

Letter to the Editor: New Observation

Detection of Post-HSV Autoimmune Encephalitis and Nonconvulsive Status Epilepticus Using Ictal Subtraction SPECT

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Autoimmune encephalitis after herpes virus simplex encephalitis (HSVE) is a relatively frequent occurrence with 30%–42% of patients developing neuronal cell surface antibodies,¹ and up to 27% developing autoimmune encephalitis post-HSVE.^{1,2} Of those that develop autoimmune encephalitis, 82% in one large cohort had anti-N-methyl-D-aspartate receptor (NMDAR) antibodies and the remainder unidentified cell surface antibodies.² Rarely GABA-A Receptor and Dopamine-Receptor 2 antibodies have been reported as well.³ Post-HSVE autoimmune encephalitis typically begins within 2 months of initial infection and frequently presents with neuropsychiatric symptoms.¹ Accompanying seizures and more rarely, nonconvulsive status epilepticus (NCSE) has been reported in patients with autoimmune encephalitis post-HSVE.³

NCSE can be difficult to diagnose with certainty, and the Salzburg Consensus Criteria are used to determine probable, possible or no NCSE based on scalp electroencephalogram (EEG) findings.⁴ In patients with NCSE, single-photon emission computed tomography (SPECT) detects NCSE with a sensitivity of greater than 80%, even in the setting of indeterminate scalp EEG patterns.^{4,5} Repeating the scan after treating seizures allows ictal-interictal subtraction, revealing the seizure onset zone.⁵ Nuclear imaging is sensitive for autoimmune encephalitis as well, with positron emission tomography (PET) abnormalities estimated in up to 86%.^{6,7} SPECT is less well studied for autoimmune encephalitis; however, perfusion abnormalities that normalize with immune therapy are reported, even in the absence of magnetic resonance imaging (MRI) lesions.^{8,9} We present a patient with an unclear clinical presentation determined to have simultaneous post-HSVE autoimmune encephalitis and subsequent nonconvulsive status epilepticus with ictal subtraction SPECT.

A 55-year-old previously healthy woman initially presented with 10 days of fever and confusion. MRI revealed bilateral mesial temporal hyperintensities without enhancement (Figure 1), and cerebrospinal fluid polymerase chain reaction (PCR) was positive for HSV-1, with 200 white blood cells (WBC)/mm³ (100% lymphocytic), protein 0.71 g/L and normal glucose. The patient

was treated with IV acyclovir for 14 days, and the admission was complicated by neuropsychiatric symptoms and focal seizures treated with increasing antiseizure medications. The patient was discharged after stabilization of seizures and other symptoms on oxcarbazepine, clobazam and lamotrigine 6 weeks following her admission.

She re-presented 2 weeks later with progressive agitation and confusion (Day 67 since first admission). Repeat EEG (day 68) was unremarkable, and MRI on day 69 showed new areas of temporal lobe enhancement compared to the prior scan during active HSVE (Figure 1). CSF on day 73 revealed 17 WBC/mm³ (82% lymphocytic), protein 0.63 g/L, negative HSV-1 and -2 PCR and 19 CSF specific bands. Comprehensive CSF and serum autoimmune encephalitis panels, which included testing for neural antibodies by mouse tissue indirect immunofluorescence as well as monospecific commercial assays, returned negative except for weak serum positivity for anti-CASPR2 cell-based assay (CBA) at 1:10 dilution only that was most in keeping with a clinically irrelevant/false-positive antibody result.¹⁰

On day 76, the patient became suddenly obtunded without any witnessed preceding seizure activity, and was placed on ventilator support with sedation. Over the following four weeks, the patient remained unresponsive without a clearly identified cause. She was treated with a pulse of steroids with prednisone taper and IV Immunoglobulins (IVIG) for possible post-HSVE autoimmune encephalitis. During this time 3 additional MRIs were done (Figure 1), showing migrating enhancement with resolution of previously affected areas on sequential scans. Serial EEGs showed nonevolving 0.5–1.5 Hz generalized periodic discharges (GPD) (possible-NCSE per Salzburg Criteria), with rare periodic discharges centered over C4-P4 (Figure 2c). Repeat CSF on day 84 revealed normal cell counts, protein, glucose and microbiology including HSV PCR. Malignancy screening with computed tomography chest, abdomen and pelvis and pelvic ultrasound were unremarkable.

