

## Commentary

### TT viruses: How much do we know?

Accumulated evidence suggests that many of the cases of viral hepatitis that occur are unrelated to the well-characterized hepatitis viruses A to E (non A-E). Candidate non A-E viruses, GB virus C (GBV-C) and hepatitis G virus (HGV) though unequivocally found to be hepatotropic, failed to show a clear association with the causation of liver disease. Hence the search for other hepatitis causing agents continued.

In 1997, Nishizawa *et al*<sup>1</sup> identified a novel virus in the serum of a patient with acute post-transfusion hepatitis of non A-G aetiology. This agent was designated as 'TT' virus (TTV), after the initials of the patient in whom it was discovered. This negative sense, single-stranded, non-enveloped DNA was placed in the *Circoviridae* family, though some researchers felt that it should be included in a new family called *Circinoviridae* (latin = circinato, meaning describing a circle). More recently however, taxonomists have further proposed that the full name for TTV be Torque Teno Virus, within the genus *Anellovirus* (ring)<sup>2</sup>.

Infection with TTV appears almost ubiquitous across different human populations, several primate species and farm animals<sup>3,4</sup>. Parenteral transmission through blood and blood products is clearly evidenced by the higher detection rates among multiply transfused individuals<sup>5</sup>. Further, the virus has been detected in stool, bile, saliva and breast milk, pointing to enteric routes of transmission<sup>6-9</sup>. Higher risk of TTV acquisition with increasing promiscuity suggests a sexual mode of transmission<sup>10</sup>, and the detection of TTV in cord blood points to vertical transmission of the virus<sup>11</sup>. TTV viraemia rates increase with age and peak in young adulthood<sup>11</sup>. Infection is believed to be largely persistent.

TTV prevalence in high-risk patient groups is noteworthy. In haemodialysed patients, TTV detection rates are significant though the clinical impact is still unclear<sup>12,13</sup>. Prevalence of TTV DNA was high in bone marrow recipients as compared to donors<sup>14</sup>. TTV detection rates in liver transplant patients rose from 16 per cent pre-transplant to 46 per cent post-transplant, which may be attributed to transfusion or recurrence of TTV viraemia due to immunosuppression<sup>15</sup>.

Phylogenetic analysis of TTV isolates sourced from different parts of the globe demonstrates a phenomenal amount of genetic diversity for a DNA virus. TT virus variants are classified into five major genogroups, comprising of at least 23 genotypes<sup>16</sup> and several subtypes.

TTV detection is primarily based on viral DNA detection. Due to the high genetic heterogeneity, detection rates depend largely on the region of the genome amplified, leading to considerable variation in prevalence rates as reported from different countries and different studies within the same country<sup>17</sup>. To date, there are no reliable commercial serological assays that can be used for large-scale screening.

The earliest reports of TTV suggested a causative link between TTV and liver disease. Okamoto *et al*<sup>5</sup> reported 10-100 fold higher viral titres of TTV DNA in liver tissue as compared to serum in patients with non A-G post-transfusion hepatitis. Likewise, in newly infected patients with non A-G post-transfusion hepatitis, TTV titres rose and fell with alanine aminotransferase (ALT) levels, becoming undetectable in patients with normalized ALT levels<sup>1</sup>. TTV DNA was also detected more frequently in

fulminant hepatitis and persons with cryptogenic liver disease than in symptom-free donors<sup>5</sup>. TTV was also more frequently seen in liver cirrhosis and hepatocellular carcinoma than in chronic hepatitis<sup>18</sup>. TTV genotype 1 has been incriminated in post-transfusion hepatitis. The predominant TTV genotype in children with fulminant hepatitis and chronic hepatitis was genotype 1a<sup>19</sup>. Desai *et al*<sup>20</sup> recently reported that abnormal liver function profiles were frequent among TTV viraemic individuals. This study showed a higher mortality among acute hepatitis patients co-infected with TTV and hepatitis B virus (HBV).

Data addressing the link between TTV and liver disease have however, turned out to be conflicting because there is a bulk of evidence pointing to the absence of such an association. The lack of morphological changes within hepatocytes that showed *in situ* hybridization signals for TTV questions the role of TTV in liver pathogenesis<sup>21</sup>. Kadayifci *et al*<sup>22</sup> compared TTV DNA detection rates in patients with elevated ALT and healthy individuals and found no statistical difference, the histological examination of liver also showing no specific features attributable to viral infection. Though TTV is frequently detected in chronically infected HBV and hepatitis C virus (HCV) infected patients, TTV appears to have no influence on the clinical and histopathological features of HBV or HCV related liver disease. In this issue of the Journal, Chattopadhyay *et al*<sup>23</sup> have shown that the clinical course and biochemical profiles of HBV and HCV related chronic hepatitis patients co-infected with TTV, were not significantly different from those without TTV co-infection. However, the possibility of TTV contributing to progression of liver disease in HBV or HCV infected individuals, over time, cannot be entirely ruled out<sup>20,24</sup>.

More recent studies demonstrate TTV replication in extrahepatic sites. TTV DNA levels have been quantitated in bone marrow, lymph nodes, muscle, thyroid, lung, liver, spleen, pancreas and kidney. DNA titres were up to 300 times higher in tissue than serum, the highest levels being in bone marrow, lung, spleen and liver<sup>25</sup>. A significant detection rate of TTV DNA in the lymphocytes of both B cell lymphomas and

Hodgkin's disease suggests a contributory role in lymphoproliferative disorders<sup>26</sup>. Co-infection with TTV genogroup 1 (comprising genotypes 1 to 6) and human papilloma virus has been associated with poor clinical outcome in laryngeal cancer<sup>27</sup>.

Those who are convinced of the lack of pathogenicity of TTV believe that it may be due to a long history of mutual adaptation between virus and host or may be due to lack of specific cellular receptor binding sites. Such researchers have dismissed TTV as "a harmless virus", "an innocent bystander virus" or even "an endosymbiont".

Clearly, TTV is widely prevalent, extremely genetically variable, showing tropism for a wide range of tissues and causes persistent infection. Some genotypes such as genotype 1 seem to have higher disease causing potential. Interestingly, studies from India suggest that genotype 1 is the predominant type<sup>20,28</sup>. Consequences of TTV infection in immunocompromised patients and in co-infections with other viruses are largely unknown. It will be interesting to discover if we are merely incubators for this clinically "unapparent" viral agent or whether there will be an ultimate price to pay!

After the discovery of TTV, five other novel circoviruses were reported. These include SANBAN virus, TTV-like mini virus (TLMV), SEN virus (SENV), Sentinel virus (SNTV) and YONBAN<sup>29</sup>. Clear disease associations for these agents are awaited.

The discovery of TTV and its related viruses has certainly paved the way for further research into novel viral agents that infect humans. However, current evidence relating to TTV does not yet warrant routine screening/testing in blood banks or in patients with acute or chronic liver disease.

**Priya Abraham**

Department of Clinical Virology

Christian Medical College

Ida Scudder Road

Vellore 632004, India

e-mail: priyaabraham@cmcvellore.ac.in

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