Hepatocellular Carcinoma in Children

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KEYWORDS

• Hepatocellular • Carcinoma • Pediatrics • Epidemiology • Histopathology • Transplant • Outcome

KEY POINTS

- The spectrum of background liver disease predisposing to hepatocellular carcinoma (HCC) in children is different from that in adults.
- In children younger than 5 years the differential diagnosis of hepatoblastoma (HB) should be considered.
- The fibrolamellar variant preferentially affects teenagers and young adults.

HEPATOCELLULAR CARCINOMA IN CHILDREN

Liver tumors are relatively rare in childhood, but may be associated with a range of diagnostic, genetic, therapeutic, and surgical challenges sufficient to tax even the most experienced clinician. This article outlines the epidemiology, etiology, pathology, initial workup, and management of HCC in children and adolescents.

Epidemiology

Primary pediatric liver malignancies comprise 1% to 2% of all pediatric tumors. HB is the commonest primary hepatic malignancy (48%); HCC is the second most common primary liver malignancy of childhood (27%) with vascular tumors and sarcomas making up the rest.[1] HCC has an incidence of 0.3 to 0.45 cases per million per year (23%) and represents an increasingly common indication for liver transplant (LT) in children. Although HCC is more common in adolescents (10–14 years), histologically

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confirmed HCC has been reported in children younger than 5 years. HCC is more common in males than in females with 3:1 preponderance and tends to present with more advanced disease in children than in adults. Childhood HCC incidence increases significantly with age; however, it has remained stable over the past few decades. Data collected from the West Midlands Regional Children's Tumour Registry[2] have indicated the incidence of liver tumors to be 1.2 per million person-years: the incidence of HCC was 0.09, somewhat lower than that reported in published series.

Cause

HCC is primarily an adult-onset disease, with only 0.5% to 1% of cases occurring before the age of 20 years. Many etiologic factors worldwide have been linked with the development of HCC including cirrhosis (due to various causes including alcohol intake), hepatitis B and C, and ingestion of aflatoxins in contaminated food. These factors produce significant geographic variation, with HCC being most common in sub-Saharan Africa and southeast Asia, where its incidence may reach 90 to 100 per 100,000 population largely as a result of hepatitis B virus (HBV) infection. There is a strong link between HCC and infection with the HBV. The incidence of HCC in chronic HBV carriers is approximately100-fold greater than that in the HBV-negative population[3] and is commoner in areas with high endemic HBV infection rates. Chen and colleagues[4] reported 100% positivity for HBV infection in Taiwan, and Chan and colleagues[5] reported 64% positivity in children with HCC in Hong Kong. Although integration of the HBV genome into the HCC genome can be demonstrated at the molecular level,[6] this event in itself is not necessarily oncogenic and a secondary, as yet unidentified, promoter is probably necessary for the development of tumor.[7] This secondary promoter could be environmental influences or genetic variations. The decrease of HBV because of neonatal vaccination has led to a reduction of cases in childhood, which will, in time, be reflected in the adult population.[8] Although hepatitis C is a known risk factor for HCC in adults, it is rare in children and there is only a single case report of this occurrence requiring transplant.[9]

Tyrosinemia I (fumarylacetoacetate hydrolase deficiency) is an autosomal recessive inborn error of tyrosine metabolism that produces liver failure in infancy or chronic liver disease with cirrhosis. Before therapy, there was a high risk of HCC in childhood or early adolescence. The development of therapy with nitisinone (2-[2-nitro-4-(trifluoromethyl)benzoyl] cyclohexane-1,3-dione), which prevents the production of cytotoxic tyrosine metabolites in combination with a tyrosine- and phenylalanine-restricted diet, has transformed the natural history of tyrosinemia and has reduced, but not eliminated the risk of HCC.[10,11] HCC is also associated with glycogen storage disease types 1 and IV.[12]

The link between cirrhosis and HCC is unclear; however, the association of cirrhosis of any origin and dysplastic regenerating nodules have long been considered as precursors of HCC. Only about 30% of pediatric cases of HCC are associated with cirrhosis or preexisting liver abnormality, in contrast to adult HCC in which cirrhosis is present in 70% to 90%. Similarly, alpha-1-antitrypsin deficiency exhibits a different mechanism for carcinogenesis, where liver injury results from abnormal and chronic regenerative signaling from the sick cells to younger less-sick hepatocytes: chronic regeneration in the presence of tissue injury leading to adenomas and ultimately to carcinomas. It is suggested that the latter mechanism may explain hepatocarcinogenesis in other chronic liver diseases, that is, genetic disorders, viral hepatitis or nonalcoholic steatohepatitis, and glycogen storage disease type III. It has been recently suggested that progressive familial intrahepatic cholestasis type 2 (PFIC 2), associated with a mutation of the ABCB11 gene resulting in deficiency of bile salt