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Should hepatitits-C virus antibody-positive donors be excluded from kidney donation?

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Abstract. In organ transplantation, virus transmitted by the donor is associated with a higher risk of severe primary infection after transplantation in the seronegative recipient. In this study, the risk of hepatitis-C virus (HCV) transmission by the kidney was determined, and the morbidity in the recipient assessed. Serum samples from all kidney donors of our Transplantation Unit between 1983 and 1988 were screened for antibodies to anti-HCV by first enzyme-linked immunosorbent assay (Ortho ELISA) and positive samples were confirmed by a second-generation ELISA and the CHIRON RIBA HCV test. Of the 164 kidney donors whose sera were available, five were positive (3%) and all of them were positive with the RIBA test. Liver function was normal in the five donors. Seven recipients received a renal transplant from the anti-HCV-positive donors. Two patients had a follow-up too short to draw any conclusions. Two patients remained anti-HCV-negative up to 36 and 48 months, respectively, but one of them had chronic hepatitis. One patient was anti-HCV-positive before transplantation and remained positive over the 4-year follow-up. The two last patients seroconverted and acute hepatitis occurred at 16 and 101 days after transplantation, respectively. In both cases, no peroperative or postoperative transfusion was given and no other cause of hepatitis could be determined. A cirrhotic evolution was observed within 15 and 36 months in both cases. Thus HCV can be transmitted by a kidney transplant and cadaveric donors positive for anti-HCV antibodies should be excluded from kidney donation.

Key words: Hepatitis C virus – Kidney transplantation – Transmission

Many viruses transmitted by transplanted organs such as cytomegalovirus, herpes simplex virus, Epstein-Barr virus, human immunodeficiency virus, human T cell lymphotropic virus type 1, hepatitis A, hepatitis B, and delta agent can be responsible for severe primary infections in the seronegative recipient [5]. The evolution of the transmitted viral disease in the recipient under immunosuppressive therapy is different from the clinical presentation in the immunocompetent host, going from a fulminant to a chronic persistent infection depending on the type of virus, on the viral charge, on the immune status of the recipient and on the type and (HCV) intensity of the immunosuppressive therapy. In organ transplantation the possible transmission of hepatitis C virus (HCV) has just been reported [7]. In 1989 the possible detection of anti-HCV antibodies against a recombinant viral antigen, C 100-3 [1, 6], then the use of the second-generation ELISA allowing the detection of antibodies against structural and non-structural recombinant antigens and the use of the CHIRON RIBA test as a confirmation test, have improved considerably the diagnosis of HCV infection. If the transmission by blood product transfusion has been proved, other ways of contamination are possible, such as sexual and fetomaternal transmission, as occurs for hepatitis B virus [3, 4, 10].

To assess the risk of HCV transmission by the transplanted kidney we analysed the prevalence of anti-HCV antibodies in 164 organ donors from 1983 to 1988. The serological, biological and clinical follow-up of the respective kidney recipients were analysed in order to determine whether anti-HCV-positive donors should be excluded from organ donation.

Patients and methods

Kidney donors and serological methods

All the stored serum samples from the organ donors from 1 January 1983 to 31 December 1988 in the Virology Department were screened for anti-HCV antibodies and HBs antigen. A first-generation enzyme-linked immunosorbent assay (ELISA) (Ortho HCV ELISA Test system, Ortho Diagnostic Systems, Raritan, N.J.) de-

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tecting antibodies against the non-structural proteins, C 100-3 and 5-1-1, was first used. Then, when it became available, the second-generation ELISA which detects antibodies directed against both non-structural proteins, C 200 including C 100-3 and C 33 c., and a structural protein (core), C 22-3, was performed in the donors positive for anti-HCV antibodies with the first generation ELISA. The confirmation test was the CHIRON RIBA second-generation assay, which is an immunoblot assay using the five recombinant antigens, 5-1-1, C 100-3, C 33 c, C 22-3 and superoxide dismutase.

