Journal of
Immunology and Vaccine Technology

Open Science Publications

Volume 1, Issue 1 - 2015

www.opensciencepublications.com

Sen and Torque Teno Virus: Putative agents of Non-A-E Viral Hepatitis

Research Article

Shafqat Jahan[1], Meher Rizvi[2], Mohd Azam[2], Fatima Khan[2]*, Asfia Sultan[2], Indu Shukla[2], Abida Malik[2], M R Ajmal[3]

[1]*Department of Microbiology, Deen Dayal Upadhyay, Delhi, India*

[2]*Department of Microbiology, Jawaharlal Nehru Medical College, AMU, Aligarh, India*

[3]*Department of Medicine, Jawaharlal Nehru Medical College, AMU, Aligarh, India*

***Corresponding author:** Dr. Meher Rizvi, Assistant Professor, Department of Microbiology, JNMCH, AMU, Aligarh, Tel: 7060317021, India; Email: rizvimeher@yahoo.co.in

Article Information: **Submission:** 20/06/2015; **Accepted:** 27/07/2015; **Published:** 06/08/2015

Abstract

Introduction: The past few decades have witnessed formidable advances in the characterization of hepatotropic viruses of humans. A proportion of acute and chronic hepatitis cases still remain that cannot be ascribed to Hepatitis A-E viruses or to other viruses like certain *Enteroviruses, Adenoviruses, Parvovirus* B19 etc. The TTV and the SEN viruses are often present in the serum of individuals at high risk of infection with bloodborne viruses. Knowledge on TTV and SEN-V is growing fast, but many fundamental aspects remain to be elucidated. This study was undertaken to study the prevalence of TTV and SEN virus in patients with acute and chronic liver disease and to assess their role in liver disorders.

Methodology: The study was conducted in Jawaharlal Nehru Medical College and hospital over a period of two years. 135 patients of liver disorder were included in the study. Screened was done for HAV, HCV, HEV IgM antibodies and HBV (anti HBsAg) by ELISA. Detection of TTV and SEN-V was done by nested PCR.

Statistical analysis: Statistical analysis was performed with the IBM SPSS Statistics 19.

Result: HBV was detected in 62(46%) cases. 34(25.2%) were positive for SEN virus, 20(15%) had TTV, 5(3.7%) had HEV, 3(2.2%) had HCV and 1(0.7%) had HAV infection. TTV was detected in 1(3.3%) healthy control while SEN-V was not detected in any of the healthy controls. Isotype SEN-H was detected in 58% of SEN-V patients and SEN-D in 38%. AVH was the most common presentation of TTV (60%) and SEN-V (64.7%). Clinically fever and icterus were consistent findings along with ascitis and abdominal discomfort. MELD score was greater than normal almost unvaryingly in all these patients.

Conclusion: Our study points to a greater potential of SEN-V in causing hepatitis compared to TTV.

Keywords: Torque Teno Virus; SEN- Virus; Viral Hepatitis Non-A-E; Liver Disorders

Introduction

The past few decades have witnessed formidable advances in the characterization of hepatotropic viruses of humans, with the discovery of five major hepatitis viruses (A-E) and the development of sensitive detection methods for each. However, a relatively small proportion of acute and chronic hepatitis cases still remain that cannot be ascribed to these viruses or to other viruses like certain *Enteroviruses, Adenoviruses, Parvovirus* B19 etc.

While attempting to shed light on these forms, Nishizawa et al., in 1997 [1], first identified Torque Teno Virus (TTV) in Japanese patients who exhibited elevated alanine amino-transaminase (ALT) levels following transfusions. It is a single stranded DNA virus

ISSN: 2455-4766

belonging to the *Anelloviridae* family [2]. At least four genotypes have been described, of which genotype 1 is the most prevalent [3]. The virus has a global distribution.