After 3 weeks of treatment with corticosteroids, a course of IVIG, continued burst suppression and escalating antiseizure

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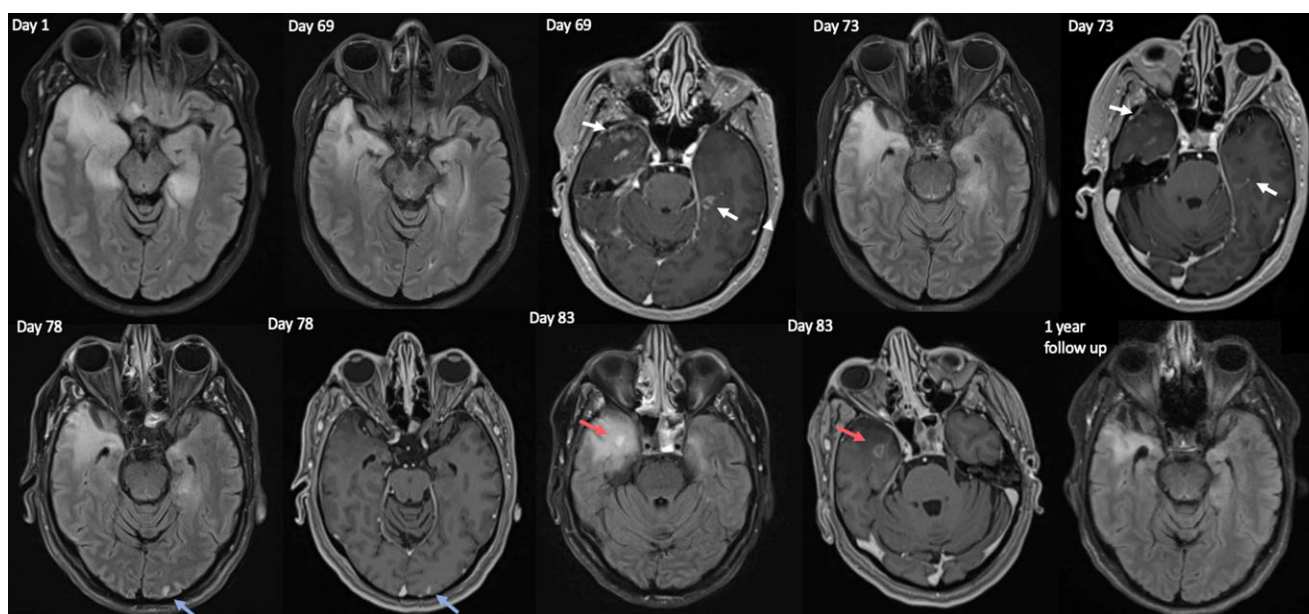


Figure 1. Serial magnetic resonance imaging (MRI) images from initial admission (Acute HSVE- day 1), and the second admission for autoimmune encephalitis (starting 6 weeks after the initial scan), on Days 69, 73, 78 and 83 since initial MRI with acute HSVE. At the time of acute HSVE bilateral mesial temporal and inferior frontal T2 hyperintensities were noted, with no diffusion restriction, hemorrhage or gadolinium contrast enhancement (not pictured). On the initial scan of the second admission (Day 69) new areas of enhancement were present in bilateral basal temporal lobes (white arrows). These areas of enhancement were improved on day 73 (white arrows) and resolved on day 78. On day 78 a new area of occipital T2 hyperintensity was seen on FLAIR (left-most blue arrow) with associated enhancement (right-most blue arrow), which resolved on the next scan on Day 83. On day 83 a new area of FLAIR hyperintensity was noted in the anteromedial right temporal lobe (left-most red arrow), with associated ring enhancement (right-most red arrow). This abnormality improved on a subsequent 3-month scan, and enhancement had resolved by 1-year follow-up. 1-year follow-up revealed gliosis of the right more than left mesial temporal lobes.

