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Retrospective study of three NORSE cases: EEG features and treatment

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Background: New-onset refractory status epilepticus (NORSE) is a clinical presentation in which patients without a history of Epilepsy suddenly develop prolonged seizures that do not respond to at least two standard anti-epileptics (AEDs) and for which the cause for the seizures remains unidentifiable beyond 72 hours. Clinicians' aim is to treat the possible cause, suppress the seizures and aim for suppression burst (SB) in EEG which has been found to be associated with less breakthrough seizures and with no increased rate of intra-hospital complications. Multi-disciplinary ward rounds are essential to avoid increasing morbidity.

We analyse the clinical care and outcome of the patients that presented with NORSE at King's College Hospital, London, UK.

Methods: This is a retrospective study of three patients who presented with NORSE during the last four consecutive years at King's College Hospital. Review of clinical notes and multi-disciplinary ward rounds are performed.

Results: The three patients were under 35. Mean length of admission in ICU was 11 days. Extensive diagnostic check list was performed. Suppression burst was achieved promptly, 0-3 days, administering 5 anaesthetics drugs and 4 AEDs. Immuno-modulation therapies were also provided. Breakthrough seizures, clinical and electrographic, reappeared within a mean of 9 days (0-22). The three patients died. The post-mortem reports could not identify the primary cause for NORSE in two patients and identified resolving encephalitis with ischaemic changes in one patient.

Conclusions: Despite achieving SB promptly, breakthrough seizures reappeared and despite multi-disciplinary ward rounds and different approaches of treatment, the three patients died. The early identification and treatment of seizures did not seem to be associated with a good outcome. Hence, the best management and treatment of NORSE remains difficult to determine. Are seizures an epiphenomenon of a more diffuse clinical entity? Should we be focusing and treating every detected seizure? Further studies with larger sample of patients' data would be helpful to agree a diagnostic and treatment pathway, and to analyse possible aetiologies that might benefit from aggressive treatment compared to others.

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The Spectrum of Electrographic Seizure Patterns in the Critically Ill

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Background: Electrographic seizures are common in critically ill comatose or encephalopathic patients. To date, there is little data regarding seizure onset patterns (SOP), seizure onset frequencies

(SOF) and other electrographic features of seizures, and whether or not meaningful associations with clinical characteristics exist in this population.

Methods: 44 subjects from 2013 to 2017 were identified from a clinical database of hospitalized patients undergoing continuous video EEG monitoring. All had documented electrographic seizures, and were altered or critically ill. Patients with focal motor seizures with intact awareness were excluded. The definitions for various ictal and periodic/rhythmic patterns were based on published criteria. Board-certified or board-eligible electroencephalographers each reviewed two seizures per patient.

Results: In this cohort of 44 subjects, the mean age was 55.5 years; 40.7% were women. 91 seizures were analyzed. Status epilepticus was present in 55.1% of patients. SOP's were most commonly rhythmic sharp waves or spike-wave complexes, followed by rhythmic evolving activity (35.9%), fast activity (>13 Hz) (12.1%), and attenuation (1.1%).

SOF was delta in 50.5%, theta in 36.3%, alpha in 12.1% and beta in 1.1%. Maximal spatial extent remained localized/focal in 47.3%, hemispheric spread in 36.3%, and generalized in 16.5% of seizures studied.

There was a significant association of SOP with the presence of acute brain injury (Pearson chi square of 9.086, $p < 0.05$) and poor outcome (trend toward significance $p = 0.074$). Higher SOF (alpha or beta) were associated with better outcome (chi 8.208, $p < 0.05$).

There was no significant association of SOP with the presence/absence of status epilepticus, or the use of therapeutic coma.

Conclusions: The most common SOP in our cohort of critically ill altered patients appears to be rhythmic discharges. Majority of seizures were delta frequency at onset and associated with a dichotomous outcome, while higher onset frequencies (alpha or beta) portended a better outcome. Larger prospective studies are further needed to explore electrographic characteristics that may predict a response to treatment or outcome.

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Improved outcome on early immunotherapy in new onset refractory status epilepticus (NORSE). Experience in Qatar

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Introduction: New-onset refractory status epilepticus (NORSE) is defined as refractory status epilepticus without an obvious cause after initial investigations. Refractory status epilepticus (SE) is a condition in which patients suddenly experience continuous seizures or a flurry of very frequent seizures that do not respond to standard anticonvulsant medications. Seizures are thought to be due to an excess of pro-inflammatory molecules in the brain, perhaps triggered by a simple viral infection, although no clear cause has ever been demonstrated.

Materials and Methods: This is a descriptive, retrospective review of 10 previously normal adult patients (age between 28 and 56 years) with NORSE admitted to Hamad Medical Corporation MICU in Qatar from 2012 to 2018.