In 1999, a previously unidentified DNA virus was detected in the blood of a human immunodeficiency virus (HIV) infected injection drug user and named SEN virus (SENV). SENV is distantly related to the large TTV family [4]. SENV earlier belonged to the family *Circoviridae*, genus *Anellovirus*, a group of small, single-stranded, non-enveloped circular DNA viruses. SENV, TTV and TTV-like mini viruses TUS01, SANBAN and YONBAN may have evolved from a common ancestor [5]. Recent changes in nomenclature have classified *Anelloviruses* capable of causing human infection into *alpha torque virus* (*Torque Teno virus*, TTV), *beta torque virus* (*Torque Teno-like mini virus*, TTMV) and *gamma torque virus* (*torque teno-like midi virus*, TTMDV) genera of the other *Anelloviridae* family of viruses [6]. SENV has a strong association with transfusion transmitted non A-E hepatitis [7]. The prevalence of SEN virus in serum samples of otherwise healthy persons in different geographical regions ranges from 1.8% in the United States to 28.6% in Japan [8,9]. As many as 30% of blood transfusion recipients have SEN virus in their serum [4], with a significant association between transfusion volume and the occurrence of SEN virus infection [8]. Eight genetic variants of the virus (A-H) have been described, each differing from the others by more than 25% of the total nucleotide sequence [11] but only two of these variants (SEN virus-D and SEN virus-H) have a significant association with transfusion-transmitted hepatitis and chronic liver disease [11].

The TT virus has been detected in the serum of patients with non-A-E fulminant hepatitis, chronic hepatitis, cirrhosis and HCC [12]. Despite its presence in the serum of individuals with a number of conditions and in a variety of circumstances, there is no unequivocal evidence that TTV causes hepatitis [13]. Knowledge on TTV and SEN-V is growing fast, but many fundamental aspects remain to be elucidated. This study was undertaken to study the prevalence of TTV and SEN virus in patients with acute and chronic liver disease and to assess their role in liver disorders.

Material and Methods

A prospective study was carried out on individuals presenting with clinical hepatitis at Jawaharlal Nehru Medical College and hospital, AMU, Aligarh during January 2010 to June 2011.

Study Group

A total of 135 patients of liver disorder [90 acute viral hepatitis (AVH) cases, 18(13.3%) chronic viral hepatitis (CVH), 9(6.7%) fulminant hepatic failure (FHF) cases, 17(12.6%) liver cirrhosis (LC) cases and 1(0.7%) hepatocellular carcinoma (HCC)] were included in the study. Patients with autoimmune liver disease, drug-induced hepatitis and alcoholic liver injury were excluded. The cases were recruited from Gastroenterology clinic and wards after informed consent. All the cases were subjected to detailed history, clinical examination and investigations. The study protocol was approved by the Institutional Ethical Committee of Jawaharlal Nehru Medical College.

Model end stage liver disease (MELD) score was calculated. Formula for calculating MELD score was as follows: MELD Score = 10 {0.957 LN (S. creatinine mg/dl) + 0.378 LN (T bilirubin mg/dl) + 1.12 LN (International normalized ratio) + 0.643}[14]. The four MELD levels were: greater than or equal to 25, 24-19, 18-11, less than or equal to 10 on the basis of which patients were classified as severe, modertae, mild and normal. The results were further confirmed using the MELD calculator at http://www.unos.org/resources/MELD calculator [15].

Healthy Controls

The control group comprised of 30 healthy voluntary blood donors of comparable age among which 22 (73.3%) were men and 8 (26.7%) women; mean age being 37 years ± 3.8.1 These individuals were negative for HBsAg as well as for anti-HCV and anti-HIV antibodies.

Serological investigations

Blood samples (10 ml) were collected in DNAase free containers, taking all aseptic precautions. Serum was separated and stored at -80 °C until use. All the patients were screened for IgM anti-HAV antibodies (DRG International Inc., USA), HBsAg (SD Bio standard diagnostic,India), IgManti-HCV antibodies (J. Mitra& Co. Pvt. Ltd., India), IgM anti-HEV antibodies (M.B.S.S.R.L.Medical Biological Service, Milano).

Other Investigations

Liver function and kidney function tests along with prothrombin time and international normalized ratio (INR) were performed. Specific investigations like ultrasonographic examination of liver, upper GI endoscopy and liver biopsy were performed wherever feasible.

