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ORIGINAL ARTICLE

Features predicting adverse outcomes of status epilepticus in childhood

可預期兒童癲癇持續發作導致不良後果的特徵

Objective. To examine variables that might predict abnormal outcome of status epilepticus among children.

Design. Retrospective study.

Setting. Regional hospital, Hong Kong.

Patients. All children younger than 15 years who were admitted to the paediatric intensive care unit with status epilepticus between 1997 and 2002.

Main outcome measures. Neurodevelopmental outcomes.

Results. Two of the 25 patients died, resulting in a mortality rate of 8%. No deaths were due to status epilepticus itself. No patient with febrile or idiopathic status epilepticus developed epilepsy. Neurological deterioration was observed in a quarter (six of 23) of the survivors. Symptomatic aetiology (acute or remote) and refractory status epilepticus were associated with adverse outcomes (P<0.05). Young age at status epilepticus (<12 months) and duration of status epilepticus (>60 minutes) tended to be more frequent among those who developed adverse outcome. Rectal diazepam was given before hospital arrival in only four patients.

Conclusions. Paediatric patients with status epilepticus who had normal neurodevelopmental status before the onset of an attack and who did not sustain an acute insult to the central nervous system or have progressive encephalopathy, had favourable outcomes. Prompt use of rectal diazepam or buccal midazolam administered by caretakers or paramedics should be encouraged.

目的：研究可以預期兒童因癲癇持續發作而引致不良後果的變量。

設計：回顧性研究。

安排：地區醫院，香港。

患者：由 1997 至 2002 年間，所有因癲癇持續發作被送入兒科深切治療部的 15 歲以下兒童。

主要結果測量：腦神經發展方面的結果。

結果：25名病人中有2人死亡，死亡率為8%。兩人都不是因持續癲癇發作而導致死亡。沒有發熱性或自發的持續癲癇的病人發展成癲癇症。23名獲救的病人中有四分之一（6名）出現神經損傷。症狀病因學（急性或遙因的）及難治的癲癇持續發作，均與不良後果有關(P<0.05)。出現不良後果的病人中，較多為發病時年紀較小（年紀少於 12 個月），或癲癇持續發作的時間較長（多於 60 分鐘）。只有 4 名病人入院前經直腸給 diazepam 。

結論：在癲癇持續發作的兒科病人中，發作前神經發展正常的、沒有中樞神經系統急性損傷或持續惡化的腦病者，其結果較為良好。應鼓勵看護及護理人員及時讓病人經直腸給 diazepam 或口服 midazolam 。

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Introduction

Status epilepticus (SE) is a major neurological emergency that causes an estimated direct mortality of 1% to 2%.[1] It can occur in association with epilepsy and in the context of acute central nervous system (CNS) or systemic insults. Short-term mortality is higher when SE occurs because of an acute insult. Aggressive management protocols for SE have been introduced during the 1980s and 1990s.[2-4] The importance of rapidly terminating prolonged seizures has been well recognised. Treatment protocols, however, vary between different hospitals. It is estimated that SE is refractory in 9% of adults, and shown that the mortality associated with refractory SE is substantially higher

than that for non-refractory SE.[5] In this study, we review the cases of SE that were managed in the paediatric intensive care unit of a regional hospital, with the aim of examining various variables that might predict abnormal outcomes.

Patients and methods

We retrospectively identified all children younger than 15 years with SE who were admitted to the Paediatric Intensive Care Unit at the Tuen Mun Hospital between 1997 and 2002. The hospital is the only tertiary paediatric centre in the northwest district of Hong Kong. Patients with neonatal SE and non-convulsive SE were excluded from the analysis.

Status epilepticus was defined as a single seizure lasting for at least 30 minutes, or recurrent seizures lasting more than 30 minutes, without the full return of consciousness.[6] Seizures were classified as generalised or partial, according to the International League Against Epilepsy revised classification system.[7] The aetiology of SE was classified as follows: (1) idiopathic: no acute CNS or metabolic dysfunction; (2) febrile: SE provoked only by fever (>38.4°C); (3) acute symptomatic: SE occurring during acute illness with known CNS or systemic metabolic dysfunction; (4) remote symptomatic: SE occurring without an acute cause in a patient with a history of a CNS insult that was known to be associated with increased risk of convulsion; and (5) progressive neurological: SE occurring during a progressive neurological (eg metabolic or neurocutaneous) disease.[8] Refractory SE was defined as seizure that was refractory to initial therapy with a benzodiazepine, followed by an adequate loading dose of a standard intravenous anticonvulsant (either phenytoin or phenobarbitone) for at least 60 minutes.[9]

The treatment protocol for SE consisted of the following steps: (1) intravenous diazepam at 0.2 mg/kg or lorazepam at 0.1 mg/kg or rectal diazepam at 0.5 mg/kg followed, if it fails, by (2) intravenous phenobarbitone at 15 to 20 mg/kg or phenytoin at 15 to 20 mg/kg, and if this also fails, by (3) midazolam or thiopentone infusion or rectal paraldehyde. The goal of treatment was to completely control the seizure and to achieve a burst-suppression pattern on an electroencephalogram if possible.

