Chapter 18

Liver Tumors in Infancy

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1. Introduction

Hepatic tumors in children are relatively rare, accounting for 1 to 4% of all pediatric solid tumors. [1] Primary liver masses constitute the third most common group of solid abdominal tumors of childhood [2] with an incidence of 0.4 to 1.9 per million children each year. [3,4]

Liver masses in children can be malignant, benign, or indeterminate and they are a diverse group of epithelial and mesenchymal tumors whose incidence can vary considerably with patient age. [5] Two thirds of liver tumors in children are malignant. [6] Unlike liver tumors in adults, in which the predominant histology is hepatocellular carcinoma, hepatoblastoma accounts for two thirds of liver tumors in children. [7] Other liver malignancies in children include sarcomas, germ cell tumors, and rhabdoid tumors, as well as the more familiar hepatocellular carcinoma. Benign tumors of the liver in children include vascular tumors, hamartomas, adenomas, and focal nodular hyperplasia. The histology and anatomy of a pediatric liver tumor guides the treatment and prognosis. [8]

In this chapter we outline the epidemiology, etiology, pathology, clinical presentation, diagnosis and management of each of the most important types of liver tumor. Also aspects of the surgical anatomy and resection techniques and other ways to improve ressecability in liver tumors in childhood will be described such as portal vein thrombosis, chemotherapy and transarterial chemoembolization (TACE).

2. Epidemiology

The incidence of hepatic tumors in childhood is consistently quoted from many series as being in the region of 0.5-2.5 per million population [9] and approximately 100–150 new cases

of liver tumors are diagnosed in the U.S. annually. [7] Two thirds of liver tumors in children are malignant. [6] acounting for slightly more than 1% of all pediatric malignancies and among those there is a male preponderance of 1.8 : 1. [7,10]

Hepatoblastoma presents in a younger age group, being a uncommon diagnosis over the age of 4 years. Hepatocellular carcinoma has its peak onset in early adolescence, although the range is wide. The older age at onset for hepatocarcinoma may well reflect its close association with other underlying disease processes. [10]

There are several suggestions that the incidence of malignant liver tumors is increasing in the U.S. Surveillance, Epidemiology, and End Results data from 1972–1992 showed a 5% annual increase. [7] Liver cancer represented 2% of all malignancies in infants in the early 1980s with the incidence doubling to 4% 10 years later. [11]

At a population level, there has been a dramatic increase in survival in countries in which a modern health system has been implemented, although the increased survival is lower for hepatocarcinoma in comparison with hepatoblastomas. [10] According to Litten & Tomlinson [8], it has been suggested that the improvements in technology, care, and outcomes for premature infants have been driving forces in the increase of the incidence in hepatic tumors. Hepatoblastoma is more commonly diagnosed in children with a history of prematurity than in full-term infants. Interestingly, those tumors that arise in ex-premature infants do not present at a younger age than those of term infants. [8]

3. Hepatoblastoma

Hepatoblastoma is the most common malignant tumor of the liver in children and is an embryonal tumor in the classic sense of incomplete differentiation; [12] accounts for 1% of all pediatric malignancies and for 79% of all liver cancers in children under age. [13] Its overall incidence is 0.5–1.5 per million, however the incidence in children under the age of 18 months is 11.2 cases per million. [14]

Hepatoblastoma is diagnosed in very young children with a peak in the newborn period reflecting those tumors that developed prenatally, and an overall median age at diagnosis of 18 months; 90 percent of cases are manifest by the fourth birthday, several have been present at birth, and there is an hypothesized association with prematurity. [15] Only 5% of new hepatoblastoma cases are diagnosed in children >4 years of age. [8]

The increased incidence of HB in children born before 28 weeks gestation (with birth weight <1500 g) compared with term gestations, may be explained by the exposure of rapidly dividing hepatoblasts to endogenous metabolites and hormones as well as exogenous chemicals that would normally be eliminated via the placenta. Inefficiency and compromise of the immature detoxification mechanisms could produce multiple somatic mutations and epigenetic (ie, methylation) modifications of the genome. [16, 17]

For poorly understood reasons, hepatoblastoma occurs in males significantly more frequently than it does in females with a male:female ratio that ranges from 1.2 to 3.6:1. [14] Most

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commonly, these tumors present in the right lobe of the liver. [18] There is an increased incidence of hepatoblastoma in Beckwith-Wiedemann Syndrome, which has a relative risk of 2280 suggesting a role for genetic aberrations of chromosome 11 in the pathogenesis of hepatoblastoma,[19, 20] hemihypertrophy, and familial adenomatous polyposis (FAP) witch has a relative risk of 1220 suggesting a role for aberrations of chromosome 5 in the pathogenesis. [21] Screening for cases in FAP kindred families is recommended by testing for germline mutations in the APC tumor suppressor gene. [22, 23] Inactivation of the APC tumor-suppressor gene (found on chromosome 5) is found in 67–89% of sporadic hepatoblastoma [24, 25] This gene is known to regulate B-catenin and modulate the wnt signaling pathway, suggesting a role for this signaling pathway in the development of hepatoblastoma. [26] Additional biologic markers may include Trisomy 2, 8, and 20 and translocation of the NOTCH2 gene on chromosome 1. [27]