DNA Extraction

Total DNA from 100 µl serum was extracted by standard phenol chloroform isoamyl alcohol method [16]. The extracted DNA was subjected to PCR for amplification of SEN V DNA and TTV DNA using Labnic thermal cycler (MJ Research Inc., USA)

Detection of SEN virus and its genotypes SENV-D and SENV-H DNA

SEN virus-DNA (349 bp) was detected using nested-PCR procedures specific for the detection of specific sequences for SEN virus and its genotypes SENV-D (193bp) and SENV-H (118bp) [17]. The sequences of primers are as follows: SEN-V common primers: SP1-5' TWCYCMAA CGACCAGCTAGACCT3'; SP2-5'GTTTGTGGTGAGCAGAACGGA3'. SENV-D primers: SP3-5'CTAAGCAGCCCTAACACTCATCCAG-3'; SP4-5'GCAGTTGACCG CAAAGTTAC AAGAG3'. SENV-H primers: SP5-5'TTTGGCTGCACCTTCTGGTT3'; SP6-5' AGAAAT GATGGGTGAGTGTTAGGG3'. (W=A/T, Y=C/T, M=A/C)

The outer PCR for SEN-V was carried out with a reaction mixture consisting of 12.5 µl of 2x PCR master mix (MBI Fermentas, USA) containing 0,05 units/µlTaq DNA polymerase in reaction buffer, PCR buffer, 4mM $MgCl_2$, 0.4mM dATP, 0.4mM dCTP, 0.4mM dGTP and

Citation: Jahan S, Rizvi M, Azam M, Khan F, Sultan A, et al. Sen and Torque Teno Virus: Putative agents of Non-A-E Viral Hepatitis. J Immunol Vaccine Technol. 2015;1(1): 104.

0.4mM dTTP, 5 pmol concentration of SP1 and SP2 primers and 5 µl DNA sample. The reactions consisted of preheating at 94 °C for 4 min, 40 cycles of denaturation at 94 °C for 15 sec, annealing at 55 °C for 50 sec, extension at 72 °C for 50 sec, and a final at 72 °C for 7 min. The first nested PCR for SENV D was carried out with the same reaction mixture with SP3 and SP4 primers and 5 µl outer PCR product. The second nested PCR for SENV H was carried out with the same reaction mixture used as above with SP5 and SP6 primes and 5 µl outer PCR product. Cycling conditions were the same as for SEN-V for both SENV D and SENV H.

TTV DNA Detection

16S rRNA genes were targeted for amplification of TTV specific nucleic acid by nested PCR. Primers were synthesized from Operon, Germany (Genetix).

First set of primers wereNS1 5'-GGGTGCCGAAGGTGAGTT-TAC-3', NS2 5'-GCGGGGCACGAAGCACAGAAG-3' while second set of primers were: NS3 5'-AGTTTACACACCGAAGTCAAG-3' and NS4 5'-AGCACAGAAGCAAGATGATTA-3' as described by Biagini et al., [18].

The first round PCR was carried out for 40 cycles with pre heating of 96 °C for 2 min., each cycles consisting of denaturation at 94 °C for 15 seco, primer annealing at 55 °C for 45 sec and extension at 72 °C for 45 sec, followed by an additional extension at 72 °C for 7 min in a solution containing NS1(5pmol), NS2(5pmol), DNA Template(5µl), nuclease free water (3µl), 2x PCR master mix (10µl).The second round PCR was carried out for 40 cycles, each cycles consisting of denaturation at 94 °C for 15 sec, primer annealing at 50 °C for 45 sec and extension at 72 °C for 45 sec, followed by an additional extension at 72 °C for 7 min in a solution containing NS1 (5pmol), NS2 (5pmol), PCR Product (2µl), nuclease free water (6µl), 2x PCR master mix (10µl). The 2x PCR master mix contained the reagents as described above.

Amplified PCR products (5 µl) were subjected to electrophoresis and visualized under Gel Documentation systems (Biorad, USA).

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics 19. Results were expressed as means ± standard deviation or as percentages. Means were compared between groups by using the *t –test*, and frequency distributions were compared by using the chi-square test. Wilcoxon sign ranked test and Mann Whitney U test were the non parametric tests used for non-normally distributed data.

Results

One-hundred and thirty five patients of liver disease, either admitted in Medicine wards or attending the outpatient Department and Gastroenterology clinic, along with thirty healthy age and sex matched controls were included in the study. The age distribution revealed that maximum number 28.88% were in the age group 21-30 years. The mean age distribution was 33.90±18.15 years in the study group and 40.2±6.42 years in controls. Overall male to female ratio was 2.8:1.

