Cryptogenic New Onset Refractory Status Epilepticus (NORSE) in adults—Infectious or not?

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ABSTRACT

Introduction: In the majority of cases of New Onset Refractory Status Epilepticus (NORSE) in adults, a cause is discovered. However, some cases of NORSE remain undiagnosed, i.e. cryptogenic. They are usually presumed to be due to infectious encephalitis and typically have devastating consequences. We describe our experience with six adults who presented with NORSE and raise the possibility of non-infectious causes.
Methods: Retrospective case series from an epilepsy service in a tertiary care urban hospital. We compare the clinical features of these cases with patients who develop NORSE in the setting of clinically-defined encephalitis from the California Encephalitis Project (most of whom are etiologically cryptogenic) as well as with patients who develop NORSE in the setting of proven infectious encephalitis.
Results: We describe 6 previously-normal adults with NORSE where a cause was not established despite an exhaustive search. With an average duration of 36 days (range 6–68), the in-hospital and long-term morbidities were high; one patient died of the propofol infusion syndrome. In contradistinction to NORSE in the setting of etiologically-proven infectious encephalitis, these patients were afebrile and the abnormalities evident during their evaluation could be attributed to the ictal activity itself. Neuropathological examination revealed non-specific findings in 4 patients.
Conclusions: Though an underlying etiology remains unproven in these patients, we contend that NORSE is etiologically heterogeneous, with a proportion of cases due to non-infectious causes. Further study of this poorly understood form of status epilepticus is needed.

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1. Introduction

Status Epilepticus (SE) is a common and frequently devastating neurological emergency. In the vast majority of cases, a cause for SE is evident but in a small fraction of cases, the underlying aetiology is not apparent despite extensive evaluation. Among these cases of *cryptogenic* SE, perhaps the most difficult to understand are patients who present *de novo* with highly refractory SE, which others have called NORSE ('new onset refractory status epilepticus') [1]. Most neurologists have encountered previously-healthy adults with present with status epilepticus and subsequently prove to be (a) highly refractory to standard first and second line agents and infusion therapies, and (b) no clear cause is found. These patients usually have a very protracted clinical course and sometimes die in the ICU. Typically, the working or presumptive diagnosis is that of viral encephalitis. This cause of NORSE is difficult to prove or refute because in many cases of *bona fide* infectious encephalitis, an infectious agent is not proven [2]. Hence, many cases remain poorly understood despite their catastrophic course and outcome. Surprisingly few cases of cryptogenic NORSE have been specifically described in the literature, even though cases of refractory SE due to 'presumed viral encephalitis' are not uncommon in neurological practice. The working diagnosis of 'viral encephalitis' is generally made on the basis of CSF pleocytosis, MR imaging abnormalities and the absence of an alternative explanation. However, in the final analysis, a specific pathogen is frequently not isolated (also not uncommon for encephalitis without associated seizure activity) and, in some cases, the CSF pleocytosis and imaging abnormalities can be ascribed to the seizure activity itself [3].

A recent paper from the California Encephalitis Project (CEP) described the clinical features of NORSE in the setting of clinically-diagnosed encephalitis [4] but, in the majority of patients, an infectious etiology was not discovered. However, NORSE does occur in 10–20% of patients with etiologically proven infectious encephalitis [5–7], usually in the setting of a febrile illness, typically with meningismus and encephalopathy. The use of clinical criteria for case ascertainment of encephalitis without need for definitive proof of a causative organism is likely to be over-inclusive as non-infectious illnesses such as Acute Disseminated Encephalomyelitis (ADEM) may clinically mimic infectious encephalitis.

Recognizing the difficulties of making a definitive diagnosis of infectious encephalitis and the increasing awareness of non-infectious causes of NORSE and epilepsy in adults [8], we propose that a fraction of cases of NORSE due to presumed infectious encephalitis do not have an

infectious cause. We report our experience with 6 adults with NORSE where an underlying cause was not established despite an exhaustive work-up. We emphasize that much is unknown about NORSE in adults, a search for non-infectious causes is important, and therapeutic considerations should address both infectious and non-infectious etiologies.

