■ Clinical commentary

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# Non-convulsive status epilepticus as an initial manifestation of herpes simplex virus encephalitis

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**ABSTRACT**

Herpes simplex encephalitis (HSVE), manifesting with non-convulsive status epilepticus (NCSE), normocellular CSF findings and CT features of acute ischemic stroke, is a rare finding that can be hard to diagnose accurately. We present a case of HSVE and compare our results to those of previously published cases with the same pathology, in order to provide information to support more rapid and effective diagnosis and treatment. A Pubmed search of reported cases was conducted and five cases of HSVE manifesting with NCSE were found. Each of the cases, including ours, was compared in terms of clinical manifestations and CSF, CT and EEG findings. The clinical manifestations in our patient correlated with those of the other cases. EEG showing sharp fronto-temporo-centro-parietal waves was only observed in our patient. Similar CT manifestations were found in one other patient, normocellular CSF was registered in three other cases and positive PCR for HSV in four patients. Information about the possible clinical manifestations and CT, EEG and CSF findings in patients with HSVE manifesting with NCSE is crucial for a fast diagnosis and successful treatment, leading to higher survival rates and fewer complications and neurological deficits.

**Key words:** non-convulsive status epilepticus, herpes simplex virus encephalitis, diagnosis, treatment, normocellular cerebrospinal fluid

Herpes simplex virus encephalitis (HSVE) is a devastating and deadly illness that can be caused by HSV-1 or HSV-2 [1]. HSV-1 is the most common cause of sporadic encephalitis worldwide with an estimated incidence of between 2 and 4 cases/1,000,000 [1]. The most common manifestations of HSVE are fever, headache, altered mental status, seizures, and focal neurological deficits [2]. Seizures can be present in about 55% of patients with HSVE at the time of hospital admission [3]. However, non-convulsive status epilepticus (NCSE) appears to be rare and, to the best of our knowledge, has been described so far in only a few cases [4-8]. Herein, we report a case of a 71-year-old female patient with NCSE caused by HSVE, with a comparison to all previously published cases.

## Case study

A 71-year-old female presented to our centre in July 2016 due to altered mental status and fever. She was found in bed confused, unable to communicate, stiff, with head backwards in a non-physiological position and had urinated on herself. Her first complaints started

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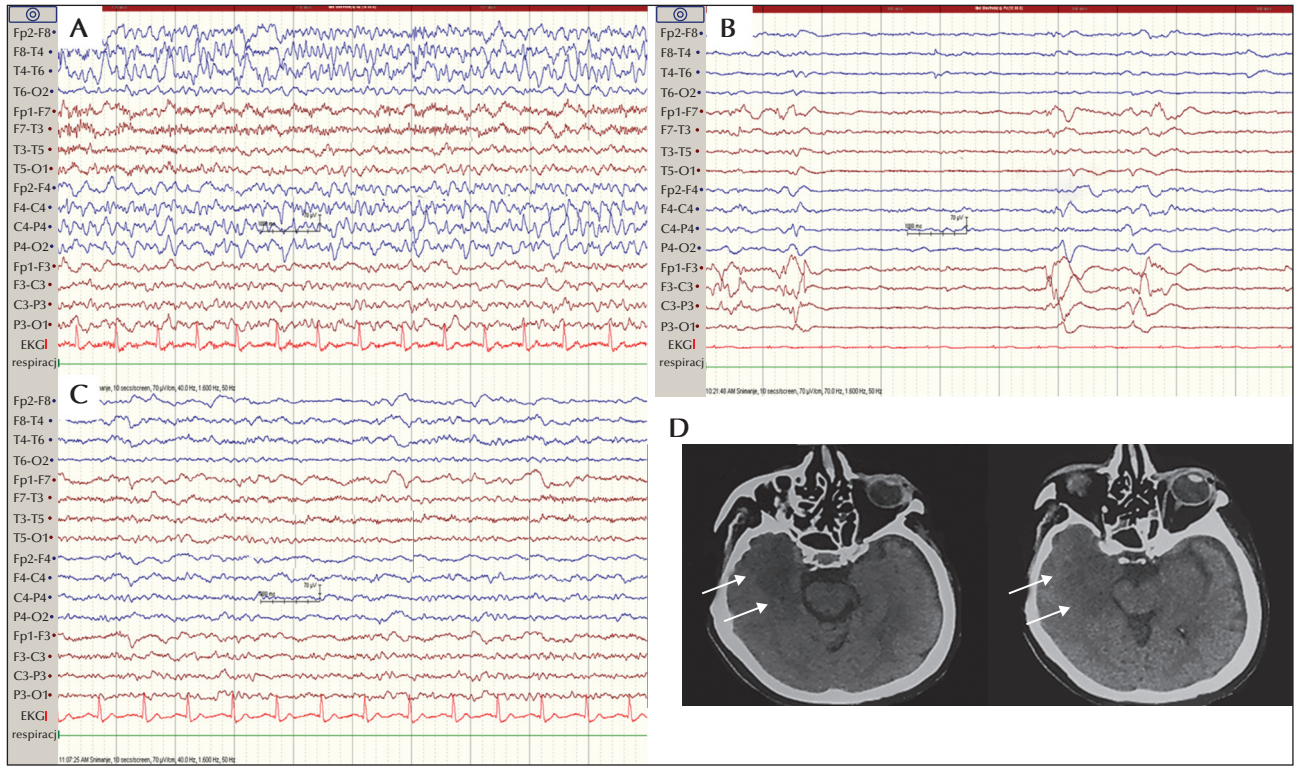
approximately 36 hours earlier at home with a feeling of fatigue and generalized weakness followed by fever. Personal history revealed that she was diabetic and had hypertension.