Hepatitis A-E, TTV and SEN-V prevalence in patients with liver diseases and in healthy controls

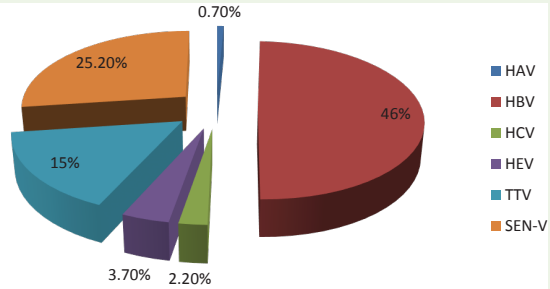
HBV was most prevalent with 62(46%) cases. A statistically significant number 34(25.18%, 95% CI: 20.1-30.3) were positive for SEN virus ($p<0.01$) (Figure 1). Prevalence of TTV was lower at 20(15%, 95% CI: 10.8-19.2) (Figure 2). A much lower prevalence was observed for HEV 5(3.7%), 3(2.2%) for HCV and 1(0.7%) for HAV (Graph 1). TTV was detected in 1(3.3%) healthy control while SEN-V was not detected in any of the healthy controls.

Graph 2 shows the distribution of HBV, TTV and SEN-V among the different categories of liver diseases. Out of 62 HBV positive patients, 32(51.6%) had AVH, 9(14.5%) had CVH, 14(22.6%) had cirrhosis, 6(9.7%) had FHF and 1(1.6%) had HCC. Among 20 TTV patients 60% were in the age group 20-40 years and most of them 12(60%) suffered from AVH, 5(25%) had CVH, 2(10%) had cirrhosis and 1(5%) had FHF.

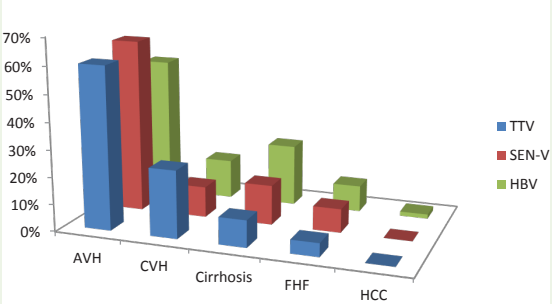
Among the 34 SEN-V positive patients 55.2% were in the age group 20-40 years. Most of the SENV positive patients had AVH 22(64.7%), 4(11.4%) had CVH, 5(14.7%) had cirrhosis and 3(8.8%) from FHF (Graph 2). On genotyping, the prevalence of SEN-D and SEN-H isotypes was found to be 38% and 58% respectively (Figure 3). 85% of SEN-D positive patients had AVH, while 15% had CVH. Among SEN-H positive patients AVH was noted in 53% followed by cirrhosis, FHF and CVH in 26%, 16% and 5% respectively.

Clinical and biochemical profile of patients with TTV and SEN-V infection

Amongst the TTV and SEN-V positive patients, fever was the



Graph 1: Distribution of Hepatitis A-E, TTV and SEN-V in patients with liver disorders.



Graph 2: Distribution of HBV, TTV and SEN-V in different disease groups.

Citation: Jahan S, Rizvi M, Azam M, Khan F, Sultan A, et al. Sen and Torque Teno Virus: Putative agents of Non-A-E Viral Hepatitis. J Immunol Vaccine Technol. 2015;1(1): 104.

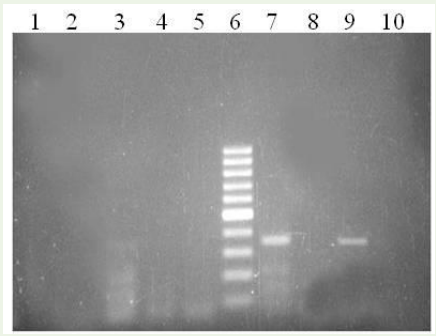


Figure 1: Amplification of PCR products for SEN-V detection.

