Super-refractory status epilepticus in children: what happens when anesthetic therapy is not enough?

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Abstract

***Introduction*: to describe the clinical features, treatment options and outcome of Super-Refractory Status Epilepticus (SRSE) in a population of children aged ≤16 years with different etiology.**
***Methods*: we retrospectively analyzed the population with status epilepticus admitted to the "Bambino Gesù" Pediatric Hospital between 2007 and 2016, identifying patients with SRSE. We examined medical history before SRSE including neurological status, preceding epilepsy, antiepileptic treatment, SE episodes. Etiology was classified as progressive/ metabolic (PM), remote symptomatic (RS), acute symptomatic (AS). We evaluated clinical and EEG features of SRSE, and all treatments including anesthetics, antiepileptic drugs and "other" treatments administered according to the single case. Outcome (further epilepsy/SE and neurological status) was assessed after ≥6 months.**
***Results*: We identified 20 children (12 male/8 female) with SRSE with a mean age at SRSE of 5.9 years (0.7-16.6). Before SRSE 16 patients (80%) had epilepsy with episodes of SE in 8 (50%). According to etiology 9 patients (45%) were classified as PM (8 mitochondrial, 1 folate deficiency), 7 (35%) as RS (4 genetic epilepsy, 3 focal cortical dysplasia), 4 (20%) as AS (2 CNS vasculitis, 1 stroke, 1 GABA-A receptor encephalitis). SRSE mean duration was 23 days (4-92). The most used anesthetics were midazolam (18), thiopental (15), propofol (11), ketamine (4). Treatments other than conventional AEDs were steroids (17), immunosuppressants (7), Vitamins (8), KD (5), Bromide (3), hypothermia (2), VNS (1). At last follow-up (mean 3.8 years), 12 patients (60%) showed a worsening of the neurological status, 9 (45%) presented further episodes of SE and 4 (20%) SRSE, 2 (10%) underwent epilepsy surgery and 2 (10%) died.**
***Significance*: SRSE is a severe condition affecting mostly children with acute imbalance of the neuronal functions due to energy failure (progressive pathology), immune-mediated damage and symptomatic epilepsy; although the treatment remains daunting, the use of "other" treatments can be very helpful in selected cases.**

KEY WORDS: Pediatric Status Epilepticus, Super-refractory status epilepticus (SRSE), etiology, treatment, Pediatric Intensive Care Unit (PICU).

Introduction

When Status Epilepticus (SE) persists despite first and second line treatments becomes Refractory (RSE) and a more aggressive therapeutic approach is needed (1, 2).
Admittance in the Pediatric Intensive Care Unit (PICU), endotracheal intubation, mechanical ventilation and induction of therapeutic coma are necessary to prevent irreversible systemic and brain damage.
Although in most cases anesthetic therapy is sufficient to control seizures (3-5), in a minority of patients with RSE the status continues despite pharmacological coma or persists unchanged at the weaning of the anesthetic drugs. This condition has only recently been referred to the term Super-Refractory Status Epilepticus (SRSE) (6). In the past decade, before the term SRSE was adopted, many difficult to treat SE were referred to "severe pharmacoresistant SE" or "malignant" SE, a condition encompassing cases with poor prognosis, high risk of mortality and, in most cases, unknown etiology (7-9).
However, once SRSE is established there is no consensus on how to treat these patients and additional treatments such immune-modulating therapies, ketogenic diet and hypothermia, are considered useful in some instances (10, 11).
We here report our experience with pediatric SRSE with particular focus on the possible etiologies and to the "other" treatments that can be useful when anesthetic treatments become ineffective.

Methods

We retrospectively analyzed the population with status epilepticus admitted to the "Bambino Gesù" Children Hospital between 2007 and 2016, identifying 213 patients with SE. We included in the present study children ≤16 years with scarce response or relapse of SE after pharmacological coma induction with anesthetic drugs (SRSE). Newborns were excluded. Data collection included an accurate examination of the medical history before SRSE including neurological status, number and types of AEDs administered, previous SE episodes.

All investigations including magnetic resonance (MRI), lumbar puncture, metabolic and genetic tests, skin or muscle biopsies were reviewed to assess the etiology.

