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Original Research Article

Predictors of status epilepticus duration and short-term outcome in Bulgarian patients treated in a neuro-intensive care unit

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Abstract

Our purpose was to identify predictors of SE duration and short-term outcome. We performed a prospective study of 95 consecutive patients diagnosed with SE and treated in a neuro-intensive care unit over a period of 3 years. Demographics and clinical data concerning established epilepsy and SE were collected and their relationship to SE duration and short-term outcome was analyzed. The predictive role of non-convulsive SE type, SE treatment with polytherapy, and prior epilepsy with polymorphic seizures for longer SE duration was confirmed on multivariate analysis P < 0.001 (F = 10.89). The longer duration of prior epilepsy and SE proved to be predictors of the rate of recurrent seizures P < 0.001 (F = 14.52). The 1unfavourable functional outcome correlated with older age, existing neurological abnormalities, mental retardation, prior symptomatic epilepsy, remote symptomatic etiology of SE, non-convulsive SE, and longer duration of SE. Existing neurological abnormalities, mental retardation, SE etiology and duration were confirmed as functional recovery predictors on multivariate analysis P < 0.001 (F = 16.70). The study confirms the predictive value of some clinical factors for SE duration and short-term outcome. Our results are useful for finding more successful strategies in SE management.

Keywords: Duration, outcome, predictor, recurrent seizures, status epilepticus

INTRODUCTION

Status Epilepticus (SE) is a life-threatening condition of ongoing or repetitive seizures which carries high mortality and severe disability. In cases with refractory SE seizures do not respond to first and second line antiepileptic drugs and usually last for more than 60 minutes.

A number of studies have focused attention on various aspects of SE – epidemiology, clinical characteristics, and outcome. The latter has been usually characterized by functional recovery, neurological consequences, and mortality. The rate of seizure recurrence is another important aspect of short-term outcome, which has received scarce attention by few studies (Besli et al., 2010; Kravljanac et al., 2011; Tsetsou et al., 2015). The risk factors and predictive role of seizure recurrence for the other outcome aspects have not been verified yet.

The significance of SE preventative strategies development motivated many investigators in their efforts to identify predictors of refractory SE (Agan et al., 2009; Mayer et al., 2002; Murthy et al., 2007; Novy et al., 2010; Rossetti et al., 2006; Sutter et al., 2015; Towne, 2007; Tsetsou et al., 2015) and SE outcome (Chen et al., 2009; Chin et al., 2004; Drislane et al., 2009; Hocker et al., 2013; Holtkamp et al., 2005; Holtkamp et al., 2005; Hui et al., 2003; Hui et al., 2005; Joyalakshmi et al., 2014; Kang et al., 2014; Kravljanac et al., 2011; Kumar et al., 2014; Lambrechtsen and Buchhalter, 2008; Murthy et al., 2007; Rossetti et al., 2006; Towne, 2007; Vooturi et al., 2014). The predictive role of SE duration for outcome has been supported by lots of studies (Drislane et al., 2009; Holtkamp et al., 2005; Holtkamp et al., 2005; Kumar et

al., 2014; Lambrechtsen and Buchhalter, 2008; Murthy et al., 2007; Towne, 2007), although the risk factors for longer duration of SE appeared to receive little attention. Predictors of outcome have been also sought among age, gender, SE etiology and type, comorbidity, pre-existing neurological abnormalities, timeliness of SE diagnosis and treatment, and EEG findings. Female gender (Koubeissi and Alshekhlee, 2007; Murthy et al., 2007), delayed treatment (Hui et al., 2003) and diagnosis (Drislane et al., 2009), lack of response to first-line antiepileptic drugs (Murthy et al., 2007), acute symptomatic comorbidity (Chen et al., 2009; Hocker et al., 2013; Koubeissi and Alshekhlee, 2007), specific EEG findings (Hocker et al., 2013; Kravljanac et al., 2011), and 2nfavourable neurological abnormalities (Kravljanac et al., 2011) have been described to predict poor SE outcome. The 2nfavourable effect of other variables (etiology, age, SE type) is controversial (Kravljanac et al., 2011; Lambrechtsen and Buchhalter, 2008; Rossetti et al., 2006).

The abovementioned gaps and contradictions in the current knowledge about SE duration and outcome predictors were a starting point for our study. No similar study has been performed in Bulgaria.

