



**Cairo University**  
Faculty of Medicine  
Department of Pediatrics

# **PEDIATRIC LIVER MASSES**

**BY**

**Mohammad El-Sayed El-Refay Ghalwash**  
(M.B.B.Ch)  
Mansoura University

***Essay***

Submitted for Fulfillment of the Master Degree  
In Pediatrics

***Supervisors***

***Prof. Dr.***

**Mortada Hasan El-Shabrawi**  
Professor of Pediatrics  
Faculty of Medicine  
Cairo University

***Dr.***

**Ranya Aly Hegazy**  
Lecturer of Pediatrics  
Faculty of Medicine  
Cairo University

***Dr.***

**Naglaa Mohammad Kamal**  
Lecturer of Pediatrics  
Faculty of Medicine  
Cairo University

**2007**

## ACKNOWLEDGMENT

"Thanks first to *Allah*, who has given me everything I have"

I wish to express my great thanks to *Prof. Dr. Mortada H. El-Shabrawi*, Prof. of Pediatrics, the head of pediatric hepatology unit, Faculty of Medicine, Cairo University, one of the pioneers of pediatric hepatology in Cairo University, for his honest advice, sincere cooperation, meticulous observations, and continuous guidance during this work, unlimited help, and generous support.

I am grateful to *Dr. Ranya Aly Hegazy*, Lecturer of Pediatrics, Faculty of Medicine, Cairo University, for suggesting the points investigated and for her advice, sincere cooperation, meticulous observations, continuous guidance during this work and generous support.

I would like to forward my grateful appreciation to *Dr. Naglaa Mohammad Kamal*, Lecturer of Pediatrics, Faculty of Medicine, Cairo University, for her sincere cooperation, and support.

No words could express my deep thanks to *Dr. Nehal Mohamed Al-Koofy*, Assistant Prof. of Pediatrics, Faculty of Medicine, Cairo University, for her honest advice, encouragement, unlimited help and generous support.

I also extend my thanks to all my colleagues, without their help this work has never seen light.

# ***DEDICATION***

To the spirit of my mother,

Spirit of My father,

My brother Shaban,

My sisters Mervate and Alliaa,

And to all of my family,

I dedicate this work

*Mohammad Ghalwash*

# CONTENTS

SUBJECT	PAGE
<b>Introduction and Aim of the Work</b>	<b>1</b>
<b>(1) Liver Anatomy &amp; Histology</b>	
• Embryology of the Liver	5
• Gross Anatomy of the Liver	7
• Microscopic Anatomy of the Liver	31
<b>(2) Benign Neoplastic Liver Masses</b>	
• Infantile Hemangioendothelioma	40
• Cavernous Hepatic Hemangioma	46
• Mesenchymal Hamartoma	50
• Focal Nodular Hyperplasia	61
• Hepatocellular Adenoma	65
• Hepatic Teratoma	67
<b>(3) Malignant Liver Masses</b>	
• Hepatoblastoma	69
• Hepatocellular Carcinoma	84
• Undifferentiated Embryonal Sarcoma	90
• Angiosarcoma	94
• Rhabdomyosarcoma	95
• Metastatic Hepatic Tumors	99
<b>(4) Nonneoplastic Liver Masses</b>	
• Simple Hepatic Cyst	101
• Polycystic Liver disease	104
• Hepatic Hematoma	105
• Peliosis Hepatis	106
• Parasitic Hepatic cyst	109
• Pyogenic Liver Abscess	113
• Amebic Liver Abscess	116
• Inflammatory Pseudotumor	119
• Nodular Regenerative Hyperplasia	121
• Choledochal Cyst	124
<b>Summary and Conclusion</b>	<b>130</b>
<b>References</b>	<b>137</b>
<b>Arabic Summary</b>	<b>168</b>

