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Evaluation of Aetiological Causes, Clinical Features, Treatment and Prognosis in Patients Diagnosed with and Treated for Status Epilepticus: An Epidemiological Study

B ***Gürbüz***, F ***Gürbüz***, A ***Cayır***, A ***Değerliyurt***, A ***Güven***, G ***Köse***

Abstract Due to its high levels of morbidity and mortality, status epilepticus is an important paediatric emergency condition. The purpose of this study was to determine aetiological causes in patients diagnosed with and treated for status epilepticus in our hospital, to assess these patients in terms of clinical features, treatment and prognosis and to establish the efficacy of drugs used in treatment. One hundred sixty-two patients diagnosed with status epilepticus and aged 0-18 years were included. Generalised seizure was the most common form at 85.2%. In terms of aetiology, 59 patients (36.4%) were acute symptomatic, 40 (24.7%) febrile, 23 (14.2%) chronic symptomatic and 9 (5.6%) progressive. In conclusion, concluding the seizure in as short a time as possible with early, aggressive and appropriate treatment in cases of SE and the prevention of probable complication if seizures are prolonged is important in terms of reducing probable morbidity and mortality levels.

Key words Child; Seizure; Status epilepticus

Introduction

Status epilepticus (SE) refers to single epileptic seizure activity lasting 30 minutes or more or two or more seizures in series without the patient regaining consciousness between them.[1,2] SE is a neurological emergency frequently seen in children with an approximate incidence of 18-20 per 100,000 children per year.[3] SE may result in high levels of morbidity and mortality. As with epilepsy, the causes of status vary. It may appear following acute brain damage or in the form of epilepsy findings. SE needs to be diagnosed and treated quickly due to its life-threatening nature and since it may lead to serious sequelae.[1-3]

Central nervous system infections, electrolyte disorders, head traumas, acute and chronic encephalopathies and idiopathic seizures, (febrile or afebrile) are the most common causes in children. Appropriate treatment must be initiated in the early period in SE. Seizure duration is known to be prolonged if treatment is delayed, while the risk of morbidity and mortality increase. An urgent approach to treatment and concurrent appropriate drug use are important. Tests aimed at identifying the aetiology should also be performed.[1-5]

The purpose of this study was to determine aetiological causes in patients diagnosed with and treated for SE in our hospital, to assess these in terms of clinical features, treatment and prognosis and to establish the efficacy of drugs used in treatment.

Department of Pediatry, Ankara Children's Health and Diseases, Hematology-Oncology Hospital, Ankara, Turkey
B **Gürbüz** *MD*
F **Gürbüz** *MD*

Department of Pediatrics, Region Training and Research Hospital, Erzurum, Turkey
A **Cayır** *MD*

Department of Pediatric Neurology, Ankara Children's Health and Diseases, Hematology-Oncology Hospital, Ankara, Turkey
A **Değerliyurt** *MD*
A **Güven** *MD*
G **Köse** *MD*

Correspondence to: Dr F **Gürbüz**

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Materials and Methods

This retrospective study involved 162 paediatric patients aged 0-18 diagnosed with and treated for SE between December 2006 and May 2009. The medical records of 11,565 patients presenting with seizures between these dates were examined from hospital computer database recorded as seizure diagnosis. For each patient, the records were available in the type of seizure. Epileptic seizure of any type exceeding 30 minutes or seizures recurring too rapidly to permit neurological improvement were regarded as SE, and seizures not meeting that description were excluded from the study.[6,7]

Patient age, sex, seizure control durations, aetiological factors, drugs used in treatment, magnetic resonance imaging or computerised tomography of the brain findings, EEG findings and prognoses were recorded during the study.

