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Refractory and Super-Refractory Convulsive Status Epilepticus of Children in the west of Algeria: Risk factors.

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ABSTRACT:

Introduction

Refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE) are serious and frequent neurological emergencies in children associated with high morbidity and mortality. Despite this, we note the absence of published Algerian data. The aim of this work is to determine the demographic data, the etiologies and the factors of progression in RCSE and Super-RCSE as well as the short-term prognosis.

Design: Prospective observational study with retrospective analysis of all the episodes of RCSE and Super-RCSE treated between January 1, 2008, and April 30, 2016.

Setting: Pediatric Intensive Care Unit, University Hospital of Oran, Algeria.

Patients:

RCSE is defined as seizure activity that persists after administration of a first-line benzodiazepine (BZD) and a second-line antiepileptic drug (AED). Super-RCSE is defined as «SE that has continues or recurred despite 24 hours of general anesthesia. »

Factors independently associated with Refractory and Super-RCSE were established through univariate and multivariable analyses. The outcome was evaluated using the Glasgow Outcome Score.

Results:

Among 443 patients with status epilepticus, 140 patients (31.6%) were afflicted with refractory status epilepticus and 25 (5.6%) with SRSE. The mean age of the entire cohort was 40.65 ± 2.16 months [1 – 180 months].135 patients (33.8%) had suffered previous seizures;

RCSE was related to younger age (< 3 years) (OR 1.76; 95% CI 1,018 – 3,058) p=0.043, duration of status epilepticus >2 h (OR 3.096; 95% CI 1, 77 – 5, 39) p= 10^{-4}, acute symptomatic etiologies (OR 3.609; 95% CI 2,112 – 6.166), Severe consciousness impairment (GCS < 13/15) before treatment (OR 18.55; 95% CI 8,202 – 41.972) p= 10^{-4} and Non respect of the therapeutic protocol upstream of PICU (OR 3.659; 95% CI 1,926 – 6.949) p= 10^{-4}.

Super-RCSE was independently associated with age greater than 3 years (OR 3.28; p=0.018), indeterminate etiology (OR 6.628; p=0.009), encephalitis (OR 4. 782; p=0.003) and use of Vasopressor medications (OR 4.239; p=0.007). Overall mortality was 83 (20.75%).

Conclusion

The etiologies of CSE are heterogeneous, with significant incidence of RCSE in acute symptomatic group.

Encephalitis was the determinant of progression of CSE to Super-RCSE.

The therapeutic success of which depends on whether or not the cause of CSE can be treated.

Keywords: Refractory status epilepticus; Super-Refractory status epilepticus; Etiology; PICU; Outcome; Children.

Abbreviations:

SE: Status Epilepticus, RCSE: Refractory Convulsive Status Epilepticus, NRCSE: Non Refractory Convulsive Status Epilepticus, Super-RCSE: Super-Refractory Convulsive Status Epilepticus**,** BZD: Benzodiazepine, AED: Antiepileptic Drogue, CNS: Central Nervous System.

1. INTRODUCTION

Status Epilepticus (SE) is defined as a seizure lasting more than 30 min or recurrent seizure activity without recovery (returning to baseline) between seizures. **[1]**

The annual incidence of convulsive SE in population-based studies ranges from 10 to 61 cases per 100,000 persons per year, **[2][3]** with peak incidences reported during first year of life, and after the age of 60. **[4]**

Refractory status epilepticus (RSE) is an important pediatric neurological emergency associated with significant morbidity and mortality. RSE is defined as seizure activity that persists after administration of a first-line benzodiazepine (BZD) and a secondline antisepileptic drug (AED). **[5]**

Alternately, it is also defined as the duration of seizure activity that lasts for 1 or 2 h. **[6]**

SE that persists for 24 h or more following onset of therapy with third-line agents (e.g. propofol, high-dose midazolam, barbiturates) or after the reduction or withdrawal of third-line agents is defined as super-refractory Status Epilepticus (Super-RSE). **[7]**

Risk factors associated with RCSE are less clearly known in children. Risk factors for RCSE include young age, delay in onset of treatment and being afflicted with focal motor seizure. **[8]7**

This article presents a unique center experience concerning the etiology, the response to antiepileptic treatment and the factors of progression in RCSE and Super-RCSE of large number episodes of CSE.

2. MATERIALS & METHODS

- **Study design and setting.**

This is a prospective observational study with a retrospective analysis of all the episodes of RSE and SRSE treated in Pediatric Intensive Care Unit, University Hospital of Oran, Algeria, between January 1, 2008, and April 30, 2016.