## LIST OF TABLES

	<b>Title</b>	<b>Page</b>
<b>Table 1</b>	Classification of Liver Masses.	<b>2</b>
<b>Table 2</b>	Presenting symptoms of hepatic hemangioendothelioma	<b>42</b>
<b>Table 3</b>	Difference between hemangioma and Hemangioendothelioma.	<b>47</b>
<b>Table 4</b>	Current Pathologic Classification of FNH.	<b>64</b>
<b>Table 5</b>	Conditions associated with Hepatoblastoma.	<b>70</b>
<b>Table 6</b>	Clinical Staging of Hepatoblastomas.	<b>76</b>
<b>Table 7</b>	Conditions Associated With HCC.	<b>85</b>
<b>Table 8</b>	Classification of hepatic hydatid cysts.	<b>112</b>
<b>Table 9</b>	Conditions associated with NRH.	<b>122</b>

## LIST OF FIGURES

	<b>Title</b>	<b>Page</b>
<b>Fig 1</b>	<b>Embryology of the liver</b> & development of hepatic blood vessels.	<b>6</b>
<b>Fig 2</b>	<b>External gross anatomy of the liver</b> , anterior view.	<b>8</b>
<b>Fig 3</b>	<b>Schematics illustrate the normal portal vein (PV) branches.</b>	<b>11</b>
<b>Fig 4</b>	<b>Diagram of the hepatic segments (I-VIII)</b> with their portal venous branches.	<b>23</b>
<b>Fig 5</b>	<b>Subxiphoid, oblique sonogram and Corresponding CT scan</b> shows the left (L), middle (M), and right (R) hepatic veins.	<b>24</b>
<b>Fig 6</b>	<b>Anatomy of the segmental portal veins;</b> there is one H for each lobe.	<b>25</b>
<b>Fig 7</b>	<b>Subxiphoid sonogram and the corresponding CT scan</b> shows the H of the left lobe. Arrows show the ligamentum venosum.	<b>26</b>
<b>Fig 8</b>	<b>A sagittal-oblique intercostal sonogram obtained at the midaxillary line</b> shows the H of the right lobe.	<b>28</b>
<b>Fig 9</b>	<b>CT scan</b> shows the falciform ligament (Fl), separating segment 4 (IV) from segment 2 and 3 (II / III).	<b>29</b>
<b>Fig 10</b>	<b>Subxiphoid sonogram (above) and Corresponding CT scan (below)</b> show, the ligamentum venosum (LV).	<b>30</b>
<b>Fig 11</b>	<b>Normal portal tract from human liver</b> shows small bile ducts (B), hepatic artery (A), a portal vein (P), and occasional lymphocytes (H & E).	<b>31</b>
<b>Fig 12</b>	<b>Normal liver histology</b> , shows classic hepatic lobule, H terminal hepatic vein, P portal tract (H & E).	<b>32</b>
<b>Fig 13</b>	<b>Diagram of classic liver acinus.</b>	<b>34</b>
<b>Fig 14</b>	<b>Diagram of hepatocyte.</b>	<b>36</b>

