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Baseline and outcome assessment in pediatric status epilepticus

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ABSTRACT

Purpose: To summarize different aspects of short and long-term outcomes associated with SE, including mortality, recurrence, subsequent epilepsy, neurocognitive dysfunction, imaging abnormalities, and health-related quality of life.
Methods: We searched MEDLINE for studies that assessed the short-term and long-term outcome of status epilepticus in pediatric population, including mortality, recurrence of seizure and status epilepticus, neurological, cognitive, or behavioral impairment, and health-related quality of life. We excluded studies that exclusively assessed the adult population.
Results: Mortality in pediatric SE is relatively low, while morbidity poses more challenges. The underlying cause of SE has been shown to be a major determinant in the outcome after SE. However, it is difficult to establish the net effect of SE on outcome due to the heterogeneity of the studies. Notably, this review highlights that health-related quality of life, an important aspect of long-term outcome in pediatric SE, is under-addressed and merits further investigation.
Conclusion: There is a need to acquire high-quality long-term data evaluating QoL, neuroimaging, use of continuous infusions, and cognitive and behavioral outcome of children who experience SE.

1. Introduction

Status epilepticus (SE) is one of the most common neurologic emergency in pediatrics. The estimated incidence is about 20/100,000 per year [1]. It is generally believed that SE is associated with poor short- and long- term outcomes, including mortality and morbidities such as recurrence, development of subsequent epilepsy, and neurological or cognitive impairment. However, the extent of the effect of SE on the outcome is not well understood. There are many obstacles to define the net effect of SE on the observed outcome given potential confounding factors, namely the underlying etiology of SE, in addition to differences in study design, study populations, and outcome measures.

In this paper, we review the available data on the outcomes of SE in the pediatric population and focus on key aspects of outcome, including morbidity and mortality. Different aspects of the observed outcomes based on available data are discussed.

2. Methods

We searched MEDLINE using the term "status epilepticus", combined with "outcome", "mortality", "morbidity", "recurrence" and "quality of life". Search matches were reviewed to select relevant articles. We included studies that assessed the short-term and long-term outcome of status epilepticus in pediatric population, including mortality, recurrence of seizure and status epilepticus, neurological, cognitive, or behavioral impairment, and health-related quality of life. We excluded studies that exclusively assessed the adult population. All the included articles were then reviewed in full text. References of relevant articles were also searched. Only publications in English language were included in this review.

3. Results and discussion

3.1. Mortality

Short-term mortality rate in 30 days or until discharge ranged from 2.1% to 6% in studies conducted after 2000s, and from 2.7% to 11.5% in studies conducted before 2000. The reported short-term mortality rate was higher in some studies conducted in developing countries [2,3] (7.1%–17.5%) (Table 1). The advent of modern

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Table 1
Mortality and associated risk factors in pediatric CSE.

Author	Year	Design	Number	Age	F/u	Mortality	Risk factors
Pujar [22]	2017	Prospective	226	1 month-18 years	median 8·9 years (IQR 8·2–9·5)	10% (3% within 1 month)	
Hommady [42]	2017	Retrospective	116	1 month- 10 years (median 4.5 years)	NA	2.6%	Symptomatic SE etiology
Santhanam [43]	2017	Retrospective	610	1 month-12 years	NA	4.6%	Respiratory symptoms (grunt, rales, retractions), cardiovascular dysfunction, shock requiring fluid resuscitation, delayed capillary refill, inappropriate prehospital management.
Hassan [44]	2016	Prospective	84	21.3 ± 19.9	Discharge-1 year	14%	Risk factors for mortality and morbidity: Etiology, age, delay in treatment, absence of past history of epilepsy
Prins [45]	2014	Prospective	119	95% between 2 and 9 years	3–4 years	7.6%	
Jayalakshmi [46]	2014	Retrospective	177	31.6 ± 19.2 years	6 months	6.7%	Mortality was higher in refractory SE (40.0%) and super-refractory SE (35.7%) than non-refractory SE (6.7%) Encephalitis had higher mortality than other etiologies.
Bhalla [47]	2014	Prospective	80	13–78	2 weeks	5%	
Shatirishvili [48]	2014	Prospective	48	1 month–18 years	30 days	8.3%	Etiology
Loddenkemper [11]	2012	Retrospective	12,365	<20 years (mean 6.2 years)	–	0.9%	Near drowning, hemorrhagic shock, sepsis, massive aspiration, mechanical ventilation, transfusion, structural brain lesion, hypoglycemia, sepsis with liver failure, and admission in December
Pujar [6]	2011	Prospective	206	1 months – 16 years (mean 32.3 months)	8 years	11%	Presence of clinically significant neurological impairment prior to CSE
Lin [2]	2009	Prospective	141	2 months –18 years	1 month	7.1%	Etiology, age
Molinero [49]	2009	Prospective	47	1 months –16 years (mean 4.5 years)	13 weeks	13%	Infectious cause, cerebrovascular accident, long duration of SE
Mpimbaza [50]	2008	Randomized clinical trial	330	3 months – 12 years	Discharge	6%	Malaria, severe malnutrition, immunosuppression, pneumonia
Saddarangani [8]	2008	Prospective	138	1 month – 13 years	Discharge 3 years	15% 21%	Acute bacterial meningitis, age, hypoglycemia, focal onset seizures
Siddiqui [51]	2008	Descriptive cross-sectional	125	2 months – 15 years		12%	Acute intracranial infections, age, prolonged SE
Hayashi [52]	2007	Retrospective	358	Mean 48.6 (SD 46.5) months	Discharge	2.1%	Encephalitis, cerebrovascular disease
Muchochi [53]	2007	Non-Randomized study	26 (children with severe malaria)	6 months – 13 years	Discharge	11.54%	Pre-existing cerebral malaria, convulsions
Chin [13]	2006	Prospective	226	29 days – 15 years	2–26 months	3% (2–7%)	
Ahmad [54]	2006	Open randomized trial	160	2 months – 12 years	Discharge	17.5%	Progressive infection, cerebral malaria, febrile convulsions, acute bacterial meningitis, metabolic derangements
Morrison [55]	2006	Retrospective	17 (refractory SE)	0–17 years (median 3.5 years)	Discharge	18%	Subdural hematoma, birth asphyxia, post cardiac arrest
Maegaki [56]	2005	Retrospective	241	1 month –18 years		3.8%	Prolonged SE, moderate to severe asthma
Kang [57]	2005	Retrospective	189	<15 years	Mean: 17 months	3%	Higher mortality in acute symptomatic SE vs. remote symptomatic SE
Asadi-Pooya [58]	2005	Retrospective	135	1 month – 15 years		10·4%	Prolonged febrile seizure, CNS infection, metabolic, AED withdrawal, symptomatic epilepsy, prolonged stay
Brevoord [59]	2005	Retrospective	122	0.5–197.4 months (median: 24.4 months)	3 months	5.7%	Near drowning episode, pneumococcal meningitis, cardiac failure, brainstem tumor, hemorrhagic shock, metabolic defect
Gualti [60]	2005	Retrospective	30	1–120 months (mean: 56.6 ± 46.5 months)	Discharge	30%	Prolonged SE, septic shock
Berg [61]	2004	Prospective	613	1 month – 15 years	Median: 8.0 years	8.9%	Neurodegenerative disorder, epileptic encephalopathy, prolonged SE
Kwong [14]	2004	Retrospective	25	< 15 years	36 months	8%	
Wu [62]	2002	Retrospective	2885	All age groups children and adult	Discharge	1.9%	Female sex, older age
Logroscino [10]	2002	Retrospective	184	children and adult	10 years	7.4% (pediatric)	Prolonged SE, acute symptomatic etiology, myoclonic SE
Koul [63]	2002	Retrospective	68	2 months – 14 years		1.5%	
Sillanpaa [64]	2002	Prospective	41	< 16 years	30y	17%	
Singhi [65]	2002	Prospective		2–12 years	Discharge	25%	

