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CLINICAL STUDY

TT Virus Infection in Patients on Peritoneal Dialysis in Taiwan

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Many studies have reported the prevalence of transfusion-transmitted virus (TTV) infection in hemodialysis patients, but few reports studied the prevalence of TTV infection in peritoneal dialysis patients. In this study, we determined the prevalence of TTV in a peritoneal dialysis population in Taiwan and related its prevalence with history of blood transfusion, serum hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), and serum aminotransferases (AST and ALT) levels. Serum samples from 47 peritoneal dialysis patients and a control group of 43 patients at health examination were studied for TTV viremia by using polymerase chain reaction. The rate of blood transfusion exposure ($p < 0.0001$), female gender ($p = 0.001$), younger age ($p=0.0014$), and serum AST level ($p=0.012$) were significantly higher in peritoneal dialysis patients. The prevalence of TTV viremia was not significantly different between peritoneal dialysis patients and the control group (23.4% vs. 37.2%). TTV infection was not associated with evident liver diseases in peritoneal dialysis patients, and the infection rate was not different between automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD) patients. There was no statistically significant association between TTV infection and age, gender, transfusion history, duration of peritoneal dialysis, AST level, ALT level, HBsAg, or anti-HCV seropositivity in peritoneal dialysis patients. Our results suggest that TTV infection is not associated with evident liver diseases, and there is no difference between TTV infection in healthy individuals and peritoneal dialysis patients. TTV transmission probably occurs via routes unrelated to peritoneal dialysis.

Keywords transfusion-transmitted virus (TTV), peritoneal dialysis, prevalence

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INTRODUCTION

The TT virus (TTV) was discovered recently by molecular biological methods in a serum sample from a

patient suffering from non-A to E hepatitis. It was first isolated in 1997 in a Japanese patient with acute post-transfusion hepatitis and was considered a transfusion-transmitted and hepatotropic virus.[1] The virus was named TT both to stand for the initials of the index patient and as an abbreviation of "transfusion-transmitted." TTV can be transmitted by blood products and other parenteral routes;[2] however, a non-parenteral route of viral transmission cannot be ruled out, such as fecal-oral exposure or maternal-fetal transmission.[3,4]

Many studies have reported the prevalence of TTV infection in hemodialysis patients.[5–9] Patients on hemodialysis are at risk of parenteral infections, including viral hepatitis. Patients on peritoneal dialysis are also prone to infections via contamination during exchange of peritoneal dialysate. Peritonitis is a frequent complication of peritoneal dialysis. There are only a few reports of the prevalence of TTV infection in peritoneal dialysis patients,[10,11] and there were no such reports from Taiwan. The aims of this study are to survey the prevalence of TTV viremia among peritoneal dialysis patients in Taiwan and compare the results with those of previous studies.

METHODS

Patients

Serum samples were collected from 47 patients on peritoneal dialysis in a medical center in Hualien in eastern Taiwan in December 2004. During the same period, 43 subjects at health examination were enrolled as control group. The Protection of Human Subjects Institutional Review Board of Tzu-Chi University and Hospital approved this study. Thirty-five patients had been on continuous ambulatory peritoneal dialysis (CAPD, dianeal, Baxter Health Care, Singapore), with three to five dialysate exchanges per day for more than three months. The other 12 patients performed four to five dialysate exchanges each night with an automated device (automated peritoneal dialysis, APD). Patients were excluded if they had any acute infection at the time of blood sampling, such as peritonitis and peritoneal catheter exit site infection, or the duration of peritoneal dialysis was less than three months. Serum samples taken from each subject were stored at −70°C until use.

Laboratory Tests

Serum samples were immediately centrifuged at 3,000 g for 10 minutes. Serum aminotransferases (AST and ALT) were measured with an autoanalyzer (Hitachi 747, Tokyo, Japan). The serum hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (anti-HCV) were tested with commercially available enzyme immunoassays (Abbott Laboratories, North Chicago, Illinois, USA). All samples were processed at room temperature and prepared according to the manufacturer's directions.

