Does delta infection play a part in the pathogenesis of hepatitis B virus related hepatocellular carcinoma?

The delta (δ) agent is a defective RNA viral agent which requires helper functions from the hepatitis B virus for its replication and transmission. The agent plays an important part in the pathogenesis of severe acute hepatitis and chronic active hepatitis (and perhaps cirrhosis) in people who have or have had hepatitis B infection. Because about 80% of cases of hepatocellular carcinoma world wide are related to hepatitis B virus and in most there is coexisting cirrhosis, we investigated the possible role of coinfection with the δ agent in these patients.

Patients, methods, and results

Serum from the following groups was examined for δ antigen and anti-δ:

107 South African blacks who were positive for hepatitis B surface antigen (HBsAg) and had hepatocellular carcinoma; 144 black carriers of HBsAg; and 17 multiply transfused renal transplant recipients who were positive for HBsAg. The examinations, using radioimmunoassay, were performed in the laboratory of Dr M Rizzato in Turin, Italy. The patients with cancer were aged 13-74 years (mean 38 years); there were 101 men and six women. Of the chronic HBsAg carriers 137 were asymptomatic and seven were known to have cirrhosis or chronic active hepatitis. They were aged 3-57 years; there were 132 men and 12 women.

HBsAg, anti-HBs, antibody to the core antigen (anti-HBc), e antigen (HBeAg), and antibody to the e antigen (anti-HBe) were measured by radioimmunoassay (Austria II, Ausab, Corab, and HB/anti-HBe, respectively, Abbott Laboratories).

Liver and tumour tissue from a further 80 patients with hepatocellular carcinoma was examined for δ antigen by the direct immunoperoxidase technique using a peroxidase conjugated anti-δ antibody. Serum samples were also taken from 55 of these patients. The mean age of the 80 patients was 53-2 years (range 12-81 years) and there were 66 men and 14 women. In all of these patients we performed histochemical staining of the tissues to locate HBsAg.

Serum studies—The serum of all of the 107 patients with hepatocellular carcinoma was positive for HBsAg and anti-HBc; HBeAg was present in 34 and anti-HBe in 66. HBsAg was detected in 19 (13%) of the chronic HBsAg carriers and in 15 (88%) of the transplant recipients. Neither δ antigen nor anti-δ was detected in the serum of any of the patients with hepatocellular carcinoma, the chronic carriers of HBsAg, or the renal transplant recipients.

Tissue studies—HBsAg and anti-HBc were present in the serum of 19 of the 55 patients with hepatocellular carcinoma in whom both tissue and serum were studied. Three of these patients were positive for HBeAg and 15 for anti-HBe. A further three patients were positive for anti-HBc in the absence of HBsAg and anti-HBc. Anti-HBs with or without anti-HBc was present in 24 patients and anti-HBe in six of these. Six patients had no markers of hepatitis B infection. Of the 19 patients with HBsAg antigenic tissue HBsAg was detected in 14. One patient with anti-HBe and anti-HBc alone was positive for tissue HBsAg. Of the 25 patients in whom tissue alone was studied six showed HBsAg. In all, 26 patients showed either serological or tissue evidence of HBsAg and one further patient had anti-HBe alone in the serum. δ Antigen could not be shown in either non-neoplastic liver tissue or in tumour tissue in any of the patients.

Comment

δ infection does not play a part in the pathogenesis of hepatocellular carcinoma in South African blacks. Serological evidence of δ infection was not found in a substantial number of chronic carriers of HBsAg who lived in several areas of South Africa, and thus the agent could not be expected to have a causal role in chronic liver disease, including hepatocellular carcinoma, in this region. We cannot, of course, exclude the possibility that the δ agent has a pathogenic role in the hepatocarcinoma that occurs in other populations with a high prevalence of infection with this agent. Nevertheless, δ antigen was shown immunohistochemically in only 14% of HBsAg positive Greek patients with hepatocellular carcinoma (compared with 29% of patients with HBsAg positive chronic active hepatitis and 28% of those with HBsAg positive cirrhosis) and infrequently in Italian and North American patients.

This work was supported in part by grants from the National Cancer Association of South Africa and the South African Chamber of Mines. We thank Drs Mario Rizzato and Antonio Bonino for performing tests for δ antigen and anti-δ in patients’ serum.


(Accepted 9 March 1984)

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