TT Virus

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Abstract. TT virus (TTV) is a newly described DNA virus that was first detected in the blood of three patients with elevated serum aminotransferases following transfusion who tested negatively for all known hepatitis viruses. The virus has been found worldwide with a high prevalence in the general population. However, accumulating evidence suggests that the virus is not a significant cause of acute or chronic liver disease. No other disease associations with infection have been described.

After the discovery of the hepatitis A and B viruses in the 1960s and 1970s, it became apparent that an unidentified agent was responsible for hepatitis in a number of patients suspected of having acute or chronic viral hepatitis. The unknown pathogen was referred to as non-A non-B hepatitis until the hepatitis C virus was identified in 1989 and was found to account for hepatitis in the majority of these patients (1).

However, in approximately 5% of patients with liver disease, no cause can be identified (2). It has long been suspected that additional hepatotropic viruses will be discovered to account for some of these cases, especially since approximately half of these patients have a history of blood transfusion (2). The hepatitis G virus, identified in 1996, has proven to be an unlikely candidate since an association with hepatitis or any other disease has not been consistently demonstrated (3).

A novel virus associated with posttransfusion hepatitis was identified in 1997 in three patients from Japan who developed elevated serum aminotransferase concentrations following transfusion and tested negatively for all known hepatitis viruses (4). The virus (referred to as TT virus for the initials of the patient in whom it was isolated or “transfusion transmitted virus” [TTV]) exhibited hepatotropism, and its titers correlated with elevation in serum aminotransferase concentrations suggesting that it was a true hepatitis virus.

Accumulating data have demonstrated a high prevalence of the virus in the general population, demonstrating that it is capable of producing chronic infection. TTV DNA has been detected in approximately 2% of blood donors in the United Kingdom, 1 to 10% in the United States (5,6), 12 to 40% in Japan (7–9), 14% in Korea (10), 13% in Germany (11), 62% in Brazil (12), 11% in Spain (13), and 10% in Columbia (14). TTV may be acquired early in life, particularly in countries with a high prevalence of infection in the general population. A series from Japan found that 5% of 197 children seen in a general pediatric center had TTV DNA detectable in serum (15). In another report from the Democratic Republic of Congo, TTV was found in 61 of 105 women (58%) attending an antenatal clinic and 36 of 68 (54%) of infants (16). The virus can be detected in the stool and bile of infected patients, suggesting that it may be transmitted enterally (17,18).

A high prevalence of infection has been found in patients with parenteral exposure to blood. TTV DNA was detected in 44% of patients with hemophilia in the United Kingdom (19), and up to 75% in Japan (20,21). A report from China found a prevalence of 22% among those with a history of intravenous drug use (22). TTV was present in 84% of Italian patients with transfusion-dependent beta thalassemia (23).

Despite its high prevalence, an association between TTV infection and acute or chronic hepatitis or other diseases has not been consistently observed. Furthermore, the initial observation of hepatotropism has not been confirmed (24), and injection of the virus into chimpanzees, while capable of causing infection, did not produce clinical illness (25).

Phylogenetic Analysis

TTV is an unenveloped, single-stranded DNA virus that has similarities to the Circoviridae viruses known to infect plants and vertebrates (25). However, it has been classified as a member of a new family of viruses, the Circinoviridae, based on its distinct biophysical and molecular characteristics.

Phylogenetic analysis of isolates pooled from worldwide sources has demonstrated at least three genotypes and multiple subtypes (designated 1a, 1b, 1c, 2a–f, and 3); the different genotypes do not appear to be geographically clustered (21,25–33). A possible fourth genotype has been reported in Columbia, Belgium, and Korea (10,14,31).

The majority of patients are infected by genotype 1. However, coinfection with multiple genotypes is common, particularly in patients who have had multiple exposures to blood products (28). No differences in clinical outcomes among the various genotypes have been observed (32).

Natural History

The natural history of TTV infection has not yet been defined. The presence of TTV infection has been based on the detection of its DNA in serum or tissue samples. Thus, little is known about the immune response to the virus or the frequency
with which an acute exposure leads to viral clearance. Antibodies against TTV have been detected and will help to clarify these issues (34).

Preliminary reports in patients who have been followed longitudinally have suggested a low rate of viral clearance. As an example, TTV DNA remained persistently detectable for 3 yr in a cohort of 19 patients (35). In another report, 97% of 93 patients who were followed for 3 yr remained viremic (23). A third series suggested an annual clearance rate of approximately 7% (36). However, many of the patients in these series had exposure to blood products. Thus, the extent to which the persistence of TTV DNA represents chronic infection by a single genotype or the acquisition of new genotypes remains uncertain.

**Clinical Significance**

The presence of TTV has been sought in a number of clinical settings, which will be summarized below. However, much of the information has been reported only in preliminary form. Thus, an understanding of its possible clinical significance is evolving.

**Hemodialysis**

A number of series have found a high prevalence of TTV infection among patients undergoing hemodialysis particularly in Japan (30,36–39). As an example, in a series of 115 patients from Japan, TTV DNA was detected in 51%, compared to 13% in healthy blood donors (37). Serum alanine aminotransferase concentrations were similar between those with and without TTV DNA.