Nucleic Acid Extraction and Polymerase Chain Reaction (PCR)

The presence of TTV DNA was determined by PCR. The viral nucleic acid was extracted from 150 ul serum using Macherey-Nagel NucleoSpin RNA Virus kit (Macherey-Nagel GmbH & Co. KG, Duren, Germany). The viral nucleic acid was then dissolved in 50 ul RNase-free water. These nucleic acids were used directly for PCR for the detection of TTV DNA. The nested PCR primers and the PCR program for the detection of the 197-bp TTV DNA fragment were the same as previously described.[1,12]

Statistical Analysis

Unpaired t-test was used as the significance test for continuous variables and the Fisher exact test was used for categorical data. All test statistics were two-sided. A p value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the results of the comparisons of clinical background between peritoneal dialysis patients and the control group. There were significantly higher proportions of blood transfusion exposure ($p < 0.0001$), female gender ($p = 0.001$), and higher mean serum AST level ($p = 0.012$) in peritoneal dialysis patients. The mean age of peritoneal dialysis patients at enrollment was significantly younger than that of the controls ($p = 0.0014$). The prevalence of TTV infection is 37.2% in control group and 23.4% in peritoneal dialysis patients. There were no statistically significant differences in the prevalence of TTV viremia between peritoneal dialysis patients and controls ($p > 0.05$). None of the TTV-infected peritoneal dialysis patients had overtly clinical or biochemical signs of liver disease such as jaundice, spider nevi, splenomegaly, or other abnormal liver biochemical tests.

Table 2 shows the results of the comparisons of clinical background between patients with and without TTV infection. There were no statistically significant differences in the mean age, gender distribution, duration of hemodialysis, transfusion history, mean AST/ALT level, and positive rates of HBsAg or anti-HCV.

Table 1
Comparisons of clinical background between peritoneal dialysis patients and controls

Background characteristics	Age (years)*	Gender (F, %)†	Transfusion (%)†	HBsAg (%)†	Anti-HCV (%)†	TTV (%)†	AST (IU/L)*	ALT (IU/L)*
Control group (n=43)	63.5 ± 14.3	32.6	10.3	14.0	4.7	37.2	15.0 ± 9.9	15.8 ± 12.9
Peritoneal dialysis (n=47)	53.6 ± 14.2	68.1	91.5	17.0	14.9	23.4	22.1 ± 10.0	18.2 ± 11.0
p value‡	0.0014	0.001	<0.0001	>0.5	0.16	0.17	0.012	0.30

*Data are expressed as means ± SD.
†Data are expressed as positive % (number).
‡two-sided.
Abbreviations: Anti-HCV=antibodies against hepatitis C virus, HBsAg=hepatitis B surface antigen, TTV=transfusion-transmitted virus.

Table 2
Comparisons of clinical background of peritoneal dialysis patients with and without TTV infection

Background characteristics	TTV (-) (n=36)	TTV (+) (n=11)	*p* value
Age (years)*	51.7 ± 15.3	59.7 ± 7.5	>0.1
Gender (female %)†	69.4	63.6	>0.1
Duration of peritoneal dialysis (months)*	29.9 ± 20.6	22.3 ± 21.2	>0.1
Transfusion history (%)†	91.7	90.9	>0.1
HBsAg (%)†	16.7	18.2	>0.1
Anti-HCV (%)†	13.9	18.2	>0.1
AST (IU/L)*	21.9 ± 9.6	22.7 ± 12.7	>0.1
ALT (IU/L)*	17.0 ± 8.2	23.1 ± 17.1	>0.1

*Data are expressed as means ± SD.
†Data are expressed as positive % (number).
Abbreviations: Anti-HCV=antibodies against hepatitis C virus, HBsAg=hepatitis B surface antigen, TTV=transfusion-transmitted virus.

Table 3 shows the results of the comparisons of clinical background between patients on APD and patients on CAPD. There were no statistically significant differences in the mean age, gender distribution, duration of dialysis, transfusion history, mean levels of serum AST and ALT, seropositivity of HBsAg and anti-HCV, and prevalence rates of TTV viremia.

DISCUSSION

TTV is a single-stranded circular DNA virus that lacks an envelope and contains approximately 3800 nucleotides. Sequence alignment of several near full-length TTV genomes revealed the presence of three conserved open reading frames and sequence motifs consistent with a rolling circle mode of replication.[13] Sequence analysis confirms that the TTV genome contains a high degree of genetic variability and can be classified into at least six major genotypes and several subtypes.[14] The genotype-specific pathogenicity of TTV remains unclear.

