Frequency and Prognosis of Convulsive Status Epilepticus of Different Causes

A Systematic Review

Aidan Neligan, MSc, MRCP; Simon D. Shorvon, MD, MA, FRCP

We conducted a systematic review of all studies of status epilepticus (SE) with more than 30 patients published between January 1, 1990, and December 31, 2008, to determine the frequencies of the common underlying causes and the extent to which the underlying causes affect the prognosis of an episode of SE. The frequencies of underlying causes vary among studies and show marked geographic differences, but in most studies, the most common underlying causes were cerebrovascular disease and low antiepileptic drug levels. A relatively good prognosis of SE is found when the underlying cause is associated with low antiepileptic drug levels or alcohol abuse, and a relatively poor outcome occurs when the underlying cause is cerebrovascular disease, particularly in the case of SE due to acute cerebral anoxia, but in most conditions, the reported prognosis is variable. Also, when SE occurs in the context of an acute cerebral insult, such as cerebral infection or cerebrovascular disease, the prognosis of the acute cerebral event is worsened.

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It is a prevalent view that the frequency and prognosis of status epilepticus (SE) largely depend on its underlying cause. We examined recent studies providing data on this topic to determine to what extent this view is correct. In this review article, we consider prognosis in relation to mortality (and severe morbidity). We begin the survey at 1990 because one of us (S.D.S.) has previously reviewed all major studies up to 1990.1 We considered in detail only the common causes of SE in the developed world.

SEARCH CRITERIA

We searched the MEDLINE and PubMed databases for all articles published between January 1, 1990, and December 31, 2008, with the term status epilepticus combined with the terms outcome, mortality, morbidity, fatality, prognosis, coma, death, incidence, prevalence, and epidemiology. Only articles written in English or French were reviewed. Of 3043 articles initially identified, all but 529 were excluded on the basis of the title and abstract. The exclusion criteria included case reports, review articles, commentaries, treatment protocols, and studies with fewer than 30 patients. Articles specifically concerned with nonconvulsive SE were excluded, but articles in which data for convulsive SE (CSE) and nonconvulsive SE were given were considered. Inevitably, a distinction between CSE and nonconvulsive SE was not always made in some series, and these articles were included. Prospective and retrospective population- and hospital-based series were included. The search identified 7 population-based studies, with the remainder of the studies cited being hospital based. The reference lists of the identified articles were then examined for additional relevant studies. Common causes of SE were defined as causes listed in at least 1 of the population-based studies of SE that had an incidence greater than 1%. The major studies of CSE in the developing world are also reviewed to identify the predominant causes of CSE, although no attempt is made to analyze prognosis by cause, as is done for studies from the developed world.

