

The NORSE (New-onset Refractory Status Epilepticus) Syndrome: Defining a Disease Entity

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Abstract

Introduction: To characterise a homogeneous group of patients with new-onset refractory status epilepticus (NORSE syndrome). **Materials and Methods:** This is a descriptive, semi-prospective review of all cases of NORSE syndrome seen between 2000 and 2004 at a tertiary care public hospital in Singapore. A review of the literature was performed to identify possible additional similar cases for comparison. **Results:** Seven patients with NORSE syndrome were identified. Characterising features were female gender, young age, previous good health, cerebrospinal fluid pleocytosis (in 4), antecedent febrile illness (in 5), extraordinarily prolonged status epilepticus (average 32 days), failure of extensive investigations to reveal an underlying cause, catastrophic outcome as well as temporal lobe and leptomeningeal abnormality on brain magnetic resonance imaging. A review of the literature identified 12 similar patients, comprising both adults and children. **Conclusions:** Based on our patients and those described in the literature, we characterise the NORSE syndrome. Increased recognition of this clinical entity is needed to help delineate the underlying aetiology of this unique severe illness.

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Introduction

Status epilepticus (SE) describes a clinical condition characterised by an epileptic seizure or a series of seizures that lasts for at least 30 minutes without consciousness being regained.¹ Some authors have added a time line of 60 minutes. The incidence of generalised convulsive status epilepticus (GCSE) is between 40 and 80 per 100,000.² The associated mortality rate has been estimated to be as high as 22%³ and may vary from 7.6% to 19% within the first 30 days.^{1,3,4} After 30 minutes to 60 minutes of continuous seizures, the physiologic compensatory mechanisms break down, resulting in an increased risk of neuronal damage as the seizures persist due to systemic and metabolic disturbances as well as a direct excitotoxic effect of neuronal discharges during the seizure.¹ Refractory status epilepticus (RSE) is a life-threatening condition, which is characterised by the failure to respond to first- and second-line anticonvulsant therapy.⁵ Risk factors predisposing patients to RSE include delay in receiving treatment, infections of the central nervous system (CNS), metabolic enceph-

halopathy and hypoxia.^{3,5} Most episodes of status are thought to develop without a prior history of epilepsy, and are almost always secondary to discernible underlying cerebral pathology.¹ We describe a new clinical syndrome, consisting of cases with new-onset refractory status epilepticus (abbreviated to NORSE) seen in 7 patients over the last 3 years in our institution. The impressive clinical features of female gender, young age, previous good health, very long-lasting status epilepticus, extensive negative workup, including neuropathology in 2 patients and catastrophic outcome, caused us to review the literature in search of a possibly more widespread occurrence of this clinical syndrome.

Materials and Methods

After noticing 3 similar cases of young women with new-onset RSE, with no discernible underlying cause and all of whom died within 3 months of presentation without abolition of seizures despite multiple medical interventions, we performed a retrospective review of the medical records of

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all cases of SE seen between 2000 and 2002 at our tertiary care public hospital in Singapore, after which we prospectively assessed 4 more cases who presented within the next year. We defined SE as persistent clinical generalised epileptic activity lasting more than 30 minutes, without restoration of consciousness.¹ RSE has widely varying definitions in the literature. We classified epilepsy as refractory when seizures did not respond or only partially responded to treatment with institution of 2 treatment regimens. All cases coded under the International Classification of Diseases (ICD) coding for SE (345.2, 345.3 and 345.7) were included for analysis. To identify similar cases of new-onset SE, the literature was reviewed using PubMed and the key index words of “epilepsy”, “status epilepticus”, “seizures”, “continued seizures”, “refractory epilepsy” and “refractory status epilepticus”.

Results

Patient Profiles

Apart from the already identified 7 patients with NORSE syndrome, a retrospective case sheet analysis failed to pick up any additional cases. In total, we screened 355 patient files coded as SE. All of our patients were female, varying in age from 20 to 52 years, with a mean age of 33 years. Six patients were of Chinese ethnicity, and one was Malay. All save one (who had completed primary school) had completed secondary school (high school equivalent) education.

None of the patients had previous seizures or a family history of epilepsy, nor a significant past medical or psychiatric history. Five out of 7 had fever in the week prior to the onset of seizures. All required ventilation during their prolonged admission. Except for extensor plantar responses, none of the patients had localising neurological signs. Table 1 is an overview list of the clinical characteristics. Six of the patients presented with a generalised tonic clonic seizure (GTCS), one with non-convulsive SE manifesting as altered consciousness. Initial electroencephalogram (EEG) captured ictal discharges in all. In 3, initial EEG showed repeated ictal discharges originating from both fronto-temporal regions with no

clear side preference. In 1, there was continuous parasagittal ictal discharge and 3 showed frontotemporal epileptiform waves originating from the right on 2 occasions and once from the left. In all patients, repeated EEGs showed the presence of multifocal SE.