Sequelae of SE were classified as follows: (1) epilepsy: onset of any type of unprovoked recurrent seizures after SE in patients without prior epileptic seizures; (2) major neurological sequelae: neurological dysfunction, such as mental retardation or paresis, that emerged after SE in previously normal patients; (3) minor neurological sequelae: school or learning problems, behavioural problems, or difficulty with concentration, memory or linguistic skills after SE; and (4) increased neurological disability: major or minor new neurological deficits in patients with previous neurological abnormalities.[10] Case records were
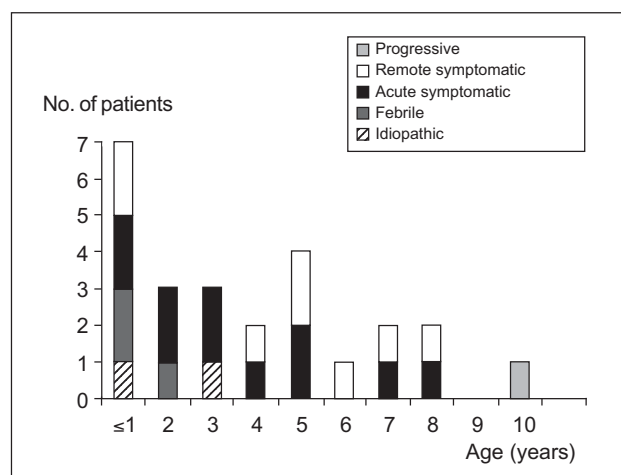

Fig 1. Aetiology of status epilepticus in various age-groups

Table. Aetiology of status epilepticus in different age-groups

Aetiology	Age (years)	
	1-3	≥ 4
Idiopathic	2	0
Febrile	3	0
Acute symptomatic	6	5
Meningitis/encephalitis/encephalopathy	3	2
Stroke	1	0
Electrolyte disturbance	2	2
Drug intoxication	0	1
Remote symptomatic	2	6
Congenital malformation	1	2
Prior central nervous system insult	0	2
Unknown	1	2
Progressive	0	1
Metabolic	0	1

retrieved and all aspects of disease treatment and outcome analysed. We performed univariate analyses of potential predictors of abnormal outcome using Chi squared tests; P values of less than 0.05 were considered significant.

Results

Clinical profile

Twenty-five children (11 boys and 14 girls) with SE were identified during the study period. The mean age at the time of SE was 2.6 years (range, 0.5-10.0 years). The highest incidence of SE was in the first year of life. Approximately one half of patients were younger than 3 years at the time of SE (Fig 1).

Eleven patients had a history of seizure disorders: seven had epilepsy, three had had febrile convulsions, and one had had a single afebrile seizure. Pre-existing neurological abnormalities were present in 15 patients. The type of SE was generalised in 13 cases and partial in 11 cases; the type of seizure could not be clearly classified in one patient. Among the cases of SE, 11 were of the acute symptomatic type, whereas eight were remote symptom-
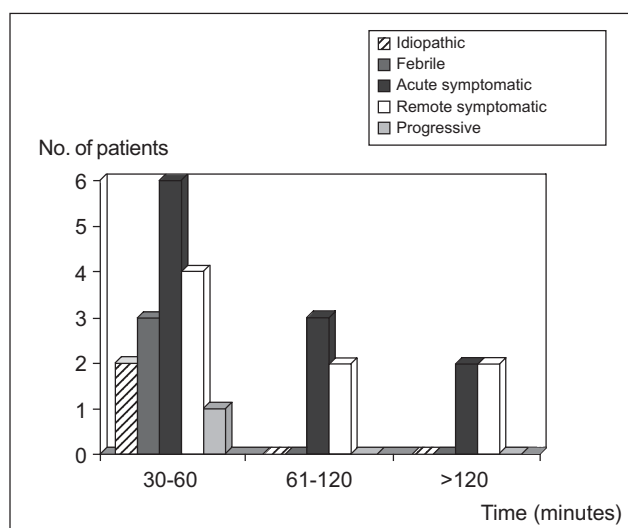
Fig 2. Duration and aetiology of status epilepticus

atic, three were febrile, two were idiopathic, and one was progressive neurological (Table). Acute symptomatic and febrile aetiologies accounted for two thirds of children younger than 3 years and two fifths of children older than 4 years.