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Table 1. Summary of 7 Population-Based Studies of SE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Richmond, Virginiaa</th>
<th>Rochester, Minnesotaa</th>
<th>French-Speaking Switzerlanda</th>
<th>Hessen, Germanya</th>
<th>Californiaa</th>
<th>Bologna, Italya</th>
<th>London, United Kingdoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population, denominator, No.</td>
<td>202 774</td>
<td>1 090 655</td>
<td>1 735 420</td>
<td>743 285</td>
<td>NA</td>
<td>336 767</td>
<td>605 230</td>
</tr>
<tr>
<td>Cases, No.</td>
<td>166</td>
<td>199</td>
<td>172</td>
<td>150</td>
<td>19 491</td>
<td>44</td>
<td>226 total: 176</td>
</tr>
<tr>
<td>Incidence of SE, per 100 000 per year</td>
<td>41 (raw): 61 (adjusted)</td>
<td>18.3 (adjusted)</td>
<td>9.9 (raw): 10.3 (adjusted)</td>
<td>15.0</td>
<td>6.2 (4.9-8.5)</td>
<td>13.1</td>
<td>17-23 (adjusted): 12.5-14 (adjusted first-ever episode of SE)</td>
</tr>
<tr>
<td>Sex ratio, F:M</td>
<td>1:1.2a</td>
<td>1:1.9b</td>
<td>1:1.7b</td>
<td>1:1.9c</td>
<td>1:1.1</td>
<td>1:0.74b</td>
<td>1:1.12</td>
</tr>
<tr>
<td>History of epilepsy, %</td>
<td>42</td>
<td>46</td>
<td>42.4</td>
<td>33</td>
<td>NA</td>
<td>39</td>
<td>7d</td>
</tr>
<tr>
<td>Case fatality, %</td>
<td>22</td>
<td>19</td>
<td>7.6</td>
<td>9.3</td>
<td>10.7</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>Inclusions/exclusions</td>
<td>Patients ≤1 mo old were excluded</td>
<td>Patients with postanoxic encephalopathy were excluded</td>
<td>Only patients ≥18 y old were included</td>
<td>Only generalized CSE cases were included</td>
<td>Only patients ≥20 y old were included</td>
<td>Only CSE was included; only children (&lt;15 y old) were included</td>
<td>Only CSE was included; only children (&lt;15 y old) were included</td>
</tr>
<tr>
<td>Case ascertainment</td>
<td>Prospective hospital record review</td>
<td>Retrospective review using a record linkage system</td>
<td>Prospective hospital record review</td>
<td>Prospective hospital record review</td>
<td>Prospective hospital discharge record review</td>
<td>Prospective active surveillance of hospital admissions</td>
<td>Prospective active surveillance through A&amp;E and hospital admissions</td>
</tr>
</tbody>
</table>

Abbreviations: A&E, accident and emergency; CSE, convulsive status epilepticus; NA, not available; SE, status epilepticus.

a Raw data.
b Adjusted ratio.
c Adjusted figures from the regions with the best case ascertainment (and least prone to selection bias).
d Excludes febrile seizures.

Status epilepticus was defined, according to the International League Against Epilepsy guidelines for epidemiological studies on epilepsy, as a single seizure lasting longer than 30 minutes or a series of epileptic seizures during which function is not regained between ictal events for longer than 30 minutes.2 This definition was adapted by most studies reviewed, when a definition was given.

FREQUENCY AND ETIOLOGY OF SE

Frequency of SE in Population-Based Studies

This review found 7 population-based studies of SE published from Richmond, Virginiaa; Rochester, Minnesotaa; Switzerlanda; Hessen, Germanya; Californiaa; Bologna, Italya; and London, United Kingdoma(Table 1 ). All but the Rochester study3 were prospective and confirmed to the International League Against Epilepsy recommendations for epidemiological studies in epilepsy.2 These studies defined SE as a single epileptic seizure lasting longer than 30 minutes or a series of epileptic seizures during which function is not regained between seizures for longer than 30 minutes; the minimum incidence of SE was 10 to 20 per 100 000, although a higher incidence was reported in the Richmond study3 (41.61 per 100 000 per year). Evidence that the incidence of generalized CSE (GCSE) requiring hospitalization is decreasing is provided in a retrospective study by Wu et al.7 This study was performed using a statewide hospital database to identify all hospitalizations for GCSE in California between 1991 and 1998. Overall, the incidence rate for GCSE was 6.2 per 100 000 population, but this rate decreased by 42%, from 8.5 to 4.9 per 100 000, between 1991 and 1998, a time when the policy of urgent therapy for generalized tonic-clonic seizures lasting more than a few minutes was being promulgated. The incidence of SE was slightly higher in males in all the studies except the one from Italy.8

Race/ethnicity have been recognized as important factors since Delorenzo et al7 noted that the incidence of SE was 3 times higher in the black population compared with the white population (80% nonwhite vs 20% white), a finding that was replicated in the study by Wu et al.7 This may, in part, reflect different socioeconomic or etiologic factors. Age is a dominant factor, with SE incidence forming a U-shaped graph with peaks in the very young and the elderly.

