Status epilepticus

Can the incidence be reduced?

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ABSTRACT

Objectives: To identify high risk groups for the development of convulsive status epilepticus (CSE) in an attempt to decrease the incidence and to determine both the time to access to medical care and the use of prehospital treatment in an attempt to reduce the duration of seizing.

Methods: Retrospective study record analysis of all cases of CSE in children, at the King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia from June 1997 to June 2000.

Results: During the study period there were 24 cases of CSE. The major etiologic factors were chronic neurological disorders, idiopathic epilepsy, and acute cerebral insults. All but one of the chronic epileptics in the study group had at least one identifiable risk factor for the evolution of breakthrough seizures into status epilepticus (SE). Mortality was 12.5% and chronic neuro-behavioral morbidity in previously normal children was 17%. The average total duration of seizing was 2.3 hours, with an average of 52 minutes prior to arrival in the hospital. Prehospital rectal diazepam was administered by the family in only 2 instances, and in both cases the patients were overdosed.

Conclusion: The identification of risk factors for CSE can serve 2 purposes: Focus targeted patient and family education, and a checklist for emergency room personnel to recognize those presenting with breakthrough seizures who are susceptible to SE, aiding in management decision making. The incidence of SE can be reduced by abbreviating the duration of breakthrough seizures. This can be achieved both by more widespread yet proper use of rectal diazepam at home, and by auditing the process of patient or family education.

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Status epilepticus (SE) is a potentially life threatening emergency with significant physiologic sequelae and neurologic deficits.[1] This study was designed to determine the characteristics of SE in our group of patients and to identify potential areas for intervention to reduce the incidence of SE in our center. A significant proportion of children with epilepsy (1.7-16%) are expected to develop SE.[2] Many known epileptics develop breakthrough seizures,[3,4] some of which may evolve into SE. Identifying those patients with breakthrough seizures that are more likely to develop SE, will help target the high-risk group. These groups' of families can then receive specific instructions for the prevention of breakthrough seizures and the appropriate action in their event. Furthermore, the availability of specific checklists of risk factors can aid the emergency room (ER) personnel in triage, and decision making during the management of breakthrough seizures regarding admission criteria and promptness of seizure control. The specific risk factors we searched for included: the use of multiple anti-epileptic drugs (AED), poorly controlled seizures, poor compliance, and a

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previous history of SE. The acute precipitating factors that we considered were intercurrent infections and abrupt withdrawal of an AED. Breakthrough seizures may also be prevented from evolving into SE by reducing the time interval from onset of seizing until arrival in the hospital and by using rectal diazepam at home (prehospital treatment). These objectives can be met through family education.

Methods. King Abdul-Aziz University Hospital, is an academic tertiary care center in Jeddah, Kingdom of Saudi Arabia (KSA), serving children and adults. Retrospective analysis of all cases admitted with a diagnosis of SE, or developed SE in hospital, in association with other disorders, from June 1997 to June 2000 was undertaken, and the following data was collected: demographic data, underlying etiologies, possible precipitating factors, duration of fitting, prehospital rectal diazepam administration and outcome. The data was then analyzed in order to determine the morbidity and mortality, and comparison with international standards; to identify possible predicting factors for the risk of SE and factors affecting prognosis; to assess for delays in accessing treatment, and potential areas for intervention to decrease the incidence and duration of fitting.

Results. During the study period, there were 24 cases with a diagnosis of SE. Twenty were admitted through the ER and 4 developed SE while in the hospital for other reasons. The male:female ratio was 0.7:1, with a mean age of 4.45 years and age range from 4 months to 14 years. Underlying diagnoses are shown in **Table 1 & 2**. Interestingly, 2 sisters with systemic lupus erythematosus (SLE) were admitted with SE at different times. Possible predicting factors for the risk of developing SE in those with a chronic neurologic disorder included: Poorly controlled epilepsy (despite therapy with multiple AED in many cases) in 56%, non-compliance with prescribed AED (25%), abrupt withdrawal of the AED (19%), mild intercurrent infection outside the central nervous system (CNS) in 50%, and a previous history of SE in 12% (**Table 2)**. There were 7 cases of refractory SE (RSE) (seizures continuing for 60-90 minutes after the initiation of therapy; or failure of termination of seizures with normally adequate doses of diazepam or lorazepam, phenytoin, phenobarbitone, or both). The remainder were in established SE (ESE). The mean duration of convulsion for all 24 cases of CSE was 2.3 hours. For the following durations, one child whose family initially refused medical care was not included. The mean duration for RSE was 3.8 hours, compared to 1.35 hours for ESE (**Table 3 & 4**). In order to assess patient's access to treatment for patients developing SE outside the hospital (20 patients), the average duration from the onset of the convulsions until arrival in the hospital was determined from the physicians' notes. It ranged from 30-130 minutes with a mean of 52 minutes. The triage time (time from arrival in the hospital until medical treatment was started) was difficult to determine given the current state of documentation. The average time from arrival until fits were aborted was 23.9 minutes for patients in ESE with a range of 3-45 minutes, and for patients in RSE it was 3 hours, (range 2.3-4.5 hours) **Table 3 & 4**. Prehospital treatment (rectal diazepam administered by the family), was given to only 2 patients, due to lack of parents' experience in this group. Both patients were given excessive doses by their care-givers (3 & 5 boluses). In terms of outcome, the mortality was 12.5% (3 patients of the whole group). The underlying diagnoses in these patients were: acute purulent meningitis, severe degenerative brain disease, and severe spastic quadriplegic cerebral palsy (CP) with global developmental delay. Regarding morbidity, neuro-behavioral changes unexplained by other causes were documented in 4 children (17% of the whole group). These included slow development, mainly in speech and language function, urinary incontinence, and various behavioral abnormalities. Three of these had SE as part of an acute CNS insult, and the 4th child

