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Refractory status epilepticus in adults admitted to ITU in Glasgow 1995–2013 a longitudinal audit highlighting the need for action for provoked and unprovoked status epilepticus

Hinanaz Abbasi[a], John Paul Leach[a,b,*]

[a] Department of Neurology, Institute of Neurosciences, Queen Elizabeth University Hospital, Glasgow, G51 4TF, United Kingdom
[b] School of Medicine, Wolfson Medical School Building, University of Glasgow, Glasgow, G12 8QQ, United Kingdom

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ABSTRACT

Purpose: Our primary objective was to determine incidence of status epilepticus in adults admitted to 5 ITU settings in Glasgow over 18 years. We wanted to investigate if there are any change in causes and outcomes of SE over last decade. We also compared outcomes of De Novo statuts Epilpeticus (DNSE) and Stauts Epilepticus in patients with previous Epilepsy (SEPE).

Methods: The NHS GGC Research Ethics Committee gave permission for this study to continue without a full ethics submission. Between 2013 and 2016, coding records were searched across NHS Greater Glasgow and Clyde for adults over the age of 16 years admitted to an Intensive Care Facility in any of the hospitals in Glasgow.

Results: 633 cases were included in study. Cases were separated depending on whether there had been previous epilepsy (SEPE n = 214) or De Novo Status Epilepticus (DNSE, n = 419). Causes in both groups were listed, with 52% of those with DNSE having some contribution from substance misuse. In SEPE, this was felt to play a role in 33.7%. Duration of stay in both groups was similar, but the longest in-patient stays were in the DNSE group. Admission mortality was significantly higher in DNSE than in SEPE (13.8% versus 7.5%). This mortality risk was most closely associated with substance misuse in the group with DNSE.

Conclusion: DNSE has a worse prognosis than SEPE. A presentation with DNSE is sign of a system in peril, even where episodes are provoked by alcohol and or drug use. Such episodes should spark off a chain of multispecialty care in order to address this recurring and persisting public health catastrophe.

1. Introduction

Status epilepticus (SE) is defined as continuation of seizures for more than 5 min [1] and is a medical emergency that requires immediate assessment and treatment [2]. Subdivision of stages of SE have been defined depending on the degree of response to treatment and duration of treatment needed. The ILAE's classification [1] defines two 'operational dimensions', being the intial seizure duration requiring treatment (T1) of five minutes, and the seizure duration associated with neurological sequelae (T2) of 30 min.

Refractory status epilepticus (RSE) is defined as SE that continues despite treatment with benzodiazepines and at least one antiepileptic drug, while Super Refractory Status Epilepticus (SRSE) consists of continuous or recurrent seizures lasting for 24 h or more despite administration of an intravenous (IV) anaesthetic, or recurrence of SE on weaning from anaesthesia [3]. Preclinical studies show that persisting epileptic activity leads to changes in GABAergic function, increased glutamatergic stimulation, as well as changes in mitochondrial function in receptor trafficking, leading to a rapid escalation of epileptogenicity with persisting epileptic activity [4,5,6]. Such SE-related changes may underly the morbidity and mortality of prolonged seizures. There are many recognised causes of status epilepticus [7,8] and in approximately 50% of cases, this will be the first presentation of seizures or epilepsy. There are a range of causes of status epilepticus, and it may result from a range of causes including exposure to alcohol and drugs [9,10]. The risk factors for morbidity and mortality related to SE have not previously been well-defined, although small cohort studies [11,12,13,14,15] have suggested that older age at onset, generalised seizure at onset, treatment delay, impaired consciousness at presentation, or lack of electroencephalograhic (EEG) monitoring may all impair prognosis. Several studies [13,14,16,17], have shown an immediate mortality of SE of between 7 and 39%, while long term mortality has

* Corresponding author at: School of Medicine, Wolfson Medical School Building, University of Glasgow, Glasgow, G12 8QQ, United Kingdom.
E-mail address: john.leach@glasgow.ac.uk (J.P. Leach).