Table 1 (*Continued*)

Author	Year	Design	Number	Age	F/u	Mortality	Risk factors
			40 (refractory SE)				Early intubation and ventilation, meningoencephalitis, acute hyponatremia, hepatic encephalopathy
Shinnar [27]	2001	Prospective	180	1 month – 10 years	1 month	0%	
Tabarki [66]	2001	Retrospective	139	1–24 months, (mean 11 months)	4 years	15.8%	Acute symptomatic seizure, progressive encephalopathy
Kim [67]	2001	Retrospective	23(severe refractory SE)	0–15 years	4 years	43.5%	Acute symptomatic etiology, anoxia
Sahin [68]	2001	Retrospective	22(severe refractory SE)	4.5 months–18 years	31·2 months	31.8%	Remote symptomatic and progressive encephalopathy
De Lorenzo [69]	1999	Prospective	228	>1 month (pediatric and adult)	1 month	Overall 19%, Pediatric 4%	
Mah [70]	1999	Retrospective	59	Mean: 2 years and 10 months	5 y	2%	
Bernard [71]	1999	Retrospective	52	1 month- 15 years	Discharge ≥ 3 months	9.6% 15.4%	Brain tumors, metabolic disorder, multi-organ failure
Waterhouse [72]	1999	Prospective	212	Adults and pediatric		5.2% in pediatric	CNS infection, hypoxia, drug withdrawal, continuous SE
Eriksson [73]	1997	Retrospective	65	Under 16 years	3–6 years	0%	
Scholtes [74]	1996	Retrospective	112	6 months – 15 years	Discharge	11.5%	Anoxia, presence of complication, Insufficient therapy, prolonged duration
Lacroix [75]	1994	Retrospective	147	3 days – 18 years	Discharge 1 year	6.1% 9%	
Verity [7]	1993	Prospective	37	Cohort followed from birth to 10 years	Discharge 10 years	2.7% 5.4%	
Shinnar [76]	1992	Prospective	95	1 months – 18 years	4–60 months	4.2%	
DeLorenzo [77]	1992	Retrospective	546 (171 pediatric)	from birth to >80 years		2.3%	Tumor, hematological disease, anoxia, metabolic and congenital malformations
Maytal [25]	1989	Retrospective with prospective follow-up	97	1 month – 18 years	13.2 months	7.2%	Prolonged SE
Dunn [78]	1988	Prospective	97	Children	Discharge	8.24%	Severe pre-existing brain damage, meningitis and encephalopathy
Yager [28]	1988	Prospective	52	Median 2 years	18 months	5.8%	
Cavazzuti [79]	1984	Prospective	66	<5 years	5–10 years	3%	
Chervie [80]	1978	Prospective	334	28 days – 1 year	1 year	6.3%	Symptomatic seizures, age
Aicardi [81]	1970	Retrospective	239	< 15 years	Discharge After a few weeks to several years	4.2% 11.2%	Prolonged SE, cerebral disease

neurocritical care and improvement of out-of-hospital emergency medical care probably contributed to the decreased mortality. In a systematic review conducted in 2007, the short-term mortality rate of SE ranged from 2.7–5.2% considering only the high-quality studies [4]. Long-term mortality ranged from 2.3% to 11% depending on the duration of follow-up (Table 1) [5].

Several study design factors could influence the results, including the definition of SE, age groups enrolled, duration of follow-up, population-based versus hospital-based settings, and the quality of the studies (sample size and power, and selection or information biases).

Different factors have been described to be associated with mortality in SE including etiology, age, SE duration, and neurological and other non-neurological co-morbidities (Table 1).

3.1.1. Etiology

Studies evaluating acute symptomatic etiologies (including CNS infection, trauma, metabolic derangements, hypoxia) consistently demonstrated worse outcomes compared to those without a clear underlying etiology or with febrile seizures [5]. For previously neurologically healthy children, all deaths occurred in patients who had acute symptomatic convulsive status epilepticus (CSE) in a population-based study in London, with febrile SE having an overall very good short and long-term outcome [6]. Likewise, in another national cohort, mortality in unprovoked or febrile CSE was lower compared to acute symptomatic cases [7]. The finding that mortality is related to the presence of a symptomatic etiology is not surprising as there can be more varied injury secondary to the underlying etiology versus febrile status epilepticus, e.g. – a large hemispheric stroke with cerebral edema may be expected to have a worse outcome than a small lacunar stroke. The bigger challenge is determining what effect status epilepticus has on mortiality independent of the etiology.

3.1.2. Age

The association of age and mortality due to SE in pediatric patients have been examined in different studies (Table 1). Several studies have shown higher risk of mortality in younger patients, especially in the first year of life [4,8–10]. Some other studies have shown no association between age and mortality [6,11], or an

increased odds ratio for mortality in the second decade of life compared to the first decade [12]. However, the underlying etiology is a major confounder of the effect of age on mortality. The distribution of etiologies is different among age groups. Acute symptomatic etiology, which is associated with higher mortality as discussed in the etiology section above, is more common in patients under one year old [8,13–17]. Thus, the higher mortality rate in the infants under one year old could be at least in part due to the higher prevalence of acute symptomatic etiologies, including CNS infection and metabolic derangements, in this age group.

3.1.3. Prior neurological abnormality

The presence of a prior neurological abnormality has been associated with a higher mortality in patients with SE. In a large population-based study of children with prior CSE conducted by North London Epilepsy Research Network with a follow-up duration of 8 years, CSE patients experienced a mortality 46 times higher than an age-matched population, with a history of prior neurological abnormality being the only independent factor that significantly predicted the mortality. Seven of 206 (3%) children died within 30 days after CSE, and the mortality rate during the 8-year follow-up was 11%. Overall, children with a prior history of neurological impairments had a seven times higher risk of death within 8 years following CSE compared with previously neurologically healthy patients. Considering only the subgroup of patients who survived beyond 30 days after CSE, the mortality within 8 years was 19 times higher in those who had prior neurological deficits compared with the previously healthy children [6]. The authors of this study point out that the mortality rate for these patients is similar to mortality in patients with severe cerebral palsy suggesting that the underlying neurologic abnormality may play a larger role than the episode of status epilepticus itself in long term outcome.

