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Aetiologies and characteristics of Refractory Status Epilepticus cases in different areas of the world: results from a Global Audit.

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Running title: Aetiologies of RSE.
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Key points

- We collected information about 776 cases of RSE treated with continuous IV anaesthetic drugs in 50 countries around the world

- Good outcome was associated with younger age and a prior history of epilepsy; aetiology strongly influenced the outcome.

- Patients from Asia were younger, more frequently presented with convulsive SE, and were more frequently affected by infectious aetiologies

- Important differences exist among patients with RSE from different regions of the world, but these do not seem to influence patient outcomes

Figure legend:

Fig. 1: Map of involved countries

Fig. 2: Origin of patients

Fig. 3: Outcome of SE episodes

Fig. 4: Neurological outcome of patients at the end of anaesthesia

Abstract

In order to describe the demographics, aetiologies, types of status epilepticus (SE) and outcomes in people with refractory and super-refractory status epilepticus from around the world, we collected prospectively cases of refractory status epilepticus (RSE) treated with continuous intravenous anaesthetic drugs (CIVADs) in an intensive care unit setting, through online questionnaires using “active surveillance". We collected information about 776 cases of RSE in 50 countries over 4 years. Control of SE was achieved in 74% of the cases. Neurologic outcomes were poor in 41% of patients and 24% died. Good outcome was associated with younger age and a prior history of epilepsy. Aetiology strongly influenced the outcome. Patients from Asia were younger, more frequently presented with convulsive SE, and were more frequently affected by infectious aetiologies when compared with patients from Europe and the Americas. Despite these differences, outcomes were similar in all countries. Demographics of patients with RSE in a global audit are similar to those in prior single centre series providing evidence of generalizability of those studies. Important differences exist among patients with RSE from different regions of the world, but these do not seem to significantly influence patient outcomes.

Introduction

Refractory status epilepticus (RSE) is a dangerous condition, with a mortality rate of 24-38% in recent series, [1, 2] higher in prolonged episodes.[3]A generally accepted definition of RSE is a seizure that persists after 2 antiseizure drugs, typically including a benzodiazepine. At this stage, most protocols suggest treatment with continuous intravenous anaesthetic drugs (CIVADs), in order to promptly stop seizure activity, prevent long-term neuronal damage, further refractoriness [4, 5] and severe acute systemic consequences, especially in convulsive SE. The current evidence base guiding optimal management of RSE is mostly based on small series given the rarity of the condition. [6] For these reasons, there has been an increasing interest in multinational registries.[7, 8]

The underlying aetiology of SE is considered the most important prognostic factor determining outcome.[9] Apart from the treatment, aetiology itself significantly differs in developing countries

as compared to the western world, with acute symptomatic aetiologies being more frequent in developing countries.[10,11] In this study, we prospectively collected information about cases of RSE treated with continuous IV anaesthetic drugs in different regions of the world.

Methods

Details about the audit procedures have been published previously.[12] Briefly, this was an anonymized online registry, collecting information prospectively from neurologists and intensivists caring for patients with RSE not responding to first-line therapy, admitted to an intensive care unit (ICU) and treated with continuous IV anaesthetic drugs, through online questionnaires. The "active surveillance" method, which utilized monthly reminders sent to all participating physicians, ensured maximal reporting. A modified Rankin scale (mRS) of 0-3 was considered a good outcome.[13]

All data were analysed using statistical software (IBM SPSS Statistics, version 20). When comparing continuous variables, Student's *t*-test and Mann-Whitney test were used. The analysis of categorical variables was performed using Chi-square and Fisher exact and analysis between groups with Anova and Kruskal Wallis.

Results

The data collection started on the 1st of March 2013 and was terminated after 4 years. In total, 776 cases were collected from 166 different physicians (see list of all contributors in appendix 1). A map of the 50 countries involved is shown in Figure 1, and the number of cases contributed per country in Figure 2. Patients were from Europe (n=408, 56%), Asia (n=169, 23%), the Americas (n=131, 18%), Australia and New Zealand (n=17, 2%) and Africa (n=9, 1%). The clinical characteristics of patients are summarized in Table 1. The majority of patients (n=x, 63%) had no history of epilepsy and the most common single etiology was cryptogenic (n=200, 26.1%). Among those with cryptogenic RSE, 78 (39%) had a positive history of epilepsy, 119 (59.5%) were new-onset refractory status epilepticus, and in 3 (2%) history of epilepsy was uncertain.