Classification of SE was performed according to the new ILAE classification updated in 2001 and based on type of seizure and aetiology.[8]

Cases were classified as generalised SE (GSE) or focal SE (FSE) depending on type of seizure and as febrile SE, acute symptomatic SE, chronic status encephalopathy and idiopathic SE depending on aetiology. Seizure lasting >30 minutes associated with fever due to a cause other than central nervous system infection in a child with no previous history of afebrile seizure was regarded as febrile SE. SE in which no cause that might give rise to seizure was identified in a neurologically normal child was regarded as idiopathic. SE developing with no other acute cause in a child with neurological compromise was regarded as chronic symptomatic SE. SE emerging during diseases leading to acute neurological injury, such as bacterial meningitis, encephalitis, hypoxia or cerebrovascular diseases or during metabolic defect was regarded as acute symptomatic SE. SE appearing during the course of progressive neurodegenerative diseases such as subacute sclerosing panencephalitis, neuronal ceroid lipofuscinosis, or mitochondrial diseases was defined as progressive encephalopathic SE. Patients with seizures still lasting longer than 60 minutes despite starting SE treatment were regarded as resistant SE. Medical file investigation and individual patient examination were performed for patient monitoring. Patients unable to attend check-up were telephoned to ascertain their status.

Statistical Analysis

Data analysis was performed on SPSS 15.0 software. Descriptive statistics were expressed as mean ± standard deviation, number and percentage (%). The chi square, Fisher's exact or Pearson's chi square tests were used to examine whether variables had significant effects, depending on the patient. Means were compared between groups using the Mann-Whitney test and Kruskal-Wallis test. $P<0.05$ was regarded as significant.

Results

Seventy-eight patients (48.1%) were female and 84 (51.9%) male. No statistically significant difference was determined in terms of gender. Twenty-four patients (14.8%) were aged 0-12 months, 51 (31.5%) 13-36 months, 13 (8%) 37-72 months and 74 (45.7%) more than 72 months. There was no significant difference in terms of age groups ($p>0.05$). Aetiological causes by age groups are shown in Table 1. In terms of specific aetiological causes in the acute symptomatic group, SE developed due to metabolic causes in 9 (15.3%) patients (6 hypocalcaemia, 3 hypercalcaemia), due to head trauma in 5 (8.5%), intoxication in 4 (6.8%), meningitis in 7 (11.9%) and encephalitis in 10 (16.9%), during antiepileptic drug withdrawal (known epileptic patients) in 6 patients (10.2%)

Table 1 Aetiological classification by age group

	0-12 months n (%)	13-36 months n (%)	37-72 months n (%)	>72 months n (%)
Idiopathic	2 (6.5)	12 (38.7)	5 (16.1)	12 (38.7)
Febrile status epilepticus	8 (20)	23 (57.5)	1 (2.5)	8 (20)
Acute symptomatic	12 (20.3)	9 (15.3)	4 (6.8)	34 (57.6)
Chronic symptomatic	1 (4.3)	6 (26.1)	2 (8.7)	14 (60.9)
Progressive	1 (11.1)	1 (11.1)	1 (11.1)	6 (66.7)

and due to irregular drug use among patients diagnosed with epilepsy in 18 patients (30.5%). The most common cause in the acute symptomatic group was irregular drug use among patients diagnosed with epilepsy.

A previous history of seizure was present in 106 patients (65.4%), while first seizure occurred in the form of SE in 56 (34.6%). In terms of distribution by age groups while first seizure occurred, the most common SE seizure was in children aged under 1 year, at 83.7% (p=0.000). In terms of distribution of type of seizure, the most common type was generalised seizure at 85.2%, with partial type seizure at 14.8% (p=0.01). The most common subtype of generalised seizure was tonic-clonic in 126 patients (91.3%), and the most common partial seizure subtype was epilepsia partialis continua in 19 patients (79.1%). Other partial seizure subtypes were aura continua in one patient and partial SE with hemiparesis in 3 patients. Aetiological classification by seizure type is given in Table 2.