On physical examination, she was found to be febrile (38.0°C), hypertensive (180/90 mmHg) and hyperglycaemic (25.8 mmol/L). At the time of examination, she was disoriented in time and place with behavioural fluctuations. Apart from the divergent strabismus of the right eye present since childhood and symmetrically elevated muscle tonus, the rest of the neurological examination was normal. Brain CT scan showed multiple chronic ischemic changes and leukoencephalopathy. After blood pressure and hyperglycaemia were corrected, neurological and mental status did not change.

She was admitted to the Department of Emergency Neurology. Initial EEG performed after admission revealed NCSE from the right hemisphere (fronto-centro-temporal spike waves) (*figure 1A*). The patient was immediately administered intravenous therapy with diazepam at a dose of 20 mg and valproic acid at a dose of 1,000 mg. As the NCSE persisted, intravenous phenobarbitone therapy at a dose of 880 mg was also administered. Control EEG showed low-voltage global activity with bilateral burst-suppression patterns (*figure 1B*). The patient's respiratory pattern changed, leading to intubation and mechanical ventilation (MV), and intravenous therapy with broad-spectrum antibiotics and acyclovir at a dose of 10 mg/kg, three times a day, was administered. Globally, control EEG showed moderate lower-voltage electrocortical dysfunction with predominant theta-alpha waves (*figure 1C*). Lumbar puncture revealed clear and colourless cerebrospinal fluid (CSF) with three leucocytes, hyperproteinorachy (2.99g/L) and normal-range glycorachy. The repeat brain CT showed an extensive hypodense zone with frontotemporal flattened sulci on the right (differential diagnosis: subacute ischemic lesion and early cerebritis [less likely]) (*figure 1D*). Additional laboratory analyses demonstrated a discrete increase in inflammatory parameters, as well as subclinical hypothyroidism, while tumour markers and immunological analyses were within normal range.




■ **Figure 1.** (A) Initial EEG performed after admission revealing NCSE from the right hemisphere (fronto-centro-temporal spike waves). (B) Control EEG showing low-voltage global activity with bilateral burst-suppression patterns. (C) Control EEG showing overall moderate lower-voltage electrocortical dysfunction with predominant theta-alpha waves. (D) Repeat brain CT showing an extensive hypodense zone with frontotemporal flattened sulci on the right.

Serology analyses for CMV, HSV1/2, VZV and EBV were negative based on the CSF and serum. Bacteriological examination of the CSF and TPHA analyses from CSF and serum were also negative, and the direct native composition of the CSF was normal. However, PCR for herpes simplex virus (HSV) DNA from the CSF was positive. The control brain CT showed chronic ischemic temporo-basal changes on the right and bilaterally in the insulas. During hospitalization, the patient's condition fluctuated, and while on transfer to the Clinic for Infectious Diseases she remained on MV, but was able to open her eyes and shift her right extremities in response to verbal stimulation. Later on, her condition was complicated by pulmonary infection and sepsis, which led to a lethal outcome two months after the onset of the disease.