2. Methods

2.1. Case ascertainment

We screened those patients admitted to the neurological intensive care unit at our institution with refractory SE. We excluded patients who had a history of seizures or epilepsy prior to the episode of SE and those with incomplete diagnostic evaluations or follow-up information. The inclusion criteria for case ascertainment were as follows: normal pre-morbid functioning, highly refractory status epilepticus of duration greater than 7 days despite appropriate therapy, unrevealing comprehensive and appropriate diagnostic evaluation and complete follow-up data. Status epilepticus was designated as 'refractory' when it was not terminated by appropriate doses of appropriate 1st and 2nd therapies (usually i.v. benzodiazepine followed by i.v. phenytoin or fosphenytoin). We designate status epilepticus as 'highly refractory' if the electrographic seizure activity is not terminated within 24 h of achieving a burst-suppression EEG pattern through continuous infusion therapy (with propofol, pentobarbital or midazolam, or combinations thereof). The list of diagnostic investigations performed during the course of each patient's admission is shown in Table 1. Not every test was performed in each patient. Of note, testing for HHV6 was not performed in patients 1 and 5 due to lack of awareness of this infectious agent as a cause of encephalitis at the time of admission. The clinical features, details of investigations and treatment and clinical outcome were tabulated. At least one of the authors was directly involved in the care of each patient. The medical literature was surveyed for other well-characterized cases.

3. Results

3.1. Pre-morbid clinical characteristics and initial clinical presentation

Six adults who fulfilled the criteria were identified. Four patients were female. The average age was 28.5 years with a range of 24–36 years. One patient had a prior history of depression. Two patients used marijuana on an irregular basis. No other risk factors for acute symptomatic seizures or SE were identified in the patients. Of note, four cases had a well-described recent mild febrile illness within 2 weeks of development of NORSE. The illness consisted of fever and coryzal (nasal congestion, sore throat, myalgias) symptoms in 3 patients while the remaining patient had a persistent dry cough. However, none of the patients were febrile or exhibited meningismus on admission.

In four patients, the first clinical presentation was that of serial convulsive seizures without recovery in between. This led to intubation in the emergency department setting and transfer to an ICU. Two patients (cases 4 and 6) presented with abrupt onset of non-convulsive complex partial status epilepticus without generalized convulsive activity. This primarily manifested as confused behaviour with obtundation and intermittent focal motor seizure activity. In all cases, the seizure activity was recognised and treated with intravenous (i.v.) lorazepam (0.1 mg/kg) and i.v. phenytoin or fosphenytoin 15–20 mg/kg in conjunction with intubation and transfer to an ICU setting, all within 2 h of presentation to the emergency department. There were no undue delays in recognition or treatment of the SE. All 6 patients were transferred to our hospital Neurological ICU (NICU) within 12 h of first presentation to the emergency services. One patient (case #6) had experienced a number of complex partial seizures with recovery between individual seizures during the 72 h prior to the onset of sustained complex partial SE, where the patient did not recover to baseline. Patients were deemed to be in refractory SE when emergency EEG monitoring, initiated upon arrival to our hospital, confirmed the presence of electrographic seizure activity, by which time each patient had received i.v. lorazepam and phenytoin/fosphenytoin.

3.2. Electroencephalography and imaging findings

Continuous EEG monitoring was initiated within 4 h of admission to our hospital in all patients, either in the emergency department or in the NICU. The EEG recording was reviewed and interpreted by an experienced electrophysiologist at least twice per day. In this study, an electrographic seizure was operationally defined as a paroxysm of rhythmic EEG activity lasting at least 10 s distinctly different from

Table 1
Diagnostic investigations considered in patients with refractory status epilepticus, prior to designation of a diagnosis of cryptogenic 'New Onset Refractory Status Epilepticus' (NORSE)