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been shown to be higher at 35–43% [11,16,17]. It has been suggested that RSE has a higher short-term and long-term mortality than SE, although this is not invariably replicated [17]. The increased 1-year mortality in SRSE has been associated with older age, or poorer neurological status on discharge from hospital [17].

Other studies have looked at incidence of SE, but we wanted to look at patients with SE which had been sustained enough to merit admission to an Intensive Therapy Unit (ITU) setting, each one thereby fulfilling the definition of RSE, and in some cases SRSE. We looked at the incidence of RSE spanning the decades following the introduction of newer antiepileptic drugs (AEDs). We aimed to consider the effect of different baseline AEDs and assess the management and outcome of SRSE lasting for very extended periods (this will be discussed in a subsequent paper). We had hypothesised that increasing use of newer antiepileptic drugs (AEDs), with their more predictable pharmacokinetics, would reduce the incidence of RSE in the population of patients with treated epilepsy.

2. Methods

The Research Ethics Committee for our regional Health Board (NHSGGC) was contacted and gave permission for this study to continue without a full ethics submission. Between 2013 and 2016, coding records were searched across NHS Greater Glasgow and Clyde for adults over the age of 16 years admitted to an Intensive Care Facility in any hospitals in Glasgow. Local records from the ITU in the Institute of Neurological Science provided additional data.

Coding for admission depended on the World Health Organisation's International Classification of Diseases in 9th and 10th Revisions (ICD 9 and ICD 10 respectively). ICD9 codes, which were used up to 31st March 1996, had no specific code for Status Epilepticus. From April 1996, ICD 10 codes were used, and to ensure we captured all settings for high intensity medical care we sought admissions to ITU, High Dependency Units and Coronary Care Units with primary diagnosis of ICD10 codes G40 ('Epilepsy'), G41 ('Status Epilepticus') & R568 ('Other & Unspecified Convulsions'). Patients with a specific diagnosis of hypoxic brain injury were not specifically excluded from analysis. Patients where duration of seizure was too short (ie admission to ITU had occurredas a precaution after seizure cessation) were excluded from the study. Patients with a final diagnosis of Pseudostatus Epilepticus or prolonged dissociative attacks were excluded from this audit but will be presented separately in a later paper. Separate publications will outline the individual treatments used and their effects

Demographic information was collected in each case. The outcome after admission was recorded, and for each case we recorded death during admission, at 1 year after admission, and - where appropriate - 5 years and 10 years after admission.

Where patients had died more than 5 years before coding identification, paper records may have been destroyed, leaving only electronic records available. Where necessary, demographic and admission data were collected from the NHS GGC audit department (n = 280).Those presenting with RSE who had no prior diagnosis of epilepsy were termed De Novo Status Epilepticus (DNSE). Those who had a prior diagnosis of epilepsy were designated SE with Prior Epilepsy (SEPE). The causes, treatments, and outcomes (including short-term and long-term mortality) of those with DNSE and SEPE were compared. The existence of alcohol or drug dependency was either noted from a direct statement to that effect or inferred from other supporting information (e.g. previous admission for detoxification, deranged LFTs before admission, ongoing treatment with methadone, or treatment required for alcohol withdrawal syndrome).

We used clinical notes to ascertain whether there was any neurological deficit by the time of discharge or (where data was available) if full recovery occurred later. Mortality data was gained form the notes and timed as occurring during ITU admission or at 1, 5, or 10 years after the date of admission to ITU.

The Glasgow incidence of SE-related admissions per 100,000 was calculated using population estimates for Greater Glasgow from the census nearest the mid

point of the sample incidence, being the 2011 census figure of 577,869. Statistical comparisons were carried out using Microsoft Excel 2016 and Mini Tab version 18. Comparison of mortality rates between groups was carried out using a Two Tailed Z test, producing a p value and 95% confidence intervals.