The duration of SE was 30 to 60 minutes in 16 patients, 61 to 120 minutes in five, and longer than 120 minutes in four. The extreme long duration (3 days) in one patient was because the parents had failed to recognise partial-motor SE. Older age at SE was associated with prolonged duration of seizure: two of the 13 children younger than 3 years, compared with seven of the 12 children older than 3 years, had seizure durations of longer than 60 minutes (15% versus 58%; P<0.05). Duration of SE was also somewhat related to aetiology (Fig 2): none of the patients with idiopathic or febrile aetiology had an episode of SE of longer than 60 minutes, and all seizures that lasted for more than 60 minutes somewhat belonged to the symptomatic (acute or remote) category (P=0.06).

Rectal diazepam was given before hospital arrival in only four cases, which were all cases of chronic epilepsy. Our treatment protocol was able to end seizure within 120 minutes in four fifths of patients. Status epilepticus was refractory in 10 cases. Eleven patients received rectal paraldehyde, four required midazolam infusion, and one received an infusion of thiopentone. The longest treatment duration was 14 days in one patient, who had symptomatic frontal lobe epilepsy. She ultimately underwent epileptic surgery for cortical dysplasia.

Two patients in our series died. One had Wolf syndrome and developed multi-organ failure, and the other died of encephalitis. Neither death was directly related to seizure. There was no neurological deterioration in 17 of the 23 survivors. Among the remaining quarter of survivors, new onset of major neurological deficits or deterioration were

evident in three, and minor sequelae were observed in a further three. New-onset epilepsy developed in three of the survivors. Another patient, who had known seizure history, had recurrent SE. The mean duration of follow-up was 36 months (range, 12-70 months).

Predictors of neurological deterioration

All patients with major neurological sequelae belonged to the symptomatic (acute or remote) group (P<0.05). Young age at SE predicted regression: three of the seven patients aged 1 year or younger showed deterioration, compared with three of the 16 patients who were older than 1 year (43% versus 19%; P=0.2). Duration of SE also predicted deterioration: two of the 14 children with seizure durations of less than 60 minutes showed a deterioration in SE, compared with four of the nine children with seizures lasting longer than 60 minutes (14% versus 44%; P=0.1). Furthermore, refractory SE was associated with neurological deterioration: only one of the 13 children with non-refractory SE had minor neurological sequelae, whereas the condition in five of the 10 children with refractory SE deteriorated (8% versus 50%; P<0.05).

Discussion

This study showed that SE had an acute mortality of 8%. However, all children who died had acute life-threatening conditions, and these conditions rather than SE itself accounted for the two deaths in our series. More than 70% of the survivors showed no neurological deterioration. These results are consistent with those reported by recent clinical studies of SE in children.[1,10-13] The significant associations between aetiology, duration, and neurological deficit are also in accordance with findings of previous clinical and experimental studies.[14-16]

Sixty percent (15/25) of the children were neurologically abnormal prior to SE. This proportion is comparable to that reported by Barnard and Wirrell.[17] Children with an underlying neurological abnormality were more prone to SE than others. However, our study has some limitations. Firstly, it was retrospective: developmental histories were obtained retrospectively rather than by prospective psychological testing. Milder delays in younger children might not be obvious to the family. Hence, the number of children with neurodevelopmental deterioration after SE was probably overestimated.

Much controversy still surrounds the question of whether SE can cause brain injury. Low morbidity and mortality rates in children with SE have been reported, especially in those with idiopathic or febrile aetiology.[11,13] However, there are contradictory studies showing that SE is a predictor of poor neurological outcome.[18,19] The critical duration of SE in the production of irreversible long-term sequelae in humans remains unknown. A duration of 1 to 2 hours has been proposed to be critical in some studies.[20,21] The purpose of aggressive treatment

of SE is to minimise neuronal damage caused by systemic and electrical effects of SE. Our treatment protocol was able to end SE within 120 minutes in 80% of cases. This proportion is comparable to that reported by Eriksson and Koivikko.[10] Only four (16%) of the 25 patients in our series—all four with chronic epilepsy—received rectal diazepam before hospital arrival. Prompt diagnosis and management of SE provide the best outcome. The longer an episode of SE continues, the more likely that it will be refractory to treatment. Approximately 80% of seizures will stop if treatment is administered within 15 minutes, compared with only 60% if treatment is administered after 15 minutes of the start of SE.[22] Alldredge et al[23] reviewed 45 episodes of convulsive SE in 38 children who were given prehospital treatment with rectal or intravenous diazepam; treatment shortened the duration of SE by one half and reduced recurrence by one third. Hence, rectal diazepam or buccal midazolam administered before hospital arrival should be considered, because they shorten the duration of SE. However, even prompt use of rectal diazepam may not necessarily prevent SE in certain cases; a large controlled study is needed to clarify the proper treatment of SE.

