CASE REPORT

New onset refractory status epilepticus (NORSE) as the heralding manifestation of herpes simplex encephalitis

Rajesh Verma,¹ Tushar Premraj Raut,¹ Prithvi Giri,¹ Heramba Narayan Praharaj²

¹Department of Neurology, King George Medical University, Lucknow, Uttar Pradesh, India

²Department of Neurology, CSM Medical University, Lucknow, Uttar Pradesh, India

Correspondence to

Professor Rajesh Verma, drrajeshverma32@yahoo.com

SUMMARY

New onset refractory status epilepticus (NORSE) is a relatively novel concept used to describe a cohort of previously healthy young adults mostly women presenting with *denovo* refractory status epilepticus which has a miserable impact on the outcome. Various infectious and non-infectious causes have been considered to be responsible for this dreaded syndrome; however, many a times the exact cause is not identified. As therapy with antiepileptic and anaesthetic drugs is not so successful, identifying and treating the exact cause could improve the outcome. Here the authors describe a woman who presented with NORSE. Investigations confirmed the diagnosis of herpes simplex encephalitis (HSE) and she responded drastically to acyclovir along with complete control of seizures. In this case, NORSE was the presenting feature of HSE and the refractoriness of her seizures was terminated only after treating the exact cause, that is, encephalitis.

BACKGROUND

Status epilepticus (SE) is a commonly encountered neurological emergency that can have fatal consequences if not treated promptly. Refractory SE is a condition in which the first and second line therapy (benzodiazepines and phenytoin/phenobarbitone) fails and the seizures continue to occur.¹ New onset refractory status epilepticus (NORSE) is a relatively newly coined term for previously healthy adults who present with *de novo* refractory SE.² It is usually associated with a prolonged course, high morbidity and mortality. Presumption of an infectious aetiology like viral encephalitis is considered for NORSE but it still lacks convincing evidence.³ The role of antibodies to voltage-gated potassium channels, glutamate receptors and N-methyl-D-aspartate receptors have been identified.³ It can also occur due to precipitous unmasking of an 'epileptic' diathesis due to a channelopathy or covert mitochondrial disorder by a benign febrile illness or due to an infectious or parainfectious phenomenon. Among the viral encephalitis, herpes simplex encephalitis (HSE) is the most important and treatable cause of sporadic encephalitis in children above 6 months and adults.⁴ It can present with a myriad of features like fever, headache, behavioural abnormality, memory disturbances, hallucinations, seizures and focal deficits.⁵ Although seizures occur commonly in HSE, presentation of HSE as a NORSE at the onset is rare. Here we report a PCR confirmed case of HSE who presented with

NORSE. Her seizures were not controlled despite the use of multiple antiepileptic drugs (AEDs) and intravenous anaesthetics. She improved clinically along with complete remission of seizures only after receiving acyclovir.

CASE PRESENTATION

A 35-year-old woman presented to our department with multiple episodes of generalised tonic clonic convulsions (GTCS) for past 8 days. She had a history of moderate to high-grade fever with cough that lasted for 2–3 days. Next day she had 8–10 episodes of generalised tonic clonic seizures which occurred over a period of 1 h without any gain of consciousness in between. After admission to a hospital, her seizure frequency increased leading to convulsive SE, which was not controlled with a full dosage of intravenous lorazepam, phenytoin and phenobarbitone. She was intubated and was on ventilatory support for 2 days. The patient received continuous infusion of injection midazolam and propofol. Tablet leviteracetam was given through the Ryle's tube and her seizure frequency reduced but she continued to have occasional multifocal seizures with persistent altered sensorium. Her biochemical parameters were within normal range and EEG revealed epileptiform discharges. She was extubated and referred to our hospital. The patient then developed in the form of visual and auditory hallucinations. She had behavioural changes in the form of irritability and irrelevant talking. She still continued to have 4–5 episodes of GTCS per day with altered consciousness.

On examinations, her vitals were stable. She was afebrile. The patient was confused; however, she responded to simple commands intermittently. There was fluctuation in her sensorium with an impairment of recent memory. Cranial nerve examination was normal. There was no other focal neurological deficit on examination.

INVESTIGATIONS

Haematological, biochemical parameters (blood sugar, serum electrolytes, liver functions, renal function, thyroid profile) were within normal range. Previous EEG showed bisynchronous spike and sharp wave discharges in temporal leads with a spread to adjacent leads along with background slowing (figure 1). An EEG at our institute revealed bilateral periodic lateralised epileptiform discharges (figure 2). MRI brain revealed T2 hyperintensities involving hippocampi and left temporal, insular

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Figure 1 Initial EEG record during status epilepticus showed bisynchronous high-amplitude spike and sharp wave discharges involving temporal leads with background slowing.

cortex and medial frontal lobe (Figure 3). Cerebrospinal fluid (CSF) examination was normal.

TREATMENT

In view of her clinical, EEG and MRI features, the patient received injection acyclovir and within 24 h, there was a dramatic response to acyclovir. Her sensorium improved completely; there were no hallucinations or behavioural changes. Her memory was normal and no further episodes of seizures were observed. A PCR analysis of CSF for herpes simplex virus 1 (HSV1) turned out to be positive and we continued parenteral acyclovir for 14 days.

OUTCOME AND FOLLOW-UP

The patient was discharged on oral leviteracetam 500 mg twice a day and is seizure free.