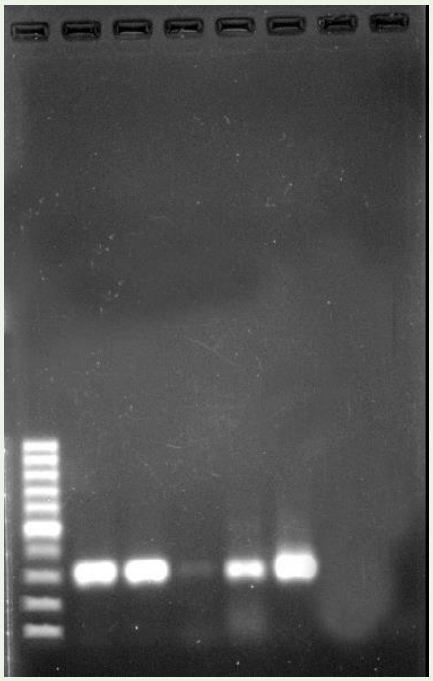


Figure 2: 2,3,5,6- Showing amplified TTV(295bp) DNA, 1- 100bp DNA ladder,4-negative control.

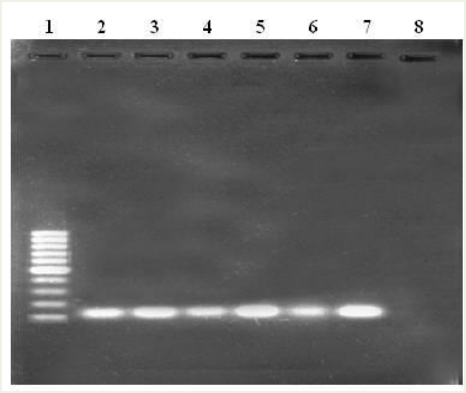


Figure 3: Lane 2-7 showing amplified SEN-H PCR product of 193 bp, lane 1 showing 100 bp DNA ladder, lane 8 showing negative control.

most common presenting complaint (85% and 79% respectively). The other significant complaints on presentation were weight loss, abdominal discomfort and high coloured urine. On examination, icterus was present in 90% of TTV and 82% of SEN-V positive patients. Ascitis and splenomegaly was more common in patients positive for TTV (67% and 60% respectively) than the SEN-V positive patients (26% and 12% respectively).

On analyzing liver function tests of the TTV positive patients, majority (60%) had deranged AST and ALT level. 70% of the patients had deranged INR and MELD score greater than normal. Among the SEN-V positive patients 73.5% had deranged AST level and 79.4% had deranged ALT levels. INR was deranged in 76.5% patients and almost all the SEN-V positive (97%) patients had MELD score higher than normal (Table 1,2).

Co-infection of TTV and SEN-V with Hepatitis A-E

Co-infection of TTV and SEN-V was highest with HBV (55%/44% for SENV and TTV). HCV co-infection was found in 5% and 6% of TTV and SENV positive cases and for HEV it was 10% and 11% respectively. None of the TTV or SENV positive cases was co-infected with HAV. Co-infection of TTV with SENV was noted in 5(14.7%) patients (Table 3).

Discussion

Despite the five known hepatitis viruses (A-E) 5-30% patients still present with acute and chronic hepatitis of unknown origin (Non A-E hepatitis). TTV and SEN-V are being considered as putative agents of post-transfusion non A-E hepatitis [4,19]. However, the exact role of these viruses in the pathogenesis of liver diseases still remains unclear.

TTV viremia is an extremely frequent occurrence in apparently healthy individuals worldwide, a feature so unusual among viruses that it has even been proposed that TTV might be a commensal virus [20]. In our study, prevalence of TTV in liver disease patients was 15% and 3.3% in healthy controls. A relative high prevalence of TTV DNA in liver diseases, in comparison to the healthy persons suggests that TTV might play an important role in causation of liver disease. Report by Irshad et al. [21] demonstrated little role of TTV in causation of liver diseases. Several studies have revealed high (1.9 to 36%) TTV DNA prevalence in healthy control groups [22-24]. Its prevalence in healthy populations in India is lower than those previously reported for Turkish (51.6%), Japanish (92.0%) and Polish (78%) blood donors [21].

Prevalence of SEN-V in our study was higher (25.2%) than TTV amongst the liver disease patients while none of the controls was found positive for SEN-V. Prevalence of SEN-V reported in previous studies, for SEN-V DNA ranged from 17 to 92% in patients with liver disease [8]. The explanations for these differences are unknown, but they may result from interactions between behavioral, social and biological factors.

A notable finding among the TTV and SEN-V positive patients was that they were associated with significant morbidity. Fever and icterus were a consistent finding in these patients, along with ascitis and abdominal discomfort. Most of the patients with TTV and/or

Citation: Jahan S, Rizvi M, Azam M, Khan F, Sultan A, et al. Sen and Torque Teno Virus: Putative agents of Non-A-E Viral Hepatitis. J Immunol Vaccine Technol. 2015;1(1): 104.