Screen	Disease or agent tested
Infectious	*HSV I, *HSV II, *VZV, *EBV, *HHV6, *St. Louis Encephalitis virus, *Western Equine Encephalitis virus, *West Nile virus, *Eastern Equine Encephalitis, *Measles virus, *Enterovirus, *Adenovirus, *Influenza A, *Influenza B, *Chlamydia species, *Mycoplasma Pneumoniae, *HIV, *RPR-VDRL, *Lyme serology, *CMV, JC virus, *Mycobacterium TB, Toxoplasma serology, Ehrlichia, Cryptococcus Neoformans, *Bartonella, Fungal culture, prion disease, Rocky Mountain Spotted fever, Tularemia, Babesiosis
Toxicological	Marijuana, *benzodiazepines, *amphetamines, *cocaine, LSD, Heroin, PCP, ecstasy, marine toxins, occupational and iatrogenic drug history, heavy metals
Immunological	*ANA, *anti-thyroid antibodies, *anti-dsDNA, ANCA, Jo-1, Ro, La, Scl-70, Rheumatoid factor, *ESR, *C-reactive protein, serum ACE level, *CSF immunoelectrophoresis, anti-GluR3, andi-GAD65, anti-VGKC antibody
Neoplastic	*CXR, *CT thorax, abdomen, pelvis, *whole body PET, bone marrow biopsy, *CSF cytology, *CSF flow cytometry
Paraneoplastic	*Anti-Hu, *Ma2, *CV2/CRMP5, *anti-amphiphysin, *anti-VGKC, anti-NMDA receptor antibody
Metabolic	*Renal panel, *liver panel, *electrolytes, *Ca/Mg, *ammonia level, B12 level, folate, lactate level, pyruvate level, CPK, Thyroid function, glucose levels, *porphyria screen, *celiac disease (anti-tTG, anti-endomysium)
Haematologic	*CBC, blood smear, *hypercoagulable screen including anti-cardiolipin and anti-phospholipid antibodies
Vascular	*CTA or MRA, *MR venography
Genetic	Skin and muscle biopsy, serum and CSF lactate and pyruvate, genetic screen for known MERRF and MELAS mutations, muscle respiratory chain enzyme assay, very long chain fatty acid screen, lysosomal enzyme screen, blood and urine amino acid screen, urine organic acid panel, serum copper and caeruloplasmin, urine sulphites, blood and urine urate levels, white cell enzyme studies, serum lipids, MR spectroscopy
Other	18-FDG PET brain, SPECT, Biopsy (meninges, cortex, white matter), *CSF biochemistry and cell counts, urinalysis

Those investigations performed in every patient are highlighted by an asterisk. The remaining tests were considered on a case-by-case basis.
HIV: human immunodeficiency virus; RPR: rapid plasma reagin; VDRL: venereal disease research laboratory; HSV: herpes simplex virus; EBV: Epstein–Barr virus; CMV: cytomegalovirus; VZV: varicella zoster virus; TB: tuberculosis; HHV: human herpesvirus; ANA: anti-nuclear antibody; dsDNA: double-stranded DNA; ANCA: anti-cytoplasmic antibody; GluR: glutamate receptor; GAD: glutamic acid decarboxylase; VGKC: voltage gated potassium channel; CXR: chest x-ray; CT: computer tomography; PET: positron emission tomography; CSF: cerebrospinal fluid; NMDA: N-methyl-D-Aspartic acid; CK: creatine kinase; MERRF: myoclonus epilepsy with ragged red fibers; MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; FDG: fluoro-deoxyglucose; SPECT: single photon emission computed tomography.

background EEG activity with a temporospatial evolution characterized by an initial 'build-up' of regularly repetitive sharp wave or rhythmic sinusoidal activity of gradually increasing frequency and amplitude, progressing to a slowing in frequency and a more irregular appearance with post-ictal disorganization and slowing in the same region.

Continuous infusion therapy was titrated to achieve a burst-suppression pattern on the EEG, aiming for approximately 1 burst per 10–15 s of EEG recording. We made decisions about tapering (by 25% decrements in rate of infusion) or stopping infusion therapy every 12–24 h, based on the EEG findings and clinical situation. If SE was not terminated after 24 h of a suppressed EEG pattern, infusion of another agent was begun. Decisions on therapy were made after consensus was reached between the epileptologists/neurophysiologists and NICU physicians based on the EEG findings from the previous 12–24 h and the clinical status of the patient. Particular attention was paid to avoid misinterpretation of EEG patterns, especially electrographic seizures.

At the time of admission, the EEG recording revealed generalized or multifocal electrographic seizure activity in 4 patients while patients #1 and 6 had focal electrographic seizures from the onset. In patient 6, the consistently focal electrographic seizures prompted consideration of surgical intervention when it became apparent that medical therapy was ineffective.

