Cerebrospinal Fluid Compartmentalization of Hepatitis B Virus in Chronic HIV-1 Coinfected Patients

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Abstract

Introduction: The central nervous system (CNS) can function as a unique compartment for various types of viruses leading to neuroinvasiveness. In this study we investigated the presence and compartmentalization of hepatitis B virus (HBV) in the cerebrospinal fluid (CSF) of chronic HIV-1 coinfected patients.

Methods: Paired plasma/CSF samples from 26 HIV/HBV coinfected patients (mean age 47.1 years, 18 males) with various neurological manifestations were collected during routine follow-up visits. The presence of HBV DNA in the CSF was determined using the Inno-LiPA HBV assay (Innogenetics, NV, Ghent, Belgium). HBV DNA levels were measured using the Amplicor system (Roche Diagnostics, Basle, Switzerland). HBV genotypes were determined using the INNO-LiPA HBV test (Innogenetics, NV, Ghent, Belgium) and Sanger sequencing. Reverse transcriptase (RT) sequencing was performed in selected cases.

Results: HBV DNA was detected in the CSF in 11 of 26 patients (42.3%), with plasma HBV DNA levels ranging from 5 × 10³ to 3.27 × 10⁶ copies/mL. Intrathecally synthesized HBV DNA and RNA were detected in 10 patients. HIV RNA levels were below the detection limit in 15 patients. HBV genotype a was detected in 10 patients, while genotype d was found in 5 patients. We identified 12 unique HBV drug-resistant variants in the CSF of 3 patients, with resistance mutations at positions L181, M204, and L180/A181. The prevalence of HBV DNA in the CSF was significantly higher in patients with detectable HBV DNA in plasma compared to those without (p = 0.02). The presence of HBV DNA in the CSF was associated with lower CD4 counts and higher HIV RNA levels (p = 0.02). The presence of HBV DNA in the CSF was also associated with neurological symptoms, including dementia, encephalopathy, and MIBEs.

Discussion: We report:

- the presence and high rate of HBV DNA in the CSF of HIV patients with productive HBV infection (61.1%)
- the presence of viral genotypic compartmentalization of HBV between blood and CSF

In our study, all subjects with HBV DNA in the CSF had detectable HBV RNA in the CSF, suggesting a relationship between the two.

Concerning CNS compartmentalization:

- We detected HBV DNA in the CSF of more than half of the subjects who had detectable blood plasma HBV RNA, and in all cases, the viral loads of CSF HBV DNA were lower than in the blood, and there was a positive correlation between them, suggesting that there may not always be compartmentalization of HBV infection between the blood and CNS.

- With genotypic analysis, we found evidence of CNS compartmentalization, at least in the setting of HBV drug resistance.

- Interestingly, we found that most of our subjects with current exposure to lamivudine had undetectable HBV in the CSF.

The demonstration of HBV CNS compartmentalization in the setting of lamivudine associated resistance lends evidence that HBV replicates independently in the CNS and that CNS may function as a sanctuary for HBV in the development of HBV drug resistance, similar to what has been demonstrated in HIV.

Limitations:

- Small study group – we lacked the power to determine the clinical significance of the presence of HBV in the CSF, although the surprisingly high number of adolescents with stroke could suggest a vasculitic mechanism.

- Interference of other neurological conditions - the association with HIV-associated encephalitis could suggest a facilitator role of HBV in the development of neurocognitive impairment, as previously demonstrated for HIV.

Further research

- These findings may be important in identifying HBV-related impact on CNS disease, especially in the setting of HIV co-infection and the understanding of HBV entry into the CNS.

- The consequences of 3TC treatment during HIV/HBV co-infection and the development of HIV and HBV 3TC resistance remains unclear.

- If HBV plays a role in neurocognitive impairment, and most of the co-infected patients are already resistant to 3TC, there will be a need of adressing the problem of 3TC-penetrating treatment for HBV.