## Discussion

Non-convulsive status epilepticus is a very rare manifestation of HSVE. So far, only five cases of NCSE in patients with HSVE have been described [4-8]. Our patient was a 71-year-old woman. All five previously reported patients were also female of different ages, which correlates to previously published data showing that NCSE is more frequent in females [4-9]. Among them, the youngest patient was only 11 months old, while our patient was the oldest [4-8]. The initial manifestations in our patient were fever, fatigue, generalized weakness, and altered mental status. Fever and altered mental status were described as initial manifestations in all previously published cases [4-8]. Although signs of focal neurological deficits may be present as an initial manifestation in patients with HSVE, they were not observed in our patient initially, but did occur later on. In another two described cases, there were also no signs of focal neurological deficit on admission [7, 8].

Considering the course of the disease of our patient, in which the altered mental status was the main feature, an EEG was performed immediately after admission in which NCSE was detected over the right hemisphere with fronto-temporo-centro-parietal (FTCP- predominantly FT) sharp waves. Paroxysmal sharp waves, slow-wave activity and/or tri-phasic complexes originating from the temporal lobe may be recorded in patients with HSVE on EEG [10]. This may be because HSV usually affects these areas of the brain and the temporal lobe is susceptible to epileptic discharges [11]. One of the most effective treatment options for refractory NCSE is eliminating EEG seizure activity by treating with burst-suppression patterns [12]. There are a number of different approaches for treatment NCSE. The use of anaesthetic agents has rarely been used because the risks associated with intubation and ventilation may out-weight the benefit of this approach [13]. Other authors agree that treatment depends on the aetiology of status epilepticus, and the decision of clinicians is based on their own clinical practice, judgment and through choice regarding the risks and benefits associated with each therapeutic decision [14]. In this particular case, the approach with phenobarbital was not contraindicated, since the patient suffered refractory status epilepticus. Potential risks associated with intubation and mechanical ventilation were considered, since these are not standard approaches.

In our patient, brain CT showed an extensive hypodense zone with flattened frontotemporal sulci on the right. CT hypodensities in the basal frontal and temporal area, bilaterally, have also been described in another patient [5]. Non-contrast CT and MRI of the brain are of great importance for the diagnosis of HSVE [1]. CT may show hypodense lesions of the frontal or temporal lobe, oedema, or contrast enhancement [1]. A hyperdense middle cerebral artery (MCA) sign, which refers to focal hyperdensity of the MCA and usually indicates its occlusion, was described on non-contrast CT in our patient [15]. This was also described in the HSVE series of Shoaib *et al*., in which brain CT showed a stroke-like lesion with midline shift and a hyperdense right MCA sign, while perfusion CT and CT angiography performed later did not show any abnormalities, implying that the false-positive hyperdense right MCA sign originated from the surrounding cerebral parenchyma [16].

In our case, lumbar puncture showed clear and colourless CSF with three leucocytes, hyperproteinorachy and normal-range glycorachy. Normocellular CSF was also obtained in three of the five previously described cases [5, 7, 8]. In two of these cases, repeat lumbar punction yielded hypercellular findings [5, 8]. A usual CFS finding in HSVE consists of lymphocytic pleocytosis, hyperproteinorachy, and normal glycorachy [1]. Normocellular CSF can be found in up to 26% of patients which indicates that normocellular CSF should not exclude HSVE diagnosis [17]. Repeat lumbar punctures should be performed, as CSF pleocytosis can develop in the later course of the disease [17].

Our patient had a positive PCR for HSV-1 based on CSF. Four of the five previously described cases of NCSE caused by HSVE also had a positive PCR for HSV-1 based on CSF [5-8]. PCR is the golden standard for HSVE diagnosis with a sensitivity of 98% and specificity of 100% [18], although negative PCR based on CSF of HSVE patients can be seen in some cases [19]. This may be due to early CSF analysis or prior acyclovir treatment [19].

Both HSVE and NCSE are serious and potentially life-threatening diseases [3, 20]. Untreated HSVE can lead

to mortality in over 70% of cases, and in patients with acquired NCSE, the rate of mortality is as high as 27% [3, 20]. One HSVE patient from previously published cases with NCSE died [8], and another had a significant neurological deficit after 21 days although the final outcome was not reported [5]. Prompt diagnosis and initiation of treatment with acyclovir and antiepileptic drugs are key to successful recovery [1, 21]. ■

**Supplementary material.**
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

**Disclosures.**
None of the authors have any conflict of interest to declare.

## References


1. Bradshaw MJ, Venkatesan A. Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis and management. *Neurotherapeutics* 2016; 13(3): 493-508.