Table 1 - Patients developing status epilepticus as a part of an acute central nervous system trigger with no previous neurologic impairment.

Patient	Age (months)	Sex	Underlying etiology	Outcome
1	11	F	Acute purulent meningitis	Died 3 days later
2	11	M	Febrile convulsions	Recovered
3	72	F	CVA – sickling crisis	Learning disability, behavior abnormality
4	12	F	Acute encephalopathy	Complications of original disorder
5	18	M	Acute meningoencephalitis	Learning disability, behavior abnormality
6	54	F	CNS – lupus	No new insult
7	168	F	SLE- hypertensive encephalopathy	Learning disability
8	72	M	Acute hypoxic ischemic insult	Post-hypoxemic vegetative state

Poor prognosis except for febrile convulsions.
Prognosis is related to severity of insult causing SE, but may improve prognosis by lessening the added damage of prolonged SE.
CVA - cerebrovascular accident, CNS - central nervous system, SLE - systemic lupus erythematosus, SE -status epilepticus.

Table 2 - Cases of status epilepticus developing on a background of "chronic" neurologic illness.

Patients	Age (year)	Sex	Underlying diagnosis	AED	Poor compliance	Control	Abrupt withdrawal of AED	Intercurrent fever or Infection	Previous SE	Outcome
1	8.5	M	Cerebral palsy	Clob, VPA, CBZ, LMT	-ve	Well	-ve	+ve	+ve	Died
2	5	M	Degenerative disease	Clonazepam, VPA	-ve	Well	-ve	-ve	+ve	Died
3	14	F	Cerebral palsy	CBZ	-ve	Well	-ve	+ve	-ve	No change
4	7	F	Idiopathic epilepsy	VPA	-ve	Well	-ve	-ve	-ve	No change
5	1.5	M	Shunted hydrocephalus	CBZ	-ve	Well	-ve	+ve	-ve	No change
6	3	F	Idiopathic epilepsy	Clonazepam, VPA	+ve	Poor	+ve	-ve	-ve	Speech or behavior changes
7	3	M	Hemimegalencephaly	VPA, CBZ	+ve	Poor	-ve	-ve	-ve	No change
8	5	F	Cerebral palsy*	-	-ve	NA	-ve	+ve	-ve	No change
9	1	F	Shunted hydrocephalus*	-	-ve	NA	-ve	+ve	-ve	No change
10	1	F	Shunted hydrocephalus	Clob	-ve	Poor	-ve	-ve	-ve	No change
11	0.3	F	Sturge-Weber syndrome	Clob, VPA, CBZ	-ve	Poor	-ve	-ve	-ve	No change
12	4.5	M	Idiopathic epilepsy	Clob, VPA, Phenobarb	-ve	Poor	-ve	+ve	-ve	No change
13	1.2	M	Idiopathic epilepsy	Clob, VPA, Phenobarb	-ve	Poor	-ve	+ve	-ve	No change
14	3.7	M	Degenerative disease	VPA, CBZ, LMT	-ve	Poor	-ve	+ve	-ve	No change
15	4.5	F	Shunted hydrocephalus	VPA, Clob	-ve	Poor	+ve	-ve	-ve	No change
16	9	F	Idiopathic epilepsy	CBZ, Clob	-ve	Poor	+ve	-ve	-ve	No change

Each patient had at least one predicting risk factor except patient 4.
* - no previous history of seizures, AED - antiepileptic drug, Clob - Clobazam, CBZ - Carbamezapine, Phenobarb - Phenobarbitone, VPA - Valproic acid, LMT - Lamotrigine, NA - not applicable; -ve - negative; +ve - positive

Table 3 - Cases of refractory status epileptus arriving in the emergency room.