3. Results

We identified a total of 800 admissions to ITU with relevant diagnostic codes. We excluded 167 cases with insufficient information available, or with no supportable diagnosis of RSE, leaving 633 admissions to ITU with RSE with supporting information. Two hundred and fourteen (34%) patients had experienced prior seizures or a diagnosis of epilepsy (Status Epilepticus with Previous Epilepsy – SEPE), while 419 (66%) patients were admitted to an ITU for an index seizure (De Novo Status Epilepticus - DNSE). The nature of the SE was assessed (Supporting Table 1) 590 (93.20%) being generalized tonic colonic SE, and 24 (3.79%) were focal SE. Thirteen cases (2.1%) were eventually thought to be non-convulsive SE. In 6 cases (0.9%) no information on type of SE was available.

Table 1
Demographic Data, nature of Status Epilepticus and identified Causes.

	Total n = 633 (100%)	DNSE n = 419 (66%)	SEPE n = 214 (34%)
Age (years)	48	50	44
Mean, Range	15–91	15–91	15–90
Interquartile range	25	23	26
Female :Male	249:384 1.0:1.54	162:257 1.0:1.58	87:127 1.0:1.46
Documented Drug abuse	103 (16%)	71 (17%)	32 (15%)
Documented Alcohol abuse	312 (49%)	227 (54%)	85 (40%)
Previous ITU with neurological condition	108 (17%)	27 (6.40%)	81 (38%)
Days in hospital	21.4, 8	28, 10	8.7, 6
Mean, Median (Range)	(0.5 – 1497)	(0.5 – 1497)	(0.5- 30)
Interquartile range	17	20	11
Days in ITU	3.6	3.65	3.7
Mean, (Range)	(0.5 -165)	(0.5-165)	(0.5-26)
Interquartile range	3	3	3
Number of Deaths over 10 years following admission	303 (47.86%)	220 (52.50%)	83(38.7%)
Deaths during index admission	74 (11.69%)	58 (13.80%)	16(7.47%)
Deaths within 1-year following date of Admission	141 (22.0%)	106(25.0%)	35(16.0%)

DNSE = DeNove Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy.

3.1. Demographic information

The demographic details of the whole cohort and subgroups are shown in Table 1. Age and gender distributions were similar in both DNSE and SEPE groups. There was a male preponderance in both groups, which may reflect the incidence of causative factors seen in subsequent tables. The incidence of alcohol-related problems was slightly higher in DNSE than among SEPE patients. Analysis of addiction issues and other risk factors (Table 3) show increased rates related solely to addiction and abuse in the group with DNSE compared to SEPE (41% versus 18%).

3.2. Annual incidence

The annual number of cases of RSE (both SEPE and DNSE) in Glasgow showed wide variation, and we have for clarity formed 3-year cohorts. Both DNSE and SEPE show a parallel pattern of a steady rising incidence up to the 2007-09 epoch, peaking at just under 20/100,000 per year followed by a slight drop (Supporting figure 1).

3.3. Baseline AED treatment

Among 214 cases with SEPE, 170 (89%) were being prescribed AEDs at the time of admission, but the exact nature of this treatment was only known in 163 patients. Of these, 93 (57%) were receiving only established AEDs, with 24 (15%) solely on new AEDs and 46 (28%) on a mixture of established and new AEDs.

Table 2 shows baseline AED use in patients with SEPE before and after 2003. In later years the use of newer AEDs increases markedly. AED use was also grouped by effect on hepatic enzymes (Supporting Table 2). Enzyme inducing AEDs (EIAEDs - Carbamazepine, phenytoin, phenobarbitone and primidone) were being prescribed in 104 (63.8%) at the time of admission. Valproate (Supporting figure 2) was the single most commonly prescribed AED, used in 68 patients (41.7%). Phenytoin was the second most commonly prescribed (n = 53, 32.5%) and levetiracetam the 3rd most common AED 31 (19.0%).