Etiology of SE in Population- and Hospital-Based Studies

In an analysis of the largely hospital-based literature in 1994,1 of 1679 patients in 13 hospital series, SE had no obvious cause in only 19% of patients (11% in children and 13% in the elderly). Febrile SE accounted for 12% of cases and acute metabolic, toxic, and anoxic causes for 14%. Stroke, tumor, trauma, infection, and perinatal causes accounted for 7% to 10% each. When CSE occurs in patients with a history of epilepsy, many cases are due to antiepileptic drug (AED) reduction or withdrawal. In these patients, an acute brain insult is much less commonly the precipitating factor.
More recent population-based studies have reported similar findings as these hospital series (Table 1 and Table 2). Overall, 30% to 44% of patients with SE have a history of epilepsy. Acute symptomatic causes, especially febrile illness, account for up to 60% of cases.

Lowenstein and Alldredge retrospectively reviewed the clinical course of adult patients treated for generalized SE at the San Francisco General Hospital between 1980 and 1989. One hundred fifty-four patients were included, and the 4 most common causes were anticonvulsant drug withdrawal (n=39), alcohol related (n=39), drug toxicity (n=14), and central nervous system (CNS) infection (n=31). No cause was identified in 105 patients.

In the population-based survey of children with first-ever episodes of SE from London, the most common cause of SE was febrile illness (febrile SE), accounting for 32% of all patients, of whom 12% had bacterial meningitis. Seventeen percent of these children had acute symptomatic SE, with acute metabolic disturbance or CNS infections predominating. The contention that the major determinant of outcome in SE is the underlying cause is supported by a study by Rossetti et al, who looked at the effect of treatment on prognosis in 47 patients with SE. They found that outcome was independent of the anesthetic agent used or the extent of the electroencephalographic burst suppression achieved.

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Cause of SE in the Developing World

Studies from Africa, Trinidad, India, and, more recently, China have looked at the incidence, etiology, and prognosis of SE (Table 3). These were all case series, not epidemiologically based, and although the range of causes was different from that in Western Europe and the United States, no frequency data can be derived. Thus, although it seems likely that frequency is higher in the developing world primarily because of the high rate of infection, no data confirm this.

In the study of SE from Trinidad, none of the patients died, and morbidity was 4.9%. In a retrospective study from Senegal, 697 patients with SE were identified during an 11-year period, of whom 48% were younger than 5 years. Infections were responsible for 67% of cases, followed by poorly controlled epilepsy (10%) and cerebrovascular disease (8%). Overall mortality was 25%, with an average delay from onset of symptoms to treatment of 16.6 hours.

In a prospective study from India over 2 years, 85 patients with SE were identified with etiologies as given in Table 3. The mean duration of symptoms prior to treatment was 18.02 hours (range, 1-72 hours). Overall mortality was 10.5%, with lack of response to first-line treatment being a predictor of mortality (P < .001). Longer duration was associated with increased morbidity (P = .001).

Two studies have recently been published from Africa. In a retrospective study from Ethiopia, overall mortality was 20.2% (n=24), with another 4 patients having deteriorated from baseline; therefore, 23.5% (n=28) had a poor outcome overall. Predictors of poor outcome were acute symptomatic etiology, stroke, systemic disease, and human immunodeficiency virus/AIDS and its CNS complications. Idiopathic SE and SE due to AED noncompliance.

