Letter to the Editor

Pediatric Hepatocellular Carcinoma: Metabolic Causes and Possible Prevention

Hakim Rahmoune[1,2*], Nada Boutrid[1,2], Mounira Amrane[2] and Belkacem Bioud[1,2]

[1]*Department of Pediatrics, University Hospital of Setif, Setif-1 University, Algeria;*
[2]*Genetic, Cardiovascular & Nutritional Diseases Laboratory, Setif-1 University, Algeria*

Dear Editor,

Hepatocellular carcinoma is a devastating malignancy in childhood. We highlight some specific aspects in the pediatric population, especially involving metabolic diseases like tyrosinemia type 1.

Pediatric hepatocellular carcinoma is the second most common malignant liver cancer and differs from the adult form in its etiologies, biological behavior, and low frequency of cirrhosis.[1,2] The main pediatric causes of hepatocellular carcinoma are hepatitis B virus infection and genetic/metabolic disorders, such as hepatorenal tyrosinemia, familial progressive intrahepatic cholestasis, glycogen storage diseases, and Alagille's syndrome.[2]

The age that hepatocellular carcinoma typically affects children is 10–14 years (median), and it is often metastatic or locally advanced at diagnosis. However, due to mass immunization against hepatitis B virus, the epidemiologic and clinical profiles of pediatric hepatocellular carcinoma are shifting; younger patients with congenital and metabolic liver disease now make up the major portion of patients with hepatocellular carcinoma.[3] Thus, management of any predisposing liver disease is highly recommended for preventing and detecting hepatocellular carcinoma.[2,4]

Currently, the most important metabolic disorder leading to hepatocellular carcinoma is tyrosinemia type I (hepatorenal tyrosinemia), an autosomal recessive condition resulting in hepatic failure with renal and neurological comorbidities and long-term risks for hepatic carcinoma.[5] In fact, due to the enzyme deficiency (fumarylacetoacetate hydrolase deficiency) in hepatorenal tyrosinemia, the substrate fumarylacetoacetate accumulates. This accumulating fumarylacetoacetate and its precursor, maleylacetoacetate, is mutagenic and causes chromosomal instability, cell cycle arrest, and apoptosis, leading first to liver cirrhosis and later on to hepatocellular carcinoma.[6] The molecular basis of the pathogenic liver process in hepatorenal tyrosinemia is still unclear. Multiple signaling pathways involved in cell proliferation, differentiation, and cancer have been found to be rapidly deregulated in hepatorenal tyrosinemia-model mice. The p21 and mTOR pathways, critical regulators of proliferation and tumorigenesis, have also been found to be dysregulated.[7]

Interestingly, an effective medical treatment with 2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione exists.[5–7] 2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione prevents the development of hepatocellular carcinoma when started early but fails to stop this malignancy if prescribed at a later stage, stressing the importance of a prompt diagnosis and management of hepatorenal tyrosinemia.[8] Prior to the availability of 2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione for the treatment of hepatorenal tyrosinemia, the only definitive therapy of liver damage was transplantation. Nowadays, hepatic grafting is reserved for hepatorenal tyrosinemia pediatric cases with severe liver failure who fail to respond to 2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione therapy or those with documented evidence of malignant changes.[9–10]

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptualization (HR, MA), writing the original draft (HR, NB), review and editing (HR, BN, BB).

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[*]**Correspondence to:** Hakim Rahmoune, Department of Pediatrics, University Hospital of Setif, Setif-1 University, 19000, Setif, Algeria. E-mail: rahmounehakim@gmail.com
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