In terms of imaging techniques, CT of the brain was performed on 41 patients (25.3%) and magnetic resonance imaging on 36. CT of the brain was normal in 28 patients, while cerebral edema was identified in 3 patients, space-occupying mass in one patient, and other anomalies in 9 patients. Fourteen patients examined using MRI were assessed as normal, while focal edema was determined in one, generalised edema in 2, bleeding in 2, infarct in one and other anomalies in 16. EEG was performed on 97 patients (59.9%), 54 in the first 3 days after SE, 32 in 4-7 days and 11 after more than 7 days. EEG results were normal in 49 patients (50.5%). Basal activity irregularity was determined in 12 (12.3%) of the patients receiving EEG, focal epileptic disorder in 17 (17.6%), widespread generalised slowing in 5 (5.2%) and generalised epileptic disorder in 14 (14.4%).

In terms of duration, seizure lasting 30-45 minutes was determined in 47 patients (29%), 46-60 minutes in 49 (30.3%), 61-75 minutes in 26 (16%) and more than 75 minutes in 40 patients (24.7%). Although there was no statistically significance relation between aetiology and duration of seizure, 39.4% of the patients with seizure lasting more than 60 minutes were in the acute symptomatic group (p>0.05). Seizure concluded in less than 60 minutes in 72.5% of patients presenting with febrile SE. A significant increase in morbidity and mortality was determined in patients with seizure duration exceeding 60 minutes (p=0.000 and p=0.002, respectively). Complication level in patients with seizure duration exceeding 60 minutes was 92.4% (p=0.032), while response to treatment was more difficult and length of hospitalisation increased with duration of seizure (p=0.001).

We learned that 37 patients had received various forms of treatment, predominantly rectal diazepam, at home before presentation, in the ambulance or at initial presentation; 77.8% of the patients with mortality had received treatment before reaching hospital. A statistically significant correlation was determined between receipt of treatment before arrival at hospital and mortality (p=0.001) (Figure 1). However, no significant increase in morbidity was observed between patients receiving treatment before hospital and those not receiving treatment (p>0.05).

Seizures were resistant in 64.9% of patients receiving treatment before hospital (p=0,001), but no correlation was determined between pre-hospital treatment and response to treatment administered in hospital and duration of hospitalisation. Time between onset of seizure and presentation to hospital was 30 minutes or less in 37 patients (22.9%), 31-60 minutes in 91 (56.2%) and over 60 minutes in 34 (20.9%). Time to presentation exceeded 60 minutes in all patients with a fatal course. In addition, length of hospitalised increased with time to presentation, and morbidity developed in 90.5% of patients with a time to presentation of more than 60 minutes (p=0.03). The distribution of cases for duration of hospitalisation with

Table 2 Aetiological classification by seizure type

	Generalised n (%)	Partial n (%)
Febrile status epilepticus	36 (26.1)	4 (167)
Acute symptomatic	48 (348)	11 (458)
Idiopathic	26 (188)	5 (208)
Chronic symptomatic	21 (152)	2 (83)
Progressive	7 (51)	2 (83)

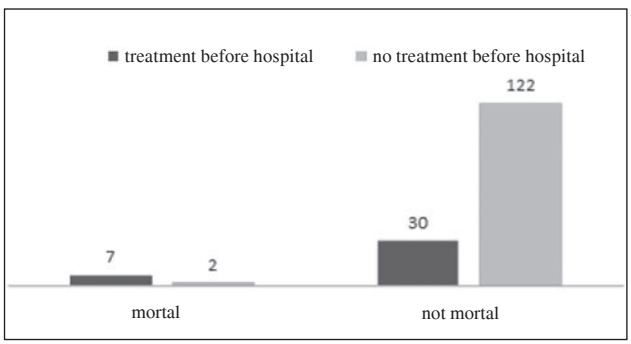

Figure 1 Comparion of mortality with treatment before hospital.

aetiological causes is given in Table 3.