Purpose

Our purpose was to identify predictors of SE duration and short-term outcome in patients treated in a neuro-intensive care unit.

METHODS

All study procedures were performed after the approval of the Local Ethics Commission at the Medical University – Plovdiv. All patients or their relatives were introduced to the study design and signed an informed consent form before participation in the study procedures.

The study included 95 consecutive patients aged 18 years and above, diagnosed with SE, and treated in the neuro-intensive care unit at the University Hospital in Plovdiv, Bulgaria over a period of 3 years. We defined status epilepticus as an epileptic state of a prolonged seizure (lasting for more than 5 minutes) or repeating seizures without gaining consciousness between them. Demographics (age, gender) and clinical data concerning established epilepsy (duration, etiology, epilepsy type, seizure type, antiepileptic drugs type and serum level), mental retardation, existing neurological abnormalities, and SE (type, etiology, trigger factor, antiepileptic drugs for SE treatment, recurrent SE experience, EEG findings after SE management) were collected by a trained health professional by means of a purposeful interview of a reliable patient's relative or attendant and review of patients' medical records. During hospitalization patients were monitored by a neurologist who is a specialist in epilepsy.

The relationship of the abovementioned characteristics to SE duration and short-term outcome was analyzed. SE short-term outcome assessment was based on the rate of recurrent seizures during hospitalization (single seizures, seizure clusters and/or status epilepticus) and functional recovery according to the Glasgow Outcome Scale results. We accepted 4 main types of SE etiology: 1. Idiopathic – in cases with absence of acute precipitating central nervous system insult or systemic metabolic dysfunction; 2. Remote symptomatic – in cases without acute provocation, but with a prior history of central nervous system insult known to be associated with increased risk for convulsions, e.g. stroke, head trauma, meningitis, static encephalopathy; 3. Acute symptomatic – during an acute illness (stroke, encephalitis, head trauma, electrolyte imbalance); 4. Progressive encephalopathy – during a progressive neurological disease (malignancies, neurodegenerative diseases) (Kumar et al., 2014).

The Glasgow Outcome Scale was used to assess objectively the functional recovery of patients with brain injury in five categories: 1. Death; 2. Persistent vegetative state (no obvious cortical function); 3. Severe disability (permanent need for help in daily living); 4. Moderate disability (no need for assistance in everyday life, employment is possible but may require special equipment); 5. Good recovery and resumption of normal activities (26).

Data were processed using STATA version 10 (Stata Corp., College Station, TX, USA) and SPSS (Statistical Package for the Social Sciences) version 14.0 (SPSS Inc., Chicago, IL, USA). The results for quantitative variables were expressed as means ± SE (standard error) and the results for qualitative variables as percentages. The association of SE duration and short-term outcome with demographics and clinical findings was tested by means of $\chi 2$-tests and F-tests. The predictive role of the significant demographics and clinical findings was determined by multivariate regression analysis. The level of significance was set at $P < 0.05$.

RESULTS

In our study fifty-one (53.68%) of participants were men, 44 participants (46.32%) were women. Their mean age was 50.32 ± 1.72 years. Most patients (53.68%) were above 50 years of age. The clinical findings concerning established epilepsy and SE of the participants are shown in Table 1 and Table 2.

There was a history of learning disability or other type of retardation in 13 (13.68%) patients. Preexisting neurological abnormalities had been described in 42 (44.21%) of study participants.

The most common causes of SE with remote sympto-

Table 1. Clinical findings concerning established epilepsy of the study participants

Clinical findings concerning established epilepsy	n	P (%)	SE
Epilepsy duration			
- epilepsy start	22	23.16	4.35
- ≤ 10 years	37	38.95	5.03
- > 10 years	36	37.89	5.00
Etiology of epilepsy			
- idiopathic	9	9.47	3.02
- symptomatic	56	58.95	5.07
- cryptogenic	30	31.58	4.79
Epilepsy type			
- partial	42	44.21	5.12
- generalized	53	55.79	5.12
Seizure type			
- partial	11	11.58	3.30
- generalized	51	53.68	5.14
- polymorphic	33	34.74	4.91
AEDs for epilepsy treatment			
- monotherapy	32	33.69	4.88
- a combination of 2 AEDs	13	13.68	3.54
- ≥ 3 AEDs	11	11.58	3.30
- untreated	17	17.89	3.95
- NA (epilepsy start)	22	23.16	4.35
AEDs' serum levels			
- in therapeutic range	23	24.21	4.42
- in subtherapeutic range	17	17.89	3.95
- unknown	15	15.79	3.76
- NA (epilepsy start or AEDs cannot be routinely investigated)	40	42.11	5.09