Patient	Underlying diagnosis	Duration of seizing (hours)			Outcome	Findings on brain CTS
		Before arrival to ER	After arrival to ER	Total		
1	Cerebral palsy	1	2.2	**3.2**	Died	Not done
2	Meningitis	1.1	2.7	**3.8**	Died	Brain edema
3	Cerebral palsy	1	2.5	**3.5**	No change	Brain atrophy (no change)
4	Idiopathic epilepsy*	10	4	**14**	Speech affected	Normal
5	Degenerative brain disease	2	4.5	**6.5**	Died	Brain edema

Two cases of RSE developing SE in the hospital are not included. Table shows poor prognosis of RSE. Delay seeking medical advice may have contributed to resistance of SE to treatment. * - family refused treatment, ER - emergency room, CTS - computed tomography scan, RSE - refractory status epilipticus, SE - status epilepticus

Table 4 - Duration of episodes of established status epilepticus in patients attending the emergency room (1997-2000).

Patients	Underlying diagnosis	Duration of seizing (minute)			Outcome
		Prior to arrival in ER	After arrival in ER	Total	
1	Febrile convulsions	45	30	**75**	Normal
2	Cerebrovascular accident	50	60	**110**	Behavior abnormality, urine incontinence
3	Idiopathic epilepsy	45	15	**60**	No change
4	Hydrocephalus	30	40	**70**	No change
5	Systemic lupus erythematosus	125	55	**180**	Behavior abnormality
6	Systemic lupus erythematosus	60	25	**85**	No change
7	Hemimegalencephaly	60	55	**145**	No change
8	Cerebral palsy	60	15	**75**	No change
9	Hydrocephalus	50	3	**53**	No change
10	Hydrocephalus	130	20	**150**	No change
11	Degenerative brain disease	50	10	**60**	No change
12	Idiopathic epilepsy	35	10	**45**	No change
13	Idiopathic epilepsy	50	10	**60**	No change
14	Hydrocephalus	45	0	**45**	No change
15	Idiopathic epilepsy	45	10	**55**	No change

No patients had brain edema on CTS. Prognosis is better that RSE. Two cases of ESE developing in hospital are not included. ER - emergency room, CTS - computed tomography scan, ESE - established status epilepticus, RSE - refractory status epilipticus

Table 5 - Mortality in relation to underlying etiology of status epilepticus.

Variable	Symptomatic SE	Idiopathic epilepsy or FC
n of patients	18	6
n of deaths	3	0

Mortality is mainly predicted by the underlying diagnosis
n - number, SE - status epilepticus, FC - febrile convulsions

had idiopathic epilepsy, but her family refused proper treatment of her status episode. Their ages were 3, 5, 14 and 3 years. New epilepsy occurred in 5 out of 8 children not previously known to have seizures.

Discussion. Status epilepticus is a well-recognized pediatric neurologic emergency with significant morbidity and mortality. It is classically defined as continuous seizure activity or intermittent convulsive activity with failure to regain consciousness between attacks for a duration of more than 30 minutes. The estimated incidence of SE is 41 per 100,000 population.[5,6] The estimated incidence of RSE is 2000-6000 cases per year.[4] The total number of cases of SE seen in our center over a period of 3 years was 24, with an average of 8 cases per year. Underlying diagnoses were chronic neurological disorder in 11 cases, idiopathic epilepsy in 5, and an acute neurologic insult in 8 cases. Previously, SE was associated with a mortality of up to 20% in children[2] (much higher in adults). More recent mortality rates of 3-11% may be due to early aggressive treatment of SE, proper management of the underlying disease process, vigilance to supportive care and maintenance of homeostasis during the attack, and in particular the lower mortality of 3% has been hypothesized to be the result of such factors and the fact that fewer children in the population have severe underlying neurologic abnormality[8,9] at least in developed countries.[9] Appropriate early management may also lessen morbidity. "New" morbidity (presumed to be the result of the SE episode) has been reported to be 9.1%. This compares with earlier findings (4% incidence of neurologic sequelae, 48% of mental deterioration, 44% incidence of epilepsy).[2] Maytal et al[11] states that "in the modern emergency department, the outcome is primarily a function of the underlying etiology". This view has been supported by other workers,[10] although a recent study by Barnard & Wirrel[1] has found more discouraging results (79% neurologically abnormal and 36% epilepsy), but the worst outcome occurred in those with non-idiopathic, nonfebrile SE, especially in those of a younger age. In our group of patients the mortality rate was higher when compared with the above figures (12.5% or 3 patients out of 24). The deaths were felt to be more related to the underlying disease process that led to the SE event in at least 2 of the 3 patients, (acute purulent meningitis, and severe degenerative brain disease) both of these showed evidence of brain edema on computerized tomography (CT) scan of the brain. The 3rd child had severe spastic quadriplegic CP with severe global developmental delay as a result of a previous hypoxemic-ischemic insult. He had a previous history of SE, and was receiving multiple anti-convulsants. These findings relating to mortality are in keeping with the opinion that when