Table 2. Major Etiologies of SE by Population-Based Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Richmond, Virginia</th>
<th>Rochester, Minnesota</th>
<th>French-Speaking Switzerland</th>
<th>Hessen, Germany</th>
<th>California</th>
<th>Bologna, Italy</th>
<th>London, United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low AED levels</td>
<td>21 (P)/24 (A)</td>
<td>1</td>
<td>8.1</td>
<td>8.7</td>
<td>3.9 NA</td>
<td>NA</td>
<td>0.5</td>
</tr>
<tr>
<td>CNS infections</td>
<td>52 (P)/3 (A)</td>
<td>8.5</td>
<td>NA</td>
<td>0.6</td>
<td>NA</td>
<td>10.2</td>
<td>32</td>
</tr>
<tr>
<td>Febrile</td>
<td>NA</td>
<td>8</td>
<td>14.9</td>
<td>0.6</td>
<td>NA</td>
<td>10.2</td>
<td>32</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10 (P)/22 (A)</td>
<td>19.1</td>
<td>30.5</td>
<td>66.7</td>
<td>12.4 41</td>
<td>0.5</td>
<td>32</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>13 (A)</td>
<td>NA</td>
<td>NA</td>
<td>7.3</td>
<td>3</td>
<td>10.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Trauma</td>
<td>3 (A)</td>
<td>4.5</td>
<td>NA</td>
<td>12</td>
<td>18</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>CNS tumors</td>
<td>7 (A)</td>
<td>NA</td>
<td>NA</td>
<td>3.5</td>
<td>13.3 0</td>
<td>3</td>
<td>17.5</td>
</tr>
<tr>
<td>Metabolic disturbance</td>
<td>5 (P)/13 (A)</td>
<td>5.5</td>
<td>NA</td>
<td>26.7</td>
<td>10 32</td>
<td>0.5</td>
<td>17.5</td>
</tr>
<tr>
<td>Degenerative brain disease/</td>
<td>38 (P)/25 (A)</td>
<td>5.5</td>
<td>NA</td>
<td>26.7</td>
<td>10 32</td>
<td>0.5</td>
<td>17.5</td>
</tr>
<tr>
<td>CNS anomalies</td>
<td>Medication induced/overdose</td>
<td>2 (P)/3 (A)</td>
<td>2</td>
<td>NA</td>
<td>10.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Anoxia/hypoxia</td>
<td>5 (P)/13 (A)</td>
<td>5 (P)/13 (A)</td>
<td>10 Excluded</td>
<td>NA</td>
<td>8 9.1 0</td>
<td>0.5</td>
<td>17.5</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>5 (P)/3 (A)</td>
<td>17.5</td>
<td>8.7</td>
<td>3.5</td>
<td>13.3 0</td>
<td>3</td>
<td>17.5</td>
</tr>
</tbody>
</table>

Abbreviations: A, adults; AED, antiepileptic drug; CNS, central nervous system; NA, not available; P, pediatric; SE, status epilepticus.

a Some studies give only percentages for some etiologies.

b In the Richmond study, etiologies were separately given for the pediatric and adult populations.

c Pediatric population.

d Percentage of the total cohort (low AED levels were the cause of SE in 18.9% of patients with epilepsy).

e Patients with epilepsy only.

f Nonepileptic patients.

g Combination of systematic metabolic disorders and postanoxic encephalopathy.
were associated with a good prognosis. The mean and median durations of SE at hospital arrival were 44.7 and 24.0 hours, respectively. The other is a retrospective study of all pediatric patients with CSE admitted to a rural district hospital in Kenya. Overall, there were 388 episodes of CSE, of which 155 (40%) were confirmed (directly by the authors). Infectious causes were responsible for SE in 274 patients (71%). Fifteen percent of patients (n = 59) died in the hospital (75% [n = 44] within the first 48 hours). Another 22 patients died during 3-year follow-up (overall mortality of 21%). Death before discharge was more common in those with confirmed CSE (36 [23%] vs 23 [10%], P < .001). Another 46 patients (12%) had neurological deficits at discharge, of which motor deficits were the most common (87%). As before, the proportion with a neurological deficit was higher in those with confirmed CSE (28 [18%] vs 18 [8%], P = .002). Subanalysis of those with confirmed CSE using multivariate analysis showed acute bacterial meningitis and focal-onset seizures to be the only significant risk factors for mortality, whereas hypoglycemia and age younger than 1 year were significant risk factors for morbidity.

In summary, studies of SE from the developing world, where resources are inevitably poor, typically demonstrate prolonged seizure duration prior to presentation. Overall, infectious causes constitute most cases of de novo SE, whereas AED noncompliance is an important cause for those with previous epilepsy. The overall prognosis, though, is not appreciably worse than that in studies from Europe.