SE was convulsive in 55% of cases, non-convulsive in 19%, convulsive evolving to non-convulsive in 21%, of other semiology (epilepsia partialis continua, absence status, other) in 4%. Mean duration of ICU stay was 18.41 ± 22.8 days.

Regional differences

There were too few patients from Africa and Oceania to justify subgroup analyses. Patients from Asia were significantly younger than those from Europe and the Americas (Mean age 22.4, 48.2, and 40.5 years, $p<0.001$) and more frequently presented with convulsive SE compared with non-convulsive forms (71%, 53% and 44%, $p<0.001$). The ICU duration was longer in Asia (mean 22.8 ± 24.1 days) than in Europe (16.3 ± 18.9 days, $p<0.05$) or in the Americas (19.31 ± 26.3 days).

There were some notable differences regarding aetiologies of SE (Table 2). In Asia, the most frequently reported aetiology was infectious (n=59, 30.1%), compared with while this represented only (n=23, 15.4%) of cases in the Americas and (n=56, 12.3%) in Europe. In particular, the percentage of cases with acute encephalitis was significantly higher in Asia (n=41, 20.9%), than in Europe (n=26, 5.7%) or the Americas (n=7, 4.7%), $p<0.01$). Vascular aetiologies were more frequent in Europe (n=75, 16.6%) than in Asia (n=11, 5.6%), $p<0.01$. There was a non significant trend towards a higher incidence of traumatic etiologies in Europe (n=28, 6.2%) and the Americas (n=7, 4.7%) than in Asia (n=1, 0.5%).

Outcomes

In 686 cases information about the outcome was provided: 510 patients (74%) recovered, 148 patients (22%) died during treatment, and 28 patients (4%) had therapy actively withdrawn. The neurological status of the patients at the end of anaesthesia was good in 35% of patients, poor in 41%, and 24% of patients died. Outcomes in patients with a long-term outcome data provided (n=208) are shown in Table 3. There was a higher proportion of patients with a better outcome at six-month follow up.

No differences were found in outcome with respect to gender or type of SE. Prior history of epilepsy and younger age was positively associated with recovery from SE ($p<0.001$). As expected, aetiology strongly influenced outcome (Table 4). Patients with post-anoxic SE had the worst outcomes, as did those with metabolic aetiologies or acute encephalitis when compared

with other etiologies. The patient with the best long-term outcomes were those where the etiology of the status was classificed as due to 'antiseizure drug withdrawal' and the worst outcomes statistically were those classified as due to anoxia (Table 5).

In the analysis between geographical regions, we did not find any significant differences in rate of success in controlling SE, or in the neurological outcome of patients (fig. 3 and 4).

Discussion

In studies on RSE, the setting (ICU, academically-driven, general hospital, rural hospital) and the geographical region may have an important impact on the results.[10, 14, 15] Observational studies are almost the only ones available in RSE, and the validity of such studies depends on the range of participation and the quality of their data. This is to our knowledge the largest and most widely collected series of RSE treated with continuous IV anaesthetic drugs, although we acknowledge limitations in drawing conclusions about associations given the non-systematic method of collection. Our case definition requires the administration of IV anesthetic drugs and not all definitions of RSE have this stipulation. We introduced this stipulation to avoid confusion from the participants and to ensure that all the participants in the audit are referring to severe cases (albieit in the recognition that status stops in some milder cases withour continuous IV anaesthetic drugs and there are also cases which would be treated with IV anaesthetic drugs in some countries but not in others (especially in the poorest regions of the world).

To ensure accuracy and completeness of the data, we modified the format of the questionnaires several times, but as increasing complexity reduced the number of cases reported and we had to compromise on a limited data set. We also did not make any complex statistical analysis of the data of the limitations of case selection bias. [16] Despite these limitations, this registry adds important information to our knowledge of the demographics, types and aetiologies of RSE treated with continuous IV anaesthetic drugs around the world.