In all patients, MR imaging was performed within 24 h of admission to hospital. In all but one patient (#6), the initial MRI was unremarkable. Patient #6 showed early and sustained left frontal peri-ictal abnormalities. Subsequent MR imaging revealed peri-ictal hippocampal abnormalities in case #1 while 3 patients had normal imaging despite ongoing SE. We differentiated 'local' peri-ictal imaging abnormalities where the MRI findings were localized to the same region (midline, frontal, anterior temporal, posterior temporal, occipital, centroparietal) as the electrographic seizure activity (as defined by maximal amplitude activity on a referential EEG montage recording at the same time as the MR imaging was performed), from 'remote' peri-ictal abnormalities where the MRI findings were evident in brain region(s) distant from the region of electrographic seizure activity. Peri-ictal abnormalities included swelling of the cortical ribbon with loss of grey-white matter differentiation (Fig. 1), and increased T2 signal intensity in areas of cortex and adjacent subcortical white matter, sometimes correlating with restricted diffusion in the same region.

3.3. Cerebrospinal fluid analysis

All patients had at least two lumbar punctures for CSF analysis. A modest lymphocytic pleocytosis with normal glucose and normal or mildly elevated protein level was seen in all patients. The EEG, imaging and diagnostic findings and clinical course of the NORSE are summarized in Table 2.

3.4. Other investigations

In each of the six patients, an exhaustive diagnostic work-up was unrevealing (Table 1). An infectious screen, particularly focused on searching for infectious causes of encephalitis, was performed on more than one occasion in all patients. One patient (patient 4) had modest titers of anti-thyroglobulin and anti-thyroid peroxidase antibodies, raising the possibility of 'steroid-responsive encephalopathy associated with autoimmune thyroiditis' (SREAT).

3.5. Therapeutic intervention

In all cases, after initial prompt treatment with i.v. benzodiazepine and phenytoin or fosphenytoin therapy, the patients received a 20 mg/kg loading dose of phenobarbital and were maintained of maintenance phenytoin and phenobarbital therapy during the initial days of admission. Continuous infusion therapy was initiated in the NICU setting and titrated to produce a sustained burst-suppression pattern with bursts every 10–15 s of EEG recording. Continuous infusion therapy typically began with propofol for at least 24 h, followed by sequential 24–48 h trials of midazolam or pentobarbital if electrographic seizures persisted. Ketamine infusions were initiated if the SE proved refractory to propofol, pentobarbital and midazolam. In addition to the infusion therapy, patients were always maintained on 'maintenance' enteral anti-seizure medications. These typically involved at least two of the following agents—phenytoin, topiramate, carbamazepine, levetiracetam, or phenobarbital. Patients # 4 and 5 received intravenous methylprednisolone 1gm/day for 3 days during the course of their illness. In addition, patient 4 received 3 days of plasmapheresis followed by intravenous immunoglobulin 0.4gm/kg per day for 5 days, because of the elevated titers of anti-thyroglobulin and anti-thyroid peroxidase antibodies, but did not respond to these treatments. None of the patients received immune-based therapies
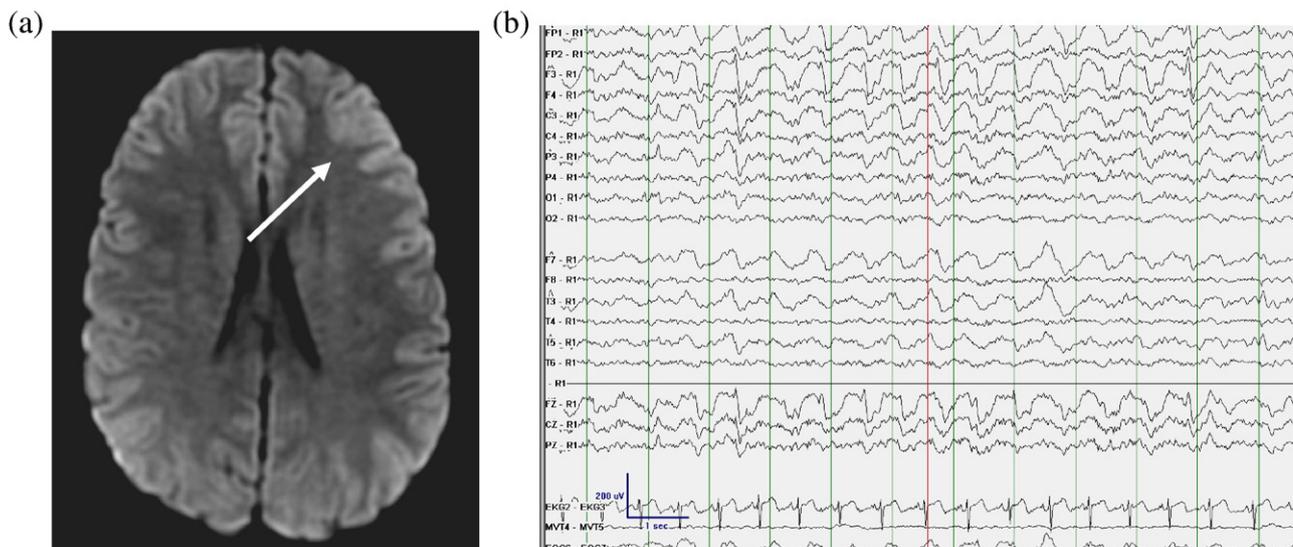