3.4. Identified causes of SE

Where specific causes were identified, these are listed in Table 3. As expected, SEPE and DNSE have a different spread of contributory and causative factors.

Provocation by alcohol +/or drug misuse is significant in 54.9% of those with DNSE and 33.7% of those with SEPE. In the SEPE group a wide range of causes was found. In those with a prior diagnosis of epilepsy, the progressive nature of the epilepsy syndrome and incomplete adherence or loss of effect of AED made up the majority of the SEPE. No cause was identified in 13.8%. Only 6 patients with hypoxic brain injury and associated status were identified, 4 of whom had no history of prior seizures.

3.5. Outcomes of RSE – admission to ITU and total hospital stay

The median duration of stay in ITU (i.e. time to discharge or death) was similar in both groups, with more than half staying in for 2 days or less (Table 4). While the median stay is similar across SEPE and DNSE groups, 10.5% and 13.8% of those with DNSE and SEPE respectively had an ITU admission lasting longer than 7 days or more. The longest-term stays arose only among those with DNSE, with 0.5% requiring ITU admission for longer than 6 weeks. Median duration of total in-patient hospital stay was slightly longer in DNSE (10 versus 6 days), which was also associated with the longest stays.

3.6. Outcomes of RSE – death, residual neurological deficit, or full recovery

As can be seen in Table 5 and Supporting Table 3, the admission mortality rate was higher in DNSE than SEPE (13.8% versus 7.5%) (p = 0.0195, 95% CI 1%–11.59%). At 1 year, 5 years and 10 years post-

Table 3
Causes of Status Epilepticus.

	DNSE (N = 419) n, (%)	SEPE (N = 214) n, (%)
Sole Contributor being Alcohol +/or drugs	171 (40.80%)	39 (18.00%)
Cerebrovascular / trauma	55 (13.1%)	0
Alcohol +/or drugs + Other contributors	48 (11.5%)	34 (15.7%)
Metabolic (e.g. renal / hepatic failure)	27 (6.5%)	3 (1.4%)
CNS Lesion	17 (4.1%)	15 (6.9%)
CNS infection	17 (4.1%)	3 (1.4%)
Idiopathic	16 (3.8%)	30 (13.8%)
CNS inflammation	11 (2.6%)	3 (1.4%)
Post Op	10 (2.40%)	6 (2.8%)
Systemic Sepsis	9 (2.10%)	17 (7.8%)
Medication	6 1.40%)	3 (1.4%)
Cardiovascular	4 (1.0%)	2 (0.9%)
Pregnancy	3 (0.70%)	0
Electroconvulsive Therapy	2 (0.50%)	0
Neurodegenerative	2 (0.5%)	1 (0.5%)
Progressive epilepsy syndrome	n/a	24 (11.1%)
Poor adherence or loss of drug levels	n/a	25 (11.5%)
No Information Available	21 (5.0%)	12 (5.6%)
	419	214

DNSE = DeNove Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy.

Table 4
Duration of Hospital and ITU Admission for SE.

ITU Stay (days)	Total n = 633	DNSE n = 419	SEPE n = 214
Median **(days)**	1.0	1.0	2.0
Mean **(days)**	3.6	3.7	3.7
Range **(days)**	0.5-165	0.5-165	0.5-26
1-7 days n (%)	556 (87.8%)	370 (88.3%)	186 (86,2%)
> 7 days n (%)	72 (11.4%)	44 (10.5%)	28 (13.8%)
> 28 days n (%)	3 (0.5%)	3 (0.7%)	0
> 42 days n (%)	2 (0.3%)	2 (0.5%)	0
Hospital Stay (days)			
Median **(days)**	8.0	10.0	6.0
Mean **(days)**	21.4	28.0	8.7
Range **(days)**	0.5-1497	0.5-1497	0.5-30
1-7 days n (%)	146 (23.1%)	23 (5.5%)	123 (57.5%)
> 7 days n (%)	330 (52%)	240 (57.3%)	90 (42%)
> 28 days n (%)	92 (14.5%)	91 (21.7%)	1 (0.5%)
> 42 days n (%)	65 (10.3%)	65 (15.5%)	0

DNSE = DeNove Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy.

