Symposium (I): Carrier State and Infectivity of HBs-Ag

Co-moderators: Fumihiro Ichida (Niigata Univ.) and Nakao Ishida (Tohoku Univ.)

(1) Considerations of familial clustering of HBs-Ag carriers from e antigen and antibody system

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It has recently been clarified by Magnius and others that e antigen and antibody system is closely related to HBV infectivity, i.e., HBsAg-positive sera detected e antigen (e-Ag) have an intensive infectivity, and those detected e antibody are no infective.

Therefore, the authors tested e-Ag and e-Ab by the Micro-Ochterony's method in sera from 127 carriers, and, from the data, discussed as to intrafamilial infections with HBV and the clustering of the carriers. The results are as follows.

1. In eleven children of 6 e-Ag-positive carrier mothers, 10 children were positive for HBsAg, and 3 out of 6 children of 2 e-Ag-positive carrier fathers also were HBsAg-positive. Moreover, in one of 3 children living with their e-Ag-positive grandfather, HBsAg was detected in the serum. Accordingly, it can be said that an e-Ag-positive carrier produces new carriers at a high rate in the following generations, and the rate is extremely high in mother-to-child transmission.

2. In 103 asymptomatic carriers, the frequency of e-Ag-positive result was higher in the younger ages (75% in ages of below 10 years and 12% in ages of more than 41 years). On the contrary, the rate of e-Ab-positive carriers was higher in the older ages (17% in ages of below 10 years and 44% in ages of more than 41 years).

This result implies that, in the majority of HBsAg carriers, although there are wide differences in the individuals, HBV infectivity declines with years and finally vanishes.

(2) Clinical studies on infectivity of Hepatitis B virus

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In order to elucidate infectivity of Hepatitis B virus (HBV), transmission pattern of HBsAg in families of asymptomatic HBsAg carrier (Group I: 107 cases in 25 families) and patients with HBsAg positive liver disease (Group II: 174 in 31 families) was investigated. Correlation between eAg system and infectivity of HBV was also studied in HBsAg positive mother-child pairs.

Method employed were I.A.H.A. or RIA for HBsAg and PHA for anti-HBs. eAg and eAb were detected by Micro-Ouchterlony method. The results obtained are as follows:

1) The incidence of HBsAg in Group I and II was 28.0% and 38.5%, and that of anti-HBs was 26.1% and 18%, respectively. HBsAg positive spouses were not found in both groups, but anti-HBs was detected in 45.5% in Group I and 50% in Group II, respectively. Though all, but one, proband's father was negative for HBsAg, incidence of their mother's HBsAg was 25% (4 in 16 cases) and 36.4% (4 in 11 cases), respectively HBsAg positive children of female probands were 3 of 16 cases (18.8%) in Group I and 21 of 25 (84%) in Group II, in contrast to lower incidence of HBsAg positive children from male probands; 1 of 17 (5.9%) and 8 of 29 (27.6%), respectively. The results indicated that familial clustering of HBsAg was found and maternal transmission was dominated in both groups, especially in Group II.

2) In fourteen HBsAg carrier mothers, 2 cases were positive for eAg, 4 were positive for eAb and 8 were negative for both eAg and eAb. Both babies of eAg positive mothers were positive for HBsAg at 1M and 11M after delivery, respectively. Two babies of 4 eAb positive mothers were positive for HBsAg at 1M and 10M after delivery, but other 2 babies were negative for HBsAg. However, all, but one, babies of 8 mothers negative for eAg and

eAb were negative for HBsAg, thus suggesting that eAg and eAb system could be related with infectivity of HBV.

(3) Studies on the infectivity of HBs-Ag carriers with special viewpoint of intrahepatic HBc-Ag and Dane partilce in serum

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Intrafamiliary infection of HBV was surveyed according to the index cases of asymptomatic HBs-Ag carriers (the carriers) and HBs-Ag positive chronic liver diseases (CLD). Forty five index cases of CLD with 154 members of those akins and 28 cases of carriers with 74 family members were examined for serum HBs-Ag (by IAHA method), anti-HBs (by PHA method) and anti-HBc (by IAHA and immunofluorescent method). Index cases further underwent intrahepatic HBc-Ag by immunofluorescent technique, serum e-antigen and antibody by Ouchterlony method and serum Dane particle by IAHA method. HBc-Ag in the liver was detected in carriers as low as 34.4% comparing to 66.0% in CLD. The infectivity in parents and spouses of CLD were 3 times and 2.5 times higher, respectively, than that of carriers. One hundred per cent of spouses were infected from HBc-Ag positive and Dane particle positive carriers, comparing to 37.5% of infectivity in cases negative for both of them. While no significant difference of infectivity to the spouses were observed in CLD on the attitude of HBc-Ag or Dane particle in index cases. The infectivity to the spouses was 100% in e-antigen positive cases of both CLD and carrier groups, while in cases positive for e-antibody it was 83.3% in CLD and only 28.6% in carriers.

