A NON-A NON-B HEPATITIS EPIDEMIC IN A HB ANTIGEN-FREE HAEMODIALYSIS UNIT. DEMONSTRATION OF SEROLOGICAL MARKERS OF NON-A NON-B VIRUS


*Centre Pasteur-Vallery-Radot, Paris, **INSERM U45, CNRS LP 54.40, Hôpital Edouard Herriot, Lyon, and †Centre National de Transfusion Sanguine, Paris, France

Summary

One hundred and thirty six patients receiving haemodialysis in a HB antigen-free unit were prospectively studied over a period of 29 months for evidence of hepatitis. Twelve/one hundred and eleven patients who were dialysed in this unit for at least one month developed elevation of ALT which proved to be related to neither toxic hepatitis nor hepatitis due to any of the following viruses: hepatitis B virus (HBV), hepatitis A virus (HAV), cytomegalovirus (CMV) or Epstein-Barr virus (EBV). Therefore these cases were considered to be non-A non-B (NANB) hepatitis. In 5 patients the liver disease was of short duration, whereas in 7 others hepatitis had a chronic course with ALT remaining elevated for more than 6 months. During the same period, one/sixty staff members who were working for at least one month in this unit also developed presumed non-A non-B hepatitis. Serological markers of NANB infection tested by double immunodiffusion were present in 10/12 patients and in the one staff member.

Introduction

The discovery of serological markers of hepatitis A and B viruses which can be routinely demonstrated in patients rapidly led to the recognition of a third variety of viral hepatitis commonly known as NANB hepatitis [1,2]. NANB hepatitis accounts for 80 to 90% of post-transfusion hepatitis and is also responsible for a significant proportion of sporadic and epidemic cases. Contrasting with a mild clinical course in its acute phase, NANB hepatitis progresses with high frequency to chronic liver disease [3]. There have been few reports on outbreaks of NANB hepatitis in haemodialysis units [4–8].

Until recently, diagnosis of NANB hepatitis relied solely upon serological exclusion of the other viruses known to cause hepatitis. Shirashi et al [9] were the first to identify by immunodiffusion an antigen-antibody system associated with NANB virus. More recently, two of us [10] demonstrated also by immunodiffusion an antigen-antibody system which proved to be specific and identical to
the one described by Shirashi et al.

The aim of the present study was 1) to establish the prevalence of NANB hepatitis in patients treated in a HB antigen-free haemodialysis unit; 2) to try to detect specific immunological markers of NANB infection in haemodialysed patients with NANB hepatitis.

Material and methods

One hundred and thirty six patients treated in an HBs antigen-free haemodialysis unit from August 1st 1977 (date of the opening of this unit) to December 31st 1979 (date of the end of this study) were prospectively studied for evidence of hepatitis. One hundred and eleven patients were treated for at least one month. Blood samples were obtained bimonthly for determination of ALT and AST by a method derived from the one described by Karmen. Hepatitis was diagnosed when serum ALT exceeded twice the upper limit of normal values (≤ 20 UI/L) in two consecutive determinations. Sera from all patients with hepatitis were tested for HBV, HAV, CMV and EBV markers. HBs antigen, antibodies against HBs, HBC and HAV were tested with Abbott radioimmunoassays. Antibodies against CMV were tested by an immunoabsorbent assay (ELISA technique) and antibodies against EBV by indirect immunofluorescence with determination of antibodies against both VCA and EBNA. Hepatitis was then presumably considered as NANB when 1) treatment with hepatotoxic drugs or other causes of elevation of ALT were excluded 2) when there was no serological evidence of recent infection with either HBV, HAV, CMV or EBV.