<b>Fig 15</b>	<b>Abdominal IV contrast-enhanced CT shows a circumscribed mass in the left lobe, typical for a <b>hemangioendothelioma</b>.</b>	<b>43</b>
<b>Fig 16</b>	<b>Histology of cavernous hemangiomas</b> , shows large vascular channels packed with abundant red blood cells (H & E).	<b>48</b>
<b>Fig 17</b>	<b>Hemangioma (CT)</b> . Unenhanced and early arterial CT examination (A, B). Late venous phase (C) images.	<b>48</b>
<b>Fig 18</b>	<b>Cavernous Hemangioma (MRI)</b> . Precontrast T1-weighted image (A), T2-weighted image (B), postcontrast T1 (C, D).	<b>49</b>
<b>Fig 19</b>	<b>Abdominal CT scan</b> of a 7 year-old girl with an MHL consisting of 2 large cysts.	<b>53</b>
<b>Fig 20</b>	<b>Magnetic resonance scan</b> of a 2-month-old baby with a large, dominantly solid MHL (after gadolinium contrast).	<b>53</b>
<b>Fig 21</b>	<b>Histology of an MHL</b> showing distorted bile ductules, small cystic spaces with myxoid connective tissue (H&E).	<b>56</b>
<b>Fig 22</b>	<b>The liver of a neonate at autopsy</b> shows a discrete MHL in the right and left lobes of the liver.	<b>57</b>
<b>Fig 23</b>	<b>CT scan</b> appearance of the infant's left liver lobe <b>FNH</b> .	<b>62</b>
<b>Fig 24</b>	<b>Histopathology finding of FNH (H &amp; E)</b> .	<b>64</b>
<b>Fig 25</b>	<b>CT of hepatic adenoma</b> reveals large right hepatic lesion, with a faint pseudocapsule containing the adenoma.	<b>66</b>
<b>Fig 26</b>	<b>Enhanced CT scans of a 22-month-old male with HB</b> . <b>A)</b> At diagnosis. <b>B)</b> After four courses of chemotherapy.	<b>73</b>
<b>Fig 27</b>	<b>HB with fetal and embryonal patterns</b> . The fetal component is composed of tumor cells with abundant eosinophilic cytoplasm.	<b>74</b>
<b>Fig 28</b>	<b>PRETEXT (PRE Treatment EXTent of disease)</b> staging system.	<b>76</b>
<b>Fig 29</b>	<b>Unenhanced CT scan of a 17-year-old girl with HCC</b> shows a large mass in right lobe of liver.	<b>86</b>
<b>Fig 30</b>	<b>HCC histopathology</b> . <b>a) Moderately differentiated HCC</b> shows trabecular pattern. <b>b) Fibrolamellar carcinoma</b>	<b>88</b>
<b>Fig 31</b>	<b>Enhanced CT scan of 1-month-old boy with UES</b> of liver.	<b>91</b>

<b>Fig 32</b>	<b>Histopathology of UES (H&amp;E)</b> shows ovoid to spindle-shaped cells with pleomorphic nuclei on eosinophilic mixoid matrix.	<b>93</b>
<b>Fig 33</b>	<b>CT scan of 14-year-old boy with rhabdomyosarcoma</b> , in biliary tract.	<b>96</b>
<b>Fig 34</b>	<b>Contrast-enhanced CT scan of liver metastasis. (A) A girl</b> with right adrenal neuroblastoma. <b>B) A boy</b> with metastatic carcinoma.	<b>100</b>
<b>Fig 35</b>	<b>Unenhanced CT scan of 18-year girl</b> with a simple hepatic cyst.	<b>102</b>
<b>Fig 36</b>	<b>CT of polycystic disease of the liver.</b> CT in patient with a history of polycystic kidney disease	<b>105</b>
<b>Fig 37</b>	<b>Contrast axial CT scan</b> of peliosis hepatis. <b>(A)</b> Through the upper abdomen <b>(B)</b> At a lower level.	<b>107</b>
<b>Fig 38</b>	<b>US scan</b> showing a giant, type II liver hydatid cyst with a floating membrane appearance	<b>111</b>
<b>Fig 39</b>	<b>CT scan of hydatid cyst. (A) Plain CT</b> showing multiple liver and splenic hydatid cysts. <b>(B) Enhanced CT</b> showing enhancement of the cyst wall and septa of Type II hydatid cyst	<b>111</b>
<b>Fig 40</b>	<b>CT scans of liver abscess. (A) CT scan of 6-year girl</b> with pyogenic liver abscess (arrows). <b>(B) CT scan of 9-year boy</b> with cat scratch fever	<b>115</b>
<b>Fig 41</b>	<b>CT scans of NRH</b> illustrate multiple hypodense nodules during arterial phase <b>(A)</b> that become isodense during portal venous phase <b>(B)</b>	<b>123</b>
<b>Fig 42</b>	<b>Enhanced CT scan. A)</b> of 15-month girl with <b>Caroli disease</b> , <b>(B)</b> of 15-year boy with <b>choledochal cyst</b>	<b>125</b>
<b>Fig 43</b>	Types of choledochal cyst	<b>126</b>