Table 1: Association of SEN-V with various biochemical parameters.

AST (IU/L)				
SEN-V positive cases	**Normal (2-20) n(%)**	**Mild (20-40) n(%)**	**Moderate (40-60) n(%)**	**Severe (>60) n(%)**
AVH (n=22)	7(31.81)	8(36.36)	0	7(31.81)
CVH (n=4)	1(25)	0	1(25)	2(50)
HE/FHF(n=3)	1(33.33)	0	0	2(66.66)
Cirrhosis(n=5)	0	4(80)	0	1(20)
Total	**9(40)**	**12(35.29)**	**1(5)**	**12(25)**
ALT(IU/L)				
SEN-V positive cases	**Normal (2-15) n (%)**	**Mild (15-30) n (%)**	**Moderate (30-45) n (%)**	**Severe (>45) n (%)**
AVH (n=22)	5(22.72)	8(36.36)	2(9.09)	7(31.81)
CVH (n=4)	1(25)	0	1(25)	2(50)
HE/FHF(n=3)	1(33.33)	0	0	2(66.66)
Cirrhosis(n=5)	0	4(80)	0	1(20)
Total	**7(20.58)**	**12(35.29)**	**3(8.82)**	**12(35.29)**
INR*				
SEN-V positive cases	**Normal (0.9-1.3) n (%)**	**Mild (1.3-2.3) n (%)**	**Moderate (2.3-3.3) n (%)**	**Severe (>3.3) n (%)**
AVH (n=22)	4(18.18)	14(63.63)	2(9.09)	2(9.09)
CVH (n=4)	2(50)	2(50)	0	0
HE/FHF(n=3)	1(33.33)	0	0	2(66.66)
Cirrhosis(n=5)	1(20)	4(80)	0	0
Total	**8(23.52)**	**20(58.82)**	**2(5.88)**	**4(11.76)**
MELD Score				
SEN-V positive cases	**Normal (<10) n (%)**	**Mild (11-18) n (%)**	**Moderate (19-24) n (%)**	**Severe (>24) n (%)**
AVH (n=22)	1(4.54)	7(31.81)	9(40.9)	5(22.72)
CVH (n=4)	0	3(75)	1(25)	0
HE/FHF(n=3)	0	3(100)	0	0
Cirrhosis(n=5)	0	3(60)	1(20)	1(20)
Total	**1(2.94)**	**17(50)**	**10(29.41)**	**6(17.64)**

INR: International normalised ratio, MELD: Model end stage liver disease

Table 2: Association of TTV with various biochemical parameters.

AST (IU/L)				
TTV positive cases	**Normal (2-20) n(%)**	**Mild (20-40) n(%)**	**Moderate (40-60) n(%)**	**Severe (>60) n(%)**
AVH (n=12)	4(33.33)	4(33.33)	0	4(33.33)
CVH (n=5)	3(60)	1(33.33)	1(33.33)	0
HE/FHF(n=1)	0	0	0	1(100)
Cirrhosis(n=2)	1(50)	1(50)	0	0
Total	**8(40)**	**6(30)**	**1(5)**	**5(25)**
ALT(IU/L)				
TTV positive cases	**Normal (2-15) n (%)**	**Mild (15-30) n (%)**	**Moderate (30-45) n (%)**	**Severe (>45) n (%)**
AVH (n=12)	3(25)	5(41.66)	0	4(33.33)
CVH (n=5)	4(80)	0	1(20)	0
HE/FHF(n=1)	0	0	0	1(100)
Cirrhosis(n=2)	1(50)	1(50)	0	0
Total	**8(40)**	**6(30)**	**1(5)**	**5(25)**

Citation: Jahan S, Rizvi M, Azam M, Khan F, Sultan A, et al. Sen and Torque Teno Virus: Putative agents of Non-A-E Viral Hepatitis. J Immunol Vaccine Technol. 2015;1(1): 104.