The high prevalence among Japanese patients on hemodialysis may reflect the relatively high prevalence in the general population. A much lower prevalence of infection was found in a series from France in which TTV DNA was detected in only two of 84 (2%) patients on hemodialysis (40). In addition, the prevalence of TTV infection may depend on the number of years that patients have been receiving hemodialysis (38). This was illustrated in a series that included 50 Japanese patients with hepatitis C who were followed for 48 mo while on hemodialysis (36). TTV DNA was present in 48% at the start of the study. A history of blood transfusions was similar among those with and without infection. During follow-up, four patients developed new infection; the estimated annual infection rate was 4%. However, in other reports, the presence of TTV was unrelated to the number of years of dialysis (39).

**Renal Transplantation**

A study from Japan found that the acquisition of TTV infection after renal transplantation was common but of uncertain clinical significance (39). New infection after transplantation was detected in nine of 25 (36%) patients. Three of these patients demonstrated an elevated serum alanine aminotransferase concentration, which subsequently normalized in two. An adverse effect on graft survival has not been reported.

**Association with Acute Liver Disease**

TTV DNA has been detected in patients with acute hepatitis of otherwise unknown etiology (7,8,41–44), but a correlation of TTV titers and serum aminotransferase concentrations has been inconsistent. Thus, it remains unclear whether the virus was the cause of the liver disease or was an incidental finding.

Some reports have suggested that the virus may be associated with acute hepatitis in a subset of patients. This was illustrated in a study that included 25 Japanese patients undergoing bone marrow transplantation of whom 60% were positive for TTV DNA after transplantation (45). No significant difference was observed in the incidence of veno-occlusive disease, graft versus host disease, or biochemical evidence of liver dysfunction based on TTV status. However, in one patient serial semiquantification of TTV DNA in serum closely correlated with the serum alanine aminotransferase levels. A liver biopsy specimen was consistent with acute hepatitis, and TTV DNA was detectable in liver tissue by PCR.

**Association with Chronic Liver Disease of Unknown Etiology**

The presence of TTV DNA does not appear to be associated with biochemical or histologic evidence of liver injury of unknown cause in most reports (24,40,46–48). In one study, for example, no significant difference in the prevalence of TTV DNA was found between 99 blood donors in the United States who had an elevated serum alanine aminotransferase compared with 46 control subjects (46). Similar findings were found in Spain (13). In a report from Japan, the prevalence of TTV DNA was similar between 50 patients with chronic liver disease of unknown etiology and 106 volunteer blood donors (47).

In contrast to these reports, another series from Japan supported a potential role for TTV in the development of chronic liver disease (42). The prevalence of TTV DNA was significantly higher among 57 patients with chronic liver disease of unknown etiology compared to 96 patients known to have chronic liver disease due to hepatitis C (47% versus 18%). Similarly, in a series from the United States, the prevalence of TTV was much higher among 33 patients with cryptogenic cirrhosis compared to 100 healthy blood donors (15% versus 1%) (5).

**Association with Known Forms of Chronic Liver Disease**

Several reports have demonstrated an increased prevalence of TTV DNA in patients with a variety of chronic liver diseases compared to control populations (5,20,21,49–51). As an example, in one series from the United States, TTV was present in 27% of patients with fulminant hepatic failure and 18% of cirrhotic patients with a history of blood transfusion compared to 1% in healthy blood donors (5). However, in most reports TTV does not appear to contribute to the liver injury. In a study from Japan, for example, TTV DNA was not more common among hemophiliacs with an elevated alanine aminotransferase who were infected by hepatitis C virus compared to hepatitis C.
virus-negative control subjects, suggesting that the liver injury was due to hepatitis C virus alone (21).

In another report from the United Kingdom, the prevalence of TTV DNA among patients with chronic liver disease was similar to healthy control subjects (52). No significant difference was noted in the rate of TTV DNA among various forms of liver disease. The majority of TTV-positive patients had no biochemical or histologic evidence of significant liver disease. Thus, the increased prevalence of TTV among patients with various forms of liver disease suggests shared risk factors with TTV infection.

Similar results have been found in other centers, which have also not detected a correlation between TTV status and the severity of liver disease (9,19,35,53,54) or outcome in patients undergoing treatment of hepatitis C virus with interferon (9,36,48,55). Interferon treatment has been associated with clearance of TTV infection.

TTV DNA has been sought in a number of other settings related to liver disease. It does not appear to serve as a trigger for autoimmune hepatitis (56,57). No association between TTV DNA and cryoglobulinemia was found in a single report (58).

Liver Transplantation

TTV is frequently acquired after liver transplantation presumably because of the multiple transfusions that are often required during the procedure. In one report from the United States, for example, TTV DNA was found after transplantation in up to 44% of those who were initially negative for the virus before the procedure (59).

Despite its high prevalence, its significance in the transplant setting is uncertain. In one report, patients who were TTV-positive after transplantation were significantly more likely to have idiopathic hepatitis on protocol liver biopsies at 12 mo (60). However, in other series TTV did not appear to have any association with clinical or histologic evidence of hepatitis (48,61).

Conclusion

An understanding of the biology and clinical significance of TTV is evolving. Increasing evidence suggests that it is not a significant cause of liver disease, although it may be capable of inducing hepatitis in a subset of patients. The continued search for TTV in non-liver-related clinical settings will help to determine whether the virus contributes to other human diseases.

References


