type of sample.

Overall, nearly a third of the biopsies were diagnosed with inflammatory processes, over 25% were abnormalities of the biliary tract, and 15% were tumors. These three categories accounted for 70% of all diagnoses.

Jaundice was the most common reason for performing liver biopsies in newborns and infants while for other ages over 50% of procedures were done to study the growth of the liver either diffusely or by mass.

The most frequent pathologies among patients under one year of age were biliary tract abnormalities. They were followed closely by infectious processes, inflammatory processes and undetermined etiologies. Among the latter were cases of neonatal hepatitis. All extrahepatic bile duct atresia and most cases of ductopenia were diagnosed before six months of age, usually before four months of age. No any age group showed predilection for hepatic fibrosis or congenital choledochal cysts.

Tumors accounted for only 3.7% of the cases among newborns and infants, but among toddlers they accounted for 36.8% of all cases. They accounted for 17.2% of cases for preschoolers, 17.6% for adolescents and 29% for elementary school children. All cases of hepatoblastoma

and benign primary liver neoplasms were diagnosed in children under six years of age. The peak incidence was among toddlers. Among elementary school children and adolescents cases of hepatoblastoma are not found. The malignant tumors found are generally hepatocellular carcinomas (HCC), but we had one case of hepatic sarcoma. In our population, HCC had a higher incidence among elementary school children than among adolescents. Children more frequently develop primary neoplasms of the liver than adults do. Of the 27 cases of tumors reported, only two were metastatic: one neuroblastoma and one malignant mixed germ cell tumor. Eight cases of lymphoproliferative disease were diagnosed.

Infectious hepatitis cases were more frequent among infants while the proportion of chronic hepatitis cases increased with age: 17.2% among preschoolers, 35.5% among elementary school children and 41.2% among adolescents. Autoimmune etiologies were established for 66.7% of these cases.

Preschoolers had (58.8%) of the cases of metabolic diseases diagnosed. Of the 17 cases found, eleven were classified as glycogen storage disorder (64.7% of cases). Since it is known that some metabolic diseases show a histological pattern similar to neonatal hepatitis (9), it is likely that some cases were not diagnosed which should lower the frequency observed in infants.

One limitation of this study worth noting is that follow-up data after the biopsy was not available for some patients, and for these patients we do not have a definitive diagnosis in our database. These patients had histological diagnoses of neonatal hepatitis, chronic hepatitis, or biopsies sugges-



tive of metabolic disease or were cases referred from other institutions for review.

This is what we know. This is the first study showing the overall incidence of liver disease in a pediatric population in Colombia. A previous study that documented indications for liver transplantation in nine pediatric patients reported that six of them (67%) had atresia of the extrahepatic bile ducts (10). Another study evaluated hepatic causes of hepatosplenic syndrome in 18 children under 12 years of age. It found portal hypertension in 34% of these patients, extrahepatic bile duct atresia in 22%, neonatal hepatitis in 22% and metabolic disease in the remaining 22% (11).

A study of pediatric patients similar to ours that was conducted in Iran shows different incidences of liver diseases. In that study, the most frequent diagnosis was hemochromatosis among patients with thalassemia (17.5%) followed in order by biliary atresia (11.8%), chronic hepatitis (10.3%) and neonatal hepatitis (10.3%) (8). Zhang et al. published a study of 1,020 patients diagnosed by biopsies which found that viral hepatitis was the main cause of liver damage followed by metabolic disorders such as Wilson's disease and glycogenesis (2). The study population consisted mostly of elementary schoolchildren and adolescents which partly explains why the impact was so different from that found in this study. Ochoa and colleagues performed a similar study to ours in Mexico. The most frequent diagnoses in their series were chronic hepatitis (33%), neonatal hepatitis (10%), cryptogenic chronic hepatitis (10%) and glycogen storage disorder (9.5%) (6).

## CONCLUSION

Liver biopsies are useful and practical for diagnosis of pediatric liver disease when combined with clinical and laboratory data. The most common indication for performance of a biopsy in children under one year of age in this study was cholestasis which was mostly due to biliary tract abnormalities (atresia of extrahepatic bile ducts and ductopenia) and inflammatory processes (neonatal hepatitis and infections). Among children aged one to eighteen years,

the growth of the liver, either in the form of hepatomegaly or masses, accounted for a large proportion of the procedures. More than half of the biopsies diagnosed tumors and chronic inflammatory processes such as hepatitis. Biliary tract abnormalities such as choledochal cysts and congenital hepatic fibrosis, metabolic diseases, biopsies with minimal or normal changes and "others" were all found in similar proportions.

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