Fatal PCR-negative herpes simplex virus-1 encephalitis with GABA\(_A\) receptor antibodies

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Herpes simplex virus-1 encephalitis (HSVE) is the most common cause of fatal sporadic encephalitis worldwide. Recently, post-HSVE relapses due to autoimmune encephalitis with NMDA receptor antibodies and other synaptic autoantibodies have been reported in up to 27% of patients within 1–2 months after HSVE.\(^1,2\) We report an unusual case of a patient with refractory status epilepticus due to HSVE with antibodies against GABA\(_A\) receptors (GABA\(_AR\)).

**Case report**

A 47-year-old man was admitted with a new-onset generalized seizure. Two days before admission, behavioral changes were observed. No psychiatric symptoms, headaches, or feverish infections had occurred in the previous weeks. He had a B-cell non-Hodgkin lymphoma 5 years ago and a Hodgkin lymphoma 16 years ago, both in complete remission after radiochemotherapy. Eventually, focal status epilepticus developed provoking intensified anticonvulsive treatment.

Initial brain MRI showed hyperintense fluid-attenuated inversion recovery (FLAIR) signal of the left prefrontal gyrus without diffusion restriction (figure 1, A and D) or contrast enhancement. CSF analysis on the day of admission revealed lymphocytic pleocytosis (13 leukocytes/\(\mu\)L), elevated protein (574 mg/L), and lactate (2.74 mmol/L). IV acyclovir 750 mg TID was started. CSF herpes simplex virus-1 (HSV-1) quantitative polymerase chain reaction (qPCR) was negative. A second lumbar puncture (day 5 of admission) showed 29 lymphocytes/\(\mu\)L, normal protein, and slightly elevated lactate (2.27 mmol/L). HSV-1 DNA remained undetectable. Immunoglobulin G-HSV antibody index was unremarkable (<1.3); further analysis revealed no other infectious causes. However, GABA\(_AR\) antibodies were detected in serum (1:1,600) and CSF (1:32) of the second lumbar puncture using cell-based assays, tissue-based assays, and life embryonal hippocampal neuron cultures (figure 1, G–I);\(^3\) no other neuronal antibodies were identified.

Acyclovir was stopped, yet IV methylprednisolone did not induce clinical improvement. Follow-up MRI showed expansion of the left frontal hyperintense FLAIR lesion with accompanied diffusion restriction and new bilateral opercular diffusion restrictions (figure 1, B, C, E, F). Refractory status epilepticus continued (EEG, figure e-1, links.lww.com/NXI/A145). The patient died of bowel ischemia due to thrombosis of the mesenteric artery. Postmortem revealed extensive HSVE with necrosis, inflammation, positive HSV antigen, and tissue PCR (figure 1J). No evidence of lymphoma was found.
Discussion

We describe an unusual case of CSF-qPCR-negative HSVE with concomitant GABAAR antibodies. We confirmed presence and specificity of GABAAR antibodies in serum and CSF with high titers, typical staining on rat brain immunohistochemistry and neuronal synapses of live neurons in vitro.

Our patient was initially misdiagnosed with idiopathic GABAAR encephalitis owing to detection of GABAAR antibodies, 2...
negative HSV-1 qPCR in CSF, and characteristic clinical presentation with severe encephalitis and refractory status epilepticus. HSVE was only diagnosed postmortem by demonstration of widespread viral replication in brain tissue. Coincidental development of HSVE and GABA\(_{A}\)R encephalitis is unlikely because of the low incidence of both diseases; rather, breakdown of immunologic tolerance toward GABA\(_{A}\)R likely provoked by virus-induced destruction of neurons would be a plausible explanation.

Previous post-HSVE autoimmune encephalitis cases predominantly had a biphasic course. However, development in contiguity with HSVE symptoms similar to our case has been described in adults, and relapses have been observed as early as 7 days after HSVE in a 2-month-old boy.

Furthermore, a case of post-HSVE GABA\(_{A}\)R encephalitis was recently described in a 15-month-old child occurring 8 weeks after herpes infection, and a second case occurred following HHV6 encephalitis. We are not aware of a case of post-HSVE GABA\(_{A}\)R encephalitis in an adult patient. However, because of the unavailability of initial CSF antibody testing, we cannot exclude the presence of “premorbid” GABA\(_{A}\)R antibodies as a coincidental finding related to previous lymphoma. Although, the “premorbid” presence of high-titer CSF GABA\(_{A}\)R antibodies without a history of seizures appears less plausible than our current hypothesis of continuous post-HSVE GABA\(_{A}\)R encephalitis.

Pathologic-proven HSVE without detectable HSV-1 DNA in CSF is another unusual feature and was rarely reported. Hypothetical explanations could be early lumbar puncture and analysis under pretreatment with acyclovir. The previous lymphoma could have predisposed toward (1) the development of HSVE as has been noted in inborn errors of pattern-recognition pathways and (2) a breakdown of immune tolerance and consecutively development of systemic GABA\(_{A}\)R antibodies predisposing to rapid development of CNS autoimmunity after HSVE.

In summary, this single case illustrates the occurrence of GABA\(_{A}\)R antibodies in PCR-negative HSVE in an immuno-suppressed patient resulting in misdiagnosis of idiopathic GABA\(_{A}\)R encephalitis. Key clinical points are (1) the difficulty of ruling out HSVE with qPCR and immunoglobulin G antibody index, (2) the occurrence of GABA\(_{A}\)R antibodies in parallel to HSVE, and (3) the possibility of unusual clinical courses of HSVE and post-HSVE autoimmune encephalitis in patients with immune deficiencies.

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Appendix (continued)

| Name                  | Location                                      | Role                        | Contribution                                                                 |
|-----------------------|-----------------------------------------------|-----------------------------|------------------------------------------------------------------------------|
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| Tim Magnus, MD        | University Hospital Hamburg-Eppendorf, Department of Neurology | Author                      | Interpretation of data and revising the manuscript                         |