In agreement with the recent classification of status epilepticus from the International League Against Epilepsy (ILAE) (12) we categorized etiology of SRSE (Fig. 1) as: 1) Progressive or Metabolic (PM) in patients with degenerative or metabolic disease; 2) Remote Symptomatic (RS) in patients with structural or genetic, non-evolving, brain pathology; 3) Acute Symptomatic (AS) in patients with an acute neurological insult or systemic disturbance.

All patients were treated for SRSE in the Pediatric Intensive Care Unit (PICU) of our Hospital and followed for at least 6 months after the discharge to assess outcome in terms of further epilepsy or SE recurrence and modification of the neurological status. Pharmacological induced coma was monitored with serial Video-EEG recordings in all patients and has been protracted until clinical and electrical seizure activity ceased. All the Video-EEG recordings performed during SRSE were carefully reviewed to assess seizure semiology and EEG features. MRIs were performed at different time points in the clinical history of each patient to assess the clinical evolution. For this purpose during the status, the evidence of a new, previously undescribed, anatomic modification (i.e. cortical-subcortical atrophy, cytotoxic edema, white or grey matter hyperintense areas) was classified as "worsened" while in the non-evolving conditions the term "static" was used.

Results

General population

We identified 20 children (12 male/8 female) with SRSE treated in our PICU (9.3%). Demographic, etiological and treatment data of each patient are summarized in detail in Table 1. Before SRSE neurological status was abnormal in 60% (12 of 20), showing in 7 of 20 (35%) a neurological impairment (hypotonia in 3, tetraparesis in 2, hemiparesis in 2) associated with a variable degree of delay in the psychomotor milestones; 5 of 20 (25%) showed only a low IQ. Sixteen patients (80%) received a diagnosis of epilepsy with a mean age at seizure onset of 2.1 years (0.1 to 7.5). Eight of 16 (50%) presented a previous episode of SE, which was refractory (RSE) in 38% (3 of 8). Sixteen patients (80%) were taking one or more antiepileptic drug (AED) at SRSE. The mean age at SRSE was 5.9 years (0.7-16.6) with peaks in the early infancy and in children >5 years (Tab. 1). SRSE duration ranged from 4 to 92 days (mean 23).

Etiology

According to etiology we individuated 9 patients (45%)

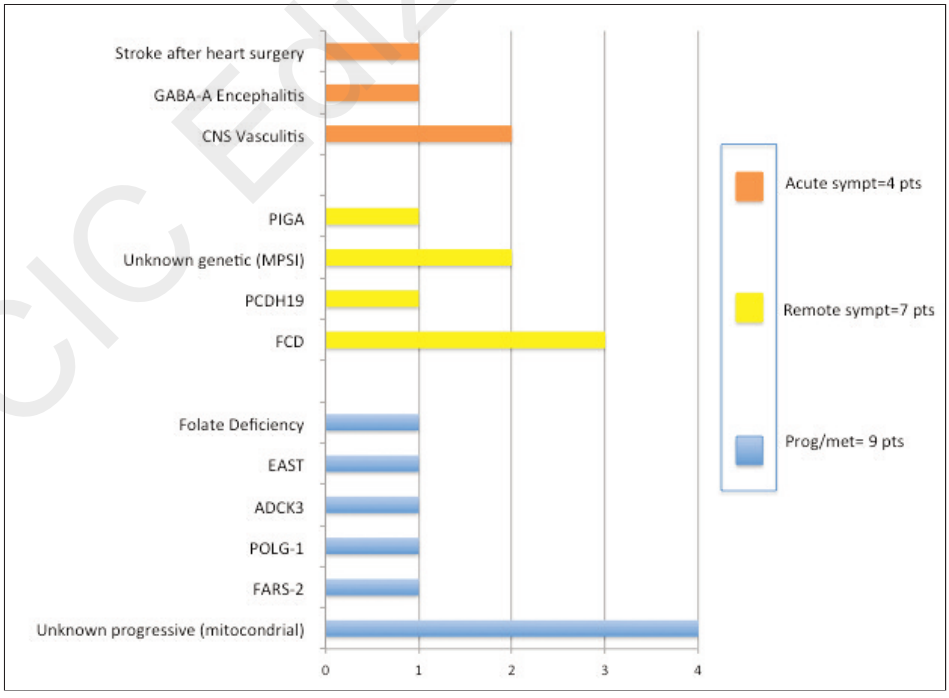

Figure 1 - Etiologies and groups.