medications (oxcarbazepine, phenytoin, levetiracetam, lacosamide, lamotrigine and clobazam), there was no clinical or electrographic improvement. To reduce diagnostic uncertainty and determine whether further escalation of immunotherapy and antiseizure medication was warranted, a SPECT scan was done off sedation on Day 93 that revealed hyperperfusion in various regions including both anterior temporal lobes, suggestive of active inflammation (Figure 2a). An ictal subtraction SPECT was done with a repeat scan while burst-suppressed with isoflurane on day 97 (Figure 2b), revealing an area of discrepancy in the right parietal lobe, suggestive of an active seizure focus in this region.

These findings confirmed both autoimmune encephalitis and NCSE, thus clobazam dose was maximized and Rituximab induction was undertaken (Day 146). The malignant EEG pattern resolved on day 101, and clinical improvement was seen from day 103 onwards, which rapidly accelerated after Rituximab induction (nonverbal and visually tracking at time of induction, speaking and following commands 3 weeks after first dose). At 1-year follow-up there was substantial improvement with residual cognitive impairment (MOCA 17/30), and repeat imaging demonstrating resolution of all enhancement (Figure 1).

The diagnosis of post-HSVE autoimmune encephalitis can be challenging as the median onset is 32 days after initial infection,¹ temporally overlapping with non-autoimmune complications of HSVE such as viral relapse or seizure disorder.² At this juncture, a cohort of 14 patients with post-HSV autoimmune encephalitis had no difference in fluid attenuated inversion recovery (FLAIR) lesion volume or CSF pleocytosis compared to those that did not develop autoimmune encephalitis. New MRI enhancement occurred without any difference between these groups 1–3 months

post-HSVE,¹ although the migrating MRI enhancement distant from initial areas of injury seen in this patient may be a more specific finding for post-HSVE autoimmune encephalitis. Additionally contributing to diagnostic uncertainty, 25%–30% of patients develop neuronal surface antibodies but do not go on to develop autoimmune encephalitis.^{1,2} While nearly all patients with autoimmune encephalitis post-HSVE have a cell surface antibody,² 18%–26% will have an unidentified antibody indicated only by CSF or serum reactivity with live neuronal culture.¹ Neural antibody detection using live cultured neurons is not routinely performed in many clinical laboratories, which may be the reason for negative neural antibody testing among a subset of patients suspected to have post-HSVE autoimmune encephalitis like in this case.

Despite its infrequent use in critical care, SPECT is an effective adjunctive test where NCSE is suspected despite unclear EEG findings,^{4,5} and in the setting of neuroinflammation.^{8,9} Although most nuclear imaging studies done to detect autoimmune encephalitis and NCSE have used PET,^{6,7} SPECT permits ictal subtraction which has greater sensitivity than PET for seizure detection¹¹ and allows the disentanglement of simultaneous inflammation and seizures. Ictal subtraction is effective in the setting of neurological comorbidities such as post-stroke epilepsy¹² but has rarely been used to detect status epilepticus.^{4,5,13} While alternating burst suppression and lifting sedation to manage NCSE provides a natural opportunity to perform ictal subtraction SPECT, producing an interictal state by burst suppression may introduce limitations including global changes to brain perfusion. Further study is required to determine the sensitivity and specificity of SPECT findings for neuroinflammation and seizure activity when both are simultaneously present.