Table 2
Number of patients on Individual Baseline AEDs in SEPE Group by Year of Admission.

	Polypharmacy	CBZ	VPA	PHT	GBP	LTG	TPM	LEV	VGB	Unknown
1995-2002 n = 51	16	10	11	11	4	2	0	0	0	29
2003-2013 n = 163	45	11	57	42	5	22	13	31	4	23

CBZ = Carbamazepine, VPA = Valproate, PHT = Phenytoin, GBP = Gabapentin, LTG = Lamotrigine, TPM = Topiramate, LEV = Levetiracetam, VGB = Vigabatrin.

Table 5
Cumulative Mortality Over 10 years.

	Total Cohort N = 633	DNSE N = 419	SEPE N = 214	95% CI for Difference between DNSE and SEPE	P value of z test
Total Number of Deaths	303 (47.8%)	220 (52.5%)	83(38.7%)		
Deaths During Index admission	74 (11.69%)	58 (13.8%)	16(7.47%)	(1.00%, 11.59%)	0.0195
Deaths within 1 year of admission for SE	141 (22.0%)	106(25%)	35 (16.0%)	(2.05%, 15.75%)	0.0109
Deaths within 5 years of admission for SE	236 (37.3%)	174 (41.5%)	62 (27.60%)	(5.04%, 20.96%)	0.0014
Deaths within 10 years of admission for SE	285 (45.0%)	206(49.0%)	79 (37.0%)	(4.11%, 20.49%	0.0033

DNSE = DeNove Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy.

Table 6
Outcome after SE in DNSE and SEPE.

	Total Group (n = 430)	DNSE (n = 265)	SEPE (n = 164)
Death during Index admission n (%)	73 (17.0%)	58 (21.9%)	16 (9.8%)
Documented recovery with residual neurological deficit n (%)	232 (54.0%)	124 (46.8%)	108 (65.9%)
Documented full recovery without residual neurological deficit n (%)	124 (28.8%)	83 (31.3%)	40 (24.4%)

DNSE = DeNove Status Epilepticus; SEPE = Status Epilepticus with Previous Epilepsy.

admission, this significant difference in mortality had persisted, (Table 5), (Supporting Figure 3). Where information was available (Table 6), we looked at the discharge status, showing incidence of full recovery in those with DNSE (31.3%) and SEPE (24.4%). Among those surviving the admission, the percentages with and without neurological deficit were very similar in both DNSE and SEPE, with approximately one third in each group surviving without neurological deficit.

3.7. Outcomes of RSE - risk of subsequent epilepsy

One hundred and thirty-four patients with DNSE (37%) were started on long term AEDs and could be inferred as having developed epilepsy. Where alcohol and/or drug misuse was a sole single cause of SE, 48/171 (28%) of patients ended up being on long term AED. Eight of 16 patients with idiopathic DNSE remained on long-term AED treatment

4. Discussion

We believe this is one of the largest studies of incidence and outcome of refractory SE [17,18,21]. We attempted to assess the longitudinal incidence of RSE in a single region spanning 6 hospitals over a period of almost two decades. The criteria for recruitment (i.e. requiring treatment in an ITU setting) ensures that these cases are at least Refractory SE with 303 patients (48%) fulfilling the criteria for Super Refractory SE. The morphology of SE is similar that seen in other studies, but the focus on ITU treatment ensures that there is a preponderance of convulsive SE.

Unlike other series, we did not exclude patients with primary hypoxic brain injury. The small numbers (n = 6) suggest that other cases may have been coded differently for general ITU admission, and that this means the recruitment is comparable to other series of SE.

We accept that other series [19,20] have found a greater proportion of cases with NCSE. Reviews [19,20] acknowledge the difficulty in diagnosis NCSE where, as in the date and setting of this series, prolonged EEG monitoring is less available.