there has been no acute or progressive CNS insult morbidity and mortality are low.[11] On comparing mortality for symptomatic cases in our study group (16.7%) to that of idiopathic cases (0%) an appreciable difference was found (**Table 5**). We did not find age to have a significant effect on the prognosis in our group of patients. Regarding morbidity in our group, slow developmental or behavioral abnormality, or both, was observed in 4 children, with no other documented impairments. This falls somewhere between the findings of other recent studies[1,10,12] although it may be an underestimation due to the fact that SE had a shorter duration (45-75 minutes) in those with no acute or chronic CNS insults (namely those with idiopathic epilepsy or febrile convulsions); while those who sustained a longer duration of seizure activity already had severe learning and neurologic defects, and any added insult may have been missed. It may also reflect underdiagnosis of subtle learning deficits in this setting. Morbidity seemed to be mainly related to the underlying diagnosis and the duration of fitting rather than age (**Tables 1 - 4**). Prolonged seizure activity in itself produces irreversible brain damage, independent of accompanying hypoxia, acidosis and consequent biochemical derangements. The excessive metabolic demands of continually firing neurons leading to depletion of essential nutrients is currently thought to be an important factor leading to cell death during continuous seizures.[13] The body is able to compensate for the stresses of CSE for approximately 30 minutes after which homeostatic regulating mechanisms deteriorate and the potential for permanent brain damage increases.[4,14] It is generally believed that the duration of the episode not only adversely affects the outcome, but the more prolonged the seizures, the more resistant they become to treatment.[3,15] Of note was the finding that in all our children with RSE, the longer the duration of seizing before arrival to the ER, the longer it took to control the seizures **(Table 3)**. This did not apply to children in ESE. Both animal and human studies suggest that the risk of brain damage is directly related to the duration of SE.[14,16] The average time for our patients to arrive in the ER from the onset of the convulsions was 52 minutes (30-130 minutes). This is dangerously high and may be due to reluctance in seeking medical advice, waiting for the seizures to die down, especially in those with several previous episodes of breakthrough seizures. This unacceptably prolonged period may be reduced appreciably by family education and the use of rectal diazepam at home.[17,18] In this study group only 2 patients' families had been instructed in the use of home administered rectal diazepam necessitating more wide spread use of this preventive modality, although this will have to be weighed against the possible risks of overdose at home and the over reliance on the home administered medication with subsequent delay in seeking medical advice, as happened with both these families. It must be fully comprehended by the care-givers that this is only a temporary measure and not a substitute for professional medical care. We feel that targeted patient and family education is central to the process of reducing the occurrence of SE, and the duration of seizing, with the ultimate goal of improving the outcome. Up to 16% of children with epilepsy may be expected to develop SE.[2] Patients most at risk are those with severe underlying CNS disorders and those with a history of frequent or refractory seizures on multiple drug therapy. These patients' families should be targeted for education regarding the possibility of SE, and the actions to be taken should it occur, including the use of rectal diazepam at home.[17] Events associated with the episode in our group of children are shown in **Table 2.** All the patients with known epilepsy excluding one had at least one risk factor, and many had more than one. These risk factors should be taken into account in family discussions regarding prevention, including vigilance during intercurrent illness for possibility of breakthrough seizures evolving into SE. A checklist of these factors can be used as alerts for attending physicians as to the possibility of a breakthrough seizure evolving into SE in these circumstances. A significant proportion of epileptics develop breakthrough seizures and many are managed on an outpatient basis. Supplying emergency room personnel with these specific checklists may serve as a guide in the decision making process regarding admission and aggressiveness of management. Of special interest was the findings of the 3 patients who died during the attack, 2 had previous medical histories of SE; ours is a small group of patients and this finding will need to be confirmed by other studies. For the meantime we recommend that patients with a past history of SE, who develop prolonged seizures be treated particularly aggressively with a lower threshold to starting 3rd line medications earlier in the process. Patients with severe acute CNS insults or moderate insults on top of systemic illness are also at high risk, and may also benefit from such policies.

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