3.1.4. Duration of SE

Longer duration of SE is associated with increased mortality. In a population based study, SE duration of greater than 24 h more than doubled the risk of mortality compared with a duration of less than 2 h [10]. It has been shown that for every minute of increase in the duration of SE, the odds ratio of mortality increased by 0.005 [18]. As with mortality, a longer duration of SE may be related to the severity of underlying etiology [19]. In addition, increasingly aggressive therapies with more potential adverse effects are typically used as the duration of SE increases. How these factors interact can be difficult to control for in retrospective studies.

3.2. Morbidity

3.2.1. Recurrence and subsequent epilepsy

According to previous studies, the risk of recurrence of SE was variable, ranging from 3.7-56% (Table 2). As with mortality, the rate of recurrence is highly dependent on the study design and characteristics of study population, such as the underlying etiology and previous history of neurological impairment. Table 2 demonstrates the risk of recurrence in the different etiologic groups as reported in different studies. In general, patients with a previous neurological impairment and symptomatic etiology were more likely to experience recurrence of SE than patients with febrile SE or an idiopathic etiology. This was demonstrated in a prospective study of 27 non-febrile CSE and 27 prolonged febrile seizures followed for one year, where one out of 27 children with prolonged febrile seizures (3.7%) experienced a recurrent episode, compared to 11.1% in the non-febrile group [20]. Furthermore, in a retrospective study of afebrile CSE, the recurrence rate in 10 years was 31.7% [21].

Patients with SE are at risk for subsequent epilepsy, with rates that vary from 12 to 82% depending on the study. The rate of subsequent epilepsy in various studies are summarized in Table 2. If we limit the studies to those with more than 100 subjects within the past 20 years, the rate of epilepsy ranges from 12 to 41% overall. In the large population-based childhood CSE cohort from North London, of 134 survivors of CSE witout prior epilepsy that were followed for a median duration of 8.9 years, 24.7% (95% CI: 16.2–35.6%) developed epilepsy. The incidence was lower in prolonged febrile seizure (14.3%) and acute symptomatic CSE (13.3%) than remote symptomatic (45.5%) and unclassified etiology (50%); however, in the multivariate analysis, absence of fever at CSE was the only predictor of subsequent epilepsy (OR:7.5, 95% CI 2.25–25.1) [22].

3.2.2. Neurological, cognitive, and behavioral impairments

There is compelling evidence in the literature that SE can result in neurological and cognitive impairment. Previous studies have reported new neurological deficits in 6 to 30% of SE patients (Table 3); however, varying outcome measures have been used to study the neurocognitive outcome, making comparison difficult.

In an early study of cognitive function after SE, 48% of patients were found to have cognitive impairment after the SE episode. Nearly two-thirds of these patients were developmentally normal prior to the insult. After one-year, the rate of neurological sequelae was 45% [16]. Moreover, a comparison of young infants with and without episodes of SE showed that the group who had experienced even one episode of SE were more impaired compared to the control group in terms of neurocognitive and developmental outcome [23]. In another study, 30% of a cohort of 147 children with SE had a neurological deficit at discharge; in a follow-up after one year, nearly two-thirds of them still demonstrated the neurologic sequelae [24]. In a different study, new-onset encephalopathy and/or neurologic dysfunction were present in 17/193 (8.8%) children who had an episode of SE; however, 6/17 (35.3%) had seizure occurrence during a progressive neurological disease. Of 17 children who sustained new motor or cognitive deficits after SE, 14 (82.3%) had residual motor findings such as hemiparesis and diparesis after the SE episode, and the other three children had cognitive deficits without any motor impairment. Seven children had cognitive deficits in addition to the motor deficit [25].

A recent study showed poorer neurocognitive outcome in patients with SE and patients with 10 or more lifetime generalized tonic clonic seizures (GTC) compared with the normal control group. However, the difference between the SE group and the multiple GTCs was not statistically significant, and the authors decided it was not possible to draw a conclusion that SE has more pronounced effect on cognitive outcome than multiple lifetime GTCs [26].

Similar to mortality and recurrence, the underlying cause and baseline neurological status likely play important roles in the neuropsychological outcome. Although the previous studies show the association of SE with neurological and cognitive impairment, the studies are very heterogeneous, and the confounding role of the underlying etiology should not be overlooked while interpreting these results.

3.2.2.1. Etiology. Febrile and unprovoked etiologies tend to be associated with fewer new neurological sequelae than acute or remote symptomatic etiologies [4,19]. In a prospective study of 180 children one month to 10 years old with febrile SE, no new cognitive or neurological impairments were observed during a one-month follow-up period [27]. Among a cohort of 54 children presenting with CSE to North London hospitals, followed for a duration of 1 year after CSE, children with prolonged febrile seizure

Table 2
Rate of recurrence and subsequent epilepsy in pediatric CSE.