Impact of the Underlying Etiology on Morality

The importance of etiology was demonstrated in a recent study from Serbia of 750 patients with 920 episodes of SE. Of the 120 patients (16%) who died, the death was judged to be due to the underlying (or comorbid) cause in 65.8% or to a combination of the underlying disease and other causes in a further 22.5%.

FREQUENCY AND PROGNOSIS OF DIFFERENT CAUSES

Stroke and SE

Stroke is a significant cause of SE in the elderly, particularly in those with no history of seizures in epidemiological studies of SE (Table 2). In the California study, acute stroke accounted for only 1.6% of cases but was associated with the second highest mortality of 25.6%. In a review of 193 patients with refractory SE, stroke was the underlying cause in 20%. In a population-based study from Germany, long-term mortality in patients with a first episode of cerebrovascular-related SE was 57% compared with 48% in patients with acute stroke without SE. Multivariate analysis showed that patients with SE had, after 6 months, twice the risk of death compared with patients with stroke with-

Table 3. Studies of Status Epilepticus in the Developing World

<table>
<thead>
<tr>
<th>Study design</th>
<th>Nigeriaa</th>
<th>Trinidadb</th>
<th>Brazia</th>
<th>Tunisiab</th>
<th>Indiaa</th>
<th>Senegala</th>
<th>Thailld</th>
<th>Iranb</th>
<th>Congoa</th>
<th>Kenya22</th>
<th>Ethiopia23</th>
<th>Chinad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study years</td>
<td>R</td>
<td>R</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R/P</td>
<td>R/P</td>
<td>R/P</td>
</tr>
<tr>
<td>Patients, No.</td>
<td>41</td>
<td>41</td>
<td>111</td>
<td>139</td>
<td>85</td>
<td>697</td>
<td>32</td>
<td>135</td>
<td>607</td>
<td>388</td>
<td>119</td>
<td>220</td>
</tr>
<tr>
<td>History of seizures, %</td>
<td>NA</td>
<td>NA</td>
<td>59.4</td>
<td>10</td>
<td>20</td>
<td>9.9</td>
<td>75</td>
<td>37</td>
<td>14.5</td>
<td>30.8</td>
<td>38.7</td>
<td>50</td>
</tr>
<tr>
<td>Etiology, %</td>
<td>Febrile</td>
<td>NA</td>
<td>5</td>
<td>5.4</td>
<td>41</td>
<td>NA</td>
<td>8.6</td>
<td>0</td>
<td>51.1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>AED noncompliance</td>
<td>NA</td>
<td>NA</td>
<td>18.9</td>
<td>10</td>
<td>20</td>
<td>9.9</td>
<td>9.4</td>
<td>28.2</td>
<td>3.8</td>
<td>5.9</td>
<td>17.6</td>
<td>15.5</td>
</tr>
<tr>
<td>CNS infection</td>
<td>41.5</td>
<td>15b</td>
<td>10.8</td>
<td>18.7</td>
<td>28</td>
<td>67</td>
<td>65.6</td>
<td>7.4</td>
<td>74.5c</td>
<td>8.0d</td>
<td>36.1</td>
<td>32.7</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>34.1</td>
<td>NA</td>
<td>10.8</td>
<td>10.1</td>
<td>11</td>
<td>4.3</td>
<td>0</td>
<td>2.9</td>
<td>NA</td>
<td>NA</td>
<td>13.4</td>
<td>11.4e</td>
</tr>
<tr>
<td>Stroke</td>
<td>14.6</td>
<td>NA</td>
<td>9.9</td>
<td>5.8</td>
<td>15</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>12.6</td>
<td>10.9</td>
</tr>
<tr>
<td>Progressive symptomatic, %</td>
<td>9.8 frontal lobe tumors</td>
<td>NA</td>
<td>2.7</td>
<td>7</td>
<td>NA</td>
<td>1.2</td>
<td>3.1</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>10.9</td>
<td>NA</td>
</tr>
<tr>
<td>Remote symptomatic, %</td>
<td>NA</td>
<td>51</td>
<td>NA</td>
<td>6</td>
<td>7</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Idiopathic, %</td>
<td>NA</td>
<td>29</td>
<td>25.3</td>
<td>6</td>
<td>19</td>
<td>NA</td>
<td>18.8</td>
<td>8.9</td>
<td>NA</td>
<td>NA</td>
<td>16.8</td>
<td>7.7f</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>100</td>
<td>0</td>
<td>19.8</td>
<td>15.8</td>
<td>10.5</td>
<td>24.8</td>
<td>6.3</td>
<td>12.6</td>
<td>26.5</td>
<td>15.2</td>
<td>20.2</td>
<td>15.9</td>
</tr>
<tr>
<td>Morbidity, %</td>
<td>NA</td>
<td>4.9</td>
<td>NA</td>
<td>36</td>
<td>NA</td>
<td>13.6</td>
<td>56.3</td>
<td>66.7</td>
<td>27.3</td>
<td>2.9</td>
<td>11.9</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiepileptic drug; CNS, central nervous system; NA, not available; P, prospective; R, retrospective.