We accept the limitations of the study in examining patient records. Reliable coding is difficult to guarantee, but we feel that this limitation may lead to reduced sensitivity rather than a reduction in specificity. Such a limitation may explain some of the variability in the incidence across the epochs.

Such data collection is time consuming and relies on accurate coding and case notification by local registers in each unit. At least some of the limitations of this method of data collection were ameliorated by the later adoption of a regional electronic system holding medical records across all hospitals in the region. Longitudinal incidence of SE across the region has shown a general increase in keeping with the increased prominence and reliance on the SIGN guidance in the late 20th Century and early 21st Century. The later dip in incidence from 2010 remains difficult to explain.

We have separated out the groups depending on a prior history of seizures and think that the approach has been validated by demonstration of the differences between the groups in causation and outcome. The male preponderance is common to both diagnostic groups which appears unusual in studies of SE [21,22]. The study by Strzelczyk et al 2017 [21] made no mention of the incidence of addiction or substance abuse in its cohort. In Glasgow over the period 1995–2013 there was an increasing incidence of RSE, involving both DNSE and SEPE. The fact that DNSE also increases avoids any suggestion that the increase in SEPE is caused by a decreased effectiveness of newer AEDs. An increasing incidence has also been shown in studies of SE in other populations [23,24,25] and it has been postulated that promulgation of guidelines and protocols have led an increasing identification and treatment that also the decreasing mortality from SE in England and Wales [20].

While such increasing recognition of the need for emergency treatment of SE may be widespread, it may be especially focussed in Scotland with the adoption of national guidelines – the first SIGN guidance in 1997, with updates coming in 2003 and 2015 (SIGN 1997, SIGN 2003, SIGN 2015) emphasising the need for emergency care. Studies of SE [22,26–28] have suggested an annual incidence of 17–20/100,000 which is similar to the peaking incidence of RSE of all causes in our population. In our study the incidence of RSE is in keeping with other geographical studies of RSE [17]. Our data would suggest a similar incidence of SRSE, at 2.7/100,000, to that described by Kantanen (2017) [17]. The pattern of SE noted in our population was similar to other studies of adults [22] with the majority of cases comprising convulsive SE. In those with SEPE, there was no emergent pattern of AED use when looking at individual AEDs or when grouping by effect on hepatic enzymes.

The increasing prior use of newer AEDs throughout the series dates was unsurprising and is in keeping with the contemporaneous change in prescribing pattern across the country. We acknowledge that other countries may have seen a more rapid uptake of the newer drugs, but tht prescribing of AEDs in the UK is heavily influenced by the national guidelines produced via SIGN and NICE. We acknowledge that there are emergent data on newer drugs such as levetiracetam, topiramate, and lacosamide in treating SE. In our series ITU treatment of SE utilised the older AEDs more than other series which reflects the period under study and the reliance on national guidelines to dictate treatment plans.

4.1. Mortality of refractory status epilepticus

As can be seen in Table 5 and Supporting Table 3, the admission mortality rate was higher in DNSE than SEPE (13.8% versus 7.5%). The other large study of RSE suggested an admission mortality of around 15% across all cases of RSE [21]. One-year post admission, this difference in mortality rates in DNSE and SEPE was maintained, but expanded in subsequent years, such that 5 years after admission 41.5% of DNSE had died compared to 27.6% of those with SEPE. It may have been anticipated that refractory SEPE would respond better than those with DNSE, since many of these would be related to reversible causes. By one-year post-admission, mortality rates in our cohort are considerable, exceeding the 25% shown by Kantanen et al 2017 [17] Most of the RSE-associated mortality arises in the first few years. Mortality from SEPE and DNSE was significant during admission, being twice as common in the former group.The diference in mortality expanded over the next 5 years, such that 5 years after admission 41.5% of DNSE had died compared to 27.6% of those with SEPE.