Figure 1. Ag : reference antigen. Ab : reference antibody. 1,2,3,4,5 : sera being tested. 1,3,4 : antigen-positive sera
Serological markers of NANB virus(es) were serially assayed in all patients suspected of having NANB hepatitis by double immunodiffusion, using a method already described [10] (Figure 1). A total number of 208 sera were tested with an average number of 16 sera tested per patient (range: 6–25). The time at which the first sample was tested varied from one patient to another, ranging from 5 months beforehand up to the actual onset of the hepatitis. The mean serological follow-up was 19 months (range: 7–23). During the same period, one out of sixty staff members (comprising doctors, nurses, ancillaries and technicians) who were working in the unit for at least one month also developed presumed NANB hepatitis and this member was also serially tested for NANB markers.

Results

According to the criteria defined above, twelve out of one hundred and eleven (11%) patients dialysed in this unit for at least one month as well as one out of sixty (1.7%) staff members who worked in the unit for at least one month developed a non-A non-B hepatitis. There were 6 males and 7 females, with a mean age of 47 years. During the acute phase, NANB hepatitis was poorly symptomatic: only 6 subjects experienced one or more symptoms which were mainly fatigue, anorexia and gastro-intestinal troubles. Hepatomegaly was found in 4 cases. Elevation of ALT was moderate, with a mean peak of 190 UI/L (range: 68–256 UI/L); the highest value was obtained in the staff member. Elevation of AST was also moderate, with a mean peak of 92 UI/L (range: 44–200 UI/L). Concomitant elevation of serum alkaline phosphatase and 5’nucleotidase were observed in 9 patients. Serum bilirubin and prothrombin time were normal in all cases. In no cases was there found any evidence of auto-immune disease. The hepatitis had an acute course and regressed rapidly in 5 patients and in the staff member, ALT returning to normal values within a mean period of time of 2 months. In contrast, 7 patients had a chronic course with protracted elevated ALT; ALT eventually returned to normal values within 8 and 17 months in 2 patients respectively, whereas it still remains elevated 8 to 21 months following the onset of the hepatitis in the remaining 5 patients. Chronic elevation of ALT was always associated with a benign and asymptomatic clinical course.

Serological markers of NANB infection were detected in ten out of twelve patients and in the staff member (Figure 2). They were absent in only 2 patients, who had an acute hepatitis. NANB antigen was detected in 5 cases and was discovered at various times with reference to the onset of hepatitis: from 2 months beforehand up to 13 months after. In 3 cases, the antigenaemia was transient, lasting from 15 to 45 days, then followed by a seroconversion. In the 2 others, antigen is still present respectively 3½ and 4 months after its first detection. In addition, antibodies were detected in 6 cases without prior antigenaemia, at times varying from 1 to 7 months after the onset of hepatitis. Development of antibodies was rapidly followed by the return of ALT to normal values in only 4 cases, whereas in the 5 others, ALT remained elevated for a long period following the appearance of antibodies. In the latter, who were observed over a long period, fluctuations in the detection of antibodies were frequently noticed.

175
Figure 2. Results of detection of serological markers of non-A non-B infection in the 12 haemodialysed patients, and the staff member

Discussion

Over a period of 29 months, NANB occurred in 11% of 111 patients treated for at least one month in a HB antigen-free haemodialysis unit. None of these patients had received potentially hepatotoxic medication; recent infection by either HBV, HAV, CMV or EBV were excluded on serological grounds. The initial phase of the liver disease was characterised by the paucity of the symptoms and the absence of icterus in all patients; elevation of ALT was the only constant abnormal liver function test. Progression to a chronic liver disease, marked by a protracted elevation of ALT, occurred in 54% of the patients. In fact, in 2 patients ALT remained elevated respectively 8 and 17 months before they returned to normal values, and in 5 others it is still elevated at a time ranging from 8 to 21 months after it was first found abnormal. We have not yet made any liver biopsy in our patients because of both the benignity of the clinical picture and the hazards of liver biopsy in the haemodialysed patient.