Thirty-seven of the 162 patients presenting to our hospital had received treatment before hospital, with a standard treatment protocol being applied in 124 cases. Seizure in one patient stopped spontaneously at presentation to our hospital. Twenty-three patients (14.2%) responded to rectal/i.m diazepam and 37 (22.8%) to diazepam + midazolam therapy. Level of response to first-stage treatment was 37%. Seizures stopped in 18 patients (11.1%) with the addition to treatment of phenytoin and phenobarbital. Midazolam infusion was performed for seizure control in 64 cases (39.5%). Seizures were also brought under control with thiopental in one patient, pentobarbital in one patient and valproic acid in 3 patients. Propofol and antiedema therapy was applied for seizure control in one patient. Antiedema therapy was required in 2 patients. Seizure was halted with appropriate replacement therapy in 3 patients entering status due to hypoglycaemia and 6 patients entering status due to hypocalcaemia. In addition, 2 patients aged less than 1 year responded to pyridoxine therapy. Response to treatment was most common in 5-10 minutes in 44 patients (27.2%), while response to treatment exceeded 30 minutes in 43 patients (26.5%). Length of hospitalisation increased with length of response to treatment (p=0.000, r=0.398). Time to response to treatment exceeded 30 minutes in 88.9% of the non-surviving patients (p=0.000). Morbidity developed in 100% of patients with a response to treatment time greater than 30 minutes (p=0.000). Twenty-one (48.8%) of the patients with a response to treatment time exceeding 30 minutes were in the acute symptomatic group, 9 (20.9%) in the idiopathic group, 5 in the (11.6%) progressive group, 4 (9.3%) in the chronic symptomatic group and 4 (9.3%) in the febrile status group. Most of the patients with response to treatment times exceeding 30 minutes were in the acute symptomatic group (p=0.011). In addition, no significant correlation was determined between age and length of response to treatment.

Mean length of monitoring in our patients was 27.5± 9.43 months (minimum 12 - maximum 41 months). Nine patients could not be monitored due to mortality and 11 due to failure to attend check-ups. One hundred forty-two (87.6%) patients were eventually monitored. Morbidity was determined in 97 (68.3%) of the monitored patients. Examination of morbidity by age groups revealed no statistically significant differences (Figure 2). No significant correlation was determined between morbidity and type of seizure or aetiological classification, but morbidity was most common in the acute symptomatic group and in generalised type SE (p>0.05) (Figures 3 and 4). No morbidity was observed in patients with tonsillitis and febrile SE; pulmonary infection was present in 63.2% of the patients with morbidity. Morbidity developed in 71.4% of patients with meningitis in the acute symptomatic group, in 80% of those diagnosed with encephalitis, 75% of those with metabolic disorder, 75% of those with intoxication, 66.7% of those entering status during discontinuation of antiepileptic drugs, in 64.7% of those with inappropriate antiepileptic drug use and 80% of patients entering status due to trauma. In contrast, seizure was not first seizure in 80% of patients developing morbidity, and no morbidity was observed in subjects in whom SE developed for the first time (p=0.011). Epilepsy was observed in 17 of the 142 followed-up patients, impairment of cognitive functions in 18, paresis in 8, moderate-medium mental retardation in 12, problems with hearing or vision in 15 and, the highest level recorded, recurrence of status in 27.

Mortality was determined in 9 (5.6%) of the total 162 patients. The distribution of mortality with age groups is given in Figure 5. In terms of aetiology of patients with mortality, 4 (44.4%) were in the acute symptomatic group, 3 (33.3%) in the idiopathic group, 1 (11.1%) in the chronic symptomatic group and 1 (11.1%) in the progressive group. No mortality occurred in the febrile status group patients (Figure 6). Although a p value cannot be given, mortality was highest in the acute symptomatic group. Encephalitis was present in 3 of the non-surviving patients in the acute symptomatic group and metabolic disorder in one. In terms of age groups, mortality was most common at age below