* NA – Not Applicable; n – number; P(%) – percentage

Table 2. Clinical findings concerning SE of the study participants

	n	P (%)	SE
SE type			
- non-convulsive	21	22.11	4.28
- convulsive	74	77.89	4.28
SE etiology			
- idiopathic	34	35.79	4.94
- remote symptomatic	45	47.37	5.15
- acute symptomatic	8	8.42	8.20
- progressive encephalopathy	8	8.42	8.20
SE trigger factor			
- poor compliance	28	29.48	4.70
- metabolic/electrolyte disorder	9	9.47	3.02
- ischemia	3	3.16	-
- alcohol	11	11.58	3.30
- inadequate treatment	7	7.37	2.69
- insomnia	1	1.05	-
- unknown	36	37.89	5.00
AEDs for SE treatment			
- Diazepam i.v.	52	54.74	5.13
- Phenobarbital i.m.	4	4.21	-
- a combination of AEDs	39	41.05	5.12
ES duration			
- < 60 min.	70	73.69	4.54
- 60 min. – 24 hours	20	21.05	4.20
- > 24 hours	5	5.26	2.30
Recurrent SE			
- yes	9	9.47	3.02
- no	64	67.37	4.84
- epilepsy start	22	23.16	4.35

Table 2. Continue

EEG after SE management			
- normal	48	50.53	5.16
- non-specific findings	24	25.26	4.48
- specific findings	23	24.21	4.42
GOS			
- dead	5	5.26	2.30
- persistent vegetative state	-	-	-
- severe disability	9	9.47	3.02
- moderate disability	24	25.26	4.48
- good recovery and resumption of normal activities	57	60.00	5.05
Recurrent seizures			
- no	54	56.84	5.11
- single seizures	26	27.37	4.60
- clusters/SE	15	15.79	3.76

*n – number; P(%) - percentage

Table 3. Results from multivariate regression analysis of the predictors of SE duration

Factor	B-coefficients	P	95% CI
SE treatment	0.331	0.001	0.057 ÷ 0.201
SE type	-0.293	0.005	-0.678 ÷ -0.123
Seizure type	0.306	0.004	0.059 ÷ 0.293
Constant	-0.081	0.645	-0.429 ÷ 0.267

matic etiology were: vascular disease (in 55.56%), cranial trauma (in 15.56%), and tumor (in 13.33%). The most common cause of acute symptomatic SE was electrolyte and/or metabolic disorder (in 75%). Most patients (87.5%) with progressive encephalopathy as SE etiology were with alcohol abuse.

We found no association between SE duration and demographics, epilepsy duration, etiology, antiepileptic drugs type and serum level, mental retardation, existing neurological abnormalities, SE etiology, trigger factor, and experience of previous SE ($P > 0.05$). The longer SE duration was more frequent in cases with non-convulsive SE ($\chi2 = 6.31$, $P < 0.01$), SE polytherapy ($\chi2 = 13.78$, $P < 0.001$), abnormal EEG findings after SE management ($\chi2 = 6.90$, $P < 0.05$), prior partial epilepsy ($\chi2 = 7.79$, $P < 0.01$) with polymorphic seizures ($\chi2 = 13.94$, $P < 0.001$). Of those with SE duration longer than 60 minutes, in 18 (72%) patients SE was treated with a combination of antiepileptic drugs, 16 (64%) participants had a history of prior epilepsy with polymorphic seizures, 17 (68%) had established partial epilepsy, in 18 (72%) patients specific or non-specific abnormal EEG findings following SE management were described. Ten (47.6%) participants with non-convulsive SE suffered SE longer than 60 minutes compared to 15 (20.3%) of those with convulsive SE. The predictive role of SE type, SE treatment, and prior epilepsy seizure type for SE duration was confirmed on multivariate analysis $P < 0.001$ ($F = 10.89$) – Table 3.