Author	Year	Design	Number	Age	F/u	Recurrence	Subsequent Epilepsy	Comparison among etiologic groups
Pujar [22]	2017	Prospective	226	1 month-18 years	median 8.9 years (IQR 8.2–9.5)		18/73 (24.7%, CI: 16.2–35.6%) History of epilepsy before CSE was the only significant predictor of active epilepsy at follow-up (OR 8·4, 95% CI 1·8–39·0)	Prolonged febrile: 14.3% (CI: 6.3–29.4%) Acute symptomatic: 13.3% (3.7–37.9%) Remote symptomatic: 45.5% (CI: 21.3–72.0%) Unclassified: 50.0)CI: 25.4–74.6)
Wagenman [29]	2014	Prospective	300 admitted with acute neurologic conditions (with and without seizures), 137 followed up	Median 3.9 years (IQR: 1.1–12.7)	Median 2.6 years (IQR: 1.5–3.2)		ESE (but not ES) associated with new onset epilepsy at follow-up (OR for ESE compared to those without seizure 13.33; 95% CI 2.49, 71.35). 12 of 13 (92%) of patients with ESE developed subsequent epilepsy.	
Prins [45]	2014	Prospective	119	95% were 2–9 years	3–4 years		14.5%	
Bhalla [47]	2014	Prospective	80	13–78 years	2 weeks	25%		
Martinos [20]	2013	Prospective	27 non-febrile CSE, 27 prolonged febrile seizures	1–42 months	1 year	3.7–11.1%		Non- febrile: 11.1% Febrile: 3.7%
Lin [2]	2009	Prospective	141	2 months –18 years	1 year	17%		Those with neurological deficit were more likely to show recurrence
Saddarangani [8]	2008	Prospective	138	1 month – 13 years	1 years		12%	
Hesdorffer [21]	2007	Retrospective	193	Pediatric and adult	10 years	31.7% (only afebrile SE)	41%	Risk of recurrence: 100% for progressive Symptomatic SE, 23.6% for remote symptomatic SE, 26.1% for idiopathic/cryptogenic SE, and 26.3% for acute symptomatic SE (log rank p = 0.09). Progressive symptomatic SE 2.4-fold more likely to recur compared with idiopathic/cryptogenic SE (this risk was no longer significant in the multivariate model (95% CI: 0.6–8.9).
Chin [13]	2006	Prospective	226	29 days – 15 years	2–26 months	13%, (95% CI 9–19) during the follow up; 1-year recurrence: 16%		Pre-existing neurological abnormality: 2·9 times (95% CI 1·01–8·45) more likely to have a recurrence within 1 year; 17% (95% CI 7–34) of children with first episode of prolonged febrile seizure had a recurrence within 1 year
Maegaki [56]	2005	Retrospective	234	1 month – 18 years	64·2 months	23%		
Kang [57]	2005	Retrospective	189	<15 years	Mean: 17 months	16%		Risk ratio for recurrence: Generalized seizure 6.83 Epilepsy 4.51 Remote symptomatic 3.21
Berg [61]	2004	Prospective	613	1 month – 15 years	Median: 8.0 years	32.1%		Recurrent rate: Idiopathic: 37.5% Cryptogenic: 14.8% Symptomatic: 52.4%
Kwong [14]	2004	Retrospective	25	<15 years	36 months		13%	None of the patients with idiopathic or febrile etiology developed subsequent epilepsy
Sillanpaa [64]	2002	Prospective	41	<16 years	30y	56%		Neither etiology nor neurological abnormality were significant predictors of

Table 2 (*Continued*)

Author	Year	Design	Number	Age	F/u	Recurrence	Subsequent Epilepsy	Comparison among etiologic groups
								recurrence in multivariate analysis
Sahin [68]	2001	Retrospective	22(refractory SE)	4.5 months – 18 years	31·2 months		100%	5/8 of subsequent seizure cases had acute symptomatic etiology, 2/8 remote symptomatic, 1/8 remote symptomatic with Acute precipitant
Tabarki [66]	2001	Retrospective	139	1–24 months, (mean: 11 months)	4 years		29%	Acute symptomatic: 5/56 developed subsequent epilepsy; Febrile 2/57; Progressive/remote symptomatic/idiopathic: 0. Another 27 cases developed mental retardation plus epilepsy
Mah [70]	1999	Retrospective	43	Mean: 2 years and 10 months	5 y	28%	72%	
Barnard [71]	1999	Prospective	52	1 month–15 years	≥3 months	50%	36%	None of the idiopathic or febrile patients developed epilepsy, but 5/8 of non-idiopathic non-febrile did
Eriksson [73]	1997	Retrospective	65	Under 16 years	3 – 6 years		23%	40% of Idiopathic, 4% of febrile, 8% of acute symptomatic, 50% of remote symptomatic, 67% of progressive developed subsequent epilepsy
Verity [7]	1993	Prospective	37	Cohort followed from birth to 10 years of age	10 years	47%	82%	Afebrile:47% Febrile: 0%
Shinnar [76]	1992	Prospective	95	1 month – 18 years	4–60 months (mean: 90 months)	17%		Remote symptomatic: 44% Progressive: 667%
DeLorenzo [77]	1992	Retrospective	546, 171 Pediatric	from birth to >80 years	2years	43%		
Maytal [25]	1989	Retrospective + prospective	193	1month – 18 years	40.2 months 32.8 months	14% 6.6%	16–44.6%	Development of subsequent seizure: Idiopathic 15/29 (51.7%), 4/16 (25%)*; Remote symptomatic 7/11 (63.6%), 1/1 (100%); Febrile 2/46 (4.35%), 1/28 (3.57%); Acute symptomatic 7/34 (20.6%), 2/21 (9.52%); Progressive encephalopathic 5/5 (100%), 3/3(100%)
Cavazzuti [79]	1984	Prospective	66	<5years	5–10 years		74%	Recurrent seizures: 43/103 (41.7%) cases were symptomatic, and 60/103 (58.3%) were cryptogenic
Aicardi [81]	1970	Retrospective	239	<15 years		10.5%	36%	

*Respectively for the retrospective and the prospective study.
ES: electrographic seizure; ESE: electrographic status epilepticus.

had a better developmental outcome than children with non-febrile CSE [20].

In a study of 52 children who presented with SE and were followed for a period of 1 to 18 months, patients with idiopathic or febrile etiology had better neurodevelopmental outcome than those with acute encephalopathic (infectious, metabolic, vascular, and toxic etiologies), and chronic encephalopathic etiologies (post-infectious, hypoxic-ischemic, CNS malformation, tumor, and degenerative). Of 13 patients who developed neurodevelopmental sequelae, only one patient had idiopathic/febrile etiology [28].

Table 3
Association of CSE with neurological, cognitive, and behavioral impairments.

