SEN virus: epidemiology and characteristics of a transfusion-transmitted virus

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SEN virus (SEN-V) is a blood-borne, single-stranded, nonenveloped DNA virus. Although its prevalence varies by geographic region, it has been detected in as many as 30 percent of postoperative transfusion recipients, compared to 3 percent of postoperative patients who did not receive transfusions. A significant association has been observed between transfusion volume and the occurrence of SEN-V infection. Transmission by transfusion also has been confirmed by the detection of greater than 99 percent homology between SEN-V in donor and recipient sera. Concurrent infections with SEN-V and hepatitis B virus, hepatitis C virus, or human immunodeficiency virus type 1 have been documented, and these observations probably reflect the blood-borne transmission of these viruses as well as SEN-V. Although SEN-V was discovered as part of a search for causes of posttransfusion hepatitis, there is no firm evidence so far that SEN-V infection either causes hepatitis or worsens the course of coexistent liver disease. Nevertheless, SEN-V appears to be transmitted by transfusion, and further studies may reveal more about its role in the future.

ABBREVIATIONS: HCC(s) = hepatocellular carcinoma(s); SEN-V = SEN virus.

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SEN virus (SEN-V) is a blood-borne virus that was discovered in 1999 by investigators at DiaSorin Biomolecular Research Institute, Saluggia, Italy, in their search for a viral cause of those cases of posttransfusion hepatitis that are not due to the hepatitis B virus (HBV) or hepatitis C virus (HCV).[1] These cases of posttransfusion hepatitis also are not caused by any other of the known human hepatitis viruses, and therefore they have often been referred to as "non-A-to-E hepatitis." Two other viruses (TT virus[2] and GB virus, type C[3] [also known as the hepatitis G virus]) previously had been identified by other investigators as possible causes of posttransfusion non-A-to-E hepatitis but a causal association has not been established.[4,5]

The discovery of SEN-V was first reported in the lay press on July 20, 1999,[1] but the discovery itself was never reported in a scientific journal or meeting. The publication of a European patent with the nucleic acid sequence of SEN-V on May 18, 2000,[6] and reports of subsequent studies by other investigators in 2001[7] were the first descriptions of SEN-V in the scientific literature. The name of SEN-V was derived with the initials of the first identified patient.[1]

DETECTING SEN-V

SEN-V is usually detected using the DNA enzyme immunoassay (EIA) method developed by DiaSorin.[7-20] In this method, viral DNA is amplified by polymerase chain reaction (PCR) and detected using biotinylated strain-specific probes in an EIA. In addition, however, SEN-V has also been detected using either PCR-Southern blot (unpublished data) or ethidium bromide gel electrophoresis after single-step PCR,[21,22] seminested PCR,[23-25] or nested PCR.[25-28] The sensitivity of the methods has been reported to be 5 copies per assay (800 copies/mL; reported in Umemura et al.[19] for the method used in Tanaka et al.,[7] Umemura et al.,[8,9,15,19] Shibata et al.,[10] Momosaki et al.,[17] Wilson et al.,[18] and Pfeiffer et al.[20]), 10 copies per assay (1600 copies/mL),[13,14] 100 copies per mL,[23] or not reported.[11,12,16,21,22,24,25,27,28] The specificity of the assays appears to be high; in some of the studies, some or all of the amplified SEN-V segments were sequenced.[7,8,12,13,18,21,23,27,28]

The Genome

The genome of SEN-V is similar to that of the TT virus and both viruses are now classified within the Circovirus family. Both are single-stranded, nonenveloped DNA viruses of approximately 3800 nucleotides.[7,29,30] Although structurally similar, the genomes of SEN-V and TT virus have less than 55 percent nucleotide sequence homology and less than 37 percent amino acid homology.[7]

Although SEN-V is a DNA virus, its rate of spontaneous mutation is closer to that of an RNA virus, suggesting the absence of effective nucleotide proofreading function.[31] The rate of synonymous substitution in SEN-V strain D has been shown to be 7.32×10^{-4} per site per year.[31] This value is closer to the rate of synonymous substitutions for RNA viruses (13.08×10^{-3} for human immunodeficiency virus [HIV] type 1;[32] 3.59×10^{-3}-13.10×10^{-3} for influenza A virus;[33] 1.35×10^{-3}-7.51×10^{-3} for HCV;[33]) than for DNA viruses (4.57×10^{-5}-7.90×10^{-5} for HBV;[34] 3.5×10^{-8} for herpes simplex virus type 1;[35] and 4×10^{-7} for JC virus[36]).