Table 1 - Showing the general characteristics of the 20 patients studied including etiology, pre-SRSE features, SRSE duration and treatment administered. EAST=Epilepsy, Ataxia, Sensorineural deafness and salt-wasting renal Tubulopathy, FCD=Focal Cortical Dysplasia, DD=developmental delay, AEDs=antiepileptic drugs, PB=phenobarbital, PHT=phenytoine, TPM=Topiramate, LEV=Levetiraceteam, VPA=valproate, CBZ=carbamazepine, LCS=lacosamide, GVG=vigabatrin, ZNS=zonisamide, LZP=lorazepam, PER=perampanel, CLN=clonazepam; MDZ=midazolam, Keta=Ketamine, TPS=Sodium thyopental, KD=ketogenic diet, PEX=plasma-exchange, IGV=i.v. immunoglobulin.

Patient n°/ sex/years	SE etiology specify	Neurological examination/cognitive assessment	Epilepsy	Previous SE	Epilepsy onset age (years)	Prior AEDs	AEDs	Anesthetichs	Other tratments	Time to SE control (days)
1/F/5.6	Presumably Progressive	Normal	Yes	No	2.7	VPA	VPA, PHT, LCS, PB, PER	MDZ, Propofol, TPS, Keta	Steroids, PEX, IgV, B6, P5P, biotin, folinic acid, Riboflavine, Q10 Coenzyme	44
2/F/6.9	EAST	Right hemiparesis, DD	Yes	No	0.2	CB:	PB, PHT, LEV, TPM	MDZ, Propofol	Riboflavine, Q10 Coenzyme	5
3/M/1.7	FOLR1	Normal, mild DD	Yes	No	0.1	CBZ, PB	PB, VPA, PHT, ZNS, CLN	TPS, MDZ, PROPOFOL	B6, P5P, Folic acid, Steroids	29
4/M/7.1	FARS2	Normal	Yes	Yes	6.5	CB:	PB, LEV, TPM, CLN, CLB	MDZ, TPS, Sevoflurane	Steroids, B6, folic acid, KD, Hypotermia	11
5/M/0.7	POLG1	Mild DD, hypotonia	Yes	Yes	0.6		PHT, PB, LEV, VPA, LCS, CBZ	MDZ, TPS	B6, Steroids	10
6/M/9.5	Presumably Progressive	Tetraparesis, DD	Yes	Yes	0.2	CBZ, PB	PB, PHT, GVG, CBZ, LZP	MDZ, TPS	-	8
7/F/16.6	ADCK3	Hypotonia, DD	Yes	Yes	7.5	VPA, CLB	PB, PHT, CBZ, VPA, CLB	TPS, Propofol, Keta	Mg, IgV, Steroids, KD, VNS, Riboflavine, Q10 Coenzyme	34
8/M/5	Possible FARS2 (biopsy)	Normal, Mild DD	Yes	Yes	3.2	PB, CBZ	CLN, LCS, LEV, GVG, PHT, TPM	MDZ, Propofol, Keta, Sevoflurane	Steroids, Hypotermia	13
9/M/3.5	Presumably Progressive	Normal	No	No	-	-	PHT, PB, LEV, VPA	MDZ, Propofol, TPS	Steroids, PEX, cyclophosphamide	32
10/M/1	Genetic (Migrating)	Tetraparesis, DD	Yes	Yes	0.4	PB, VPA CBZ, GVG, DZP	PB, PHT, CLN, LEV, ZNS, VPA, CBZ, TPM	TPS, MDZ	KD, steroids, Bromide, Folate	92