These data suggest that the infectivity may be affected by the factors of e-antigen-antibody, Dane particle and intrahepatic HBc-Ag in carriers. And these factors may be rather labile in CLD comparing to that of carriers.

(5) Anti DNA antibody in chronic HBs Ag carriers and its relation to their infectivity

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Anti DNA antibody (ADNA) was observed in two thirds of chronic HBs Ag carriers (the carriers) by passive hemagglutination using calf thymus DNA sensitized sheep red blood cells. The corresponding antigen to ADNA in the carriers was either cellular or viral DNA. If the latter is the case as mentioned by Dr. Overby, the presence of ADNA in the carriers would be a marker of the viral growth and their infectivity.

In order to examine the above mentioned possibility, correlation of ADNA to e Ag and liver function was studied. ADNA could be detected in 62.8% of the carriers, but no correlations to transaminase levels, amount of gamma globulin, or another autoantibodies such as antimitochondrial or anti smooth muscle antibodies were observed. While ADNA could not be detected in HBs Ag negative controls or HBs Ag negative acute hepatitis cases. Thus ADNA in the carriers seemed to be solely related to HBV infection, and not to hepatic cell damage or autoimmune basis. However, ADNA in the carriers did not appear to be related to infectious Dane particle formation, because any correlation between ADNA and e Ag was not observed, viz., the appearance of ADNA or e Ag was just indifferent phenomenon through the examination of 85 sera tested for both ADNA and e Ag. Thus ADNA in the carriers could not be the marker of their infectivity.

I—Special comment

e-antigen in chronic hepatic diseases

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e-antigen and antibody were measured by the method reported by Magnius & Espmak in 69 patients with histologically confirmed chronic hepatitis and 44 patients with liver cirrhosis and

additional group of 33 patients with miscellaneous chronic liver diseases. These patients were followed for averaging one year, periodically examining e-antigen and antibody at about monthly basis. e-antigen was found in 14 patients with chronic hepatitis, 8 had e-antigen alone and 5 also had e-antibody, e-antigenemia showed male preponderance and e-antibody female preponderance. The incidence rate of e-antibody was found to be higher in liver cirrhosis than in chronic hepatitis. The level of serum transaminase activity, presence of fluctuation of the same level, thymol turbidity test and zinc sulfate test as well as clinical course showed no difference in between groups with e-antigenemia and without e-antigenemia. Appearance of e-antigen and antibody in these chronic liver diseases were found to be not constant. The temporal appearance of antigen can not be anticipated from the findings of other clinical parameters studied.

I—Special comment

Transmission of acute type B hepatitis and persistence of HBs antigen —From aspects of intrafamilial infection—

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Out of 102 patients with typical icteric acute type B hepatitis, 47 cases were examined and their family members were studied for HBs antigen, HBs antibody, HBs antigen subtype, e antigen, e antibody and serum transaminase: in 6 cases among 47 index cases, their spouses were also suffered from acute hepatitis B between three and four months; in 5 cases, one of three children had acute hepatitis B at regular interval; in 5 cases, their spouses were HBs antigen chronic carrier who were either chronic hepatitis or asymptomatic carrier and all of them were e antigen positive; in 17 cases, children who were persistent HBs antigen carrier were involved; in the remaining 14 cases, none of their family had the HBs antigen.

Forty seven index cases with acute hepatitis B had HBs antigen who were predominantly subtype adw (adw: adr ratio of 7: 3). In contrast, antigenemic volunteer blood doners and patients with chronic hepatitis had exclusively subtype adr (adr: adw ratio of 8.5: 1.5).

These findings suggest the following explanation. Horizontal infection of type B virus occurs occasionally among family members. The infants whose mother has acute type B hepatitis may be easily infected to hepatitis B virus. The positive ratio of HBs antigen is higher in low age (0 to 3 years old) than in high age (6 to 7 years old). Furthermore, it seems most important that the majority of the former except icteric cases may usually constitute in persistent HBs antigen carrier. While, the close contact with the e antigen positive in HBs antigen chronic carriers may present the risk for transmitting acute hepatitis B, though less than during the incubation period or the early stage of acute hepatitis B. Subsequently, about these differences in acute hepatitis with subtype adw and chronic HBs antigen carrier with subtype adr, it is possible that adw virus might be more virulent than adr or adw infections might be prevalent in Gifu region epidemically.