Author	Year	Design	Number	Age	F/u	Outcome measure	Neuropsychological outcome
Power [26]	2017	Observational	39	≥16 years	1 year	Neuropsychological Test Automated Battery (CANTAB)	SE patients performed poorer than the normal control in memory tests, but no difference compared to patients with multiple life time GTCs.
Pujar [22]	2017	Prospective	226	1 month-18 years	median 8·9 years (IQR 8·2–9·5)	Wechsler Abbreviated Scale of Intelligence	Motor disability: 2.1% (CI: 0.6–7.4) Intellectual disability: 10.2% (CI:4.1–21.1)
Atmaca [82]	2017	Prospective	59	17–90 years	1 month		1.2% had neurological sequela
Hommady [42]	2017		116	1 month–10 years	NA	Glasgow Outcome Scale (GOS) score	Etiology and history of prior epilepsy was associated with lower Glasgow Outcome Scale score and moderate-to-severe developmental delay
Reddy [83]	2017	Retrospective	76	Median 5 months (IQR 6–37 months)	Median 5 months (IQR 2–15 months)		58% had persistent seizures or neurologic sequelae, with predictors of poor outcome being use of >3 ASMs, intubation >3 days, abnormal brain MRI.
Hassan [44]	2016	Prospective	108	21.3 ± 19.9	Discharge-1 year		22% had new neurological deficit
Abend [84]	2015	Prospective	300 with acute neurologic conditions, 137 previously neurodevelopmental normal were enrolled, comprising patients without seizure, with ES, and with ESE	Infants and children excluding neonates(median 3.9 years, IQR: 1.1–12.7)	Median 2.6 years (IQR: 1.5–3.2)	The Adaptive Behavior Assessment System—II (ABAS-II)	The Adaptive Behavior Assessment System—II (ABAS-II): median score of 73 (IQR: 48–102) for subjects with ESE; ESE and EEG background were associated with worse score in multivariate analysis (ESE coefficient: −36, p = 0.003)
						The Child Behavior Checklist (CBCL)	The Child Behavior Checklist (CBCL): median score of 61 (34, 65) for subjects with ESE; difference between the subjects with no seizure, ES, and ESE were not significant
						The Behavior Rating Inventory of Executive Function (BRIEF)	The Behavior Rating Inventory of Executive Function (BRIEF): median score 73 (59, 79) for subjects with ESE; no difference between those with no seizure, ES, and ESE
Wagenman [29]	2014	Prospective	300 patients admitted to PIU with acute neurologic conditions, 137 were followed up	Median 3.9 years (IQR: 1.1–12.7)	Median 2.6 years (IQR: 1.5–3.2)	GOS-E	Unfavorable GOS-E Peds for 35% of subjects; ESE was associated with unfavorable GOS-E Peds compared to patients without seizure After controlling for EEG background, acute neurologic disorder, age, and PICU duration (OR: 6.36; 95% CI: 1.48-27.31)
Prins [45]	2014	Prospective	119	95% were 2–9 years	3–4 years	Ten-question questionnaire (TQQ) of neurocognitive impairment	10.9% had neurological deficits at discharge, 30.9% positive in ten-question questionnaire (TQQ) of neurocognitive impairment, 13.6% of 110 screened with TQQ had neurological deficit
Shatirishvili [48]	2014	prospective	48	1 month –18 years	30 days		17% had new neurological deficits: loss of previously reached milestones, diffuse persistent hypotonia, FND-hemiparesis, cranial nerve palsy, cognitive impairment
Martinos [20]	2013	Prospective	27 non-febrile CSE	1–42 months	1 year		No differences in the performance of non-febrile and prolonged febrile seizure at baseline on the cognitive, language, and motor scales.
			27 Prolonged febrile seizures				No difference in performance from baseline to follow-up for the prolonged febrile seizure. In the non-febrile CSE group, baseline and follow-up cognitive, language, and motor composites were positively correlated
Saz [85]	2011	Retrospective	27	2.5 months–11 years	1 year		14.8% developed new motor or visual deficit none of the febrile SE patients had neurological sequelae
Roy [23]	2011	Retrospective	18	Infants (mean age: 13.1 months)		Global Developmental Quotient	Patients with SE who were developmentally normal prior to SE scored lower than the healthy controls in Global Developmental Quotient (GDQ) and the Performance and Eye–Hand Coordination subscales. The score of patients with febrile SE was lower than the healthy individuals but higher than the SE group.
Lin [2]	2009	Prospective	141	2 months –18 years	1 year	GOS	Outcome based on GOS: 9.2% death 1.4% Vegetative state

Table 3 (*Continued*)

Author	Year	Design	Number	Age	F/u	Outcome measure	Neuropsychological outcome
							37.6% Severe disability 31.2% Moderate disability 20.6% Good recovery
Molinero [49]	2009	Prospective	47	1 months –16 years, (mean: 4.5 years)	13 weeks		6% had new disability
Saddarangani [8]	2008	Prospective	138	1 month – 13 years	3 years		11% had neurological sequelae, motor and speech impairments each in 7% of children
Siddiqui [51]	2008	Descriptive	125	≤ 15 years	Discharge		8% had adverse neurological outcome
Pisani [86]	2007	Prospective	106	Neonate	24 months		Abnormal outcome in 25/26 (96.1%) of patients with SE

ES: electrographic seizure; ESE: electrographic status epilepticus; GOS: Glasgow Outcome Scale; GOS-E Peds: Glasgow Outcome Scale- Extended, Pediatric Revision.

When counselling families about the risk of neurologic sequelae, etiology appears to be a primary driver of outcome with generally low risk with febrile SE.

3.2.2.2. Age. The incidence of significant sequelae depended on the age groups, decreasing from 29% (12/41) among infants less than one-year-old to 11% (6/54) among children between 1 and 3 years of age and 6% (6/98) in those older than three years. However, the distribution of etiology was not homogeneous among different age groups, as the acute symptomatic and progressive encephalopathy groups consisted predominantly of younger patients [25].

3.2.2.3. Duration of SE. Long duration of SE has been reported to be associated with adverse outcome. In an early study, 57% of 239 children with one episode of SE lasting ≥ 1 h had some kind of disability after the episode of SE (neurological, cognitive, or both). Nearly half of the cases that had permanent neurological signs had acquired the neurological impairment either prior to the SE or as a result of the encephalopathy responsible for the convulsions (as opposed to the sequela of the CSE itself). In the other half (19.7% of the total) the child appeared to be previously neurologically healthy with no other cause directly responsible for the impairment, suggesting the SE as the culprit for the acquired neurological impairment [16].

In an evaluation of outcomes in previously developmentally normal patients who presented with SE, electrographic status epilepticus (ESE) was associated with impaired neurologic outcome at a median of 2.6 years after discharge. Shorter electrographic seizures (ES) were not associated with a worse outcome suggesting that duration of seizure activity may play a role in outcome [29].

Although the longer duration of SE is shown to be associated with increased risk of neurocognitive deficits, prolonged episodes are most often seen in more severe etiologies [19]. In our prospective cohort of 163 pediatric patients with refractory SE who had at least one year of follow-up, a longer duration of SE was identified as the main risk factor for a new neurological deficit on multivariate analysis [30].

3.3. Continuous infusion

The use of continuous infusion (CI) agents intravenously to control SE has been identified as a risk factor for worse outcome, possibly due to associated clinical factors, such as higher risk of infections or hypotension. A cohort of 171 patients were evaluated and the use of CI was associated with a 2.9-fold relative risk of death if they received a CI [31]. In the pediatric age group, it is unclear if the use of CI may play a role in worsening outcome. In our prospective study of 67 patients with pediatric SE who were previously normal prior to their episode of SE, the use of continuous infusions during refractory CSE was associated with worse outcome after adjusting for potential cofounders [32].

3.4. Imaging

MRI abnormalities are often seen in children with SE and are likely related to the underlying etiology of SE. However, MRI changes can be seen in patients with idiopathic SE suggesting that changes are related to the SE itself. Prolonged febrile convulsions can be associated with hippocampal edema within the first 48 h after seizures and asymmetry in the hippocampal volume due to hippocampal sclerosis in later follow-up studies [33]. In the FEBSTAT study [34], 22 of 226 children with febrile SE (9.7%) had abnormal hippocampal signal on their initial MRI. One-hundred thirty patients then had follow-up MRIs at 1 year with only 1 of the initial abnormal hippocampal signal changes persisting suggesting that this is an acute finding. However, 14 of the 22 (71%) with signal abnormality met visual criteria for hippocampal sclerosis on the follow-up MRI. These findings suggest that the initial episode of febrile SE can cause a cascade of events leading to later hippocampal sclerosis. Although more frequently discussed in association with prolonged febrile seizures, the hippocampal volume loss can occur after the CSE of any etiology and is not limited to the febrile etiology. The insult during the CSE episodes is believed to be crucial for the progressive hippocampal injury [35].