All patients were extensively investigated. The following tests were within normal limits in all patients: computed tomography (CT) scan of the brain (performed within 24 hours of admission), serum glucose, serum electrolytes including calcium, magnesium and phosphate, liver and thyroid function tests and collagen vascular workup (CRP, anti-dsDNA, anti-nuclear antibodies, Complement 3 & 4). Serum cryptococcal, herpes simplex virus 1 and 2 (HSV 1 and 2) and cytomegalovirus (CMV) IgG/M titres were within normal limits, as was venereal disease research laboratory (VDRL) testing. Cerebrospinal fluid (CSF) HSV 1 polymerase chain reaction, cryptococcal antigen testing and VDRL were within normal limits. CSF cultures were negative for mumps, measles, HSV 1 and 2, enteroviruses as for *Mycobacterium tuberculosis*, aerobic and anaerobic bacteria and fungi. CSF coagglutination was negative for *Haemophilus influenza B*, *Streptococcus pneumoniae*, *Neisseria meningitides*, *Streptococcus* group B and *Escherichia coli* K1 antigen. A toxicology screen was negative in all patients. In the initial phase of the EEG, 5 out of 7 patients had predominantly frontal ictal activity, which subsequently generalised. This later developed into multifocal ictal discharges. The significant positive investigations are listed in Table 2.

Treatment and Outcome

None of the initial presenting seizures were documented by medical staff, and firsthand witnesses to the initial presenting complaint described symptoms compatible with generalised tonic-clonic seizures. Subsequently, multifocal seizures were repeatedly seen. All our patients received intravenous benzodiazepines immediately (initial bolus of 5 mg to 10 mg followed by continuous intravenous delivery commencing at 3 mg to 5 mg midazolam/hour and titrating upwards), rapidly followed (within 10 to 30 minutes) by

Table 1. Clinical Characteristics of Patients with NORSE

Patient	Preceding fever/illness	Seizure type	Length of ICU stay (d)	Outcome
1	Low-grade fever (1 week), transient diarrhoea	Multifocal/GTCS	92	Survived, vegetative, frequent seizures
2	Nil	Multifocal/NCSE	11	Survived, vegetative, frequent seizures
3	Fever (1 week), headache	Multifocal/GTCS	24	Death
4	Fever (1 week), headache	Multifocal/GTCS	15	Death
5	Nil	Multifocal/GTCS	7	Death
6	Fever (3 days)	Multifocal/GTCS	11	Death
7	Fever (3 days)	Multifocal/GTCS	65	Death

GTSE: generalised convulsive status epilepticus; ICU: intensive care unit; NCSE: non-convulsive status epilepticus; NORSE: new-onset refractory status epilepticus

Table 2. Abnormal Investigations in Patients with NORSE

Patient	WBC count x10 ⁹ /L	EEG pattern/Burst suppression achieved with ACD	MRI brain (hours after admission)	CSF studies (WBC in cells/uL)
1	20	Multifocal seizures/ Achieved	Biparietal and bitemporal FLAIR hyperintensities (no contrast) (7)	WBC 18 (polymorphs), normal glucose, protein 0.86 g/L
2	18	Multifocal seizures/ Achieved	Bilateral temporal, hippocampal, cerebellar penduncular FLAIR hyperintensities, leptomeningeal enhancement (24)	WBC 63 (polymorphs), normal glucose, protein 0.25 g/L
3	16	Multifocal seizures/ Not achieved	Subarachnoid sulci FLAIR hyperintensities, leptomeningeal enhancement (72)	WBC 48 (lymphocytes), normal glucose, protein 0.27 g/L
4	9	Multifocal seizures/ Achieved	Bilateral temporal and hippocampal FLAIR hyperintensities, leptomeningeal enhancement (24)	WBC 25 (lymphocytes), normal glucose, protein 1.77 g/L
5	15	Multifocal seizures/ Not achieved	Left temporal FLAIR and T2 hyperintensities (192)	WBC 3 (lymphocytes), normal glucose, protein 0.16 g/L
6	6	Multifocal seizures/ Achieved	Bilateral temporal T2 and FLAIR hyperintensities (36)	WBC 1 (lymphos), normal glucose, protein 0.51 g/L
7	9	Multifocal seizures/ Achieved	Bilateral corona radiata, centrum semiovale T2 and FLAIR hyperintensities, bilateral temporal FLAIR hyperintensities, leptomeningeal enhancement (48)	WBC 3 (polymorphs), normal glucose, protein 0.16 g/L