Fig. 1. Example of local peri-ictal imaging findings with contemporaneous focal electrographic seizure activity, from patient #2. Panel (a) shows a swollen cortical ribbon over the left anterior frontal convexity on FLAIR sequence. Panel (b) shows electrographic seizure activity over the left frontal region (maximal amplitude at F3) on a referential montage with R1 placed over the 2nd cervical vertebra.

Table 2
Electroencephalographic, imaging, cerebrospinal fluid and neuropathological findings in 6 adults with cryptogenic New Onset Refractory Status Epilepticus (NORSE)

Patient	Early (before 5th day) and late (after day 5) EEG localization of electrographic seizures	Early (before 5th day) and late (after day 5 of NORSE) MR Imaging findings	Maximally abnormal CSF	Day of CSF analysis relative to onset of NORSE
1	Early: right temporal Late: right hemispheric	Early: normal Late: swollen right hippocampus	WCC 14/mm3 Cell type: lymphs RCC 4/mm3 Protein 23 mg/dl Glucose 101 mg/dl	Day #4
2	Early: generalized or multifocal Late: generalized or multifocal	Early: normal Late: normal	WCC 10/mm3 Cell type: lymphs RCC 7/mm3 Protein 24 mg/dl Glucose 57 mg/dl	Day #6
3	Early: generalized or multifocal Late: generalized or multifocal	Early: normal Late: normal	WCC 14/mm3 Cell type: lymphs RCC 205/mm3 Protein 39 mg/dl Glucose 74 mg/dl	Day #19
4	Early: generalized or multifocal Late: generalized or multifocal	Early: normal Late: normal	WCC 46/mm3 Cell type: lymphs RCC 43/mm3 Protein 26 mg/dl Glucose 91 mg/dl	Day #4
5	Early: generalized or multifocal Late: generalized or multifocal	Early: asymmetry in the ventricular size (R slightly bigger than L), a normal variant Late: unchanged	WCC 23/mm3 Cell type: lymphs RCC 16/mm3 Protein 40 mg/dl Glucose 63 mg/dl	Day #3
6	Early: left frontal Late: left frontal	Early: swollen cortical ribbon left frontal cortex Late: unchanged	WCC 29/mm3 Cell type: lymphs RCC 4/mm3 Protein 34 mg/dl Glucose 79 mg/dl	Day #9

Electrographic seizure activity was determined to be focal when the maximal amplitude ictal activity on a referential EEG montage recording was consistently localized to one particular region (midline, frontal, anterior temporal, posterior temporal, occipital, centroparietal). Multifocal electrographic seizure activity consistently involved more than one non-contiguous region and generalized electrographic seizure activity involved diffuse bilateral brain regions simultaneously. Imaging and EEG abnormalities were divided into those seen on the initial MRI and EEG studies ('early') and those evident after at least 5 days of treatment, when the infusion therapy was temporarily reduced or discontinued.

within the first 5 days and none received sustained (>3 days) courses of corticosteroids.