aConfirmed (n = 155) and probable (n = 233) cases of convulsive status epilepticus.
bFifteen percent of causes were listed as acute symptomatic.
cThe number of CNS tumors and developmental malformations combined.
dThe number of toxic, hypoxic, and metabolic cases combined.
eThe number of toxic, hypoxic, and metabolic cases combined.
fThe number of CNS tumors and developmental malformations combined.
out SE (hazard ratio, 2.12; 95% confidence interval [CI], 1.04-4.32; P = .04).

In a comprehensive study of the frequency of SE, Rumbach et al.28 reviewed 3205 patients with first-time stroke over an 8-year period. Of these, 159 had first-time poststroke seizures, and SE was recognized in 31 patients, with SE being the presenting epileptic symptom in 17 (SE occurring within 14 days of the stroke in 7 patients). In 4 patients, stroke began with SE, and in the remaining 10, SE developed after 1 or more seizures. After follow-up of 47 months, 15 patients had died, with 5 deaths being directly related to SE. Additional seizures occurred in 8 of the initial SE cases and in all 14 patients with SE after 1 or more seizures. The study concluded that SE in stroke has a poor prognosis but that initial SE as a first epileptic symptom was not predictive of subsequent seizures.

A smaller study29 looked at stroke as a remote symptomatic cause of SE in a cohort of patients with poststroke first-time seizures. One hundred eighty such patients were identified of 1747 patients with stroke. Of these 180 patients, 17 (9%) developed SE. The risk of SE was higher in those with higher disability (Rankin scale score >3; odds ratio [OR], 4.36). Recurrent SE occurred in 5 patients, all of whom had a first episode of SE within 7 days after stroke. Early-onset SE was associated with a higher risk of recurrence of SE (P = .003) and a higher mortality rate (P = .04).30

Bateman et al.31 using the US Nationwide Inpatient Sample over an 8-year period, identified 718531 hospitalizations for acute ischemic stroke; 1415 of these patients (0.2%) developed GCSE. Of 102763 patients admitted to the hospital with intracranial hemorrhage, GCSE developed in 266 (0.3%). In-hospital mortality was significantly higher in those with GCSE and acute ischemic stroke or intracranial hemorrhage, particularly if analysis was restricted to patients with a length of stay longer than 1 day (acute ischemic stroke: 28.4% vs 9.2%, P < .01; intracranial hemorrhage: 30.1% vs 24.3%, P = .03). Other markers of morbidity, such as pneumonia, need for mechanical ventilation, tracheotomy, and length of stay longer than 7 days, were statistically significantly associated with concomitant SE. In this study, no attempt at defining SE was made. In the Northern Manhattan Stroke Study, of 904 patients with stroke, 37 (4.1%) developed early seizures; SE occurred in 10 patients: 1.1% of the entire cohort of patients with stroke and 27% of all patients with poststroke epileptic seizures.31

Waterhouse et al.32 prospectively followed up a cohort of 83 patients with SE and stroke (44 with acute stroke and 39 with remote stroke) and compared them with 159 controls (those with acute stroke only). Acute stroke and SE had mortality of 39%, representing an almost 3-fold increase compared with those with acute stroke only (14%) and those with SE and remote stroke (5%) (P < .001). In addition, there was an almost 8-fold difference in mortality rates between the acute stroke and SE group and the remote stroke and SE group. This difference was not accounted for by age, sex, or radiographic lesion size. Logistic regression analysis demonstrated a statistically significant synergistic effect of combined injuries of cerebrovascular ischemia and SE.