INR*				
TTV positive cases	**Normal (0.9-1.3) n (%)**	**Mild (1.3-2.3) n (%)**	**Moderate (2.3-3.3) n (%)**	**Severe (>3.3) n (%)**
AVH (n=12)	2(16.66)	9(75)	0	1(8.33)
CVH (n=5)	3(60)	1(10)	1(10)	0
HE/FHF(n=1)	0	0	1(100)	0
Cirrhosis(n=2)	1(50)	1(50)	0	0
Total	**6(30)**	**11(78.57)**	**2(14.28)**	**1(7.14)**
MELD Score				
TTV positive cases	**Normal (<10) n (%)**	**Mild (11-18) n (%)**	**Moderate (19-24) n (%)**	**Severe (>24) n (%)**
AVH (n=12)	1(8.33)	5(41.66)	3(25)	3(25)
CVH (n=5)	0	4(80)	1(20)	0
HE/FHF(n=1)	0	0	0	1(100)
Cirrhosis(n=2)	0	2(100)	0	0
Total	**1(5)**	**11(78.57)**	**4(28.57)**	**4(28.57)**

INR: International normalised ratio, MELD: Model end stage liver disease

Table 3: Co-infection of TTV and SEN-V with Hepatitis A-E.

	Number of cases
HBV+HCV+TTV+SEN-V	**0**
HBV+ TTV+SEN-V	**3**
HCV+TTV+SEN-V	**1**
HBV+HCV+TTV	**0**
HBV+HCV+ SEN-V	**0**
HBV +TTV	**11**
HBV +SEN-V	**15**
HCV+TTV	**1**
HCV +SEN-V	**2**
TTV+SEN-V	**5**

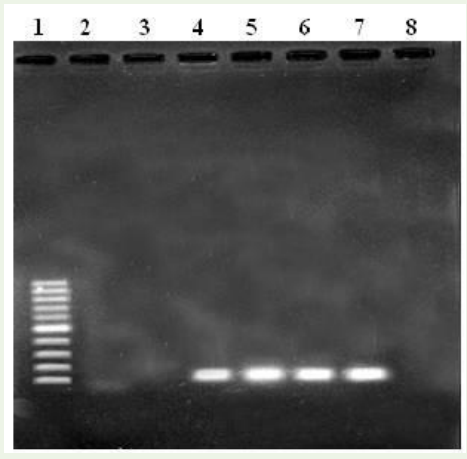


Figure 4: Lane 4-7 showing amplified SEN-D PCR product of 118 bp, lane 1 showing 100 bp DNA ladder, lane 2,3 showing negative control.

SEN-V infection had raised ALT, AST and INR levels. MELD score was greater than normal almost unvaryingly in all these patients. Abnormality in the liver functions along with clinical manifestations point to a possible role of these viruses in the pathogenesis of liver disorders. Such type of analysis has not been done in previous studies.

To assess the role of these two viruses in the causation of liver disease we compared the clinical presentation of TTV and SEN-V to HBV. It was noted that the most common presentation of all the three viruses was AVH (60%, 64.7% and 51.6% for TTV, SEN-V and HBV respectively). A significant finding of our study was that CVH was more common in patients with TTV infection, while patients with SEN-V had higher rates of cirrhosis. However there may be other yet undiscovered viruses which may be actual cause of hepatitis and SEN and TTV may be simply bystanders.

Conclusions

Our study points to a greater potential of SEN-V in causing hepatitis compared to TTV. SEN-D was associated with AVH while SEN-H was more prevalent in CVH cases. In future longitudinal studies with larger sample size will further elucidate the role of these viruses in causation of AVH and CVH.

References

1. Nishizava T, Okomata H, Konishi K, Yoshizawa H, Miyakawa Y, et al. (1997) A novel DNA virus (TTV) associated with elevated transaminase levels in posttransfusion hepatitis of unknown etiology. Biochem Biophys Res Commun 241: 92- 97.
2. Jelcic I, Holtz-Wagenblattt A, Huzaiker A, Zurhausen H, De Villiers EM (2004) Isolation of multiple TT virus genotypes from spleen biopsy tissue from a Hodgkin's disease patient: genome re-organization and diversity in the hypervariable region. J Virol 8: 7498-7507.
3. Diniz-Mendez L, DeValle S, Niel C (2004) Genomic characterization of a Brazilian TT virus isolate closely related to SEN virus F. Mem Inst Oswaldo Cruz 99: 301-306.
4. Matsumoto A, Yeo AET, Shih JW, Tanaka E, Kiyosawa K, et al. (1999) Transfusion-associated TT virus infection and its relationship to liver disease. Hepatology 30: 283-288.
5. Hino S (2002) TTV, a new human virus with single stranded circular DNA genome. Rev Med Virol 12: 151-158.
6. Biagini P (2009) Classification of TTV and related viruses (anelloviruses). Curr Top Microbiol Immunol 331: 21-33.
7. Umemura T, Donahue P, Sottini A, et al. (2000) SEN virus infection and its relationship to transfusion-associated hepatitis. Anti vir Ther 5(Suppl):11.

