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Letter to the Editor

HHV-6-associated Encephalitis should be Diagnosed only by means of PCR and after Carefully Ruling out Competing Differential Diagnoses

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Letter to the Editor

We read with interest the article by Kondo *et al*. regarding a 64-year-old patient who, six months after a liver transplant performed due to cirrhosis caused by hepatitis B and hepatocellular carcinoma, developed a probable human herpesvirus-6 (HHV-6) infection [1]. The infection followed a complicated course, leading to refractory status epilepticus, renal failure, pancytopenia, cardiac arrest, and, ultimately, death [1]. The authors concluded that the detection of HHV-6 in the cerebrospinal fluid (CSF) is difficult to interpret due to competing differential diagnoses, and that managing the toxicity of antiviral and anticonvulsant medications presents a significant challenge [1]. While the study is noteworthy, several aspects warrant further discussion.

A primary point is that the diagnosis of HHV-6-associated encephalitis should be questioned [1]. The possibility of a false-positive HHV-6 result via the BioFire system was not considered [1]. Since approximately 1% of the population carries the HHV-6 genome integrated into their chromosomes (iciHHV-6), the BioFire PCR test can detect this DNA even in the absence of an active infection or encephalitis. In immunocompetent patients, therefore, positive HHV-6 findings very often represent such false-positive or clinically irrelevant results. It is, consequently, crucial to confirm or rule out the presence of the virus using quantitative real-time PCR, the gold standard for HHV-6 diagnostics [2]. To reliably distinguish this harmless genetic predisposition from actual, active viral replication, a specialized RT-PCR (or DNA analysis using hair roots or fingernails) can be employed.

The second point is that the CSF examinations were insufficient to confirm or rule out encephalitis [1]. Given the suspicion of viral encephalitis, a comprehensive CSF analysis for neurotropic viruses, syphilis, Borrelia, helminths, parasites, and tuberculosis would have been essential. The investigation into neurotropic viruses as a potential cause of the clinical manifestations should have included PCR-based testing for HSV-1, HSV-2, VZV, CMV, EBV, mumps, measles, rubella, HIV, SARS-CoV-2, rabies, tick-borne encephalitis, echo, coxsackie, poliovirus, as well as West Nile, dengue, Zika, Japanese encephalitis, St. Louis encephalitis, eastern and western equine encephalitis, and Powassan, hepatitis, and the chikungunya virus [3]. A comprehensive CSF examination is crucial for identifying the underlying cause.

The third point is that the CSF was not tested for antibodies associated with autoimmune encephalitis (AIE) [4]. Since there was a suspicion of limbic encephalitis, which can have an autoimmune etiology, testing the CSF for AIE-associated antibodies would have been indispensable. AIE-related antibodies can target structures on the cell surface or at synapses, or they may be directed against intracellular structures. AIE antibodies directed against cell-surface or synaptic structures include those targeting NMDAR, LGI1, CASPR2, GABA-A, GABA-B, AMPA-1, AMPA-2, DPPX, the glycine receptor, D2R, IgLON5, neurexin-3-alpha, and GluR3. AIE antibodies directed against intracellular structures include ANNA-1, PCA-1, CV2, MA-2, MA-1, amphiphysin, and GAD65 [4].

A fourth point is that viral myocarditis was not considered as a potential cause of the cardiac arrest and death [1]. Given that the patient was presumably experiencing a viral infection, it is conceivable that the myocardium was also affected. Was there any clinical evidence of myocarditis?

A fifth point is that no autopsy was performed [1]. Post-mortem examinations would have been essential to clarify the circumstances.

Finally, no reference ranges were provided in either the text or the two tables. Without reference ranges, it is difficult to determine which of the reported values were truly abnormal and which were within the normal range.

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