## **Abbreviations**

AFP	alpha-fetoprotein
APC	adenomatous polyposis coli
CFTR	cystic fibrosis transmembrane conductance regulator
CK19	cytokeratin 19
CML	Chronic myeloid leukemia
CT	computed tomography
DFS	Disease free survival
EFS	event free survival
FAP	familial adenomatosis polypi
FNA	fine needle aspiration
FNH	Focal nodular hyperplasia
G-CSF	Granulocyte colony stimulating factor
HA	Hepatic artery
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCC	hepatocellular carcinoma
HD	hydatid disease
HB	hepatoblastoma
ICAM-1	intercellular adhesion molecule 1
IF- $\alpha$ 2A	interferon- $\alpha$ 2A
IGF2	insulin like growth factor 2
IPA	ifosfamide / cisplatin / doxorubicin
IPT	Inflammatory pseudotumor
IVC	Inferior vena cava
LDH	lactate dehydrogenase
MDCT	multidetector CT
MHL	Mesenchymal hamartoma of the liver
MR	magnetic resonance
MRI	magnetic resonance imaging
NHL	Non Hodgkin Lymphoma
NK	natural killer
NRH	Nodular regenerative hyperplasia
OLT	orthotopic liver transplantation
OS	overall survival
PAS	periodic acid-Schiff
PECAM-1	platelet endothelial cell adhesion molecule 1
PLA	Pyogenic liver abscess
PLS	Papillon-Lefèvre syndrome
PV	portal vein
SGOT	Serum glutamic-oxaloacetic transaminase

SIOP	International Society of Pediatric Oncology
SNPCL	solitary nonparasitic cyst of the liver
TNM	tumor, node, metastases
UES	Undifferentiated embryonal sarcoma
US	Ultrasound
U.S.	United States
VP	ventriculoperitoneal

## **Introduction**

Hepatic masses are increasingly being diagnosed, often as a result of more frequent and sophisticated imaging. Lesions can be detected during screening for primary or metastatic tumors, or as an incidental finding. Although some have distinctive radiological appearances allowing for a confident diagnosis, histological assessment of biopsy and resection specimens remains the cornerstone for the correct identification of many lesions (*Clouston, 2004*). The list of differential diagnosis, when meeting a child suffering from a hepatic mass, is long (table 1). It includes benign and malignant primary tumors, vascular tumors, metastases, cysts and abscesses. When hepatic masses are symptomatic, they most commonly manifest as a palpable mass with abdominal distention. Other signs and symptoms may include pain, anorexia, weight loss, fever, jaundice, and congestive heart failure (*Siegel, 2001*).

There are several benign and malignant processes in the liver, which are different from the normal and diffuse pathological alterations in smaller or bigger forms of hepatic nodules. Some of them are benign alterations having no clinical significance, but they have some difficulties in the differential diagnosis (*Palko, 2004*). In children, **benign** tumors constitute only 30% of liver tumors and most are vascular in origin (*Reynolds, 1999*). There is a remarkable diversity of conditions encompassed by benign liver masses in infants and toddlers. The most common **benign hepatic tumor** in this age group is infantile hepatic hemangio-endothelioma. It has no morphologic counterpart in the adult liver if one allows for the difficulty in the differential diagnosis in some cases with angiosarcoma (*Chandra, 1992*). The differential diagnosis of

benign hepatic tumors includes nonneoplastic cystic masses including biliary and simple hepatic cysts, hematoma, parasitic cysts, and pyogenic and amebic liver abscess (*Meyers and Scaife, 2000*).

***Table (1): Classification of Liver Masses.***

---

Benign liver tumors	Hemangiomas & Hemangioendothelioma Focal nodular hyperplasia Hepatic adenoma & Adenomatosis Mesenchymal hamartomas Lymphangioma & Lymphangiomatosis Nodular regenerative hyperplasia Cystadenoma Teratoma Myxoma
Malignant liver tumors	Hepatoblastoma Hepatocellular carcinoma & fibrolamellar variant Undifferentiated embryonal sarcoma Rhabdoid tumor Rhabdomyosarcoma Angiosarcoma Malignant germ cell tumor Non-Hodgkin's lymphoma Metastases: neuroblastoma, Wilms' tumor, rhabdomyosarcoma, germ cell tumor, lymphoma, leukemia, Langerhans' cell histiocytosis, choriocarcinoma, pancreatoblastoma, carcinoid
Benign bile duct tumors	Granular cell tumor Inflammatory pseudotumor
Malignant bile duct tumors	Cholangiocarcinoma Adenocarcinoma Rhabdomyosarcoma
Non-neoplastic liver masses	Cysts: simple hepatic cyst, peliosis hepatis, parasitic Hydatid cyst Liver abscesses: amebic liver abscess, pyogenic liver abscess Hematoma & biloma Inflammatory pseudotumor