To be continued

Continue from **Table 1.**

11/F/7.6	FCD	Normal	Yes	No	3.5	CB:	PB, PHT, VPA, TPM	TPS, MDZ, PROPOFOL	ACTH	25
12/M/1.7	FCD type I *	Normal	Yes	No	1.3	CB:	PHT, PB, LEV, GVG	Propofol, TPS	Steroids	4
13/F/1	PCDH 19	Normal, Mild DD	Yes	No	1.0	CB:	CBZ, PHT, PB, LEV,	MDZ, TPS	KD, B6, P5P, folic acid, Steroids, IgV	31
14/M/1	PIGA	Normal, Mild DD	Yes	Yes	0.5	CBZ, VPA, CLN	TPM, VPA, CLN, LEV, PB	MDZ	KD, Bromide	9
15/F/2.7	FCD type I *	Right Hemiparesis	Yes	No	1.7	VPA, GVG	PHT, CBZ, TPM, ZNS, CLB	MDZ, TPS	Steroids	17
16/F/1.6	Genetic (Migrating)	Hypotonia, DD	Yes	Yes	0.3	VPA, CBZ, IgV	PB, PHT, TPM, LEV	MDZ, TPS	KD, Folinic Acid, P5P, Biotin, B6, ACTH, Bromide	12
17/M/14.6	Vascular (post-stroke)	Normal, mild DD	No	No	-	PB	PHT, PB, CBZ	MDZ, Propofol, TPS	Steroids	9
18/M/5.7	Vasculitis	Normal	Yes	Yes	3.5	LEV, Steroids	TPM, GVG, PB, CLN, GVG,	MDZ, TPS	Steroids, cyclophosphamide	31
19/M/10.8	Vasculitis (confirmed biopsy)	Normal	No	No	-	-	PHT, VPA, CBZ, LEV, LCS	MDZ, PROPOFOL	Steroids, PEX, cyclophosphamide, IgV	22
20/F/13.5	Autoimmune Encephalitis	Normal	No	No	-	-	PHT, PB, LEV, LCS, LZP	MDZ, Propofol, Keta	Steroids, IGV	10

Table 2 - Main differences between groups.

	PM (n=9)	RS (n=7)	AS (n=4)	Total population (n=20)
Pre-SRSE Features				
Abnormal neurological examination (n)	6	5	1	12
*Epilepsy (n)	8	7	1	16
Epilepsy Age Mean (min-max)	2.4 (0.1-7.5)	1.2 (0.3-3.5)	3.5 (1 pt)	2.1 (0.1-7.5)
Pre-SE (n)	5	3	0	8
Pre-RSE (n)	2	1	0	3
***SESR Age Mean (min-max)**	6.3 (0.7-16.6)	2.4 (1-7.6)	11.2 (5.7-14,6)	5.9 (0.7-16.6)
SRSE Duration (days)	20.7 (5-44)	27.1 (4-92)	18 (9-31)	22.4 (4-92)
Seizure semiology (n)				
Focal Motor	8	3	4	15
*Subtle	0	3	1	4
Tonic	1	1	0	2
*EPC	6	0	1	7
Other	1	1	0	2
MRI (n)				
Worsened	7	0	3	10
Static	2	7	0	9
***Neurological outcome (n)**				
Worsened	8	3	1	12
Unchanged	1	3	0	4
Normal	0	1	3	4

*statistical significance between the three groups.

in the *PM* group, 7 (35%) in the RS group, 4 (20%) in the AS group (Fig. 1).

In the *PM* group a mitochondrial etiology was demonstrated or strongly suspected based on clinical history or diagnostic tests in 89% (8 of 9). In 4 of these patients etiology was supported by genetic analysis, which disclosed mutations in the KCN10 (EAST syndrome), FARS2, POLG1 and ADCK3 genes. The remaining patient of the group showed folate-responsive SRSE associated with FOLR1 mutation. In the *RS* group we individuated in 43% (3 of 7) a lobar or multilobar focal cortical dysplasia, in 43% (3 of 7) a severe early onset epileptic encephalopathy (EOEE), in one patient (14%) a mutation of the PCDH19 gene. In the AS group we included 2 patients (50%) with CNS vasculitis (one demonstrated with brain biopsy), 1 (25%) with SRSE secondary to ischemic stroke after heart surgery and 1 (25%) with autoimmune encephalitis with $GABA_A$-receptor antibodies demonstrated in the CSF.

