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MINI REVIEW

Hepatic neoplasms in children: A focus on differential diagnosis

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Summary Paediatric hepatic neoplasias are rare, accounting for 1—4% of all solid childhood tumors. Liver tumors in children can be classified into benign or malignant; some of the benign lesions can have the potential of malignant transformation. Two-thirds of liver tumors in children are malignant. Hepatoblastoma accounts for two-thirds of malignant liver tumors in children. Other liver malignancies in children include sarcomas, germ cell and rhabdoid tumours, and hepatocellular carcinoma. Benign tumors of the liver in children include vascular tumours, hamartomas, adenomas, and focal nodular hyperplasia. The histology and anatomy of a paediatric liver tumour guides the treatment and prognosis. Although benign and malignant liver masses share some clinical manifestations, treatment and prognosis differ.

Introduction

Pathologic masses of the liver in children constitute about 5—6% of all intra-abdominal masses and 1—2% of all paediatric tumours. Two-thirds of such masses are malignant, emphasizing the importance of systematic approach to children with a liver mass. The differential diagnostic pathway includes a stepwise approach involving the age and gender of patient, clinical presentation, underlying liver disease, serum alfa-fetoprotein (αFP) level and imaging characteristics [1,2].

Symptoms

Most children with liver masses present with abdominal distension and a palpable abdominal tumour. On occasion,

Abbreviations: AFP, Alfa-fetoprotein; BSEP, Bile salt export pump; CT, Computer tomography; DIC, Disseminated intravascular coagulation; FNH, Focal nodular hyperplasia; HBL, Hepatoblastoma; HCA, Hepatocellular adenoma; HCC, Hepatocellular carcinoma; HNF1a, Hepatocyte nuclear factor 1α; IHE, Infantile haemangioendothelioma; LFABP, Liver fatty acid-binding protein; LTx, Liver transplantation; MRI, Magnetic resonance imaging; NRH, Nodular regenerative hyperplasia; SEER, Surveillance, Epidemiology, and End Results; SIOPEL, International Childhood Liver Tumours Strategy Group; US, Ultrasonography.

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the patients are asymptomatic and the mass is discovered incidentally. Chronic fatigue due to anaemia and lack of appetite are often reported. Occasionally, severe symptoms and complications such as pain, biliary obstruction, inferior vena cava obstruction, dyspnea, feeding intolerance, sudden intra-abdominal haemorrhage due to ruptured tumour, high output heart failure, disseminated intravascular coagulation (DIC) and sepsis can occur.

Diagnostic approach

Liver tumours identified in children include primary benign and malignant neoplasms, inflammatory masses, cysts and metastatic lesions (Table 1).

The most common malignant tumours are hepatoblastoma (HBL) and hepatocellular carcinoma (HCC). Infantile haemangioendothelioma (IHE) and focal nodular hyperplasia (FNH) are also seen in children [2]. Although benign and malignant liver masses share some clinical manifestations, treatment and prognosis differ.

In addition to patient age, characteristic symptoms and serum AFP level, different imaging techniques are critical to delineate the appearances and spread of the tumour, and guide follow-up after treatment. Standard diagnostic techniques are ultrasonography (US) and magnetic resonance imaging (MRI), but contrast computerised tomography (CT) is still the most informative technique at presentation. US is the recommended technique for follow-up. A recent study suggests that contrast enhanced ultrasound (CEUS) is safe and useful in demonstrating the benign nature of focal liver lesions that are indeterminate on grey-scale sonography in children, potentially reducing the use of CT and MR imaging [3].

CT and MRI are instrumental in evaluating intra- and extra-hepatic extent of disease. Positron-emission tomography (PET) CT offers a greater sensitivity for residual and relapsed disease and may facilitate surgery [4]. T1/T2-weigthted MRI can further improve diagnosis by defining features such as density, vascularity, stromal component and intra-lesional necrosis and haemorrhage [5]. On average, diagnosis is possible on radiological findings alone in 58% of cases, while in remainder histology is necessary [6].

Table 1 Benign and malignant liver masses.

Benign
Infantile haemangioendothelioma (IHE)
Mesenchymal hamartoma
Focal nodular hyperplasia (FNH)
Hepatocellular adenoma
Nodular regenerative hyperplasia
Primary hepatic teratoma
Others: non-neoplastic cystic masses: including biliary, simple, parasitic, pyogenic and amebic hepatic cysts and abscess
Haematomas
Lymphangioma
Infarction
Cystadenoma (biliary duct cell in origin)
Vascular malformations
Polyarteritis nodosa
Granuloma
Malignant
Hepatoblastoma
Hepatocellular carcinoma
Embryonal sarcoma (undifferentiated)
Epitheloid haemangioendothelioma
Angiosarcoma
Embryonal rhabdomyosarcoma
Metastatic lesions

Infantile haemangioendothelioma

Infantile hepatic haemangioendothelioma is the most common benign liver tumour in children with a peak presentation between 3—6 months of age. Many of these lesions are discovered antenatally. Clinical features at presentation may include abdominal distension, vomiting, hepatomegaly, congestive heart failure, anaemia, thrombocytopenia and consumptive coagulopathy and occasionally skin haemangiomata. Thyroid hormone catabolism by the tumour can cause clinical hypothyroidism [7]. Jaundice may be present if there is biliary obstruction or due to the presence of arteriovenous or portohepatic shunts inside the tumour.

Histologic studies suggest that two different histologic subtypes can be distinguished. Type 1 is an orderly proliferation of small blood vessels lined by a single layer of plump endotheial cells. This type is histologically benign, with a pattern identical to that of the cutaneous haemangiomas, whereas type 2 haemangioendothelioma is more aggressive in appearance with irregular budding and branching structures, larger endothelial cells, and mitotic figures, considered histologically equivalent to angiosarcoma with more uncertain long-term prognosis [8].

Medical treatment options include corticosteroids, vincristine, and propranolol (2 mg/kg/d), which has recently become the first-line treatment [7]. Treatment with interferon-alpha seems to have become obsolete due to reported development of spastic diplegia in some of the treated infants [9].

Focal nodular hyperplasia, nodular regenerative hyperplasia and hepatocellular adenomas

FNH and hepatocellular adenoma (HCA) are extremely rare during childhood. FNH is considered to be an unspecified hyperplastic reaction to different vascular abnormalities. On histology, there is a nodular proliferation of normally differentiated hepatocytes around a central fibrovascular scar. Bile ductular reaction is usually present at the interface between hepatocytes and fibrous bands, which facilitates distinction from HCA.

One third of children with FNH show symptoms. Two-thirds of the patients with tumours larger than 7 cm are symptomatic. The most frequent symptom is abdominal