---

*(Stringer, 2000)*

**Primary hepatic neoplasms** in children are relatively infrequent, accounting for between 0.5 and 2.0% of all pediatric neoplasms. They are a diverse group of epithelial and mesenchymal tumors whose incidence can vary considerably with patient age. They are clinically relevant tumors however as two thirds of them are malignant (*Emre and McKenna, 2004*). The liver is one of the most common sites of primary abdominal neoplasm in children. **Hepatoblastoma** (HB) represents up to 85% of primary pediatric liver tumors and is followed in frequency by hepatocellular carcinoma (HCC) and infantile hemangioendothelioma. Pediatric liver masses require accurate characterization and estimation of extent relative to hepatic segmental and vascular anatomy, which have been improved with the use of multidetector CT (MDCT) and MRI. Histologic examination is still needed to characterize some benign liver tumors (*Van Beers et al., 2003*).

**Metastatic hepatic lesions** such as neuroblastoma, Wilms' tumor, and lymphoma are the most common neoplasms seen in the liver. Some distinct primary liver tumors may be seen rarely, including leiomyosarcoma, rhabdoid tumor, and endodermal sinus tumor. But five of the primary hepatic neoplasms--hepatoblastoma, infantile hemangioendothelioma, mesenchymal hamartoma, undifferentiated embryonal sarcoma, and embryonal rhabdomyosarcoma of the biliary tree--commonly occur only in children (*Stocker, 2001*). An important differentiating factor in the evaluation of pediatric hepatic masses is the age of the patient. Hemangioendotheliomas, hepatoblastomas, mesenchymal hamartomas, and metastatic disease from Wilms tumor or neuroblastoma are usually seen in the first 3 years of life, whereas HCC, focal nodular hyperplasia, hepatic adenoma, and metastases from lymphoma are more common in older children (*Siegel, 2001*).

## **Aim of work**

The aim of this essay is to review the various aspects of liver masses in the pediatric age group. We mean to highlight the different types of masses, the most novel methods of their diagnosis and all the options of their management.

## **Chapter 1**

### **Embryology, Anatomy and Histology**

#### **Embryology of the liver**

The liver arises from the hepatic diverticulum of the foregut during the fourth week of gestation (*Severn, 1971 and Couinaud, 1989*). As the embryo develops, the blood supply to this region evolves in an elaborate manner to deliver nutrients from three different sources in the sequence: yolk sac, placenta, and gut (*Strasberg, 1997*). Hepatocyte precursors, the hepatoblasts, arise from endodermal cells at the advancing front of the diverticulum and invade the mesoderm of the caudal portion of the septum transversum. The vitelline veins traverse the region, bringing blood from yolk sac and digestive tube to the heart (Fig. 1). As hepatoblasts invade the mesenchyme, they disrupt the vitelline veins, tapping their blood supply. This supply is from the vitelline veins, segments of which later become the portal vein (PV). The hepatic bud is subdivided into cords by new capillaries called sinusoids. The sinusoidal flow coalesces into three major hepatic veins (*Wanless, 2003*).

At the time the main hepatic veins are developing, the entire liver is composed of only two lobules, and there is no artery and no left or right bile duct. As the hepatic and portal veins (PVs) begin to branch, the branches interdigitate to remain equidistant from each other, and the parenchyma is subdivided into numerous lobules, or acini (*Ekataksin and Wake 1991*). The hepatoblast cords develop into anastomosing tubular structures with central bile canaliculi that eventually communicate with the bile ducts. Most hepatoblasts differentiate into hepatocytes, but those adjacent to the portal mesenchyme differentiate into a layer of duct