As expected, aetiology of SE and characteristics of patients can significantly differ in Asian countries as compared to the western world.[10, 14] In this study, patients from Asia were younger: this could simply reflect the lower mean age of the Asian population. We found less prevalence

of non-convulsive status in Asian countries, presumably because of lower availability of continuous EEG monitoring. Globally, cryptogenic SE was the most frequent cause of RSE around the world. As most of these cases had no prior history of epilepsy, future research must focus on identifying causes of cryptogenic RSE and in particular on autoimmune aetiologies, which probably account for a significant number of these cases. As expected, anoxic SE has the worst outcome; acute encephalitis and metabolic aetiologies are also associated with poor outcomes.

Aetiologies differ remarkably among continents. In Asian countries infectious aetiologies were the most commonly reported, with acute encephalitis occurring significantly more frequently than in other regions of the world. Acute encephalitis has been associated with refractoriness to treatment and higher mortalities in prior studies. [17, 18, 19] A fascinating finding of this audit is that, despite such great differences in patients' and SE characteristics, outcomes around the world were largely similar. It is possible that such great differences in aetiologies and SE characteristics are somehow compensated by other factors, like younger age, and the nature of this study does not allow for a full exploration of these relationships.
Data from this audit have been reviewed with all the participant doctors at the 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures, where further analyses have been planned and future research discussed.

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Disclosure of conflicts of interest
None of the authors has any conflict of interest to disclose.
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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Table 1. Clinical Characteristics of the 776 Patients[1]

	N	%
Age	39.8±25.9 years (mean±SD) 0-92 years (range)	
Gender		
Male	423	55%
Female	353	45%
Prior history of epilepsy		
Yes	288	38%
No	474	63%
Etiologies (can be multiple per patient)		
Unknown (cryptogenic)	200	26.1%
Infections, all	148	19.6%
Acute encephalitis	81	10.6%
Acute meningitis	19	2.5%
Other infections	50	6.5%
Vascular (incl. stroke)	111	14.5%
Anoxic (incl. cardiac arrest)	85	11.1%
Antiseizure drug reduction/withdrawal	56	7.3%
Cerebral tumour	47	6.1%
Miscellaneous[2]	43	5.6%
Trauma	42	5.5%
Metabolic	36	4.7%
Alcohol	35	4.6%
Immunological, all	24	3.1%
NMDA R Ab	8	1.0%
VGKA Ab	2	0.3%
Lupus (seropositive)	3	0.4%
Other	11	1.4%
Genetic/chromosomal	18	2.3%
Other toxins	12	1.6%

Mitochondrial disease	11	1.4%

[1] Percentages calculated from available data with denominators provided

[2]Include: eclampsia, posterior reversible encephalopathy syndrome, cortical dysplasia, or not classified

Table 2. Etiologies among continents (N, %)[1]

	Asia	Europe	Americas
Unknown (cryptogenic)	50 (25.5%)	98 (21.6%)	34 (22.8%)
Vascular (incl. stroke)	11 (5.6%)	75 (16.6%)	17 (11.4%)
Anoxic (incl. cardiac arrest)	13 (6.6%)	51 (11.3%)	17 (11.4%)
Trauma	1 (0.5%)	28 (6.2%)	7 (4.7%)
Infection, all	59 (30.1%)	56 (12.3%)	23 (15.4%)
Acute encephalitis	41 (20.9%)	26 (5.7%)	7 (4.7%)
Acute meningitis	6 (3.1%)	9 (2.0%)	3 (2.0%)
Other infection	12 (6.1%)	21 (4.6%)	13 (8.7%)
Alcohol	0 (0%)	28 (6.2%)	6 (4.0%)
Other toxins	4 (2.0%)	3 (0.7%)	3 (2.0%)
Metabolic	11 (5.6%)	17 (3.8%)	7 (4.7%)
Cerebral tumour	5 (2.6%)	33 (7.3%)	6 (4.0%)
Antiseizure drugs reduction/withdrawal	16 (8.2%)	20 (4.4%)	14 (9.4%)
Genetic/chromosomal	6 (3.1%)	8 (1.8%)	2 (1.3%)
Immunological, all	7 (3.5%)	9 (1.9%)	6 (4.0%)
Mitochondrial disease	4 (2.0%)	4 (0.9%)	3 (2.0%)
Miscellaneous[2]	9 (4.6%)	23 (5.1%)	4 (2.7%)