Five of our patients who developed NANB hepatitis, as well as the staff member, had received no blood transfusions within the 6 months preceding the hepatitis. In contrast, blood transfusions may have been the source of contamination
in the 7 remaining patients. Hepatitis B immune globulin (HBIG) seems efficient in reducing the incidence of NANB hepatitis which developed in only one of 22 patients who had received HBIG during the 9 months following the beginning of haemodialysis, whereas it occurred in five of 10 patients who had not received HBIG during an equivalent period (p < 0.005).

Markers of NANB infection were found in 10 of our 12 patients and in the one affected staff member. The absence of markers in 2 patients may be explained either by the relative lack of sensitivity in the method or by the fact it detects only one virus when 2 different viruses may be implicated in NANB infection [11]. The specific antigen was present in 5 (39%) of our cases. It was only transient in 3 cases, whereas it is still present 3½ to 4 months respectively after its first detection in 2 cases who may become chronic carriers. The specific antibodies were detected with a higher frequency and were present in 9 (69%) of our cases. They appeared after the disappearance of antigen in 3 cases, and without prior anti-genenaemia in 6. The development of antibodies was associated with the recovery from hepatitis in less than half of the cases. The significance of this observation is not yet clear. Fluctuations in antibody detection with time were often observed. They may be explained either by the lack of sensitivity of the method or at times by the presence of immune complexes masking the detectability of antibodies [12].

In conclusion, NANB hepatitis seems to be endemic among patients receiving chronic haemodialysis and does not always follow blood transfusions. Progression to a chronic liver disease is frequent. Its diagnosis may now rely upon the detection of specific markers of NANB virus (or viruses). HBIG seems efficient in reducing the incidence of NANB hepatitis. However, it could be useful to have a specific vaccine at our disposal in the future.

Acknowledgment

This study was supported by a grant from AURA (Association pour l’Utilisation du Rein Artificiel dans la Région Parisienne).

References

1 Hoofnagle JH, Gerety RJ, Tabor E, Feinstone SM, Barker LF, Purcell RH. Ann intern Med 1977;87:14
3 Berman M, Alter HJ, Ishak KG, Purcell RH, Jones EA. Ann intern Med 1979;91:1
5 Coursaget P, Maupas P, Dubois F, Drucker J, Coueau A. Nouv Presse méd 1978;7: 3515
6 Avramid MM, Feinfeld DA, Gan AC. Proc EDTA 1979;16: 141
7 Méry JP, Simon N, Couroué AM. Nouv Presse méd 1979;8: 3973
8 Galbraith RM, Dienstag JL, Purcell RH, Gower PH, Zuckerman AJ, Williams R. Lancet 1979;i: 951
10 Vitvitski L, Trépo C, Prince AM, Brotman B. Lancet 1979;ii: 1263
12 Dienstag JL, Bhan AK, Alter HJ, Feinstone SM, Purcell RH. Lancet 1979;i: 1265
Open Discussion

DE WARDENER (London) We have had this epidemic since 1967 and we are struck by the way it comes and goes. At the present moment I would say that about one quarter of our 140 patients on dialysis have this disease and quite a few of them have it chronically. Have you done any biopsies of the liver on any of your chronic ones? Is your hepatitis B immune serum useful at stopping a chronic hepatitis from continuing?

SIMON We did not perform any liver biopsies in our patients as the course of the disease was always benign and asymptomatic. In some patients ALT returned to normal values later so we did not perform liver biopsies. To your second question, we did not use Hepatitis B immune serum as a treatment of non A non B hepatitis.

ZIMMERMANN (Vienna) Did you find hepatitis B antibody in a system with non-A, non-B hepatitis?

SIMON Five out of the 12 patients who developed non-A, non-B hepatitis had anti-\( \text{HB}_8 \) antibodies.

BONE (Liverpool) Do you separate the patients who have had hepatitis from those who have not and did your first patient with hepatitis have a blood transfusion? Do you re-use dialysers?

SIMON To the first question, no, we did not.