Our study shows that symptomatic aetiology was related to prolonged and often resistant SE: seizures lasting longer than 60 minutes were associated with neurological deficits. All patients with prolonged seizures belonged to the symptomatic (acute or remote symptomatic) category. It is difficult and often impossible to distinguish neuronal damage caused by aetiological factors from damage as a result of SE itself. We found that young children were more prone to neurological regression following SE than older children. This observation is consistent with those of other studies.[11,14,18] One possible explanation is the correlation of SE aetiology with age; acute symptomatic aetiology tended to be more common in young patients who developed SE than in older children.

New-onset epilepsy developed in three survivors, all of whom had symptomatic disease. It is not surprising that a specific insult, either acute or remote symptomatic, causes brain injury that predisposes the patient to further seizures. Barnard and Wirrell[17] have reported a similar observation. None of the patients in our study who had idiopathic or febrile SE developed epilepsy. However, one would presume that those with idiopathic SE would have a lower threshold for seizures, and that although SE might be the initial presentation, epilepsy would develop subsequently. Furthermore, febrile SE in relation to mesial temporal sclerosis often presents as refractory epilepsy in adolescence or early adulthood. A low patient number and inadequate follow-up time might explain our unexpected observation.

We conclude that SE predominantly affects neuro-logically abnormal children. Most new neurodevelopmental deficits are related to the underlying aetiology of SE. Children with idiopathic or febrile SE have a very favourable outcome. The prompt use of rectal diazepam or buccal midazolam administered by caretakers or paramedics should be encouraged.

References

1. Shorvon SE. Status epilepticus: its clinical features and treatment in children and adults. Cambridge: Cambridge University Press; 1994.
2. Delgado-Escueta AV, Wasterlain C, Treiman DM, Porter RJ. Current concepts in neurology: management of status epilepticus. N Engl J Med 1982;306:1337-40.
3. Leppik IE. Status epilepticus: the next decade. Neurology 1990;40(5 Suppl 2):4S-9S.
4. Tunik MG, Young GM. Status epilepticus in children. The acute management. Pediatr Clin North Am 1992;39:1007-30.
5. Bleck TP. Advances in the management of refractory status epilepticus. Crit Care Med 1993;21:955-7.
6. Gastaut H. Classification of status epilepticus. In: Delgado Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, editors. Status epilepticus: mechanisms of brain damage and treatment. Advances in neurology. New York: Raven Press; 1983:15-36.
7. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:388-99.
8. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and un-provoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993;34:453-68.
9. Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. Epilepsia 2001;42:1461-7.
10. Eriksson KJ, Koivikko MJ. Status epilepticus in children: aetiology, treatment, and outcome. Dev Med Child Neurol 1997;39:652-8.
11. Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83:323-31.
12. Gross-Tsur V, Shinnar S. Convulsive status epilepticus in children. Epilepsia 1993;34(Suppl 1):12S-20S.
13. Verity CM, Ross EM, Golding J. Outcome of childhood status epilepticus and lengthy febrile convulsions: findings of national cohort study. BMJ 1993;307:225-8.
14. Dunn DW. Status epilepticus in children: etiology, clinical features, and outcome. J Child Neurol 1988;3:167-73.
15. Lothman E. The biochemical basis and pathophysiology of status epilepticus. Neurology 1990;40(5 Suppl 2):13S-23S.
16. Wasterlain CG, Fujikawa DG, Penix L, Sankar R. Pathophysiological mechanisms of brain damage from status epilepticus. Epilepsia 1993; 34(Suppl 1):37S-53S.
17. Barnard C, Wirrell E. Does status epilepticus in children cause developmental deterioration and exacerbation of epilepsy? J Child Neurol 1999;14:787-94.
18. Aicardi J, Chevrie JJ. Consequences of status epilepticus in infants and children. Adv Neurol 1983;34:115-25.
19. Hauser WA. Status epilepticus: frequency, etiology, and neurological sequelae. Adv Neurol 1983;34:3-14.
20. Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. Am J Med 1980;69:657-66.
21. Simon RP. Physiologic consequences of status epilepticus. Epilepsia 1985;26(Suppl 1):58S-66S.
22. Knudsen FU. Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children. Arch Dis Child 1979; 54:855-7.
23. Alldredge BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. Pediatr Neurol 1995; 12:213-6.