The Pediatric Intensive Care Unit has nine beds and an emergency room. Receives children aged 1 month to 16 years from all the west Algerian provinces.

Since the study is purely observational, informed consent is waived.

The study was conducted according to the ethical principles of the Helsinki Declaration. Personal data were coded.

- **Patients, SE definition and classification.**

Inclusion criteria were the following: (1) Patients aged between 1 month and 16 years; (2) Convulsive Status Epilepticus (CSE).

Exclusion criteria were psychogenic SE, simple partial SE, and absence SE.

Convulsive Status epilepticus was defined as the occurrence of continuous or repetitive seizures, between which there is incomplete recovery of baseline clinical conditions for at least 30 min. **[1]**

Refractory Convulsive status epilepticus was defined if first- and second line antiepileptic treatments failed to control seizures, without a given time span, implying the need to prescribe an additional specific treatment. **[9]**

Non-refractory Status Epilepticus: SE which ends with anticonvulsant drugs defined as **non-refractory Status Epilepticus (NRSE).**

Super-refractory convulsive status epilepticus was defined as continuous or recurrent seizures lasting 24 h or more following administration of a first course of anaesthetics for therapeutic coma induction **[7]**

The state of consciousness: Was estimated using the Glasgow score (Teasdale and Jennett, 1974), defined as severe when the GCS ≤ 8/15.

Etiology was classified according to the International League Against Epilepsy (ILAE) criteria, as Prolonged febrile seizures, acute symptomatic, remote symptomatic, Acute on remote symptomatic, progressive symptomatic, Idiopathic/cryptogenic epilepsy-related and Unclassified. **[4]**

Outcome was measured by the condition on discharge using the **Glasgow Outcome Score** which ranges from 1 to 5, defined as follows: **1** = death, **2** = vegetative state, **3** = severe disability, **4** = moderate disability, and **5** = good recovery. **[10]**

For the purpose of analysis, patients with score 4 and 5 were defined as having good outcome and patients with score 1 to 3 were defined as having bad outcome.

Hospital treatment protocol

Status epilepticus treatment followed the in-house protocol and included following intravenous administrations: as first line, a bolus of clonazepam 0.015 mg/kg, diazepam 0.2 mg/kg, or midazolam 0.2 mg/kg; as second line, phenobarbital 20 mg/kg; as third line, midazolam 0.2 mg/kg followed by 0.2–1.9 mg/ kg/h or thiopental 2–5 mg/kg followed by 1–5 mg/kg/h.

Additional treatments, such as oral topiramate and levoteracetam, intravenous propofol, intravenous kétamine and immunomodulation were prescribed in selected cases.

- **Variables definition**

Demographic details, developmental history, history of coexisting medical diseases, history of epilepsy, antiepileptic drug use, and seizure type. Also, general and neurologic examinations were performed. Investigations including full blood count, blood sugar, serum calcium, serum electrolytes, blood urea, serum creatinine, lumbar puncture, electroencephalography (EEG), Brain imaging (computed tomography and/or magnetic resonance) were performed.

The latency between onset of SE and treatment was categorized as < 1 h vs ≥1 h.

- **Statistical analyses**

The data were summarized using descriptive statistics: mean, standard deviation, median, and interquartile range values for quantitative variables and number and percentage for qualitative values.

Statistical differences between groups were tested using chi-square test for qualitative variables, and independent sample t test for quantitative normally distributed variables, whereas a nonparametric Mann-Whitney test was used for quantitative variables that are not normally distributed.

Logistic regression analysis was used to determine factors associated with the development of RSE and SRSE in patients presented with SE.

P value less than or equal to 0.05 was considered statistically significant.

Calculation was performed with the Epi-info 7 and SPSS, version 19.0.

3. RESULTS

- **Patients and demographics**

We identified 443 consecutive episodes of CSE in 419 patients. They constituted 11.87% of total ICU admission during this period.

16 patients had two or more SE episodes during the years of observation, thus the recurrence rate was 3.6%.

Two hundred thirty five (53%) episodes were classified as **NRCSE,** 140 (31.6%) as **RCSE** and 25 (5.6%) as **Super-RCSE.**

43 (9.7%) episodes were **not classified** because it was not possible to define the response to treatment, as there was no therapeutic escalation with direct use of general anesthesia and tracheal intubation

These 43 cases were not taken into account when comparing the results as a function of refractoriness. So A total of 400 episodes of SE were included.