Results: Ten patients with NORSE syndrome were identified, where a cause was not established despite an exhaustive search with an

average duration of 27 days (range 14-32). Characterizing features were male gender, young age, previous good health, cerebrospinal fluid pleocytosis (in 7), antecedent febrile illness (in 7), extraordinarily prolonged status epilepticus, failure of extensive investigations to reveal an underlying cause, catastrophic outcome as well as T2 hyperintense signal in temporal lobes (in 5), BL symmetrical putaminal T2/flair high signals (in 1) and leptomeningeal enhancement (in 1) on brain magnetic resonance imaging. Treatment modalities included at least 3 antiepileptic drugs (in all patients), anesthetics (in all patients), intravenous immunoglobulin (IVIG, 8 patients), steroids (4 patients), plasmapheresis (1 patient). Five patients improved completely without neurological deficit and three of them survived with moderate to severe disability. Two patients who were not given early immunotherapy, died from complications associated with prolonged ICU stay. One of the survivors received long term immunotherapy.

Conclusions: The cause of NORSE syndrome may often be difficult to find. NORSE carries a poor prognosis and early recognition and treatment may improve outcomes. Epilepsy and cognitive issues are common among survivors although a small minority of them eventually return to a normal lifestyle. Affected individuals are most often treated for weeks in an intensive care unit because they require prolonged anesthesia to control their seizures. In this case series, we have shown that immunotherapy seems to be a helpful treatment option when conventional therapy fails.

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Association between initial therapy of refractory generalized convulsive status epilepticus in adults and its outcome

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Objective: to analyze outcomes of refractory (R) generalized convulsive status epilepticus (GCSE) in adults.

Materials and Methods: The study included 23 women with RGCSE, aged from 19 to 76 years. Patients presented with RGCSE in acute symptomatic form (n = 5) and as a complication of epilepsy (n = 18), of them 14 with structural focal epilepsy, 3 with focal epilepsy of unknown etiology, 1 with combined idiopathic generalized and structural focal epilepsy. Intravenous (iv) ivLorazepam, ivPhenytoin, ivPhenobarbital are unavailable in Russia, however iv Diazepam (ivDZP), Valproic Acid (ivVPA), Levetiracetam (ivLEV), Lacosamid (ivLCM) and iv anesthetics are available. Initial GCSE treatment for patients at home and in an ambulance was started with ivBZD, with ivVPA, or with combination of ivBZD + ivVPA within 35 min to 150 min after the GCSE onset. The maximum dose (mg/kg) of all types of ivAEDs and iv anesthetics was used.

Results: 3 patients (13%) with acute symptomatic GCSE died due to multiple organ failure not related to GCSE. In the remaining 18 cases, RGCSE was relieved. Non-acute symptomatic RGCSE lasting for 3 to 132 hours was observed mainly in structural focal (frontal, fronto-temporal) epilepsy (60.9%). The main reason for the development of GCSE in adults (43.5%) was an AED withdrawal. In these cases, the basic oral AEDs were continuously administered through a nasogastric tube. Super-refractory GCSE was confirmed in 11 cases (47.8%). In the prehospital phase of GCSE treatment, ivDZP was used

in 6 patients, 5 of them developed super-refractory GCSE; ivVA was used in 8 patients, 2 of them developed super-refractory GCSE; initial therapy with ivDZP + ivVA was used in 7 patients, 3 of them developed super-refractory GCSE. During treatment with iv anesthetics, respiratory depression developed with subsequent invasive ventilation and longer recovery. In one case of RGCSE recurrence, perampanel was successfully administered through a naso-gastral tube at 12 mg/day.

Conclusions: deaths occurred only in cases of acute symptomatic RGCSE. The vast majority of refractory RGCSE in adults (43.5%) was provoked by withdrawal of AEDs. Preliminary results indicate that prehospital (initial) use of ivVPA or a combination of ivDZP + ivVA significantly increase the efficacy of RGCSE therapy.

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Prognosis in patients with brain tumor-associated status epilepticus

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Background: Tumor related epilepsy is common in patients with brain tumors and it usually starts at the onset of the disease. By contrast, status epilepticus is less frequent, occurs at later stages and it is often related with tumor progression. We aimed to investigate prognosis and associated factors in these patients.

Methods: We consecutively included 61 patients that were admitted at our hospital due to brain tumor-associated status epilepticus between 2011-February and 2018-April. Demographic and clinical characteristics (type of tumor, duration and treatment of the status epilepticus) were recorded. We analyzed status epilepticus prognosis at long-term (GOSE – Glasgow Outcome Scale) and related factors.

Results: Mean age was 62.64 years-old (± 14.9) and 59% were men. The 34.4% (n = 21) were metastasis, followed by meningiomas (24.6%, n = 15), glioblastoma multiforme (24.6%, n = 15), low grade glioma (4.9%, n = 3) and other (11.7%, n = 7). Mean follow up was 12.6 months and mean survival time 19.6 months (IC 11.4-27.4). On the multivariate analysis the presence of glioblastoma multiforme or metastasis (OR 19 (2.23 – 161.58), p = 0.007) and the status epilepticus duration > 18 hours (1.28 – 42), p = 0.025) independently predict worse prognosis at one year follow-up. Mortality at follow up was only associated with the type of tumor (HR 7.26 (2.59-20.37), p < 0.001).

Conclusions: Longer duration of status epilepticus and the presence of glioblastoma multiforme or metastasis predict poor prognosis at long-term.

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