Recipients

All the sera available from the renal transplant recipients receiving a kidney from a positive anti-HCV donor were tested for anti-HCV antibodies from the day of transplantation to the last serum available. The follow-up ranged from one week to 60 months. First- and second-generation ELISA were performed and, in cases of seropositivity, the CHIRON RIBA second-generation assay was used.

Biological parameters including the determination of alanine aminotransferase (ALAT), gamma-glutamyltranspeptidase (γ GT), alkaline phosphatases and serum protein electrophoresis, were evaluated at the time of transplantation and then at 1, 3, 6 and 12 months, and every 6 months, to detect the occurrence of liver dysfunction. Acute hepatitis was defined by an elevation of the transaminase level on two or more determinations at least 2 weeks apart and a normalization of the biology within 6 months. Chronic hepatitis was defined by a persistent elevation of the serum alanine aminotransferase level for more than 6 months. Liver biopsy was performed in cases of chronic hepatitis. All the recipients were followed by the same medical team of the Transplantation Unit and were under the same type of immunosuppressive therapy.

Results

Prevalence of anti-HCV antibodies in kidney donors

The stored serum samples from five of the 164 kidney donors were positive for anti-HCV antibodies. All the patients positive with the first-generation test were reactive with the second-generation assay. The CHIRON RIBA second-generation test confirmed the positivity in the five cases.

No significant difference was observed in the prevalence of anti-HCV antibodies in organ donors whatever the year from 1983 to 1988. All the donors had a normal aminotransferase level at the time of organ procurement, and they were all negative for hepatitis-B surface antigen.

Transmission of HCV infection in the recipients

Seven patients underwent a renal transplant from anti-HCV-positive donors in our Transplantation Department. In two patients, the follow-up was too short to allow any conclusion since one patient died at 7 days from a myocardial infarction and the other patient did not come back to the department after 1 month. Among the five other renal transplant patients, two remained anti-HCV negative on all the sera tested with a follow-up of 48 months and 36 months, respectively. However, one of them had a rise in alanine aminotransferase (ALAT) concentration 30 days after transplantation and then the liver parameters became normal. Then a rise of ALAT and of the γ GT level occurred from April 1989 to June 1990 without any blood transfusion since transplantation. A liver biopsy was performed for chronic hepatitis and showed hepatosiderosis without signs of acute hepatitis or fibrosis.

One recipient was anti-HCV positive at the time of transplantation and remained positive over a follow-up of 48 months. Anti-HBc antibodies were positive at the time of transplantation. Liver function tests remained normal from the day of transplantation to the last evaluation.

Two patients seroconverted to become anti-HCV positive at 3 and 2 months respectively. The first case was an 18-year-old boy who underwent a second renal transplant on 1 June 1984 and was HBs-antigen-positive. He did not receive any transfusion at the time of transplantation or after transplantation. Two rejection episodes occurred at 18 and 24 days after transplantation. The clinical presentation included a persistent fever from the eighth day, splenomegaly and a persistent leukopenia without active CMV infection. Poor general condition and poor renal function led to transplantectomy 82 days after transplantation. Acute hepatitis occurred from the 101st day while the liver parameters were previously normal. Anti-HCV antibodies were detected at day 101. A liver biopsy was performed 3 years later for chronic hepatitis and showed cirrhosis. He received a third transplant in July 1989 and the last biopsy performed in July 1990 showed the persistence of the cirrhosis but no hepatocellular failure occurred under low-dose azathioprine (25 mg/day).

The second case was a 42-year-old man who underwent a renal transplant on 11 August 1986. He was HBs-antigen-negative and liver function was normal at the time of transplantation. He developed cholestasis 16 days after transplantation and chronic hepatitis was evident. HBs antigen remained negative as well as DNA polymerase and HBV DNA in the serum. Anti-HCV antibodies appeared at 60 days. He did not receive any blood transfusion during or after transplantation. A liver biopsy was performed on 16 May 1987 showing acute hepatitis with minimal agressivity without cirrhosis. Six months later the patient was hospitalized for ascites and oedema of the lower limbs. Electrophoresis showed a rise in gamma globulins and a hypoalbuminaemia and the prothrombin rate was at 60%. All the other causes of chronic hepatitis had been excluded. Although liver biopsy was not repeated, a cirrhotic evolution could be suspected in the absence of cardiac failure and nephrotic syndrome. The patient has not come back to the hospital since October 1987 and a fatal outcome cannot be ruled out.