We found no association between the rate of seizure recurrence and demographics, epilepsy etiology, epilepsy type, mental retardation, existing neurological abnormalities, and SE type, etiology, and EEG findings after SE management ($P > 0.05$). The rate of seizure recurrence was significantly higher in participants with longer duration of prior epilepsy ($\chi2 = 9.62$, $P < 0.05$) and SE ($\chi2 = 15.33$, $P < 0.001$), SE polytherapy ($\chi2 = 10.77$, $P < 0.05$), recurrent SE episodes ($\chi2 = 15.58$, $P < 0.01$), established epilepsy with polymorphic seizures ($\chi2 = 9.54$, $P < 0.05$), poor compliance and inadequate antiepileptic treatment ($\chi2 = 9.85$, $P < 0.05$). Of those who experienced recurrent clusters of seizures or/and SE following SE, 10 (66.7%) suffered SE longer than 60 minutes, 10 (66.7%) had a previous history of epilepsy longer than 10 years, in 10 (66.7%) patients SE was treated with a combination of antiepileptic drugs, 10 (66.7%) had established epilepsy with polymorphic seizures, 9 (60%) were with poor compliance or an inadequate treatment as a trigger factor. There were recurrent seizures in 5 (55.6%) participants with recurrent SE. On multivariate regression analysis the predictive role of prior epilepsy duration and SE duration for seizure recurrence was confirmed $P < 0.001$ ($F = 14.52$) – Table 4.

We found no association between the functional outcome and gender, epilepsy duration, epilepsy and seizure type, antiepileptic drugs type and serum level, SE trigger factor, antiepileptic drugs for SE treatment,

Table 4. Results from multivariate regression analysis of recurrent seizures' predictors

Factor	B-coefficients	P	95% CI
SE duration	0.318	0.001	0.220 ÷ 0.860
Prior epilepsy duration	0.255	0.009	0.065 ÷ -0.432
Constant	0.163	0.208	-0.092 ÷ 0.417

Table 5. Results from multivariate regression analysis of the predictors of SE functional outcome

Factor	B-coefficients	P	95% CI
Existing neurological abnormalities	-0.349	0.000	-1.072 ÷ -0.373
SE duration	-0.344	0.000	-1.187 ÷ -0.432
SE etiology	-0.277	0.008	-0.574 ÷ -0.088
Mental retardation	-0.225	0.009	-1.163 ÷ -0.174
Constant	5.222	0.000	4.934 ÷ 5.511

recurrent SE experience, and EEG findings after SE management ($P > 0.05$). The unfavorable functional outcome correlated with older age ($\chi2 = 17.73$, $P < 0.001$), existing neurological abnormalities ($\chi2 = 25.61$, $P < 0.001$), mental retardation ($\chi2 = 12.04$, $P < 0.01$), prior symptomatic epilepsy ($\chi2 = 14.21$, $P < 0.01$), remote symptomatic etiology of SE ($\chi2 = 17.80$, $P < 0.001$), non-convulsive SE ($\chi2 = 6.35$, $P < 0.05$), and longer duration of SE ($\chi2 = 8.33$, $P < 0.05$). Of those who died or were severely disabled, 8 (57.1%) patients suffered SE longer than 60 minutes, 11 (78.57%) were older than 50 years, 13 (92.86%) had focal neurological signs before SE, 12 (85.71%) were with prior symptomatic epilepsy, 11 (78.57%) were with remote symptomatic etiology of SE. Nine (69.3%) patients with mental retardation and 13 (61.9%) of those with non-convulsive SE died or were severely/moderately disabled after SE management. Existing neurological abnormalities, mental retardation, SE etiology and duration were confirmed as functional recovery predictors on multivariate analysis $P < 0.001$ ($F = 16.70$) – Table 5.

DISCUSSION

Recent studies (Chen et al., 2009; Drislane et al., 2009; Holtkamp et al., 2005; Holtkamp et al., 2005; Kravljanac et al., 2011; Kumar et al., 2014; Lambrechtsen and Buchhalter, 2008; Murthy et al., 2007; Towne, 2007), as well as our study results, have demonstrated the undoubted negative predictive value of longer SE duration for outcome. Therefore, determinants of SE duration require extensive attention. Variables found to be significantly associated with SE duration on univariate analysis in our study were: non-convulsive SE, SE polytherapy, abnormal EEG findings after SE management, and prior partial epilepsy with polymorphic seizures. The predictive role of SE type, SE treatment, and prior epilepsy seizure type was confirmed on multivariate analysis. The predictive value of this model was 26%. We identified no other study results concerning SE duration determinants.