3.6. Clinical progress and outcome

The average duration of NORSE was 36 days (range 6–68 days) and the in-hospital and long-term morbidities were high (Table 3). Of the 5 patients that survived, the average length of stay in the ICU was 33.5 days (range 9–76 days). Patient #2 died on day 9 after receiving continuous infusion therapy with propofol (days 1–7), midazolam (days 2–6) and pentobarbital (days 3–9). Propofol was the mainstay of infusion therapy, administered for a total of 8 days. On day 7, the patient became hypotensive and oliguric with laboratory studies showing acute hyperkalaemia, metabolic acidosis, elevated creatine kinase levels (15 times normal upper limit), and hypertriglyceridae-mia (3 times normal upper limit) with normal cholesterol values. She developed profound cardiogenic failure despite support with iono-tropes and intra-aortic balloon pump placement. Post-mortem examination revealed a dilated cardiomyopathy with interstitial edema and lymphoplasmacytic infiltrates. Despite a careful search, an infectious agent was not found. The consensus opinion of her caregivers was that she died due to the propofol infusion syndrome.

3.7. Neuropathological findings

Neuropathological evaluation was available for 4 patients (patients 1, 2, 4, and 6). The neuropathological examination focused in particular on looking for evidence of vasculitis, viral encephalitis (including electron microscopy), malignancy, cortical dysplasia and non-inflammatory vascular disease. Patient 1 underwent a right temporal en bloc resection. Histopathological examination revealed non-specific gliosis within the amygdala. No other more specific findings were evident. Patient 2 underwent post-mortem evaluation. Neuropathological evaluation revealed increased microglia and scattered pyknotic neurons in both subicula and parahippocampal gyri. In addition, diffuse neuronal injury with reactive microglia and astrocytosis was evident. Patient 5 had a diagnostic right frontal brain and meningeal biopsy. Patient 6 underwent a left middle frontal gyrus corticectomy. Non-specific gliosis and microglial activation was evident in both patients but no specific diagnostic neuropathological findings were seen.

4. Discussion

In approximately 10% of cases of status epilepticus, the cause is unclear i.e. 'cryptogenic' [9,10]. In our experience, it is unusual not to discover an underlying cause for *de novo* SE, particularly when highly refractory. We describe six healthy adult patients who presented with *de novo* cryptogenic NORSE. During the course of evaluating and treating these patients, a central question was 'do they have viral encephalitis?' A parallel conundrum faces physicians when they treat patients with presumed encephalitis when the standard infectious work-up is unrevealing [2].

These cases have a number of common clinical features, namely young age of onset (average 28.5 years), female preponderance (4:2), no prior history of seizures or neurological disorder, preceding mild febrile illness in 4 patients, modest lymphocytic CSF pleocytosis, imaging abnormalities that could be ascribed to the ictal activity itself,

Table 3
Clinical outcomes after an episode of cryptogenic New Onset Refractory Status Epilepticus (NORSE)

Patient	Follow-up duration	Overall outcome	Epilepsy outcome at last follow-up	Cognitive outcome	Return to employment/driving
1	9 years	Impaired and dependent	Intractable multifocal epilepsy, on 3 AEDs	Severely impaired memory	No/no
2	Died	Death	Died	Died	No/no
3	6 years	Impaired and dependent	Intractable multifocal epilepsy, on 4 AEDs	Severely impaired memory	Yes/no
4	18 months	Good	No seizures, on 2 AEDs	Excellent recovery	Yes/yes
5	11 years	Impaired but independent	Intractable multifocal epilepsy, on 4 AEDs	Moderately impaired memory	Yes/no
6	2 years	Impaired but independent	No seizures, no AEDs	Moderately impaired executive skills	Yes/no

AED: anti-epileptic drug.

and poor clinical outcome. However these clinical features do not in any way distinguish them from many patients with presumed encephalitis where an infectious etiology is not found.

A recent report from the California Encephalitis Project (CEP) reviewed 1151 encephalitis patients in an effort to determine whether there are any distinguishing characteristics of patients with *clinically-defined* encephalitis with acute symptomatic refractory status epilepticus from those who do not. In the CEP, a case of encephalitis is reportable if an immunocompetent patient is hospitalized with altered consciousness or behavior lasting at least 24 h, and had one or more of the following: fever (>100 °F), seizure, focal neurological findings, CSF pleocytosis (>5 WBC/ml), or EEG or neuroimaging findings consistent with encephalitis. The cohort of 43 patients (4%) who developed NORSE in the setting of encephalitis were younger (median age 10 years), more likely to have fever and meningismus on admission (>90%), more likely to experience a prodromal respiratory (57%) or gastrointestinal illness (64%), and were less likely to have CSF pleocytosis (47%) or abnormal neuroimaging (16%), compared to the larger cohorts of encephalitis patients without seizures (n=649) or with medically responsive seizures (n=459).