Table 3 Distribution of cases for duration of hospitalisation with aetiological causes

	Febrile n (%)	Acute symptomatic n (%)	Idiapathic n (%)	Chronic symptomatic n (%)	Progressive n (%)	Total n (%)
0-3 days	3 (7.5)	4 (6.8)	5 (16.1)	3 (13)	0 (0)	15 (9.3)
3-7 days	18 (45)	21 (35.6)	13 (41.9)	10 (43.5)	2 (22.2)	64 (39.5)
>7 days	19 (47.5)	34 (57.6)	13 (41.9)	10 (43.5)	7 (77.8)	83 (51.2)
Total	40 (100)	59 (100)	31 (100)	23 (100)	9 (100)	162 (100)

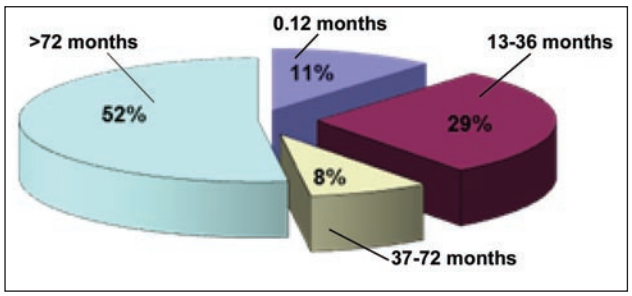

Figure 2 Distribution of morbidity with age groups.

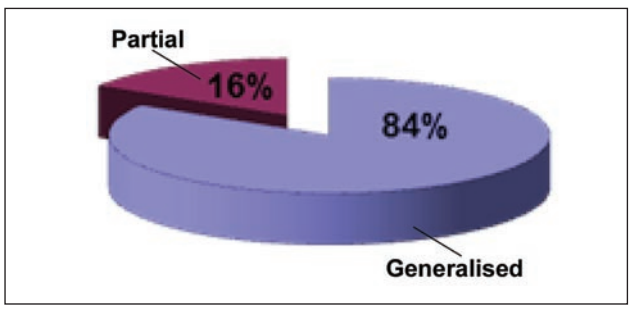

Figure 3 Distribution of morbidity with type of seizure.

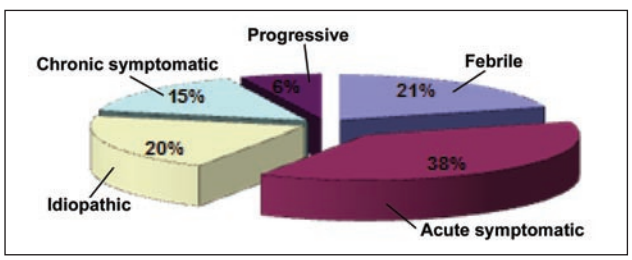

Figure 4 Distribution of morbidity with aetiological causes.

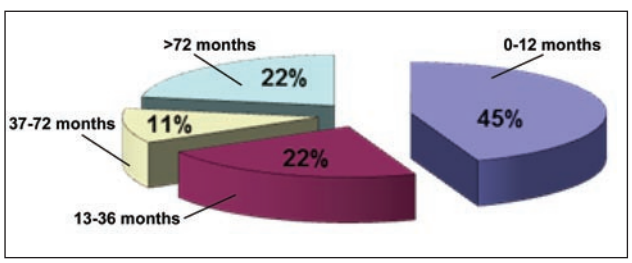

Figure 5 Distribution of mortality with age groups.

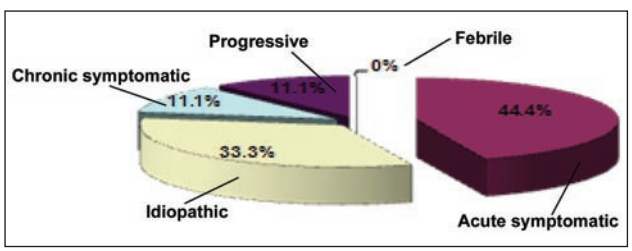

Figure 6 Distribution of mortality with aetiological causes.