DISCUSSION

NORSE is a relatively recent concept that comprises a syndrome presenting as new onset status epilepticus. Patients are young healthy adults who present with SE highly refractory to first and second line agents and usually no clear cause is identified. They commonly have abnormalities in CSF along with signal changes on neuroimaging MRI; however, no specific pathogen has been isolated.⁶ In 10–20% cases of aetiologically proven encephalitis, NORSE has been found to occur especially in the setting of febrile illness with meningismus and encephalopathy.^{7–9} Patients presenting with NORSE have a common clinical setting, which includes young age of onset, female preponderance, no prior

history of seizures or any neurological abnormality, modest CSF lymphocytic pleocytosis, EEG and neuroimaging abnormalities and a poor clinical outcome. Our case was a young healthy woman with no prior neurological disorder and who had acute onset of generalised tonic clonic SE and multifocal seizures with a history of febrile illness prior to the onset of seizures. The seizures were typically refractory to first and second line agents and the patient required intravenous anaesthetics, midazolam and leviteracetam. With these measures, seizure frequency got reduced; however, there was no improvement in the sensorium. An average duration of NORSE according to a study by Costello⁶ was 36 days (6–68 days). Our case had seizures lasting for 12 days.

EEG features include multifocal and generalised epileptiform discharges. MRI brain may reveal hyperintensities in the temporal lobe and leptomeningeal enhancement. These abnormalities seen on MRI are not sufficient to differentiate between an infectious, inflammatory or ictal encephalopathy.¹⁰ EEG abnormalities could be a result of the epilepsy or an encephalitic process that is difficult to distinguish. Also CSF abnormalities in the form of mild pleocytosis can occur as a result of encephalitis or ictal activity itself. A report from the California encephalitis project stated that 4% cases who developed NORSE in the setting of encephalitis were younger, had fever and meningismus on admission, were more likely to experience a prodromal respiratory or gastrointestinal illness and were less likely to have CSF pleocytosis or abnormal neuroimaging compared with the larger cohorts of patients with encephalitis but without seizures or with medically responsive seizures. It also stated that

Figure 2 EEG record on the 10th day of illness showing bilateral periodic lateralised epileptiform discharges.

refractory SE is uncommon in clinically defined encephalitis whereas medically responsive seizures and SE were more common.¹¹ Our case had refractory SE and initial EEG revealed bitemporal epileptiform discharges with generalisation and background slowing whereas an MRI revealed signal changes in hippocampus, left temporal, insular and medial frontal lobes.

A case of NORSE needs extensive workup to rule out infectious aetiology like encephalitis, immunological disorders like collagen vascular disorders, neoplastic, paraneoplastic, metabolic-induced and toxin-induced disorders.⁶ In our case CSF for HSV PCR was positive which has a high-sensitivity and specificity,⁵ thus confirming the diagnosis of HSE. Despite

Figure 3 (A) MRI brain T2 fluid attenuated inversion recovery (FLAIR) sequence axial view showing hyperintensities involving the left insular cortex, temporal and medial frontal lobes (marked by arrows). (B) MRI brain T2 FLAIR sequence coronal view showing hyperintensities in bilateral hippocampi, medial frontal and temporal lobes (marked by arrows).

receiving multiple AEDs, she responded clinically with complete seizure control only after receiving acyclovir. The clinical features of HSE are often non-specific and misleading, which include focal encephalitis with fever, altered sensorium and focal neurological signs. Frontotemporal involvement leads to aphasia, personality change and focal seizures. Seizures can be the presenting feature in about 50% cases because of the involvement of a highly epileptogenic frontotemporal cortex. Alteration in excitability of the hippocampal A3 neuronal network and HSV1-induced neuronal loss results in mossy fibre reorganisation which may play an important role in epileptogenesis.¹² Seizures can be acute symptomatic or remote symptomatic. Seizures include focal seizures (complex partial), focal onset generalised or generalised seizures. SE can complicate the illness, although its occurrence as a presenting feature is uncommon. According to a study by Misra¹³ UK, 39.8% cases with SE (most common type was convulsive status epilepticus) had CNS infections of which 8% had herpes simplex infection. Gunduz¹⁴ reported a case of non-convulsive SE due to HSV infection. Our case had a convulsive SE along with behavioural changes and hallucinations (auditory and visual).

A cranial MRI is essential for an early diagnosis as well as for defining the distribution of cerebral injury in HSE. The MRI scan in HSE typically shows early changes of focal oedema in the medial aspects of the temporal lobes, orbital surfaces of the frontal lobes, insular cortex and cingulate gyrus.¹⁵ An EEG is abnormal in almost all cases and may reveal focal abnormalities like slowing, spikes, lateralised or multifocal epileptiform discharges involving the frontotemporal leads; however, none of these findings are specific for HSE. The imaging features and EEG changes can resemble those occurring in NORSE as observed in our case.

Exact guidelines for the management of NORSE have not been defined; however, the treatment strategy includes intravenous infusion of propofol, midazolam and pentobarbital alone or in combination. If seizures are still refractory, intravenous ketamine and inhalational anaesthetics can be used.¹⁶ Newer agents like topiramate and leviteracetam have been tried and found to be useful. Our patient had received intravenous propofol and midazolam other than the phenytoin and lorazepam. After adding leviteracetam, her seizure frequency reduced; however, after receiving acyclovir, she was completely seizure free with normal mentation.

Contributors RV made the hypothesis and rest of the authors helped in preparing the manuscript.

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Learning points

- ▶ Adult new onset refractory status epilepticus (NORSE) is a clinical syndrome with varying aetiologies which include infectious and non-infectious causes.
- ▶ Clinical, neuroimaging, EEG and cerebrospinal fluid (CSF) profile have a great resemblance to that of infectious aetiology like herpes simplex encephalitis (HSE). CSF PCR for herpes simplex virus and dramatic response to acyclovir could help in confirming diagnosis of HSE.
- ▶ Although the prognosis in NORSE is dismal, identification of the cause and treating it at the earliest may disrupt the refractoriness of seizures and improve the outcome as in our case.

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