This large epidemiological project demonstrates that refractory SE is uncommon in *clinically-defined* encephalitis of any age (1 in 25 patients) while medically-responsive seizures and SE are much more common (~40% of all-comers). Despite early admission to hospital (median interval from onset of neurological symptoms to admission 1 day), an infectious agent was not found in the majority (72%) of patients with NORSE in the setting of presumed infectious encephalitis. An infectious cause was definitively proven in only 3 patients while 9 other patients had inconclusive evidence for an infectious cause. The clinical outcome was poor, with death in 12 patients (28%) and significant neurological impairment in the majority. Of the original cohort of 43 patients, 3 patients had brain biopsies and 3 patients underwent an autopsy. Two biopsies showed mild astrogliosis without inflammatory infiltrate or histopathology indicative of neuronal viral infection. The third biopsy showed a meningoencephalitis with marked lymphocyte infiltrates in both the cortex and overlying leptomeninges and microglial nodules. Viral inclusions were not present and no pathogen was identified. The 3 autopsy brain specimens showed anoxic-ischemic damage, including cerebral edema and neuronal necrosis, but no parenchymal infiltration or other features suggestive of encephalitis. One patient had a lymphocytic meningeal infiltrate. These findings highlight the enduring diagnostic uncertainty in many patients labeled with 'viral encephalitis' even when tissue is available.

In this study, we describe adults with cryptogenic NORSE with a presumptive diagnosis of viral encephalitis. None of these patients were febrile on admission and seizures rather than encephalopathy or meningismus were the dominant clinical manifestation in the early stages. Though 4 patients had a history of a mild febrile illness, they had all recovered prior to the onset of seizures. We contend that their clinical presentations were not typical for infectious encephalitis [5–7], though recognize that their presentation was not diagnostic of any particular entity. In these 6 adults, the clinical and neuropathological findings are very similar to the CEP patients with encephalitis and NORSE. Interestingly, similar to our cases, in the CEP study the patients with NORSE and encephalitis were more likely to have normal neuroimaging than those encephalitis patients without seizures or NORSE.

Using clinical diagnostic criteria for encephalitis is likely to be over-inclusive as it is possible than clinical entities that mimic infectious encephalitis could be included. Protracted status epilepticus itself, irrespective of cause, may lead to peri-ictal imaging [11] and CSF abnormalities [3], which can simulate the abnormalities seen in *bona fide* infectious encephalitis. Furthermore, non-infectious causes of encephalitis, often presenting with NORSE are increasingly being recognised [8,12]. In the CEP study and in our cases, the imaging, CSF and pathological findings were modest, not specific for any particular cause and could plausibly be due to the SE itself. In addition, while compelling, the EEG abnormalities reflect the epileptogenicity of the cerebral cortex but, do not distinguish SE due to a non-infectious cause from infectious encephalitis. Of the 4 patients in this case series who had histopathological assessment, the examined tissues revealed

Table 4

Summary of clinical features, treatment, outcomes and neuropathological findings in well-described adult patients with cryptogenic New Onset Refractory Status Epilepticus (NORSE)