[1] Percentages calculated from available data with denominators provided

[2]Include: eclampsia, posterior reversible encephalopathy syndrome, cortical dysplasia, others or not classified

Table 3. Neurological outcome of patients with a long-term follow-up available (percentage are calculated out of the known cases).

modified Rankin Scale	**At end of anaesthesia N (%)**	**At 6 month follow up N (%)**
0 - No symptoms.	18 (9)	31 (15)
1 - No significant disability. Able to carry out all usual activities, despite some symptoms.	30 (15)	46 (22)
2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.	21 (10)	24 (12)
3 - Moderate disability. Requires some help, but able to walk unassisted.	27 (13)	42 (20)
4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.	51 (25)	23 (11)
5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.	54 (27)	29 (14)
6 - Dead.	n.a.	13 (6)
Total	201 (100)	208 (100)

n.a.: not applicable

Table 4: Association of aetiology with outcome[1]

Aetiology of status epilepticus	**Recovered N (%)**	**Not recovered[2] N (%)**
Antiseizure drug reduction/withdrawal	44 (94)	3 (6)
Genetic/chromosomal	17 (94)	1 (6)
Trauma	31 (84)	6 (16)
Mitochondrial disease	5 (83)	1 (17)
Immunological, all	20 (83)	4 (17)
Acute meningitis	14 (82)	3 (18)
Miscellaneous[3]	32 (82)	7 (18)
Other infection	34 (79)	9 (21)
Other toxins	7 (78)	2 (22)

Cerebral tumour	33 (75)	11 (25)
Unknown (cryptogenic)	132 (75)	45 (25)
Alcohol	25 (74)	9 (26)
Vascular (incl. stroke)	74 (73)	28 (27)
Acute encephalitis	45 (64)	25 (36)
Metabolic	20 (59)	14 (41)
Anoxic (incl. cardiac arrest)	37 (52)	34 (48)

[1] Percentages calculated from available data with denominators provided

[2]Includes patients who died during treatment and patients who had therapy actively withdrawn and then died or had a severe disability

[3]Includes eclampsia, posterior reversible encephalopathy syndrome, cortical dysplasia, others or not classified

Table 5: Association of aetiology with neurological outcome at six months[1]

Aetiology of status epilepticus	**Good (mRS 0-3) N (%)**	**Poor (mRS 4-5) N (%)**	**Dead (mRS 6) N (%)**
Genetic/chromosomal	5 (63)	3 (38)	0 (0)
Antiepileptic drug reduction/withdrawal	23 (56)	15 (37)	3 (7)
Other toxins	4 (50)	3 (38)	1 (13)
Mitochondrial disease	3 (50)	2 (33)	1 (17)
Miscellaneous[2]	39 (49)	31 (39)	10 (13)
Cerebral tumour	15 (41)	16 (43)	6 (16)
Trauma	14 (40)	15 (43)	6 (17)
Other infection	14 (35)	17 (43)	9 (23)
Alcohol	10 (33)	11 (37)	9 (30)
Unknown (cryptogenic)	46 (32)	67 (46)	32 (22)
Acute meningitis	5 (31)	8 (50)	3 (19)
Immunological, all	11 (31)	15 (42)	10 (28)
Metabolic	9 (30)	9 (30)	12 (40)
Acute encephalitis	18 (26)	30 (43)	22 (31)

Vascular (incl. stroke)	23 (25)	44 (48)	24 (26)
Anoxic (incl. cardiac arrest)	13 (19)	26 (38)	29 (43)

[1] Percentages calculated from available data with denominators provided

[2]Includes eclampsia, posterior reversible encephalopathy syndrome, cortical dysplasia, others or not classified