Table 2 shows the main differences between the three groups. According to etiology in the AS group only one patient was diagnosed with epilepsy before SRSE (pt. 18), while we found that 92% (11 of 12) of the patients

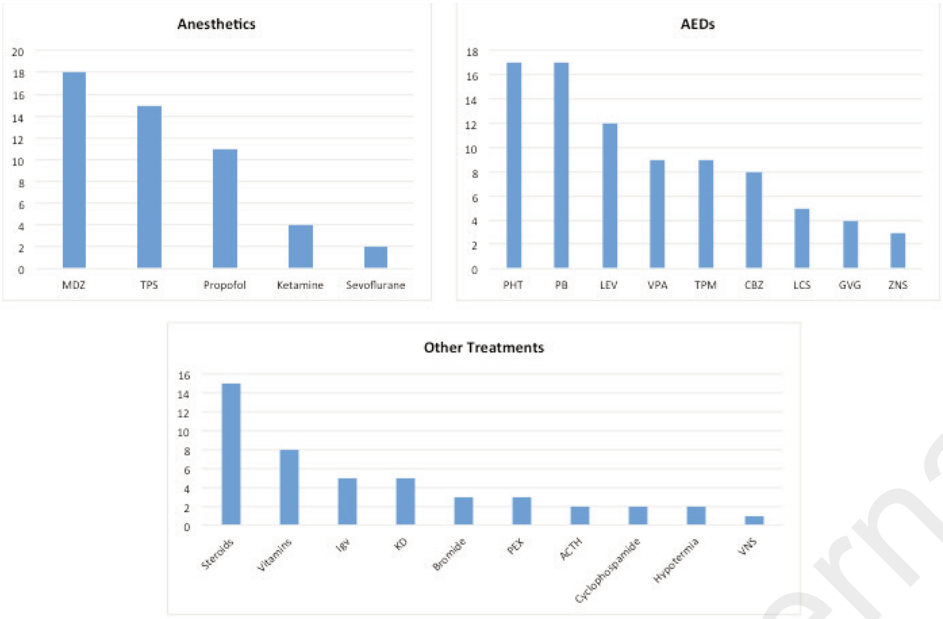

Figure 2 - SRSE treatments.

with abnormal neurological examination and 94% (15 of 16) with epilepsy were in the PM or RS groups (p=0.013). Furthermore 75% (6 of 8) of the patients with previous SE and RSE were in the PM group.
Age at SRSE is significantly different across groups (p=0.018) being lower in the RS and higher in the AS group, while we found no significant difference in the duration of SRSE.

SRSE characteristics

In the whole population, seizure semiology during SRSE was characterized by prominent focal motor signs (clonic, tonic or myoclonic) in 75% (15 of 20) and epilepsia partialis continua (EPC) was present in 35% (7 of 20); other types of seizures were found only in 5 patients (25%). In 15% (3 of 20) the prominent seizure type was characterized by vegetative signs, mild hypertonia and eye deviation (subtle seizures). Repeated tonic seizures were recorded in 10% (2 of 20). As observed in Table 2 the pattern of EPC was most frequent in the PM group (p=0,019).
EEG ictal pattern was classified as focal in 55% (11 of 20), bilateral in 45% (9 of 20), two of which with migrating focal seizures, both in RS group. Two patients (pt 5 and pt 8) showed a pattern of rhythmic high-amplitude delta with superimposed polyspikes (RHADS).
During SRSE, MRI imaging disclosed anatomic alterations in 95% (19 of 20) that were classified as worsened in 53% (10 of 19) and static in 47% (9 of 19). The only patient with normal MRI both during and after the SRSE was the patient with $GABA_A$-R encephalitis. Modifications in the MRI were found in 7 of 10 (70%) of the PM group and in 3 of 4 (75%) of the AS group (Tab. 2). MRI alterations were Flair/T2 hyperintense cortical-subcortical lesions in 12 cases (63%), atrophy in 7 (37%), cytotoxic edema in 3 (16%).

