Leading article

The delta agent comes of age

The delta agent is an RNA virus which replicates in patients with acute and chronic hepatitis B virus infection. The delta antigen is associated with the RNA genome of the virus, and is coated in HBs antigen. It was first described in the nuclei of the hepatocytes of a patient with chronic HBV infection by Mario Rizzetto in a paper published in 1977, in *Gut.*

The antigen evokes a systemic immune response initially of IgM and subsequently of IgG class. The acute infection can in some cases be diagnosed by the demonstration of the delta antigen in the serum, after cleavage of the hepatitis B surface antigen coat from the virus particles.

The most convenient diagnostic techniques in this group of patients, however, are now the immunoassays for IgM anti-delta. During the chronic infection, the delta antigen can be readily shown in unfixed and fixed liver tissue by direct immunofluorescence and immunoperoxidase techniques. Once again, chronic delta replication is usually associated with the presence of IgM anti-delta in the serum, and is closely connected with delta antigen in the liver. The recent preparation of cDNA probes has allowed the detection of the delta RNA in serum and has established a close association with this and the presence of delta antigen in the liver.

The clinical significance of this incomplete RNA virus, which requires the help of HBV in order to replicate, has now become clear. In this issue of *Gut,* Farci et al have described delta superinfection in children and have noted that it is associated with an increased level of inflammatory activity and necrosis of liver cells and hence with a more rapidly progressive form of HBV related chronic liver disease. The study confirms earlier reports of more rapidly progressive disease in adult HBV carriers superinfected with the delta virus. This superinfection can result in progression from minimal liver disease to cirrhosis in a period of one year. (Submitted). Its impact on the health of chronic HBV carriers is considerable. It was first described in patients from Southern Italy, but it has now become clear that it is of widespread distribution. In HBV carriers, the prevalence of this superinfection varies from less than 0.5% to 65% in some areas of North-Western Kenya. (Submitted).

Most adult patients infected with the delta agent will be anti-HBe positive. This serological picture is associated with either no, or little, HBV replication and indicates a state of relatively low HBV infectivity. As the delta virus can only replicate in the presence of acute or chronic HBV infection and because most delta superinfected carriers are of low HBV infectivity, it is rare for these patients to pass on the infection to normal non-HBV infected individuals. The delta agent, however, is highly infectious to patients, or chimpanzees, who are already HBs antigen carriers. In carrier chimpanzees a $10^{-12}$ dilution of delta positive serum is still infectious. For this reason, delta infection may spread...
rapidly through a family, or community with a high prevalence of chronic HBV infection.\textsuperscript{14}

Why then is delta superinfection rarely seen in Japanese and Chinese communities where 10\% of subjects are HBV carriers\textsuperscript{12} and in western European homosexual carriers who are highly promiscuous.\textsuperscript{11} It seems probable that the association of delta superinfection with low level HBV replication (anti-HBe positivity) is not always because of the inhibitory effect of delta on HBV replication, but may reflect a greater susceptibility of anti-HBe carriers to delta superinfection or a resistance of HBe antigen positive HBV carriers to superinfection.

The delta agent has now acquired the status of 'hepatitis D virus' (HDV). Its clinical importance as a cause of rapidly progressing chronic liver disease is established. The genome has been cloned and sequenced and the tools are thus available to monitor attempts at anti-viral therapy.

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\textbf{References}


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*Gut* 1985 26: 1-3
doi: 10.1136/gut.26.1.1

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