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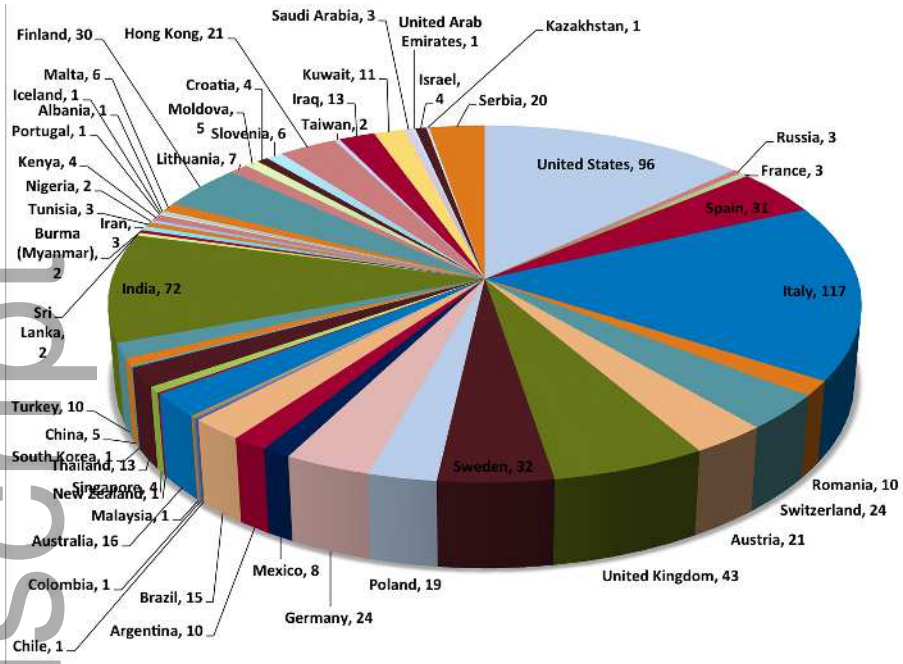

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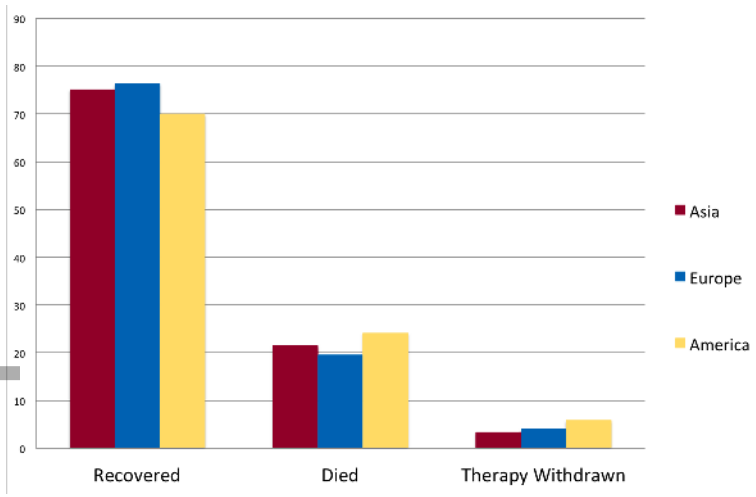

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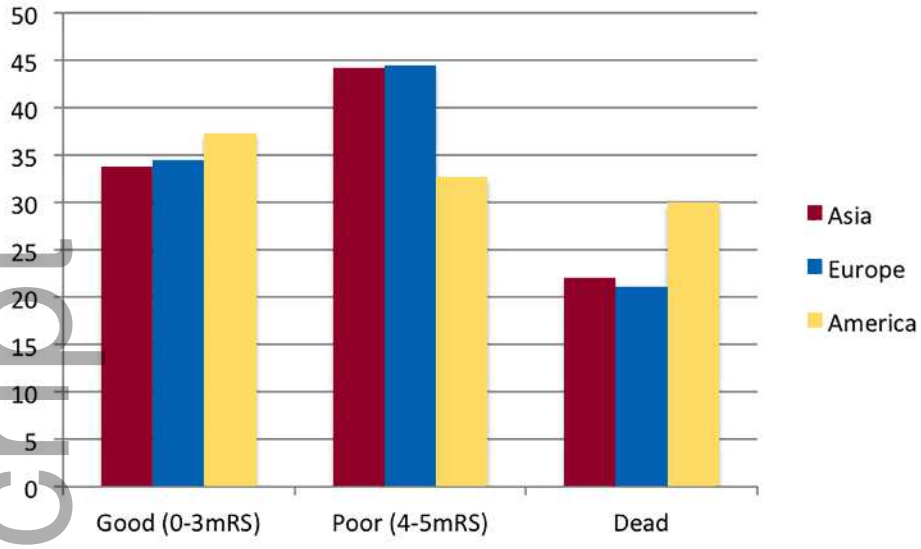

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