Patients with non-febrile CSE had a higher rate of abnormal MRI in the acute setting than those with prolonged febrile convulsion [20]. Abnormal neurological examination, continuous CSE, and non-prolonged febrile SE were shown to be predictive of an abnormal MRI in a study of 80 children with CSE [36]. The preferential white matter involvement on MRI in the aftermath of SE suggests additional glial dysfunction [37]. Increased fluid attenuated inversion recovery (FLAIR) signal associated with CSE has been shown to represent cytotoxic edema caused by the seizure, leading to neuronal damage [38].

While the FEBSTAT study followed patients with febrile status epilepticus, there are few long-term outcome studies that serially follow neuroimaging after symptomatic pediatric status epilepticus. In a recent study of 29 patients diagnosed with febrile infection-related epilepsy syndrome (FIRES), 18/29 (62%) of patients had a normal MRI at initial presentation, while only 3/23 (13%) had a normal follow-up MRI performed within 6 months after disease onset [39]. Imaging findings included brain atrophy and/or signal changes in various brain regions [39]. In addition, there was a suggestion that the extend of periventricular white matter signal change correlated with clinical outcome [39]. In a similar study of seven children with FIRES, most patients had moderate to severe cerebral atrophy after 6–12 months [40]. Most other studies evaluating long-term MRI outcome are case series in adult patients. There is a clear need to perform additional studies to address neuroimaging changes following pediatric status epilepticus.

3.5. Quality of life

Quality of life (QoL) is an increasingly important measure that utilizes a variety of spheres in a person's life to determine the quality of their well-being. While QoL is a very important outcome measure, it has rarely been published in pediatric SE. In a study of QoL in children with epilepsy, using the 76-item parent-report "Quality of Life in Children with Epilepsy" (QOLCE) Questionnaire, children who had experienced CSE were compared with those who did not have CSE, with a follow-up period of 24 months. Health-related QoL was poorer in the CSE group compared to controls [41]. In another study, children with normal neurodevelopment who were admitted to PICU with acute neurologic conditions were assessed after a median follow-up of 2.6 years (IQR: 1.5–3.2 years). The results showed that children who had a history of ESE had lower scores on health-related QoL, as measured by the Pediatric Quality of Life Inventory (PedsQL), compared to patients without seizure, while controlling for the cofactors such as EEG background, neurological disorder, age, and the duration of PICU stay. Of note, patients who had electrographic seizures without proceeding to SE did not score lower on PedsQL compared to patients without seizure [29]. QoL is dependent on many multi-dimensional factors that are hard to quantify individually, but are critically important for determining how health status affects a person's well-being. Future prospective studies evaluating QoL following SE should be undertaken to address this important outcome measure.

4. Future directions

Outcome measures are an important tool to determine effectiveness of therapy, but these are generally only focused on short term outcomes. In additions, there is a significant gap in the literature in terms of long-term outcome assessment in CSE. Research in this area is often hampered due to methodological complexities inherent in these studies, including variations of the instruments and studies, difficulty in obtaining large sample sizes, and the need to collect data in a course of time rather than single time-point measurements. However, there is a need to acquire high-quality long-term data evaluating QoL, neuroimaging, use of continuous infusions, and cognitive and behavioral outcome of children who experience SE. Combining the data on management protocols and long-term outcome could identify treatment strategies that are associated with more favorable outcome. This could permit evidence-based clinical decision-making and could result in an improved quality of care.

For future studies to assess the outcomes of pediatric CSE, prospective multi-centric studies with large sample sizes compared to a control group without SE are required to be able to carefully adjust for the confounding factors, most importantly the underlying etiology. Because there is a complex interplay between different variables and outcome, studies should be designed with carefully selected control groups that match SE patients in every aspect except for SE, to determine the net effect of SE. In addition, objective, valid, and reliable outcome measures should be utilized to obtain high-quality data, and long follow-up periods should be considered to further assess the long-term outcomes. Predictive modeling could be utilized clinically to inform parents and families more accurately about long-term outcome following pediatric status epilepticus.

References

[1] Rosenow F., Hamer HM, Knake S. The epidemiology of convulsive and nonconvulsive status epilepticus. Epilepsia 2007;48(Suppl. 8):82–4.

[2] Lin KL, Lin JJ, Hsia SH, Wu CT, Wang HS. Analysis of convulsive status epilepticus in children of Taiwan. Pediatr Neurol 2009;41(6):413–8.

[3] Ahmad S, Ellis JC, Kamwendo H, Molyneux E. Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomised trial. Lancet 2006;9522:1591–7.

[4] Raspall-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol 2006;5(9):769–79.

[5] Lv RJ, Wang Q, Cui T, Zhu F, Shao XQ. Status epilepticus-related etiology, incidence and mortality: a meta-analysis. Epilepsy 2017;136:12–7.

[6] Pujar SS, Neville BG, Scott RC, Chin RF. Death within 8 years after childhood convulsive status epilepticus: a population-based study. Brain 2011;134(Pt. 10):2819–27.

[7] Verity CM, Ross EM, Golding J. Outcome of childhood status epilepticus and lengthy febrile convulsions: findings of national cohort study. BMJ 1993;307(6898):225–8.

[8] Sadarangani M, Seaton C, Scott JA, Ogutu B, Edwards T, Prins A, et al. Incidence and outcome of convulsive status epilepticus in Kenyan children: a cohort study. Lancet Neurol 2008;7(2):145–50.

[9] Chin RF, Neville BG, Scott RC. A systematic review of the epidemiology of status epilepticus. Eur J Neurol 2004;11(12):800–10.

[10] Logroscino G, Hesdorffer DC, Cascino GD, Annegers JF, Bagiella E, Hauser WA. Long-term mortality after a first episode of status epilepticus. Neurology 2002;58(4):537–41.

[11] Loddenkemper T, Syed TU, Ramgopal S, Gulati D, Thanaviratananich S, Kothare SV, et al. Risk factors associated with death in in-hospital pediatric convulsive status epilepticus. PLoS One 2012;7(10):e47474.

[12] Koubeissi M, Alshekhlee A. In-hospital mortality of generalized convulsive status epilepticus: a large US sample. Neurology 2007;69(9):886–93.

[13] Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet 2006;368(9531):222–9.

[14] Kwong KL, Chang K, Lam SY. Features predicting adverse outcomes of status epilepticus in childhood. Hong Kong Med J 2004;10(3):156–9.

[15] Shinnar S, Pellock JM, Moshe SL, Maytal J, O'Dell C, Driscoll SM, et al. In whom does status epilepticus occur: age-related differences in children. Epilepsia 1997;38(8):907–14.

