Review

Wilson Disease and Hepatocellular Carcinoma

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Until recently, the association between Wilson disease (WD) and hepatocellular carcinoma (HCC) has been controversial. Early study showed that the incidence of HCC in patients with WD was not statistically higher than that in the general population.[1] Based on animal studies and observed rare events of HCC that developed in patients with WD, it was thought that excessive copper might have a protective effect on hepatocarcinogenesis.[2-4] However, newly emerging clinical and experimental data indicate that WD is a risk factor for HCC.[2,4-22]

WD is a rare autosomal recessive metabolic disorder with an incidence of 1:40,000.[23] To date, more than 20 cases of HCC have been reported in the setting of WD.[2,4-22] Nearly all these cases were identified in relatively young patients (mean age, 40 years) with classical presentations of WD: hepatic, neurologic, or ophthalmologic manifestations, or combinations of these manifestations. The vast majority of classic WD cases (80%) were diagnosed during the first decade of life, and the patients were treated with chelating agents or died early in life before the development of HCC, which requires an average of 18 years.[1,2,4-22] As a result, the previously low incidence of HCC that was observed in this group of young patients with classical WD may be biased.

It is well known that there is a high variability in clinical and pathologic presentations of WD, most likely related to the heterogeneity of the genetic abnormalities.[1,23-25] More than 300 distinct mutations have been identified since the gene for WD was first reported in 1993. The implicated gene encodes a transporting P-type ATPase (ATP7B).[1,23,26] Specific mutations may affect individual processes of copper sensing, copper-mediated trafficking, and copper transport, contributing to the diverse clinical manifestations of WD.[27] Mutations associated with severe impairment of copper metabolism result in grave liver disease early in life. Minor mutations may explain late onset of the disease (at 50–60 years of age), atypical clinical presentation (only hepatic or neurologic manifestations), and slow progression of the disease. These atypical cases of WD have been reported in approximately 10–15% of patients,[1,15] and some researchers have postulated that at least 50% of patients may have either atypical presentations or remain undetected for life. These patients may have normal ceruloplasmin levels, normal copper urine excretion, and normal liver function tests. Even in patients with symptomatic liver disease, liver biopsies may produce deceptively low yields for the diagnosis of WD, as histologic abnormalities may be nonspecific or may mimic other hepatic disorders such as acute hepatitis or chronic active hepatitis with or without cirrhosis.[1,18,24] Hence, atypical cases of hepatic WD may be arbitrarily classified as cryptogenic hepatitis/cirrhosis, unless a clinician diligently examines them for the possibility of WD. Patients with atypical WD are the ones diagnosed and treated with chelating agents later in life, and some patients may never be treated. As a result, they are prone to neoplastic transformation resulting from persistent direct or indirect liver injury.[1,5,24] The case described by Dr. Reyes[28] and a previously reported case are two significant examples of HCC developed under such circumstances. In the case reported by Dr. Reyes, HCC was detected by fine-needle aspiration biopsy in a 59-year-old man who had never been suspected of WD. Subsequent examinations supported the diagnosis of WD based on strong family history, histologic findings, and laboratory results. In a previously reported case of a 29-year-old man who underwent liver transplantation for cryptogenic cirrhosis, the diagnosis of WD was considered only after careful histologic examination and confirmatory quantitative liver copper analysis.[5] Therefore, the incidence of HCC in patients with atypical WD is underestimated.

The hypothetical protective effect of copper that was postulated in early reports has recently been refuted by several animal and in vitro studies. In the Long-Evans-Cinnamon rat model of human WD, a long and persistently elevated hepatic copper level resulted in the development of HCC in aged animals.[29] Copper chelation at an early disease stage in these animal models showed that neoplastic transformation of the liver could be prevented by timely treatment.[30,31] These findings suggested that copper overload is a risk factor for HCC and that chelation of copper may reduce the incidence of HCC associated with WD. The results may also explain the rarity of HCC occurring in patients with typical WD who receive early chelation therapy.

On the other hand, clinical and experimental evidence does not necessarily indicate a causative relationship

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between copper overload and HCC. The mechanism of tumorigenesis in hepatic WD is complicated and may be multifactorial.[10,11,13] Copper overload plays a critical role in the initial liver injury that eventually leads to chronic inflammation and cirrhosis; however, its direct oncogenic potential requires further investigation. It is believed that cirrhosis as a continuous process of degeneration-regeneration leads to neoplastic transformation in hepatic WD via a mechanism of tumorigenesis similar to that of other etiologies (eg, viral, alcoholism).[5,11,32] Supportive evidence comes from the fact that virtually all reported cases of HCC associated with WD developed in the setting of well-established cirrhosis.[2,4-22]

Prevention of HCC in patients with WD relies on early diagnosis and early intervention to avoid persistent liver damage. For those patients with cryptogenic cirrhosis and HCC, atypical WD should be included as a differential diagnosis.[1,32] The treatment of HCC associated with WD is no different from HCC treatment associated with other etiologies; resection, transplantation, and chemoembolization are among the treatments of choice.[5,7,8,25,33,34]

References

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