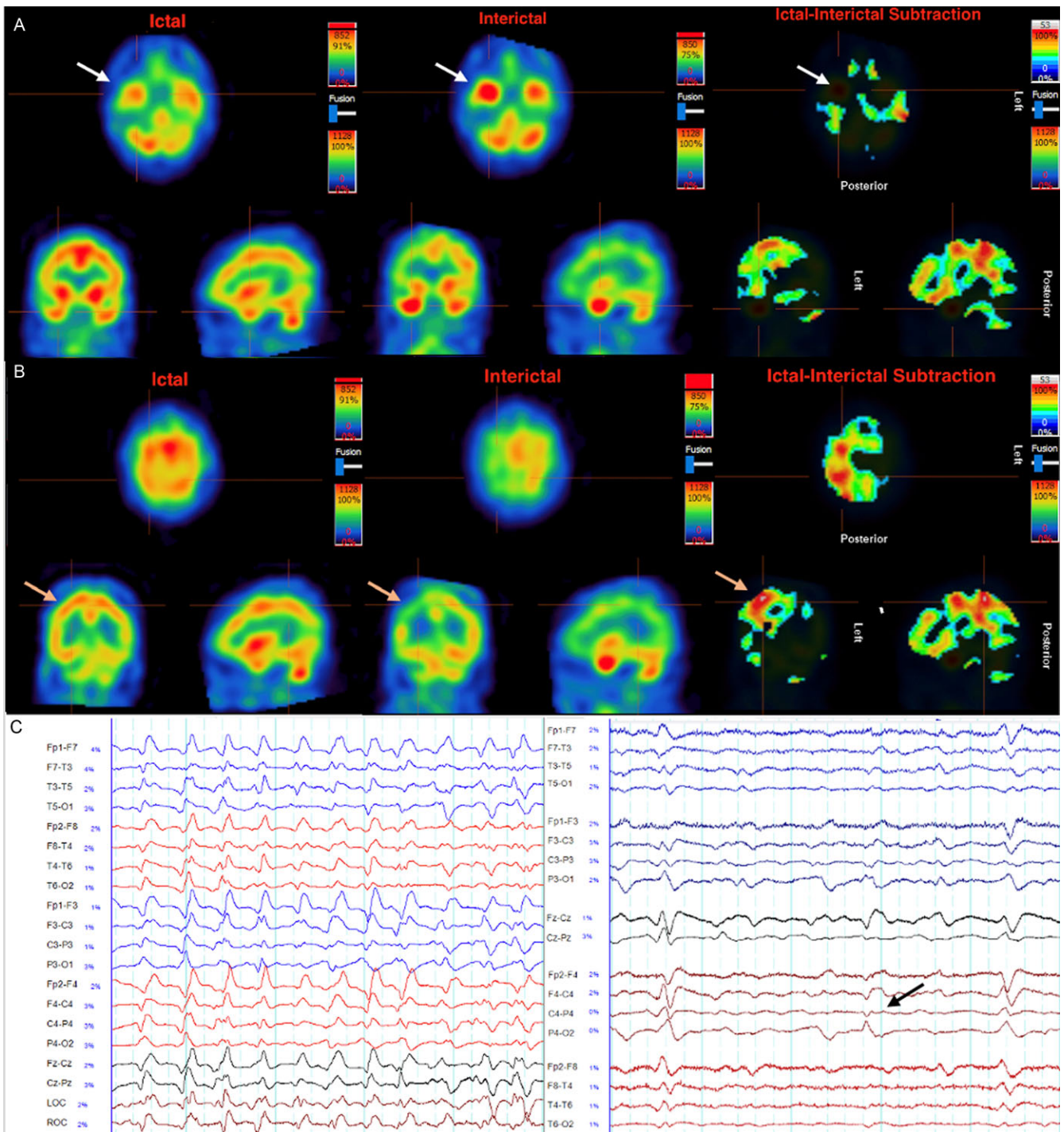


Figure 2. Ictal (A,B left), interictal (A,B middle) and ictal subtraction (A,B right) SPECT scans focusing on inflammation in the temporal lobes (A) and the seizure focus in the right parietal lobe (B). The ictal scan (Day 93) was performed after weaning anesthetic, with corresponding EEG revealing periodic generalized epileptiform discharges maximal at the biparietal regions at 1–2.5 Hz, not fulfilling Salzburg criteria for status epilepticus (C left). The interictal scan (A,B middle, Day 97) was done after achieving burst suppression. A. Significant hyperperfusion of the temporal lobes is evident in both ictal and interictal states, which is eliminated completely by ictal subtraction, reflecting inflammatory activity. B. The greatest area of discrepancy by ictal subtraction is revealed in the convexity of the right parietal lobe (orange arrows) reflecting the seizure focus. Unlike the temporal lobes, this area was not clearly hyperperfused in the ictal scan. In the interictal scan this region is hypoperfused relative to other structures, revealing an area of relative hyperperfusion when ictal subtraction is performed (B right). C. Left: Generalized periodic discharges at the time of ictal perfusion scan, which was seen for a majority of the patient’s course in intensive care. Right: Periodic lateralized discharges at C4-P4 (black arrow) briefly noted only on day 73, corresponding to where the seizure focus was identified 23 days later by ictal subtraction SPECT (B right).

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References

1. Armangue T, Spatola M, Vlagea A, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol.* 2018;17:760–72.
2. Armangué T, Olivé-Cirera G, Martínez-Hernandez E, et al. Neurologic complications in herpes simplex encephalitis: clinical, immunological and genetic studies. *Brain.* 2023;146:4306–19.
3. Armangue T, Moris G, Cantarin-Extremera V, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. *Neurology.* 2015;85:1736–43.