4.2. Causes of RSE-Associated mortality

The prognosis of RSE is thought to depend on duration of seizures and the underlying pathology [28]. In our study, addiction and substance abuse issues are associated with an increased admission and subsequent mortality in both DNSE and SEPE. It may have

been presumed that simple avoidance of any risk factor for directly provoked seizures (i.e. alcohol and / or drugs) would reduce mortality, but our data does not reflect this. Supporting Tables 4 and 5 show the contribution of addiction and abuse to deaths in the group with DNSE and SEPE. At each time point, alcohol and drugs comprise the largest contributor to mortality. In those with SEPE (Supporting Table 5) alcohol and drug use comprise a less striking contributor to mortality.

The causes of the two groups of RSE are predictably different: in SEPE, the better outcome may signal the presence of a reversible cause of epilepsy exacerbation. In DNSE, our data suggests that underlying addiction or abuse issues are not a simple reversible cause or exacerbation but are in fact a negative prognostic marker for long term mortality. In the DNSE group 28% of all deaths within 1 year were related to alcohol and drug-related complications, increasing to 34.4% of all deaths over 10 years. In the SEPE group, 1-year mortality was 20.2%, with 31.6% dying because of seizures over 10 years. Despite the longer admission with DNSE, the rate of full neurological recovery was similar in those with DNSE and SEPE. This risk of residual neurological deficit despite 'milder' RSE may reflect the cause of the underlying epilepsy in SEPE, whether that be a primary lesion, vascular event, or prior trauma or neurosurgery.

4.3. Subsequent seizures

In patients with DNSE, this index seizure was followed by a need for AEDs in 37%, a level of recurrence which would confirm that an index episode of SE or RSE is no more liable to lead to a recurrence and need for AEDs than a single shorter seizure [29].

4.4. Neurological disability

Previous studies of SE among adults [30] have suggested neurological deterioration in only 3.3% among those surviving at least 30 days. Neurological deterioration in children with SE appears to be higher [28]. While the rates of neurological deficit are raised in both DNSE and SEPE, in neither does the level of disability approach that in another larger study where only 23% were able to be discharged back to their home [17].

5. Conclusion

We argue that important messages emerge from this study of similarly and consistently severe seizures. Firstly, the separation of DNSE from SEPE is helpful in beginning to delineate prognosis, the need for further investigation, and the role of ineffective or absent AEDs in causation. The mortality rate of RSE is high, and importantly it represents a call to action for the medical community. The greater admission mortality with DNSE, which persists in the years following discharge should confirm that SE with a background of addiction or abuse should not simply be considered as a 'provoked seizure' and treated with acute support and encouragement to abstinence. Instead it suggests that a presentation with DNSE is a sign of a system in peril. While public health measures are vital in reducing the disease burden of triggers such as alcohol and addiction, each episodes should prompt a chain of multispecialty care in order to address this recurring and persisting public health disaster, which comprises of too many personal tragedies.

Bullet points

- This study looks at the causes, outcomes, and regional incidence of adults with Refractory Status Epilepticus admitted to ITU over 18 years in Glasgow
- Mortality is increased in short term and the long-term in both De Novo Status Epilepticus and Status Epilepticus Complicating Epilepsy
- There is no evidence that use of newer AEDs has reduced the incidence of Status Epilepticus complicating epilepsy
- Addressing the mortality associated with SE requires a combination of public measures and an holistic approach to individual cases of status epileptics

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.01.011.