- **Clinical features and demographics**

They were 240 (60%) boys and 160 (40%) girls.

The **mean age** was 44, 89 ± 2, 9 months (ranging from 1 to 180 months) for NRCSE group and 34.62 ± 3,125 months (ranging from 1 – 180 months) for RCSE group, respectively (P=0.019).

136 patients (34%) had suffered **previous seizures**;

The time interval between the initiation of seizure and the administration of anticonvulsant medications was 202.76 ± 20.65 min (ranging from 30 to 2880 min) in NRSE group and 717.04 ± 80.15 min (ranging from 30 to 5760 min) in RCSE group (P= 10^{-4}).

The demographic, clinical aspects and etiologies across the three CSE groups are summarized in **Table 1.**

- **Etiology**

There was a rather significant etiologic variation between the two groups.

Acute symptomatic etiology accounted for 188 episodes (47%). Acute symptomatic SE was higher in RCSE / Super-RCSE than in NRCSE (72.9%, 64% vs 29.8%, respectively) (p = 10^{-4}).

This difference was due to CNS infections (39.3% of cases of RSE, 48% of cases SRSE vs 16.6% of cases of NRSE) (p = 10^{-4}).

Acute symptomatic etiology was an associated risk factor with RCSE (OR=3.61; 95% CI 2.112-6.166, P=10^{-4}).

Prolonged febrile etiology (OR: 0.136; 95% CI 0.053 – 0.353 p = 10^{-4}), Remote symptomatic (OR: 0.119; 95% CI 0.040 – 0.357 p = 10^{-4}), Idiopathic/Cryptogenic Epilepsy-Related (OR: 0.157; 95% CI 0.052 – 0.474 p = 0.001), were against development of RSE. (**Table 3)**

Comparisons between NRCSE and RCSE (including Super-RCSE), and between RCSE and Super-RCSE are shown in **Tables 1 and 2**.

Stepwise multiple logistic regressions showed that a Severe consciousness impairment (Glasgow Coma Scale: GCS < 13/15) before treatment, symptomatic etiology, younger age under 03 years and the long duration of the SE were independently associated with RCSE. (**Table 3)**

Determinants of SRSE

On logistic regression analysis of all the variables that predict progression of RCSE to Super-RCSE: age greater than 3 years, indeterminate etiology, Encephalitis and use of vasopressor medications. (**Table 4)**

- **Complications and outcome**

Mechanical ventilation was needed in 168 (42%) patients.

The duration of ventilator care ranged from 12 to 600 hours (mean± SD; 117.4 ± 9.68 hours) days in the entire cohort.

The mean and interquartile range of intensive care unit stay was 7.44 [1-117 days].

Of the 400 patients, 83 (20, 8%) died during their hospital stay. **(Fig 1).**

4. DISCUSSION

In our study, RCSE/super-RCSE represent 31, 6% of all CSE episodes. This result is in line with previous reports showing an incidence of RSE ranging from 10% and 40% of all SE cases. **[11] [12]**

Super-RSE accounted for 5.6% of all SE episodes. Whereas in the literature, 10–15% of CSE develop super-refractory SE. **[7][9][13][14].**

However, data from analysis of children with super-refractory SE were lacking. Most of the data of pediatric super-refractory SE were only mentioned briefly in papers about refractory SE and lack details. The classifications of etiology and treatment protocol also lack consistency**. [15]**

Relative Factors of RSE

- **Acute Symptomatic etiologies**

The etiologies of SE are heterogeneous and play an important role in the formation of refractory status epilepticus. **[16]**

In our study acute symptomatic etiology was the most prevalent cause of RCSE (71, 5%). multivariate analysis showed that acute symptomatic etiology increased the risk of RSE by 3.61 times, while univariate analysis showed that central nervous system infections, meningitis and encephalitis, are more frequent in patient with RCSE.

Encephalitis was more frequent in patients with RSE and SRSE in the present study and also predicts progression to SRSE, similar to previous reports. **[17][18][19]**

Lingappa et al. **[20]** conducted a retrospective study of 73 children with status epilepticus in developing countries. They found that 45.2% developed refractory status epilepticus and 60.3% of the cases were caused by intracranial infection. **[20]**

In another study by Jainn-Jim Lin et al, (in Chang Gung, Taiwan, 2008), among the 46 children with encephalitis complicated by SE 43.4% develop a RSE**. [21]**

- **Age**

In our study, the age of less than 3 years increased the risk of CSR by 1,765 times.