2. Whitley RJ. Herpes simplex encephalitis: adolescents and adults. *Antiviral Res* 2006; 71: 141-8.

3. Sili U, Kaya A, Mert A, HSV Encephalitis Study Group. Herpes simplex virus encephalitis: clinical manifestations, diagnosis and outcome in 106 adult patients. *J Clin Virol* 2014; 60(2): 112-8.

4. Lee JH, Nam DH, Oh SY, Shin BS, Seo MW, Jeong SK, *et al*. Nonconvulsive status epilepticus presenting as epileptic nystagmus in a patient with herpes encephalitis. *J Neuroophthalmol* 2012; 32(3): 249-51.

5. Grande-Martin A, Pardal-Fernández JM, García-López FA. Utility of EEG findings in the management of a case of herpes simplex encephalitis. *Neurologia* 2017; 32(3): 193-5.

6. Sensoy G, Sayli TR, Guven A, Kanmaz G. Infantile nonconvulsive status epilepticus caused by herpes encephalitis. *J Pediatr Neurosci* 2009; 4(2): 139-41.

7. Gunduz A, Beskardes AF, Kutlu A, Ozkara C, Karaagac N, Yeni SN. Herpes encephalitis as a cause of nonconvulsive status epilepticus. *Epileptic Disord* 2006; 8(1): 57-60.

8. Baten A, Desai M, Melo-Bicchi M, Gutierrez C. Continuous electroencephalogram as a biomarker of disease progression and severity in Herpes simplex virus-1 encephalitis. *Clin EEG Neurosci* 2019; 50(5): 361-5.

9. Baker AM, Yasavolian MA, Arandi NR. Nonconvulsive status epilepticus: overlooked and undertreated. *Emerg Med Pract* 2019; 21(10): 1-24.

10. Lai CW, Gragasin ME. Electroencephalography in herpes simplex encephalitis. *J Clin Neurophysiol* 1988; 5(1): 87-103.

11. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. *Lancet* 2019; 393(10172): 689-701.

12. Jordan KG, Hirsch LJ. In nonconvulsive status epilepticus (NCSE), treat to burst-suppression: pro and con. *Epilepsia* 2006; 47: 41-5.

13. Dupont S, Kinugawa K. Nonconvulsive status epilepticus in the elderly. *Rev Neurol (Paris)* 2020; 176(9): 701-9.

14. Ferguson M, Bianchi MT, Sutter R, Rosenthal ES, Cash S, Kaplan PW, *et al*. Calculating the risk benefit equation for aggressive treatment of non-convulsive status epilepticus. *Neurocrit Care* 2013; 18(2): 216-27.

15. Maramattom BV, Wijdicks EF. A misleading hyperdense MCA sign. *Neurology* 2004; 63(3): 586.

16. Shoaib M, Kraus JJ, Khan MT. Herpes simplex virus encephalitis: atypical presentation as a right middle cerebral artery stroke. *Cureus* 2018; 10(1): e2067.

17. Bewersdorf JP, Koedel U, Patzig M, Dimitriadis K, Paerschke G, Pfister HW, *et al*. Challenges in HSV encephalitis: normocellular CSF, unremarkable CCT and atypical MRI findings. *Infection* 2019; 47(2): 267-73.

18. Aurelius E, Johansson B, Sköldenberg B, Staland A, Forsgren M. Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. *Lancet* 1991; 337: 189-92.

19. Buerger KJ, Zerr K, Salazar R. An unusual presentation of herpes simplex encephalitis with negative PCR. *BMJ Case Rep* 2015; 2015: bcr2015210522.

20. Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology* 2003; 61(8): 1066-73.

21. Kinney MO, Kaplan PW. An update on the recognition and treatment of non-convulsive status epilepticus in the intensive care unit. *Expert Rev Neurother* 2017; 17(10): 987-1002.


## TEST YOURSELF

**(1) The most common manifestation of HSVE is:**
A. fever, headache, nausea, vomitus, vertigo
B. fever, headache, altered mental status, seizures
C. seizures, fever, vertigo, vomitus, focal neurological deficits

**(2) In patients with HSVE, NCSE manifests with continuous epileptic activity on EEG that is mostly focal and predominant in the temporal lobe:**

A. very rarely
B. very often
C. only in the elderly

**(3) The golden standard for HSV detection in the CSF of patients with HSVE, with high specificity and sensitivity, is:**

A. EEG
B. lumbar puncture
C. PCR detection of viral DNA based on CSF

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.*