Treatment

Once the condition of SRSE was established we observed in most patients an intermitting-remitting course, with complete or incomplete (i.e. persistent electrical seizures) cessation of seizure activity during sedation followed by relapse of the status epilepticus at the weaning of the anesthetics.
Nineteen (95%) patients received continuous infusion with two ore more different anesthetic drugs while in the remaining patient the status reappeared at the weaning of midazolam and responded to Bromide treatment. The most frequently used anesthetics (Fig. 2) were midazolam 90% (18 of 20), thiopental 75% (15 of 20) followed by propofol 55% (11 of 20), ketamine 20% (4 of 20), and sevoflurane in 10% (2 of 20).
All patients received 3 or more different AEDs during the status. Other treatments were used in all patients (Fig. 3b-c). These consisted in steroids or ACTH in 17 (85%), vitamins (pyridoxine, pyridoxal-5-phosphate, biotin, folinic acid) in 8 (40%), ketogenic diet (KD) in 5 (25%), i.v. gamma globulins in 5 (25%), plasma-exchange in 3 (15%), Bromide in 3 (15%), cyclophosphamide in 2 (10%), hypothermia in 2 (10%), Vagal Nerve Stimulation (VNS) in 1 (5%).

Outcome

No patient died during SRSE. Middle or long-term outcome data after SRSE are available for all patients with a mean follow-up of 3.8 years (0.5 to 9.3 years).
At the last visit in all patients seizures were incompletely controlled despite multiple AED therapy. Two of the 3 patients with focal cortical dysplasia (10% of total) underwent epilepsy surgery (one multilobar resection and one hemisperotomy). In both cases histological examination confirmed the presence of a focal cortical dysplasia (FCD type Ia). Nine patients (45%) developed further episodes of RSE (4 PM, 4

RS, 1 AS) and 4 (20%) (3 PM, 1 RS) an episode of SRSE. In 60% (12 of 20) we found a worsening of the neurological status with appearance of new neurological deficits. Tetraparesis and severe cognitive impairment were found in 9 (45%), cognitive impairment with autistic behavior in 2 (10%), paraparesis in one (5%). In 8 patients (40%) neurological status was considered unchanged or remained normal as before SRSE. According to etiology an important worsening in the neurological functions was observed in 89% (8 of 9) of the PM group, in 43% of the RS group, in 25% (one of 4) of the AS group (p=0.035). Two patients of the PM group (pt. 5 and pt. 7) died in relation to progression of the pathology.

Discussion

Although rare, SRSE is a condition often encountered by the epileptologist and child neurologist engaged in the PICU.

However, the impact of SRSE during childhood is difficult to estimate from the available data of the literature. Furthermore, at the current state of art, data on the different etiologies and treatments of SRSE are mainly based on mixed adult-children populations (6, 11) and studies on children <16 years are lacking.

We observed that SRSE is a phenomenon that can appear at different age groups with peaks in the early infancy and in children >5 years. However, age at SRSE varies considerably according to etiology being lower in patients with RS etiology and higher in patients with AS etiology.

In this view our study demonstrates how important is the history preceding SRSE and which patients should be considered “at risk” for SRSE.

Despite etiology, SRSE affects mainly “complex” patients with a previous history of refractory epilepsy and neurological impairment or psychomotor delay.

It is known from other studies on patients treated in the ICU (4) that the presence of previous epilepsy itself is a negative prognostic factor in children with SE. Conversely to what is observed in adults (8, 13), in which a history of epilepsy is not so frequent, this seems to be a peculiarity of the pediatric age. On the contrary in the pediatric age a new-onset SRSE, is rare and, similarly to adults, is mostly associated to an acute symptomatic etiology such vasculitis or encephalitis (6). This confirms other studies in which a long-lasting SRSE has been observed in patients with abrupt onset seizures (7, 9).

In our study we observed that SRSE occurs frequently in children with prior episodes of SE or RSE suggesting some predisposition, at least in a few subjects, to develop long lasting and extremely pharmacoresistant SE. This is likely explained by the striking predominance of patients with progressive and genetic etiology in comparison with acute symptomatic.