Some studies indicate that age is an associated risk factor for CSR **[19][20],** this is in relation with the acute symptomatic etiology more frequent in young patients, in particular those less than one year old. **[22][23] [4]**

- **Duration of seizures**

The duration of seizures depends on prompt medical treatment, etiology and age. The longer the seizures last, the more resistant they become to the initial SE treatments. The time-dependent pharmacoresistance to BZDs has been found in animal models, **[24] [25]** and clinical studies have shown that as seizures last longer, they often become self-sustained and progressively more resistant to treatment. **[26] [27]**

And one study indicated a correlation between delay in the start of treatment and transformation of SE to RSE. **[28]**

In the present study, the type of epileptic seizure was not revealed as a associated risk factor for RSE, but in several studies, the focal seizure at the onset of the epileptic seizure was considered a risk factor related to RSE. **[29][30]**

Outcome of SE and RSE/ Super RSE

Children with SE have an overall mortality rate of approximately 0 - 3%, **[4]**

RCSE is associated with a much higher mortality. In a retrospective series of 22 children with RCSE, mortality was 32%. **[18]**

In this study, overall mortality was 20.8%, highest in SRSE (52.0%) followed by RSE (49.3%), both significantly ($p < 0.000$) higher than NRSE (0.4%).

Acute symptomatic etiology accounted for 72.3% of the deaths in the entire cohort ($p < 0.000$) when compared to all other etiologies.

A limitation of this study was the unavailability of the continuous Electroencephalographic monitoring, which represents an important tool in the diagnosis of Non Convulsive Status Epilepticus and in monitoring the response to treatments.

5. CONCLUSION

The etiologies of CSE are heterogeneous, with significant incidence of RCSE in acute symptomatic group.

Encephalitis was the determinant of progression of CSE to Super-RCSE.

The therapeutic success of which depends on whether or not the cause of CSE can be treated.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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Table 1: Demographics, clinical aspects, and etiologies of status epilepticus.

	NRSE N=235 (58.8%)	**RSE 140 (35%)**	**SUPER-RSE 25 (6.3%)**	**All 400 (100%)**	**p**
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Sexe					
Female gender	95 (40,4%)	52 (37,1%)	13 (52%)	160(40%)	**0.36**
Male gender	140 (59,6%)	88 (62,9%)	12 (48%)	240 (60%)	
Age (months) (mean, SD)	44.89 ± 2.93	31.78 ± 3.34	50.56 ± 8.12	40.65 ± 2.16	**0.009**
Age Class					
1 month – 1year	66 (28,1%)	70 (50%)	5 (20%)	141 (35,3%)	
1 – 5 years	114 (48,5%)	45 (32,1%)	12 (48%)	171 (42,8%)	**0.001**
5 – 10 years	34 (14,5%)	19 (13,6%)	6 (24%)	59 (14,8%)	
10 – 15 years	21 (8,9%)	8 (4, 3%)	2 (8%)	29 (7,3%)	
Previous history of epilepsy	103 (43,8%)	25 (18%)	7 (28%)	135 (33.8%)	10^{-4}
Previous history of SE	44 (18,7%)	6 (4.3%)	1 (4%)	51 (12.8%)	10^{-4}
Caractère des convulsions					
Intermittente	189 (80,4%)	112 (80%)	19 (76%)	320 (80%)	NS
Continue	49 (19,6%)	28 (20%)	6 (24%)	80 (20%)	
Type de convulsion					
Focal	49 (20,9%)	32 (22.8%)	8 (32%)	89 (22.25%)	NS
Généralisée	186 (79,1%)	108 (77,2%)	17 (68%)	311 (77,75%)	