1 year, although the difference was not statistically significant. SE consisted of first episodes in 66.7% of non-surviving patients, although this was also not statistically significant ($p>0.05$).

No significant correlation was determined between mortality and type of seizure ($p>0.05$). Duration of seizure exceeded 60 minutes in all non-surviving patients. In addition, mortality occurred in more than 7 days in 88.9% and in less than 3 days in 11.1% ($p=0.000$ for both). This shows that prolonged hospitalisation is associated with an increase in complications.

Discussion

Early and effective treatment in SE has a significant impact on seizure control, morbidity and mortality.[1,2] Mortality and morbidity are associated with pathology leading to status, age, length of seizure control and treatment protocols. The most common causes in the aetiology of SE in children are central nervous system infections in particular, electrolyte disorders, head trauma, chronic encephalopathies, idiopathic seizures (febrile and afebrile), trauma and brain tumours.[1,2,9,10]

The most common aetiological classification in SE in this study was acute symptomatic (Table 1). The patients in the acute symptomatic group were most commonly monitored due to epilepsy but used medications irregularly (18 cases, 30.5%). Epilepsy has been reported as the most important cause in many previous studies. Since approximately half of the cases in this study were diagnosed with epilepsy, epilepsy may be a risk factor for SE. It is very important for patients under monitoring for epilepsy to be told how to use their drugs and of the importance of fully complying with antiepileptic therapy, and for regular training sessions to be held on the subject.

In terms of age groups, the incidence was highest at age 6 and over, followed by the 1-3 years age group. Age distributions vary in the literature, but to a large extent SE is reported to be most common before the age of 5.[11,12] There is no significant correlation between SE and age, and different prevalences in different age groups have been reported in studies. Anticonvulsant therapy is known to be beneficial before arrival at hospital in SE.[13] High levels of seizure control have been achieved in studies among patients started on anticonvulsant therapy as a first intervention at home, in the ambulance or in another health institution.[12,14] Studies emphasize that this is due to a short intervention time after onset of convulsion.[15] In our study,

in contrast to the literature, seizures were resistant (patients were considered as resistant status epilepticus despite the seizures could not be controlled within 1 hour with benzodiazepines, phenobarbital, and phenytoin treatment) in 64.9% of patients receiving treatment prior to arrival at hospital, and no significant correlation was determined between receipt of therapy before hospital and time to response to treatment applied or length of hospitalisation. In addition, 77.8% of the non-surviving patients received treatment before presenting to hospital, and statistically significant correlation was determined between receipt of treatment before hospital and mortality. The reason for this difference from other studies is unclear. Poor knowledge of treatment or errors may be observed in interventions in convulsions before presentation at hospital. Although prognosis is generally associated with aetiological factors, it is known to be also directly affected by length of seizure and treatment protocol. Benzodiazepines are recommended as the first option in the majority of treatment protocols reported in the literature.[16,17] While there is no difference between benzodiazepines in terms of first seizure control, seizure recurrence is frequently observed due to the short half life of diazepam.[18] Since intravenous lorazepam is unavailable in Turkey, diazepam was the anticonvulsant drug of choice in emergency departments in Turkey.[19]

In terms of response levels in treatment steps in this study, 1st step response to treatment was similar to that in other studies. However, our levels of 2nd step response to treatment were lower compared to other studies. This may be attributed to our higher number of cases of resistant SE.