TTV has a worldwide distribution. The prevalence of TTV infection ranged from 2% to 42.4% in different countries.[6,11,15] In Taiwan, the prevalence of TTV infection is about 10% in healthy adults[16] and 11% in aborigines of eastern Taiwan.[12] In our study, the prevalence of TTV infection is 37.2% in healthy adults, which is higher than other reports from Taiwan. The reason may be that the age of our control group is higher with higher cumulative risk of TTV infection.

Blood transfusion may play an important role in TTV transmission in hemodialysis.[6,8] However, the TTV infection was not significantly associated with transfusion history in peritoneal dialysis in our report. There were also

Table 3
Comparisons of clinical background of APD patients and CAPD patients

Background characteristics	APD (n=12)	CAPD (n=35)	*p* value
Age (years)*	49.7 ± 15.5	54.9 ± 13.7	>0.1
Gender (female %)†	66.7	68.6	>0.1
Duration of peritoneal dialysis (months)*	26.7 ± 26.6	28.7 ± 18.9	>0.1
Transfusion history (%)†	75.0	85.7	>0.1
HBsAg (%)†	16.7	20.0	>0.1
Anti-HCV (%)†	16.7	17.1	>0.1
AST (IU/L)*	20.7 ± 10.0	23.8 ± 11.3	>0.1
ALT (IU/L)*	17.3 ± 11.0	18.0 ± 8.8	>0.1
TTV (%)†	25	22.9	>0.1

*Data are expressed as means ± SD.

†Data are expressed as positive % (number).

Abbreviations: Anti-HCV=antibodies against hepatitis C virus, APD=automated peritoneal dialysis, CAPD=continuous ambulatory peritoneal dialysis, HBsAg=hepatitis B surface antigen.

no statistically significant differences in the mean age, gender distribution, duration of peritoneal dialysis, mean AST level, and HBsAg prevalence between patients with and without TTV infection.

TTV infection may be acquired during hemodialysis procedure or by nosocomial transmission.[6,19] However, a non-parenteral route of viral transmission, such as fecal-oral exposure[3] or maternal transmission,[4] has been suggested. TTV genome fragments have been detected in both sera and stool.[3] During the process of dialysate exchange for peritoneal dialysis, there are also many chances of contamination. For peritoneal dialysis patients, TTV may be transmitted by fecal-oral exposure during dialysate exchange procedures or by nosocomial transmission in the hospital.

The prevalence of TTV infection in peritoneal dialysis patients is 23.4% in our study, which is around the same range as reported by Barril et al.[10] but lower than that reported by Ozener et al. (44%).[11] The prevalence of TTV viremia in peritoneal dialysis patients was not significantly different from that of the control group in our study, as well as in other reports.[10,11] The age of our control group is significantly higher than that of peritoneal dialysis patients in this survey. There may be a higher cumulative risk of TTV infection in the community. Further studies with age-matched control groups will clarify the effect of age on the prevalence rate of TTV viremia. However, the non-significantly lower rate of TTV viremia in peritoneal dialysis patients argue against an increased risk of TTV infection in the procedures involved in CAPD or APD. There were also no statistically significant differences in the prevalence of TTV viremia between APD patients and CAPD patients. It is reasonable to assume that carefully performed peritoneal dialysis may not be an effective way to transmit TTV. Accordingly, further investigations are necessary to explore the transmission route of TTV. For example, the drained peritoneal dialysate from patients with TTV viremia should be studied for the presence of TTV by PCR.

TTV infection has no effect on the severity of existing liver disease, including hepatocellular carcinoma[17] and diseases caused by chronic infection with HBV or HCV.[18] In the present study, TTV infection was not associated with HCV infection in peritoneal dialysis patients, and was not associated with a rise in ALT level, as in other reports [10,11]. None of the TTV-infected patients in this survey had signs or symptoms of liver disease.

In conclusion, TTV infection rate was not different between healthy controls and peritoneal dialysis patients in this survey in Taiwan. TTV infection was not associated with evident liver diseases in peritoneal dialysis patients, nor was the infection rate different between APD and CAPD patients. Among peritoneal dialysis patients, there was no statistically significant association of TTV infection with age, gender, transfusion history, AST level, ALT level, and the presence of serum anti-HCV or HBsAg.

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