ACD: anticonvulsant drugs; CSF: cerebrospinal fluid; EEG: electroencephalogram; FLAIR: Fluid Attenuation Inversion Recovery Sequence; MRI: magnetic resonance imaging; WBC: white blood cell

maximal doses of intravenous phenytoin (slow bolus of 1 g to 1.5 g) and valproate (800 mg 8 hourly), failing which they were treated with propafol. Four out of the 7 patients were given intravenous thiopentone when propafol failed to abort the seizures. Three received high-dose topiramate (1200 mg/day), and one of them (Patient 1) showed clinical improvement, without the complete abolition of seizures. In all patients, serum anticonvulsant levels of phenytoin and valproate were within the therapeutic range (>10 mg/L for phenytoin; >50 mg/L for valproate) during the first 2 days of treatment. If these values subsequently fell below these levels, extra dosing was given to achieve our laboratory therapeutic values. Two patients received maximal doses of levetiracetam (1500 mg bd), without obvious improvement. Three out of 7 patients received intravenous immunoglobulin therapy (IVIG) without effect (0.4 g/kg body weight per day for 3 days).

Five of our 7 patients died while on intensive care. The cause of death was multi-organ failure. Two (Patients 1 and 2) survived in a vegetative state, with frequent daily seizures.

We managed to obtain autopsy with neuropathology in 2 (Patients 5 and 6) of our patients. Brain histology was completely devoid of an inflammatory response, and apart from diffuse patchy neuronal cell loss, with reactive gliosis, no other abnormalities were detected. Autopsy excluded occult malignancy.

A literature review identified 2 groups of authors who recently described similar conditions in 6 adults (4 females and 2 males)⁶ and in a group of 6 children (4 males and 2 females) aged 5 months to 6 years.⁷

Discussion

We describe a clinically distinct and homogeneous group of 7 previously healthy young female adults with generalised SE, refractory to aggressive antiepileptic treatment, with multifocal epileptiform discharges in the EEG and hyperintensities in the temporal lobe and leptomeninges on magnetic resonance imaging (MRI). Five out of 7 patients died despite intensive medical intervention and support, with the remaining 2 surviving with severe encephalopathy and recurrent seizures. The aetiology remains obscure, although we exhaustively searched for and failed to find any infectious, inflammatory, metabolic or toxic causes. The febrile start of the illness in 5 out of 7 of our patients could suggest a possible underlying infectious or inflammatory aetiology. However, the lack of an inflammatory response in the brains of 2 of the 7 cases, absent inflammatory serum and CSF markers as well as the lack of response to IVIG make this unlikely. In the face of negative markers of infection, lacking evidence of inflammation of the brain in 2 autopsies, the mild CSF pleocytosis is probably attributable to SE, as it can occur after SE of any type.⁸ Alternatively, CSF pleocytosis could

be seen as a typical characteristic of this aetiologically enigmatic syndrome. The abnormalities seen on brain MRI are not sufficient to differentiate between an infectious, inflammatory or ictal encephalopathy. Two groups recently described similar patients in 6 adults (4 females and 2 males)⁶ and in a group of 6 children (4 males and 2 females) aged 5 months to 6 years.⁷ Extensive investigations, including brain neuropathology, were negative for infectious, inflammatory or structural brain abnormality. In these series, SE resistant to all types of antiepileptic treatment was documented with catastrophic outcome.

Recent studies suggest that subtle immunological alterations in neurotransmitter function and altered drug clearance from the brain may play a hitherto underappreciated role in the aetiopathogenesis of RSE. Tanaka et al⁹ described associated intrathecal antibodies to inhibitory neurotransmitters such as glutamate in selected patients with RSE. Similarly, studies on animals and humans with refractory epilepsy have led to the discovery of a group of proteins that extrude drugs (in particular antiepileptics) from the CNS. These proteins have been shown to be overexpressed in the cerebral vascular and parenchymal tissue of both humans and rats.^{10,11}

Recognition and further characterisation of this disease entity is crucial in gaining a better understanding of the reasons for its associated disastrous outcome and hopefully allowing for the development of better forms of treatment. Although it is a well-known fact that a large proportion of patients presenting with SE have no prior history of epilepsy, NORSE syndrome is distinct in that no identifiable underlying cause can be discerned. At present, only small numbers of patients with NORSE or a condition resembling it have been described, probably because it has yet to be recognised as a clinical entity. We speculate that anticonvulsants – although reaching normal limits in the serum – may not reach their brain target in sufficient concentrations, possibly because of a defect in the recently discovered group of efflux carrier proteins located at the blood-brain barrier. Apart from heightening awareness of this catastrophic condition, we suggest that future studies

should investigate whether antiepileptic drugs reach the CNS in sufficient concentrations in addition to whether the targets of antiepileptics, ion-channels and neurotransmitters show dysfunctional properties. Because of the early and aggressive treatment implicated both in our cases and those in the literature, it is unlikely that the timing and dosage of antiepileptics will play a major role in better managing this illness. Rather, a better understanding of the aetiopathology will result in the development of novel therapeutics useful for the treatment of RSE.

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