Citation: Jahan S, Rizvi M, Azam M, Khan F, Sultan A, et al. Sen and Torque Teno Virus: Putative agents of Non-A-E Viral Hepatitis. J Immunol Vaccine Technol. 2015;1(1): 104.

8. Viazov S, Ross RS, Varenholz C, Lange R, Holtmann M, et al. (1998) Lack of evidence for an association between TT infection and severe liver disease. J Clin Virol 11: 183-187.

9. Tanaka H, Okamoto H, Luengrojanakul F, Chainuvati T, Tsuda F, et al. (1998) Infection with an unenveloped DNA virus (TTV) associated with posttransfusion non-A to G hepatitis patients and healthy blood donors in Thailand. J Med Virol 28: 839-842.

10. Jeon MJ, Shin JH, Suh SP, Lim YC, Ryang DW (2003) TT virus and hepatitis G virus infections in Korean blood donors and patients with chronic liver disease. World J Gastroenterol 9: 741-744.

11. Unemura T, Yeo AE, Sottini E, Moratto D, Tanaka Y, et al. (2001) SEN virus infection and its relationship to transfusion-associated hepatitis. Hepatology 33: 1303-1311.

12. Mikuni M, Moriyama M, Tanaka N, Abe F, Arakawa Y (2002) SEN virus infection does not affect the progression of non-A to-E liver disease. J Med Virol 67: 624-629.

13. Charlton M, Adjei P, Poerucha J, Zein N, Moore B, et al. (1998) TT virus infection in North American blood donors, patients with fulminant hepatic failure, and cryptogenic cirrhosis. Hepatology 28: 839-842.

14. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, et al. (2001) A model to predict survival in patients with end-stage liver disease. Hepatology 33: 464-470.

15. MELD Calculator.

16. Saiki RK, Gelfand DH, Stoffel S, Scharf SJ, Higuchi R, et al. (1988) Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. Science 239: 487-491.

17. Tang ZH, Chen XH, Yu YS, Zang GQ (2008) Prevalence and clinical significance of SEN virus infection in patients with non A-E hepatitis and volunteer blood donors in Shanghai. World J Gastroenterol 14: 4204-4208.

18. Biagini P, Gallian P, Attoui H, Cantaloube JF, de Micco P, et al. (1999) Determination and phylogenetic analysis of partial sequences from TT virus isolates. J Gen Virol 80: 419-424.

19. Abe K, Inami T, Asano K, Miyoshi C, Masaki N (1999) TT virus infection is widespread in the general populations from different geographical regions. J Clin Microbiol 37: 27-35.

20. Simmonds P, Prescott LE, Logue C, Davidson F, Thomas AE, et al. (1999) TT-virus part of the normal human flora? J Infec Dis 180: 1748-1750.

21. Irshad M, Sharma Y, Dhar I, Singh J, Joshi YK (2008) Torque teno virus: Its prevalence and isotypes in North India. World J Gastroenterol 14: 6044-6051.

22. Naoumov NV, Petrova EP, Thomas MG, Williams R (1998) Presence of a newly described human DNA virus (TTV) in patients with liver disease. Lancet 352: 195-197.

23. Ikeda H, Takasu M, Inoue K, Okamoto H, Miyakawa Y, et al. (1999) Infection with an unenveloped DNA virus (TTV) in patients with acute or chronic liver disease of unknown etiology and in those positive for hepatitis C virus RNA. J Hepatol 30: 205-212.

24. Saback FL, Gomes SA, de Paula VS, da Silva RRS, Lewis-Ximmenez LL, et al. (1999) Age-specific prevalence and transmission of TT virus. J Med Virol 59: 318-322.

Citation: Jahan S, Rizvi M, Azam M, Khan F, Sultan A, et al. Sen and Torque Teno Virus: Putative agents of Non-A-E Viral Hepatitis. J Immunol Vaccine Technol. 2015;1(1): 104.