EPIDEMIOLOGY

The prevalence of SEN-V in otherwise healthy persons, including blood donors, differs markedly by geographic region. The prevalence of SEN-V isolated from serum samples of otherwise healthy persons has been reported to be 1.8 percent in the United States,[8] from 10 to 22 percent in Japan,[10,11] 15 percent in Taiwan,[21] 5 percent in Thailand,[24] from 8 to 17 percent in Germany,[15,23] 24 percent in Greece,[15] and at least 13 percent in Italy.[14]

Evidence to support the transmission of SEN-V by blood transfusion has been reported. SEN-V DNA was detected in 86 of 286 (30%) previously uninfected surgery patients after transfusion, compared with 3 of 97 (3%) patients who did not receive transfusions.[8] Transmission by transfusion was confirmed by the detection of greater than 99 percent homology between SEN-V isolates from paired donor and recipient samples. A significant association was observed between transfusion volume and the occurrence of SEN-V infection.[8] The prevalence of SEN-V is 42 to 68 percent among patients with hemophilia, who usually have been treated with multiple blood transfusions and large volumes of plasma derivatives.[21,23] (Although little is known about the effect on SEN-V of viral inactivation procedures applied during the manufacture of plasma derivatives, it is likely that SEN-V is resistant to many of these because it is a nonenveloped virus.) Among hemodialysis patients, some investigators have found a prevalence of SEN-V ranging from 13 to 68 percent,[11,21,23] although one of the reports found that dialysis patients with SEN-V had similar mean volume of prior blood transfusions and mean duration of dialysis to those without SEN-V, suggesting acquisition by another route.[11] Other individuals who are at high risk for other blood-transmitted infections also have a high prevalence of SEN-V infection, including 23 to 54 percent of injection drug users[18,21,23] and 44 to 54 percent of persons infected with HIV.[18,23]

Transmission of SEN-V from infected mothers to their newborn infants appears to occur;[13] this is a characteristic that SEN-V shares with some other blood-borne viruses such as HBV. As with HBV transmission from mother to infant, one cannot ascertain at present whether such transmission of SEN-V occurs before, during, or after delivery. SEN-V was detected in 10 of 15 infants born to 15 SEN-V–infected mothers.[13] In that study, however, SEN-V was also detected in 3 of 15 babies born to 15 uninfected mothers. Among all of the 13 infants infected in that study, SEN-V was detected in only 1 infant at the time of delivery (an infant whose mother had acute hepatitis in early pregnancy) and was detected in the others from 1 to 16 months after delivery. Cloning and sequence analysis of SEN-V DNA from matched mother-infant pairs confirmed that each infant's infection had been acquired from his or her own mother. In that study, however, some mothers were simultaneously infected with HIV; the exact number was not reported. Simultaneous infection of mothers with HIV could facilitate a much higher rate of SEN-V infections in their newborn infants. The uncertain but likely role of simultaneous HIV infections in the SEN-V–infected mothers, as well as the occurrence of three SEN-V infections in infants whose mothers were not infected with SEN-V,[13] makes it important to await replication of these findings before drawing firm conclusions concerning maternal-infant transmission of SEN-V.

SEN-V STRAINS D AND H

SEN-V consists of eight strains, designated as strains A to H.[7] Two of the strains, D and H, appear be associated more frequently than others with non-A-to-E hepatitis,[8] although it is not clear whether this observation has any significance. These two strains have been found in 30 percent of cases of transfusion-associated non-A-to-E hepatitis in the United States, compared to 1.8 percent of healthy blood donors.[8]

The distribution of SEN-V strains D and H among blood donors or other healthy populations varies geographically.[8,15,21,24] Most studies, however, have not evaluated other strains, but rather focused only on strains D and H because of their possible but unproven association with posttransfusion hepatitis.

CONCURRENT INFECTIONS WITH SEN-V AND OTHER VIRUSES

Concurrent infections with SEN-V and HIV-1 have been reported in Italy,[14] the United States,[18] and Germany.[23] The

prevalence of SEN-V was higher among those who acquired HIV through use of intravenous drugs (71%) than among those who acquired HIV by sexual transmission (26%).[14] HIV-1 infection may possibly play a role in facilitating maternal-infant transmission of SEN-V[13] referred to above. Concurrent infections with SEN-V and either HBV or HCV have also been reported.[17] These observations may simply reflect the blood-borne transmission of these viruses and SEN-V.