Thus HCV infection was implicated as the cause of acute hepatitis in both cases with a cirrhotic evolution. To summarise, HCV transmission by the kidney has been proved serologically in two patients of four seronegative patients who received a kidney from an anti-HCV-positive donor. Three patients of the four seronegative recipients had acute hepatitis and all of them developed chronic hepatitis. Two patients out of the three had a rapid cirrhotic evolution. The immunological characteristics and the immunosuppressive therapy of the patients who developed HCV infection were not different from those who did not.

Discussion

The prevalence of anti-HCV antibodies among cadaver donors was 3% from 1983 to 1988 and this rate did not decrease with time although cadaver donors are less transfused nowadays than previously. This high prevalence as compared to the prevalence of 0.6% in the population of blood donors from France or from the United States has also been found by Pereira et al. [7]. This could be due to the blood product transfusions given to the cadaveric donors and to a prolonged stay in intensive care units or in other wards with a risk of transmission. The meaning of the presence of anti-HCV antibodies is certainly not unequivocal since some donors will be able to transmit the anti-HCV antibodies and some not. The passive acquisition of anti-HCV antibodies through plasma or other blood product transfusions in cadaveric donors could not be ruled out, and the real infectivity of the organ is therefore difficult to assess depending on the viral charge and on the replication level. In organ transplantation it is difficult to discriminate between the role of the characteristics of the virus itself as it is in the donor and the role of the immunological status of the recipient in the triggering of overt hepatitis after transplantation. Two patients seroconverted 2 and 3 months after contamination without other cause of HCV transmission, especially without per- or post-operative transfusions and without other cause of hepatitis. In both cases this seroconversion was associated with biological and clinical acute hepatitis 16 and 101 days after transplantation and a rapid evolution to cirrhosis. Three patients acquired chronic hepatitis. The rapid progression of the liver disease in the recipients who became anti-HCV positive after transplantation was comparable to the evolution of HBV hepatitis acquired after transplantation under an immunosuppressive therapy [8].

The rate of seroconversion might be underestimated if a sequential follow-up of the sera of the recipients is not performed for at least 6 months after transplantation. Moreover recipients can be considered as falsely seronegative if the first-generation ELISA is the only test performed. Indeed, it has been shown that patients can have antibodies against structural proteins without antibodies detectable against non-structural proteins. These patients would be positive with the second-generation assay but seronegative with the first generation assay [9]. In the course of HCV infection some patients loose their antibodies [9, 11] against non-structural proteins and keep their antibodies against the structural proteins. This profile has been associated with normalization of the transaminase level and possibly with a decrease or a reversal of HCV replication [9]. In this study all the patients initially anti-HCV positive remained positive with the first- and the second-generation tests, suggesting a persistent viral replication. Amplification techniques should be more sensitive to detect the presence of HCV in the serum before the appearance of IgG directed against anti-C 100-3 [2, 11]. The disappearance of HCV RNA appears to correlate with the resolution of non-A, non-B hepatitis whereas viraemia persists in patients whose disease progresses to chronic hepatitis [2]. No data are available yet on the correlation between the presence or the disappearance of HCV RNA and the persistence or the disappearance of non-structural proteins.

In regard to these results anti-HCV antibody-positive donors should be excluded from organ donation, and this is the policy that we have adopted since 1 January 1990. The ELISA used for screening should be the second-generation ELISA, since antibodies against structural proteins cannot be detected with the first-generation assay, and a better evaluation of the infectivity of the anti-HCV-positive donor will be possible in the future using the HCV RNA amplification technique and the detection of direct markers of HCV replication.

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