Author (year)	Van Lierde [14]	Wilder-Smith [1]	Hoerth [15]	Costello	Total (average)
No. of patients	6	7	4	6	23
Age range (years)	18–30	20–52	20–41	24–36	(28.3)
Female:male	4:2	7:0	4:0	4:2	19:4
Preceding febrile illness	N=6	N=5	N=4	N=4	19 from 23
Fever or meningismus	Unclear	Unclear	Unclear	None	–
Pre-morbid health	Normal	Normal	Normal	Normal	–
Duration of SE (days)	6–191	7–92	10–56	9–76	(40)
EEG findings (unifocal, multifocal, generalized)	(0,6,0)	(0,7,0)	(0,0,4)	(1,1,4)	1,14,4
CSF white cell count cells/mm3 (dominant cell type)	1–28 lymphs	1–63 lymphs	1–27 'nucleated cells'	2–46 lymphs	17 cells/mm^3 (lymphocytes)
Average CSF protein, glucose in mg/dl	45 83.6	56 'Normal'	'Normal' 'Normal'	33.7 82	Protein 45 mg/dl Glucose normal
Normal early imaging findings	3/6	0/7	4/4	2/6	9/23
Late 'peri-ictal' imaging findings	3/6	7/7	0/4	3/6	13/23
Average number of AEDs and infusion therapies tried	8.5	'Multiple'	8	6.3	>6
Other therapies tried (steroids, Ivlg, plasma exchange)	1 0 2	0 3 0	2 0 0	1 1 0	Steroids 4/23 ivIg 4/23 PlEx 2/23
Surgical intervention (number)	None	None	VNS (2) CC (1)	ATL (1) Topectomy (1)	–
Died	1/6	5/7	4/4	1/6	11/23
Chronic epilepsy or encephalopathy	5/6	2/7	n/a all died	4/6	11/23
Neuropathology (biopsy, autopsy)	Biopsy: normal in 2	Biopsy: not done	Biopsy: not done	Biopsy: non-specific changes in 3	–
	Autopsy: bilateral HS in 1; bilateral hippocampal and cerebellar neuronal loss in 1	Autopsy: 'non-specific findings' in 2	Autopsy: 'non-specific findings' in 4	Autopsy: non-specific changes in 1	

VNS: vagus nerve stimulator, CC: corpus callosotomy, ATL: anterior temporal lobectomy, HS: Hippocampal sclerosis, ivIg: intravenous immunoglobulins, PlEx: plasma exchange.

mild reactive changes without features of infection, vasculitis, infiltration or cortical dysplasia.

Other authors have reported healthy adult cases with *de novo* cryptogenic NORSE [1,13–15]. Patient 6 has been described in the literature [13]. Although the numbers of patients is small, these reports collectively highlight a number of features (Table 4). The patients had normal pre-morbid health, were relatively young, had a female preponderance, and developed protracted and life-threatening status epilepticus. Again, the abnormalities evident during their evaluations can be attributed to the ictal activity itself. Typically there is a lymphocytic CSF pleocytosis with mildly elevated protein and normal glucose, MR imaging either normal or demonstrating peri-ictal changes. Probably reflecting the dynamic nature of SE, imaging abnormalities may initially be lacking but subsequently develop and the EEG may show a tendency to evolve from focal towards multifocal or generalized electrographic seizure activity. Table 3 underscores the poor prognosis with 11 of 23 (47%) fatal outcomes.

In our patients and other published cases, the neuropathological examination showed tissue changes seen in prolonged status epilepticus but did not reveal a clear cause for the SE itself [16]. The majority of cases developed chronic epilepsy and many suffered severe cognitive injury with attendant psychosocial consequences.

Though infectious encephalitis is likely to underlie many, if not the majority of cases of adult onset NORSE, we speculate that adult NORSE is likely to be more heterogenous than we appreciate with a variety of non-infectious causes. Potential, though difficult to prove, non-infectious causes might include the possibility of the precipitous unmasking of an 'epileptic' diathesis due to a channelopathy or covert mitochondrial disorder by a benign febrile illness. In these persons, the acute symptomatic seizures become self-sustaining and the patient spirals into a state of refractory SE. A second possible pathophysiological explanation for this particular electroclinical syndrome is that some forms of NORSE are a para-infectious, immune-mediated phenomenon, akin to ADEM or Guillian–Barre syndrome. In this situation, a seemingly benign infectious illness leads to an aberrant immune response due to molecular mimicry. The antigenic target may be specialized and critical to neurophysiological membrane stability (as seen with anti-VGKC limbic encephalitis) or may be multiple and non-specific leading to regional inflammation e.g. mesial temporal cortex. The importance of immune mechanisms in epileptogenesis is gaining recognition [8]. Another possibility is that of an occult epileptogenic cortical nidus such a focal cortical dysplasia [17]. In all these scenarios, the dominant clinical finding becomes the precipitous onset of SE itself, rather than an underlying illness. This is reflected in the paucity of abnormal findings of CSF analysis and other investigations.

The diagnosis of cryptogenic NORSE is essentially retrospective and made after exclusion of rare or obscure causes of refractory status epilepticus (Table 1). We postulate that cryptogenic NORSE is likely to be due to a heterogenous collection of causes, some infectious and some non-infectious. We emphasize that much is unknown about NORSE and further study of this life-threatening clinical scenario is needed.

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