Type de crise					
Tonique	70 (29,8%)	50 (35,7%)	8 (32%)	128 (32%)	NS
Clonique	29 (12,3%)	22 (15,7%)	7 (28%)	58 (14,5%)	
Tonic-Clonique	132 (56,2%)	65 (46,4%)	10 (40%)	207 (51,8%)	
Myoclonique	4 (1,7%)	3 (2.1%)	0	7 (1,8%)	
Seizure duration (min)(mean, SD) Rang [min]	202 ± 20.65 [30 – 2880]	635 ± 68.77 [30 – 5760]	1176.4± 35.93 [40 – 5760]	414 ± 37.37 [30 – 5760]	10^{-4}
Seizure duration (hours)					
≤ 02	139 (59,1%)	32 (22,9%)	4 (16%)	175 (43,8%)	10^{-4}
>02	96 (40,9%)	108 (77,1%)	21 (84%)	225 (56,3%)	
GCS at presentation					
≥ 13	123 (52.3%)	6 (4.3%)	2 (8%)	131 (32.8%)	10^{-4}
< 13	112 (47.7%)	134 (95.7%)	23 (92%)	269 (67.3%)	
Etiology classification					
Acute symptomatic	70 (29,8%)	102 (72,9%)	16 (64%)	188 (47%)	10^{-4}
Prolonged febrile seizures	59 (25,1%)	7 (5%)	0	66 (16,5%)	10^{-4}
Remote Symptomatic	49 (20,9%)	3 (2,1%)	2 (8%)	54 (13,5%)	10^{-4}
Idiopathic/cryptogenic epilepsy-related	30 (12,8%)	4 (2,9%)	1 (4%)	35 (8,8%)	**0.003**
Acute on remote symptomatic	23 (9,8%)	11 (7,9%)	1 (4%)	35 (8.8%)	**0.55**
Progressive Symptomatic	3 (1,3%)	6 (4,3%)	0	9 (2,3%)	**0.12**
Unknown	1 (0.4%)	7 (5%)	5 (20%)	13 (3.3%)	10^{-4}
CNS infections	39 (16.6%)	55 (39.3%)	12 (48%)	106 (26.5%)	10^{-4}
Encephalitis	24 (10.2%)	30 (21.4%)	11 (44%)	65 (16.3%)	10^{-4}
Meningitidis	16 (6.8%)	26 (18.6%)	1 (4%)	42 (10.8%)	**0.001**
Sepsis	0	27 (19 .7%)	3 (12%)	30 (7.6%)	10^{-4}
Vasopressor medications	2 (0.9%)	64 (46.4%)	18 (72%)	84 (21.2%)	10^{-4}

Table 2: Univariable model for factors associated with progression from SE into RSE.

Variables	Odds Ratio	95 % CI for OR	P value
Age ≤ 3 years	1.71	[1.12 – 26.20]	**0.013**
No Prior status epilepticus	5.20	[2.28 – 11.86]	10^{-4}
No Prior epilepsy	3.24	[2.04 - 5.16]	10^{-4}
GCS at presentation ≤13	21.55	[10.13 - 45.86]	10^{-4}
Seizure duration (hours) ≥ 2 hours	5.28	[3.30 - 8.30]	10^{-4}
Non-Respect of recommended escalation	2.83	[1.76 - 4.53]	10^{-4}
Etiology of SE			
Prolonged febrile seizures	0.13	[0.06 - 0.29]	10^{-4}
Remote Symptomatic	0.12	[0.046 - 0.305]	10^{-4}
Acute Symptomatic	5.918	[3.82 - 9.17]	10^{-4}
Idiopathic/cryptogenic epilepsy-related	0.21	[0.08 - 0.56]	**0.002**
Central Nervous System (CNS) infections	3.44	[2.16 - 5.46]	10^{-4}
Meningitis	2.14	[1.067 - 4.28]	**0.032**
Encephalitis	3.35	[1.96 - 5.71]	10^{-4}
Complications	22.20	[11.72 - 42.05]	10^{-4}

GCS: Glasgow Coma Scale

Table 3: Multivariable model for factors associated with progression from SE into RSE.

Variables	Odds Ratio adjusted	95% CI FOR OR	P value
Age ≤ 3 years	1.765	1.018 – 3.058	**0.043**
Seizure duration ≥ 2 Hours	3.096	1.77 – 5.39	**10^{-4}**
Non-Respect of recommended escalation	3.659	1.926– 6.949	**10^{-4}**
Acute Symptomatic etiology	3.609	2.112 – 6.166	**10^{-4}**
GCS at presentation < 13	18.55	8.202 – 41.97	**10^{-4}**

Table 4: Multivariable model for factors associated with progression from RSE into Super-RSE.

Variables	Odds Ratio ajusted	95% CI FOR OR	P value
Age > 3 years	3.280	1.221 — 8.810	**0.018**
Encephalitis	4.782	1.698 —13.465	**0.003**
Unknown etiology	6.628	1.604 — 27.383	**0.009**
Use of vasopresors drugs	4.239	1.473 — 12.204	**0.007**