4. Jaraba S, Reynés-Llompert G, Sala-Padró J, et al. Usefulness of HMPAO-SPECT in the diagnosis of nonconvulsive status epilepticus. *Epilepsy Behav.* 2019;101:106544.
5. Kutluay E, Beattie J, Passaro EA, et al. Diagnostic and localizing value of ictal SPECT in patients with nonconvulsive status epilepticus. *Epilepsy Behav.* 2005;6:212–7.
6. Lv RJ, Pan J, Zhou G, et al. Semi-quantitative FDG-PET analysis increases the sensitivity compared with visual analysis in the diagnosis of autoimmune encephalitis. *Front Neurol.* 2019;10:576.
7. Probasco JC, Solnes L, Nalluri A, et al. Abnormal brain metabolism on FDG-PET/CT is a common early finding in autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm.* 2017;4:e352.
8. Ohta K, Seki M, Dalmau J, Shinohara Y. Perfusion IMP-SPECT shows reversible abnormalities in GABA(B) receptor antibody associated encephalitis with normal MRI. *Brain Behav.* 2011;1:70–2.
9. Suárez JP, Domínguez ML, Gómez MA, Portilla JC, Gómez M, Casado I. Brain perfusion SPECT with ^{99m}Tc-HMPAO in the diagnosis and follow-up of patients with anti-NMDA receptor encephalitis. SPECT cerebral de perfusión con ^{99m}Tc-HMPAO en el diagnóstico y seguimiento de la encefalitis con anticuerpos contra el receptor NMDA. *Neurología (Engl Ed).* 2018;33:622–3.
10. Garrido Sanabria ER, Zahid A, Britton J, et al. CASPR2-IgG-associated autoimmune seizures. *Epilepsia.* 2022;63:709–22.
11. Spanaki MV, Spencer SS, Corsi M, MacMullan J, Seibyl J, Zubal IG. Sensitivity and specificity of quantitative difference SPECT analysis in seizure localization. *J Nucl Med.* 1999;40:730–6.
12. Fukuma K, Kajimoto K, Tanaka T, et al. Visualizing prolonged hyperperfusion in post-stroke epilepsy using postictal subtraction SPECT. *J Cereb Blood Flow Metab.* 2021;41:146–56.
13. Donnelly JP, Kasatwar N, Hafeez S, et al. Resolution of cryptogenic new onset refractory status epilepticus with tocilizumab. *Epilepsy Behav Rep.* 2021;15:100431.