References

[1] Trinka E, et al. A definition and classification of status epilepticus–report of the ILAE task force on classification of status epilepticus. Epilepsia 2015;56:1515–23.
[2] SIGN. Diagnosis and management of epilepsy. SIGN guidance 143. 2015www.sign.ac.uk.
[3] Trinka E, Kalviainen R. 25 Years of advances in definition, classification andtreatment of status epilepticus. Seizure 2017;44:65–73.
[4] Chen JW, Wasterlain CG. Status Epilepticus: pathophysiology and management in adults. Lancet Neurol 2006;5:246–56.
[5] Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. J Neurosci 1997;17:7532–40.
[6] Shorvon SD, Trinka E, Walker MC. The proceedings of the first london colloquium on status epilepticus – UCL. Epilepsia 2007;48(Suppl. 8):1–3.
[7] Trinka E, Hofler J, Zerbs A. Causes of status epilepticus. Epilepsia 2012;53(Suppl. 4):127–38.
[8] Tan RY, Nelligan A, Shorvon SD. The uncommon causes of status epilepticus: a systematic review. Epilepsy Res 2010;91:111–22.
[9] Shorvon S, Ferlisi M. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain

2012;135:2314.
[10] Leach JP, Mohanraj R, Borland W. Alcohol and drugs in epilepsy: pathophysiology, presentation, possibilities, and prevention. Epilepsia 2012;53(Suppl. 4):48–55.
[11] Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011;134:2802–18.
[12] Sutter R, Marsch S, Fuhr P. Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7-year observational study. Epilepsia 2013;54:502–11.
[13] Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. Epilepsia 2010;51:251–6.
[14] Kämppi L, Mustonen H, Soinila S. Analysis of the delay components in the treatment of status epilepticus. Neurocrit Care 2013;19:10–8.
[15] Vooturia S, Jayalakshmia S, Sahub S. Prognosis and predictors of outcome of refractory generalized convulsive status epilepticus in adults treated in neurointensive care unit. Clin Neurol Neurosurg 2014;126:7–10.
[16] Logroscino G, et al. Short-term mortality after a first episode of status epilepticus. Epilepsia 1997;38:1344–9.
[17] Kantanem AM, et al. Long-term outcome of refractory status epilepticus in adults: a retrospective population-based study. Epilepsy Res 2017;133:13–21.
[18] Misra UK, Kalita J, Dubey D. A study of super refractory status epilepticus from India. Front Neurol Neurosci 2017;8:636. https://doi.org/10.3389/fneur.2017.00636.
[19] Sutter R, Semmlack S, Kaplan PW. Nonconvulsive status epilepticus in adults - insights into the invisible. Nat Rev Neurol 2016;12(5):281–93.
[20] Sutter R, Fuhr P, Grize L, et al. Continuous video-EEG monitoring increases detection rate of nonconvulsive status epilepticus in the ICU. Epilepsia 2011;52(3):453–7.
[21] Strzelczyk A, Ansorge S, Hapfelmeier J. Costs, length of stay, and mortality of super-refractory status epilepticus: a population-based study from Germany. Epilepsia 2017;58:1533–41.
[22] Knake A, Rosenow F, Vescovi M, et al. Incidence of status epilepticus in adults in Germany:- a prospective, population-based study for the Status Epilepticus Study Group Hessen (SESGH). Epilepsia 2001;42:714–8.
[23] Nelligan A, Walker MC. Falling status epilepticus mortality rates in England and Wales: 2001-2013. Epilepsia 2016;57:e121–4.
[24] Wu YW, Shek DW, Garcia PA, et al. Incidence and mortality of generalised convulsive status epilepticus in California. Neurology 2002;58:1070–6.
[25] Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care 2014;20:476–83.
[26] Hesdorffer DC, Logroscino G, Cascino G, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965–84. Neurology 1998;50:735–41.
[27] Coeytaux A, Jallon P, Galobardes B, et al. Incidence of status epilepticus in French speaking Switzerland (EPISTAR). Neurology 2000;55:693–7.
[28] Nelligan A, Shorvon S. Prognostic factors, morbidity and mortality in tonic—clonic status epilepticus: a review. Epilepsy Res 2011;93:1–10.
[29] Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomized controlled trial on behalf of the Medical Research Council MESS Study Group Lancet 2005;365:2007–13.
[30] Cascino GD, Hesdorffer D, Logroscino G. Morbidity of nonfebrile status epilepticus. Epilepsia 1998;39:829–32.