Levels of systemic and neurological sequelae in prolonged and uncontrollable convulsion are known to increase in association with other organs being affected. It is therefore important for the seizure to be concluded as soon as possible and for therapeutic approaches aimed at preventing systemic damage to be determined. Although new generations drugs have begun being used alongside classic anticonvulsants in symptomatic seizure control and improvements in intensive care conditions have brought about a decrease in status-related morbidity and mortality in recent years, the desired results have still not been achieved.[20] The anticonvulsant drugs currently used in initial treatment are known to be effective in two out of three patients.[20] Improvements in standard approaches to acute convulsion and SE, will benefit health personnel in ambulances and physicians in the emergency department in practical terms, in terms of safety and time and, most important of all, by reducing morbidity and mortality. Prognosis in SE is associated with aetiology, age, length of seizure accompanying systemic abnormalities and form of treatment.[21]

The most important factors are the underlying cause and time between onset of status and treatment. Prognosis is poor in SE developing in association with cerebral hemorrhage, encephalitis, drug intoxications and severe intracranial events such as stroke.[22] A marked decrease in mortality and morbidity has been observed in the last 2 decades in paediatric patients with SE. This is due to early and aggressive interventions. The greatest contribution to this has been improvements in paediatric intensive care units. Cerebral, cardiorespiratory, autonomic and metabolic complications requiring rapid treatment may be seen in SE.[23]

The main long-term complications of SE are epilepsy, major neurological sequelae, neurological dysfunction (mental retardation or paresis), minor neurological sequelae (school or learning problems, behavioural problems, and concentration and memory disturbances) and compromise of cognitive functions. The risk of neurological sequelae such as mental retardation, behavioural disorders, focal motor deficit and resistant epilepsy is higher in young children.[22]

Both infants and older children with SE must be closely monitored in terms of these medical complications. Morbidity was determined in 97 (68.3%) of the 142 patients placed under monitoring in our study. No difference was determined in distribution of morbidity by age groups, and young age at onset of SE did not affect morbidity. Maytal et al[20] showed that neurological sequelae were correlated with age, with levels of 6% above the age of 3 years and 29% below the age of 1 year.

Prognosis can be investigated with long-term observation. Leweba et al's study,[12] one of the largest to date in that context, involved 542 patients. Due to the large number of patients, basal length of seizure in SE may be set at 10 minutes. Mean length of observation of our patients was 27.5±9.43 (minimum 12 - maximum 41 months) months. Our patient population was larger than those of other studies. While Singh et al[11] took 20 minutes as a basal value for SE and Lewena et al[12] 10 minutes, considering that our basal value for SE was 30 minutes, our patient number was higher than those of other studies. More comprehensive data concerning prognosis can be elicited as length of observation increases.

Morbidity was most common in the acute symptomatic group in this study. The reason for the greater presence of morbidity in the acute symptomatic group may be that probable aetiological factors affect duration of status as well as development of status, and that these factors also represent a direct potential risk (trauma, metabolic disorder,

intoxication, meningitis, encephalitis) in terms of morbidity. Parallel to this, patients with seizure lasting 60 minutes or more constituted the majority of the acute symptomatic group, and the incidence of mortality increased with duration of seizure. Epilepsy developed in 17 patients (12%) in our study, lower results being obtained compared to the literature. The level of epilepsy developing following status reported in the literature is 20-36%.[22,24] Our short monitoring period may have led to a lower level of epilepsy. Mortality occurred in 9 (5.6%) of our total 162 patients. A study from the USA reported mortality in 9 (6%) out of 147 children.[24] Death occurred in only 2 cases in Lewena et al's study.[12] No mortality occurred in Singh et al[11] or Hussain et al's[14] studies. Mortality in those studies in which it occurred was attributed not to status itself, but to underlying pathologies giving rise to it.[25-27]

The fact that 3 of the non-surviving patients in our study had encephalitis, one had hypoglycaemia and one had neurodegenerative disease supports that hypothesis.

In conclusion, terminating seizure as quickly as possible with early, aggressive and appropriate treatment and preventing systemic complications in prolonged seizures is important in terms of reducing morbidity and mortality rates.

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Conflicts of Interest

All authors declare that they have no conflicts of interest.

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