[16] Aicardi J, Chevrie JJ. Convulsive status epilepticus in infants and children. A study of 239 cases. Epilepsia 1970;11(2):187–97.

[17] Phillips SA, Shanahan RJ. Etiology and mortality of status epilepticus in children. A recent update. Arch.Neurol 1989;46(1):74–6.

[18] Sanchez Fernandez I, Vendrame M, Kapur K, Klehm J, Uysal S, Gedik M, et al. Comparison of pediatric patients with status epilepticus lasting 5–29 min versus >/=30 min. Epilepsy Behav 2014;37:1–6.

[19] Sheppard E, Lippe S. Cognitive outcome of status epilepticus in children. Epilepsy Res Treat 20122012: 984124.

[20] Martinos MM, Yoong M, Patil S, Chong WK, Mardari R, Chin RF, et al. Early developmental outcomes in children following convulsive status epilepticus: a longitudinal study. Epilepsia 2013;54(6):1012–9.

[21] Hesdorffer DC, Logroscino G, Cascino GD, Hauser WA. Recurrence of afebrile status epilepticus in a population-based study in Rochester, Minnesota. Neurology 2007;69(1):73–8.

[22] Pujar SS, Martinos MM, Cortina-Borja M, Chong WKK, De Haan M, Gillberg C, et al. Long-term prognosis after childhood convulsive status epilepticus: a prospective cohort study. Lancet Child Adolesc Health 2017.

[23] Roy H, Lippe S, Lussier F, Sauerwein HC, Lortie A, Sauerwein HC, et al. Developmental outcome after a single episode of status epilepticus. Epilepsy Behav 2011;21(4):430–6.

[24] Lacroix J, Deal C, Gauthier M, Rousseau E, Farrell CA. Admissions to a pediatric intensive care unit for status epilepticus: a 10-year experience. Crit Care Med. 1994;22(5):827–32.

[25] Maytal J, Shinnar S. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83(3):323–31.

[26] Power KN, Gramstad A, Gilhus NE. Cognitive function after status epilepticus versus after multiple generalized tonic-clonic seizures. Epilepsy Res 2017;140:39–45.

[27] Shinnar S, Pellock JM, Berg AT, O'Dell C, Driscoll SM, Maytal J, et al. Short-term outcomes of children with febrile status epilepticus. Epilepsia 2001;42(1):47–53.

[28] Yager JY, Cheang M, Seshia SS. Status epilepticus in children. Can J Neurol Sci 1988;15(4):402–5.

[29] Wagenman KL, Blake TP, Sanchez SM, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and long-term outcome in critically ill children. Neurology 2014;82(5):396–404.

[30] Piantino JA, Gaínza-Lein M, Chapman K, Anderson A, Arya R, et al. Long-term outcomes in pediatric refractory status epilepsy (The PSERG cohort). American Epilepsy Society Annual Meeting. .

[31] Sutter R, Marsch S, Fuhr P, Kaplan PW, Ruegg S. Anesthetic drugs in status epilepticus: risk or rescue? A 6-year cohort study. Neurology 2014;82(8):656–64.

[32] Sheehan T, Gainza-Lein M, Chapman K, Piantino JA, Anderson A, et al. Long-term outcomes in previously healthy children after refractory status epilepticus (The PSERG cohort). American Epilepsy Society Annual Meeting. .

[33] Novorol CL, Chin RF, Scott RC. Outcome of convulsive status epilepticus: a review. Arch Dis Child 2007;92(11):948–51.

