

Hepatoblastoma¹

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Abstract

Hepatoblastoma (HB) is a rare tumour but represents the commonest primary malignant tumour of the liver in childhood. It accounts for about 1% of all childhood tumours with an annual incidence of 1.5 cases per million children younger than 15 years. The onset of HB occurs at a median age of 18-24 months. Serum alpha-fetoprotein levels are frequently elevated. Main symptoms are palpable hepatic mass and abdominal pain. Systemic symptoms are rare. HB might be associated with [Beckwith-Wiedemann syndrome](#) and [familial adenomatous polyposis](#). Treatment of HB combines cisplatin-based chemotherapy and surgery. In Europe, HB is typically treated with preoperative chemotherapy, followed by tumour resection and a short course of postoperative chemotherapy, whereas primary surgery followed by adjuvant chemotherapy is the recommended treatment strategy in the United States.

Keywords

Hepatoblastoma, primary epithelial liver tumour, serum alpha-fetoprotein, cisplatin-based chemotherapy

Disease name

Hepatoblastoma (HB).

Definition

Hepatoblastoma (HB) is a rare tumour but it represents the commonest primary malignant epithelial liver tumour in children with a median age at presentation ranging from 18 to 24 months.

Differential diagnosis

Differential diagnosis involves all kinds of liver masses, including other malignant masses (*i.e.*

undifferentiated sarcoma, [rhabdomyosarcoma](#), [teratoma](#), malignant mesenchymoma

hepatocellular carcinoma) or benign ones (*i.e.* hemangioma, hemangioendothelioma, focal nodular hyperplasia, hepatic cysts: post-traumatic, congenital or echinococcal).

Etiology

The etiology of HB is unknown. HB might be associated with certain congenital syndromes like [Beckwith-Wiedemann syndrome](#), hemihypertrophy (Elliot *et al*, 1994) and [familial adenomatous polyposis](#) (Kingston *et al*, 1983).

The association between prematurity and HB development has been constantly reported (Von Behren, 2004).

Clinical description

The most common presenting symptom is an asymptomatic palpable abdominal mass discovered accidentally in an otherwise healthy baby. Systemic symptoms such as fever, weight loss are rare and usually associated with more advanced cases. The tumour can be unifocal or multifocal. HB is commonly associated with elevated alpha-fetoprotein levels (AFP). HB may be also associated with increased platelet count and, rarely, with elevated beta-chorionic gonadotrophine (β -HCG) serum level, which in males may cause a pseudo-precocious puberty.

Diagnostic methods

Diagnosis is mainly based on imaging. Initial step usually consists of abdominal ultrasonography, which is of great value for children due to its wide availability and non-invasive nature. It not only allows to make primary diagnosis but also to assess intrahepatic tumour extent.

Other standard investigations include:

- Contrast enhanced computed tomography (CT) of the abdomen or magnetic resonance imaging (MRI).
- X-Ray and/or CT of the chest to rule out eventual pulmonary metastases.
- Serum AFP and β -HCG levels.
- Platelet count since thrombocytosis is commonly found in HB

The final diagnosis however relies on tumour biopsy. In selected cases – young children with an elevated AFP and with a hepatic mass – ones can rely on clinical findings. However, in differential diagnosis of HB, rare hepatocellular carcinoma occurring in very young children can only be ruled out histologically.

Epidemiology

Primary epithelial liver tumors in children are relatively uncommon – they constitute about 1-1,5% of all pediatric neoplasm. The annual incidence of HB is of about 1.5 cases per million children aged less than 15 years. No significant geographic variation in the overall incidence of HB exists throughout the world. The median age at presentation is about 24 months with no sex prevalence. Congenital cases have been reported.

Management

Management of HB is pretty standard and the only area of controversy between American and European study groups (named SIOPEL group) remains on the timing of primary surgery. In every case, the SIOPEL and the German HB

groups recommend preoperative chemotherapy, which is followed by delayed tumour resection and a short course of postoperative chemotherapy (Fuchs *et al*, 2002a; Perilongo *et al*, 2000 & 2004; Pritchard *et al*, 2000; Shafford and Pritchard, 1994). Differently, the American Intergroup recommends whenever possible (about 50% of patients) primary surgery at diagnosis followed by postoperative chemotherapy (Ortega *et al*, 2000; Finegold, 2002). All major international groups adopt a cisplatin-based chemotherapy. The chemotherapy golden standard in Europe is represented by the combination of cisplatin and doxorubicin, which has been popularized by the SIOPEL group with the acronymus of PLADO. The American centers use the combination cisplatin, vincristine and 5-fluorouracil. Recent review of world experience has found that total hepatectomy followed by liver transplantation is a very good option for locally advanced, unresectable HB, which have shown a response to chemotherapy (Otte *et al*, 2004).

Treatment results for HB patients presenting with metastases and/or with a tumor extensively involving the entire liver and/or with evidence of intra-abdominal extra-hepatic disease (defined by the SIOPEL group as high risk HB) remain significantly inferior to those obtained in HB cases with tumor completely confined to the liver and involving at the most three hepatic sectors (called standard risk HB –Brown *et al*, 2000; Fuchs *et al*, 2002b). In SIOPEL studies, the 3-year overall survival of these two groups of HB is 50% and 90%, respectively (Perilongo *et al*, 2004). HB presenting with a normal or low AFP (< 100 ng/mL) have an unfavorable outcome.

Unresolved questions

The treatment of HB children presenting with metastases or with a low AFP at diagnosis remains a major clinical challenge. While waiting for innovative therapies to become available, the different study groups currently address this issue by using more intensively platinum-derived drugs, which seem to be the most effective agents for HB (Katzenstein *et al*, 2002, Perilongo *et al*, 2004).

HB patients presenting with a locally advanced disease not amenable to standard partial hepatectomies remain another major clinical challenge. However, it is expected that chemotherapy intensification and better use of orthotopic liver transplantation will significantly improve the outcome of these children.

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