Many etiological factors have been linked with the development of malignant hepatic tumors in childhood (Table 1). Broadly speaking, genetic influences are particularly important in the development of hepatoblastoma, whereas environmental factors and coexisting liver disease are strongly associated with hepatocellular carcinoma. [10]

Hepatoblastoma	**Hepatocellular carcinoma**
Beckwith-Wiedemann Syndrome	Hepatitis B
Hemihypertrophy	Hepatitis C
Familial adenomatous polyposis (FAP)	Hereditary tyrosinemia
	α_1-Antitrypsin deficiency
Gardner syndrome	Cirrhosis secondary to biliary atresia
Glycogen storage disease type I	Glycogen storage disease type I
Trisomy 18	Neurofibromatosis
Fetal alcohol syndrome	
Prematurity and low birth weight	Familial adenomatous polyposis
Maternal exposure to:	Drug/toxin exposure:
Oral contraceptives	Androgens
Gonadotropins	Oral contraceptives
Metals	Methotrexate
Petroleum products	Aflatoxins
Paints and pigments	
Paternal exposure to:	Fanconi anemia
Metals	
Meckel diverticulum	

Table 1. Conditions associated with hepatoblastoma and hepatocellular carcinoma.

Hepatoblastomas are composed of cells resembling the developing fetal and embryonic liver, hence the classification as an embryonal tumor. Indeed, the cells comprising hepatoblastoma mark similarly to hepatic stem cells, defined as pluripotent hepatoblasts capable of differentiating into hepatocytes or cholangiocytes. [28, 29]

According to the Childhood Epithelial Liver Tumors – International Criteria (CELTIC) group, the pathology of hepatoblastoma is classified into four groups based on the work of Weinberg and Finegold: fetal, embryonal, macrotrabecular and small-cell undifferentiated. [10]

Histologically, these tumors can be divided into epithelial (56%) or mixed epithelial/ mesenchymal tissue. The epithelial group is further subdivided into fetal (31%), embryonal (19%), macrotrabecular (3%) and small-cell undifferentiated subtypes (3%). Themajority of hepatoblastomas is epithelial and consist of a mixture of embryonal and fetal cell types (Fig. 1). [8, 30]

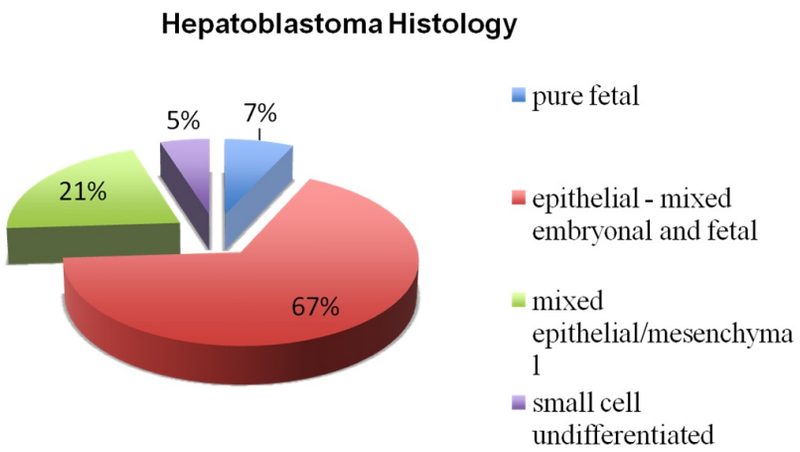

Figure 1. Distribution of histologic subtypes of hepatoblastoma. The majority are epithelial and consist of embryonal and fetal cell types. Pure fetal histology accounts for approximately 7% of hepatoblastomas and is associated with a favorable prognosis. Small cell undifferentiated hepatoblastoma accounts for 5% of hepatoblastoma cases and is associated with a poor prognosis. [8]

Of the five histologic subtypes—pure fetal, embryonal, mixed epithelial, mesenchymal/ macrotrabecular, and small cell undifferentiated—fetal carries the most favorable prognosis. [31] Approximately 5% of hepatoblastomas are of the small cell undifferentiated subtype. This subtype is associated with a worse prognosis. [32] In the mixed epithelial/ mesenchymal type, the presence of mesenchymal elements is associated with improved prognosis and the most common mesenchymal elements are cartilage and osteoid. [33]

Hepatoblastomas usually presents as a palpable asymptomatic mass with abdominal distension. [10] Less common presentations include weight loss, anorexia, emesis and abdominal pain and usually indicate advanced disease. [34] One of the more unusual presenting features of hepatoblastoma is its association with sexual precocity due to the release of human chorionic gonadotropic hormone (β-HCG) by the tumor. Osteoporosis is said to occur in up to 20% of the cases and when severe can lead to bone fractures and vertebral compression. [35] The tumor may rupture spontaneously, producing an acute abdomen and hemoperitoneum. [10]

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