Mitochondrial etiology alone represents the most frequent cause observed in our study. Notably, these patients are particularly prone to develop refractory SE (14), presumably in relation with an acute energetic failure disrupting the mechanisms involved in seizure termination (15). In some of these patients a characteristic evolution of the clinical history with repeated SE is frequently observed, likely representing an epiphenomenon of the neurodegerative underlying process. Although molecular diagnosis is often challenging, these patients often exhibit peculiar features such acute MRI lesions and typical electroencephalographic findings such as RHADS (in POLG1) and epilepsia partialis continua (14, 16).

On the other hand, other pathologies such as vasculitis or encephalitis may exhibit a similar course of illness with acute worsening (concomitant with exacerbation of the underlying disease) and remission periods.

We can therefore speculate that, despite etiology, a severe acute brain damage is a common mechanism for SRSE in childhood.

Epilepsies and epileptic encephalopathies with uncontrolled seizures are likely to be complicated with RSE[4]. Prolonged pharmacoresistant SE has been described (7, 17) but there are few studies reporting clearly etiology and treatments for SRSE (18) in these conditions.

As highlighted by Shorvon and Ferlisi (6), the identification of the etiology of SRSE is the most important factor that influences the outcome of SRSE and is closely interconnected with the choice of treatment. Unfortunately we observed as in the pediatric age the cause of SRSE is less frequently identifiable at the moment of the status and uncommon causes such mitochondrial and immunological disorders, genetic encephalopathies are the most frequent.

Consequently the final definition of the etiology, although highly suspected in some cases, is often obtained months after SRSE termination though the severity of the clinical picture requires a quick decision.

Our study shows how complex is the management and treatment of SRSE. The clinical course is often frustrating because of relapses after weaning anesthetics and apparently effective treatments. Final remission is often obtained without clear association with a new treatment and, in some cases, is apparently spontaneous.

The need to resort to treatments “other” than anesthetics and antiepileptic drugs is almost the rule in this condition and in some cases the administration of adjunctive treatments (such steroids, vitamins or KD) has been critical.

This approach is particularly relevant in the individuation of patients with SRSE due to inborn errors of metabolism that can be treated by vitamin supplementation (i.e. pyridoxine-responsive SE).

In one case (pt. 3) we observed that the resolution of the SRSE was obtained after 29 days of SRSE with folinic acid supplementation.

In our experience, due the high frequency of SE and RSE in these conditions (19), trials with pyridoxine, pyridoxal-5-phosphate (P5P) and folinic acid in young

children with unexplained drug-resistant SE are justified also outside the neonatal period.

As previously suggested (6, 11) steroids and immune-modulating treatments can be very useful in the treatment of cryptogenic SRSE when an autoimmune etiology is suspected. We observed resolution of SRSE with high dose i.v. steroids followed by plasma-exchange in the patient with $GABA_A$-receptor encephalitis. However, our study demonstrated that in some cases, second-line immunosuppressive agents could be requested. Ketogenic diet is another option suggested by different Authors in the treatment for SRSE (17). We treated 5 patients with KD (3 PM and 2 RS) obtaining complete control of SRSE only in one patient with mitochondrial disease (pt.1). This confirms that KD can show some efficacy when a mitochondrial encephalopathy is suspected.

Outcome in patients treated in the ICU for SE is often aggravated by important morbidity and mortality (7, 9). We observed as, at the last follow-up the neurological status was worsened in most patients. Worsening after SRSE was more frequent in the PM group and is unclear whether the worsening is related to progression of pathology or as sequelae of the status epilepticus; in addition only two patients (both with progressive pathology) died several months after the status likely because of progression of the neurodegenerative pathology.

Conclusions

Our study shows that SRSE is a severe condition which mainly affects children with previous history of epilepsy and SE. It recognizes a wide range of etiologies and is more often associated with acute imbalance of neuronal functions and symptomatic epilepsy, often reflecting the worsening of the underlying disease.

Although the treatment remains daunting, the use of further treatments can be very helpful in selected cases. It requires a multidimensional approach that should be as much as possible etiology-oriented and not just aimed at seizure control.

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