[34] Lewis DV, Shinnar S, Hesdorffer DC, Bagiella E, Bello JA, Chan S, et al. Hippocampal sclerosis after febrile status epilepticus: the FEBSTAT study. Ann Neurol 2014;75(2):178–85.
[35] Yoong M, Martinos MM, Chin RF, Clark CA, Scott RC. Hippocampal volume loss following childhood convulsive status epilepticus is not limited to prolonged febrile seizures. Epilepsia 2013;54(12):2108–15.
[36] Yoong M, Madari R, Martinos M, Clark C, Chong K, Neville B, et al. The role of magnetic resonance imaging in the follow-up of children with convulsive status epilepticus. Dev Med Child Neurol 2012;54(4):328–33.
[37] Okamoto R, Fujii S, Inoue T, Lei K, Kondo A, Hirata T, et al. Biphasic clinical course and early white matter abnormalities may be indicators of neurological sequelae after status epilepticus in children. Neuropediatrics 2006;37(1):32–41.
[38] Sirven JI, Zimmerman RS, Carter JL, Drazkowski JF, Larson JS. MRI changes in status epilepticus. Neurology 200360(11) p. 1866.
[39] Lee HF, Chi CS. Febrile infection-related epilepsy syndrome (FIRES): therapeutic complications, long-term neurological and neuroimaging follow-up. Seizure 2018;56:53–9.
[40] Rivas-Coppola MS, Shah N, Choudhri AF, Morgan R, Wheless JW. Chronological evolution of magnetic resonance imaging findings in children with febrile infection-related epilepsy syndrome. Pediatr Neurol 2016;55:22–9.
[41] Ferro MA. Risk factors for health-related quality of life in children with epilepsy: a meta-analysis. Epilepsia 2014;55(11):1722–31.
[42] Hommady RH, Alrifai MT, Mubayrik OK, Alayed RS, Alsemari MA, Arumayyan A, et al. Retrospective review of pediatric status epilepticus in 116 Saudi patients: predictors of outcome. Ann Saudi Med 2017;37(6):455–60.
[43] Santhanam I, Yoganathan S, Sivakumar VA, Ramakrishnamurugan R, Sathish S, et al. Predictors of outcome in children with status epilepticus during resuscitation in pediatric emergency department: a retrospective observational study. Ann Indian Acad Neurol 2017;20(2):142–8.
[44] Hassan H, Rajiv KR, Menon R, Menon D, Nair M, Radhakrishnan A. An audit of the predictors of outcome in status epilepticus from a resource-poor country: a comparison with developed countries. Epileptic Disord 2016;18(2):163–72.
[45] Prins A, Chengo E. Long-term survival and outcome in children admitted to kilifi district hospital with convulsive status epilepticus. Epilepsy Res Treat 20142014: p643747.
[46] Jayalakshmi S, Ruikar D, Vooturi S, Alladi S, Sahu S, Kaul S, et al. Determinants and predictors of outcome in super refractory status epilepticus–a developing country perspective. Epilepsy Res 2014;108(9):1609–17.
[47] Bhalla A, Das B, Som R, Prabhakar S, Kharbanda PS. Status epilepticus: our experience in a tertiary care centre in Northwestern India. J Emerg Trauma Shock 2014;7(1):9–13.
[48] Shatirishvili T, Tatishvili N, Lomidze G, Kipiani T. Etiology as a predictor of morbidity after convulsive status epilepticus in children. Georgian Med News 2014;231:60–3.
[49] Molinero MR, Holden KR, Rodriguez LC, Collins JS, Samra JA, Shinnar S, et al. Pediatric convulsive status epilepticus in Honduras: central america. Epilepsia 2009;50(10):2314–9.
[50] Mpimbaza A, Ndeezi G, Staedke S, Rosenthal PJ, Byarugaba J. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. Pediatrics 2008;121(1):e58–64.
[51] Siddiqui TS, uR Rehman Anis, Jan MA, Wazeer MS, Burki MK. Status epilepticus: aetiology and outcome in children. J Ayub Med Coll Abbottabad 2008;20(3):51–3.
[52] Hayashi K, Osawa M, Aihara M, Izumi T, Ohtsuka Y, et al. Efficacy of intravenous midazolam for status epilepticus in childhood. Pediatr Neurol 2007;36(6):366–72.
[53] Muchohi SN, Obiero K, Newton CR, Ogutu BR, Edwards G, Kokwaro GO. Pharmacokinetics and clinical efficacy of lorazepam in children with severe malaria and convulsions. Br J Clin Pharmacol 2008;65(1):12–21.
[54] Ahmad S, Ellis JC, Kamwendo H, Molyneux E. Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomised trial. Lancet 2006;367(9522):1591–7.
[55] Morrison G, Gibbons E, Whitehouse WP. High-dose midazolam therapy for refractory status epilepticus in children. Intensive Care Med 2006;32(12):2070–6.
[56] Maegaki Y, Kurozawa Y, Hanaki K, Ohno K. Risk factors for fatality and neurological sequelae after status epilepticus in children. Neuropediatrics 2005;36(3):186–92.
[57] Kang DC, Lee YM, Lee J, Kim HD, Coe C. Prognostic factors of status epilepticus in children. Yonsei Med J 2005;46(1):27–33.
[58] Asadi-Pooya AA, Poordast A. Etiologies and outcomes of status epilepticus in children. Epilepsy Behav 2005;7(3):502–5.
[59] Brevoord JC, Joosten KF, Arts WF, van Rooij RW, de Hoog M. Status epilepticus: clinical analysis of a treatment protocol based on midazolam and phenytoin. J Child Neurol 2005;20(6):476–81.
[60] Gulati S, Kalra V, Sridhar MR. Status epilepticus in Indian children in a tertiary care center. Indian J Pediatr 2005;72(2):105–8.
[61] Berg AT, Shinnar S, Testa FM, Levy SR, Frobish D, Smith SN, et al. Status epilepticus after the initial diagnosis of epilepsy in children. Neurology 2004;63(6):1027–34.
[62] Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology 2002;58(7):1070–6.
[63] Koul R, Chacko A, Javed H, Al Riyami K. Eight-year study of childhood status epilepticus: midazolam infusion in management and outcome. J Child Neurol 2002;17(12):908–10.
[64] Sillanpaa M, Shinnar S. Status epilepticus in a population-based cohort with childhood-onset epilepsy in Finland. Ann.Neurol 2002;52(3):303–10.
[65] Singhi S, Murthy A, Singhi P, Jayashree M. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. J Child Neurol 2002;17(2):106–10.
[66] Tabarki B, Yacoub M, Selmi H, Oubich F, Barsaoui S, et al. Infantile status epilepticus in Tunisia. Clinical: etiological and prognostic aspects. Seizure 2001;10(5):365–9.
[67] Kim SJ, Lee DY, Kim JS. Neurologic outcomes of pediatric epileptic patients with pentobarbital coma. Pediatr Neurol 2001;25(3):217–20.
[68] Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. Epilepsia 2001;42(11):1461–7.
[69] DeLorenzo RJ, Garnett LK, Towne AR, Waterhouse EJ, Boggs JG, Morton L, et al. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. Epilepsia 1999;40(2):164–9.
[70] Mah JK, Mah MW. Pediatric status epilepticus: a perspective from Saudi Arabia. Pediatr Neurol 1999;20(5):364–9.
[71] Barnard C, Wirrell E. Does status epilepticus in children cause developmental deterioration and exacerbation of epilepsy? J Child Neurol 1999;14(12):787–94.
[72] Waterhouse EJ, Garnett LK, Towne AR, Morton LD, Barnes T, Ko D, et al. Prospective population-based study of intermittent and continuous convulsive status epilepticus in Richmond, Virginia. Epilepsia 1999;40(6):752–8.
[73] Eriksson KJ, Koivikko MJ. Status epilepticus in children: aetiology, treatment, and outcome. Dev Med Child Neurol 1997;39(10):652–8.
[74] Scholtes FB, Renier WO, Meinardi H. Status epilepticus in children. Seizure 1996;5(3):177–84.
[75] Lacroix J, Deal C, Gauthier M, Rousseau E, Farrell CA. Admissions to a pediatric intensive care unit for status epilepticus: a 10-year experience. Crit Care Med 1994;22(5):827–32.
[76] Shinnar S, Maytal J, Krasnoff L, Moshe SL. Recurrent status epilepticus in children. Ann Neurol 1992;31(6):598–604.
[77] DeLorenzo RJ, Towne AR, Pellock JM, Ko D. Status epilepticus in children, adults, and the elderly. Epilepsia 1992;33(Suppl. 4):S15–25.
[78] Dunn DW. Status epilepticus in children: etiology, clinical features, and outcome. J Child Neurol 1988;3(3):167–73.
[79] Cavazzuti GB, Ferrari P, Lalla M. Follow-up study of 482 cases with convulsive disorders in the first year of life. Dev Med Child Neurol 1984;26(4):425–37.
[80] Chevrie JJ, Aicardi J. Convulsive disorders in the first year of life: neurological and mental outcome and mortality. Epilepsia 1978;19(1):67–74.
[81] Aicardi J, Chevrie JJ. Convulsive status epilepticus in infants and children. A study of 239 cases. Epilepsia 1970;11(2):187–97.
[82] Atmaca MM, Bebek N, Baykan B, Gokyigit A, Gurses C. Predictors of outcomes and refractoriness in status epilepticus: a prospective study. Epilepsy Behav 2017;75:158–64.
[83] Reddy Y, Balakrishna Y, Mubaiwa L. Convulsive status epilepticus in a quaternary hospital paediatric intensive care unit (PICU) in South Africa: an 8 year review. Seizure 2017;51:55–60.
[84] Abend NS, Wagenman KL, Blake TP, Schultheis MT, Radcliffe J, Berg RA, et al. Electrographic status epilepticus and neurobehavioral outcomes in critically ill children. Epilepsy Behav 2015.
[85] Saz EU, Karapinar B, Ozcetin M, Polat M, Tosun A, Serdaroglu G, et al. Convulsive status epilepticus in children: etiology, treatment protocol and outcome. Seizure 2011;20(2):115–8.
[86] Pisani F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus vs recurrent neonatal seizures: clinical findings and outcome. Neurology 2007;69(23):2177–85.