SEN-V AND LIVER DISEASE

Although SEN-V infection is found more frequently in patients with liver diseases compared with the general population, there is no firm evidence so far that SEN-V infection either causes hepatitis or worsens the course of coexistent liver disease,[8,10,15,24,28] including infections with hepatitis A virus,[21] HBV,[15,21,24] and HCV.[9,15,16,18,21-24] SEN-V infections have been reported in 20 to 60 percent of patients with HBV infection[10,15,21,24] and in 7 to 67 percent of patients with HCV infection.[9,15,18,24] There was no difference in alanine aminotransferase (ALT),[16,18,21,22] bilirubin levels,[15,18,24] or liver histologic findings[16,18,21-23] between those with SEN-V coinfection and those without. SEN-V was found in 31 to 57 percent of patients with cirrhosis in Japan,[10,27] including 45 percent in HBV-cirrhosis[10] and 22 percent in HCV-cirrhosis.[10]

In acute non-A-to-E hepatitis, patients have been found to have SEN-V in 33 to 92 percent of cases;[8,15,27] in those with chronic non-A-to-E hepatitis, SEN-V has been detected in 36 to 69 percent.[15,27,28] There was no significant difference in ALT level,[15,27,28] bilirubin level,[15,28] or histologic findings between SEN-V–positive non-A-to-E hepatitis and SEN-V–negative non-A-to-E hepatitis. ALT levels in these patients with non-A-to-E hepatitis and SEN-V infections ranged from 41 to 396 IU per L. Jaundice was not seen[8] except in one study in which 41 of 129 patients (32%) with SEN-V–associated acute non-A-to-E hepatitis had jaundice.[15]

SEN-V AND HEPATOCELLULAR CARCINOMA

Although SEN-V is found in the serum of a large percentage of hepatocellular carcinoma (HCC) patients, no carefully controlled studies have been conducted to determine if SEN-V is associated with the development of HCC. SEN-V has been found in 32 percent of HCC patients from Canada,[17] 42 percent of HCC patients from Japan,[17] and 19 percent of HCC patients from Thailand.[25] In another study from Japan, SEN-V was detected in 76 percent of patients with HCC compared to 75 percent of controls without liver disease.[26] Amplification of SEN-V replicative intermediates from HCCs from two patients has been reported.[8]

COURSE OF SEN-V INFECTION

SEN-V DNA became undetectable in serum within 6 months after transfusion in 17 of 31 (55%) cases of post-transfusion SEN-V–positive non-A-to-E hepatitis in the United States.[8] Twelve of 31 (39%) had detectable SEN-V in their serum for longer than 1 year.[8] Infections lasting as long as 12 years were documented in two cases.[8] In one other study, only 1 of 7 patients (14%) remained SEN-V–positive in serum after 1 year;[23] six of seven (86%) became SEN-V-negative within 12 months. In a study of 397 injection drug users in the United States, retesting of serum samples after a median of 9.3 years revealed that 61 percent of patients remained positive for SEN-V strain D and 27 percent remained positive for SEN-V strain H.[18]

RESPONSE TO INTERFERON THERAPY

The effect of interferon (IFN) therapy on SEN-V infection has been evaluated retrospectively in patients whose coexistent HCV infections were treated with IFN-α,[9,16] IFN-α plus IFN-β,[16] or IFN-α plus ribavirin.[12,22] SEN-V DNA became undetectable in serum after IFN therapy in 69 percent,[9] 77 percent,[16] and 32 percent[22] of patients. In these studies, a sustained response of HCV to IFN occurred as frequently in patients with SEN-V infection as in those without.[9,16,22] In one other study, there was no response of HCV to IFN-α and ribavirin in 11 of 13 (85%) patients infected with SEN-V strains D or H[12] (and SEN-V detection also was not affected by the treatment).

FUTURE DIRECTIONS

In recent years, research on SEN-V has decreased in intensity owing to lack of data showing that SEN-V causes hepatitis, despite the apparent association between SEN-V and non-A-to-E hepatitis in some studies. In addition, DiaSorin, the company that made the original discovery of SEN-V, ceased working on SEN-V after they were acquired by another company.

Nevertheless, SEN-V is a blood-borne virus that is found frequently in the blood of patients who are at risk for infections by other blood-borne viruses. It appears to be transmitted by transfusion, but so far no disease has been shown to accompany that transmission. Knowledge of the epidemiology of the virus and the availability of sensitive assays to detect it may make it possible to identify its potential role in disease more precisely in the future.

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