The rate of seizure recurrence is a rarely discussed aspect of SE outcome. The reported recurrence rate in children treated in the intensive care unit was 21% (Kravljanac et al., 2011), which was much lower compared to our study (43.6%). According to our study results the rate of seizure recurrence during hospitalization was significantly higher in participants with longer duration of prior epilepsy and SE, SE polytherapy, recurrent SE, established epilepsy with polymorphic seizures, poor compliance, and inadequate antiepileptic treatment. On multivariate regression analysis the predictive role of prior epilepsy duration and SE duration for seizure recurrence was confirmed. The predictive value of this model was 24%. In literature little attention has been directed to seizure recurrence rate as a part of SE short-term outcome and its predictors. A possible explanation for this phenomenon is the priority interest of investigators in functional outcome and the conception that recurrent seizures might not be necessarily associated with SE, but a manifestation of prior epilepsy. We found 2 studies investigating risk factors for seizure recurrence rate as an aspect of SE long-term outcome. Besli et al. (2010) have identified a significantly higher rate of seizure recurrence for a period of 6 to 18 months in cases with existing neurological abnormalities, prior epilepsy, and seizures with remote symptomatic causes (2). Tsetsou et al. (2015) provided evidence about the independent association of cumulative recurrence risk of SE over a period of 4 years with chronic etiology and female gender (Tsetsou et al., 2015).

Outcome is one of the most popular topics concerning

SE. Apart from SE duration, researchers have reported the role of lots of other determinants. Most investigators emphasize the role of acute symptomatic etiology for poor SE outcome, encephalitis and stroke being the most frequent cause (Holtkamp et al., 2005; Holtkamp et al., 2005; Hui et al., 2003; Hui et al., 2005; Joyalakshmi et al., 2014; Kang et al., 2014; Kumar et al., 2014; Lambrechtsen and Buchhalter, 2008; Murthy et al., 2007; Tsetsou et al., 2015; Vooturi et al., 2014). Kravljanac et al. (2011) have described the significance of progressive encephalopathy (Kravljanac et al., 2011), whereas our study confirmed the association of remote symptomatic etiology with unfavorable SE functional outcome. Our study results concerning the negative predictive value of preexisting neurological abnormalities and prior epilepsy are in conformity with the findings of Kravljanac et al. (2011) and Chen at al. (2009). There is no consensus which SE type is associated with poor outcome – some investigators have accepted convulsive SE as more unfavorable (Kravljanac et al., 2011), while others – non-convulsive type (Lambrechtsen and Buchhalter, 2008). The latter statement was supported by our study results. Regarding age, data in literature are also controversial. Our study results correspond to those of Rossetti et al. (2006) and Hui et al. (2003) about the unfavorable influence of older age. Kravljanac et al. (2011) and Lambrechtsen et al. (2008) have come to the conclusion that younger age is associated with poorer SE outcome. We have found no literature data about the predictive value of prior epilepsy etiology and mental retardation. Existing neurological abnormalities, mental retardation, SE etiology and duration were confirmed as functional recovery predictors on multivariate analysis in our study. The predictive value of this model was 43%.

The predictive value of other variables has also been reported in literature: coma/stupor (Kravljanac et al., 2011; Novy et al., 2010; Rossetti et al., 2006; Sutter et al., 2015), acidosis (Joyalakshmi et al., 2014), low sodium blood level (Murthy et al., 2007), respiratory depression (Chen et al., 2009) and prolonged mechanical ventilation (Hocker et al., 2013), higher comorbidity index (Hocker et al., 2013; Koubeissi and Alshekhlee, 2007), delay in treatment (Hui et al., 2003), later diagnosis of epilepsy (Drislane et al., 2009), female gender (Koubeissi and Alshekhlee, 2007; Murthy et al., 2007), abnormal EEG findings – either specific (Kravljanac et al., 2011), or non-specific ones (Hocker et al., 2013; Hui et al., 2005; Kumar et al., 2014). Our study results did not support their correlation with SE unfavorable outcome.

CONCLUSION

In conclusion, the most significant predictors of SE duration and short-term outcome are: prior epilepsy seizure type and duration, pre-existing neurological abnormalities, mental retardation, and some SE characteristics (etiology, type, duration, and treatment). Unfortunately, some of them are unchangeable. Nevertheless, enhancing the knowledge about all predictors of SE duration and short-term outcome will be helpful in the efforts to improve the outcome of patients with SE.

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