When SE occurs after stroke, it is associated with higher functional disability, and poor functional disability was the only identified predictor of SE in the study by Velioğlu et al.33 The same study found that early-onset SE (within the first 7 days after stroke) was associated with a higher risk of further episodes of SE and higher mortality rates than late-onset SE.33 Stroke severity and mortality were also found to be higher in patients with early-onset SE in the studies by Rumbach et al.28 and Afsar et al.33

In a series from Turkey,34 of 121 patients with SE, poststroke SE occurred in 30 (24.8%). Thirty percent of cases were GCSE, and the remaining were nonconvulsive SE. Sixty-seven percent of cases were defined as early onset (occurring with 2 weeks), and only ischemic stroke was associated with late-onset SE. Overall mortality was 43.3%, with disability (as defined by National Institutes of Health Stroke Scale scores) in the early-onset group significantly associated with increased mortality (P = .02). This mortality figure is similar to that found by Towne et al.35 for stroke-related SE (26.3%). In a retrospective study36 of 107 episodes of SE in China, cerebrovascular disease was the most common cause (27%) and was the strongest predictor of poor outcome after SE, with an OR of 5.57 (95% CI, 1.45-21.41; P = .001). In a large study of mortality rates in SE,37 again based on hospital coding and without clear definitions established, cerebrovascular disease was a predictor of in-hospital mortality, with an OR of 2.08 (95% CI, 1.13-3.82) and mortality of 22% (P < .001), and also of the need for mechanical ventilation (P < .001).

In summary, stroke (acute or remote symptomatic) is the cause of approximately 20% of cases of SE but is a more prevalent cause of SE with increasing age. Status epilepticus can be the first epileptic presentation after stroke; in this situation, it is found not to be a predictor of subsequent epilepsy. Patients with stroke and SE have a poorer prognosis than do patients with stroke alone.27,32 Stroke-induced SE is consistently found to have somewhat higher mortality and morbidity rates compared with other causes, especially with increasing age. For those with stroke who develop refractory SE, the prognosis is particularly poor and the mortality rate is high.

**Alcohol Abuse, Substance Abuse, and Drug-Induced SE**

Alcohol abuse (intoxication or withdrawal) has been found to be a common cause of SE in many population- and hospital-based studies, with a reported range of 8.1% to 25%, although alcohol was not reported to be a major cause in some studies, such as the Minnesota4 and Swiss5 studies. Alcohol-related SE generally has a favorable outcome, with most studies reporting mortality of 0% to 10% (9.6% in the California study).7

Alldredge and Lowenstein36 examined all 249 cases of adults with GCSE admitted to a single center during a 12-year period and identified 27 patients (10.8%) in whom alcohol abuse was the only identifiable precipitating cause. In 12 patients (44%), SE was the first presentation of alcohol-related seizures. Twenty-two patients (81.5%) had returned to baseline at the time of discharge, although time to gross recovery of mental status was at least 12 hours in 24 of the 27 patients. Four patients (14.8%) had new neu-
In summary, it can be concluded that the reduction or withdrawal of AEDs is a relatively common cause of SE in patients with a history of epilepsy and that these or low AED levels are generally associated with a good prognosis even in patients with refractory SE.

Severe Acute Cerebral Anoxia/Hypoxia and SE

Anoxia, usually after cardiac arrest in adults, can result in deep coma with myoclonic jerking, and this is assumed by some authorities, but not all, to be a form of SE. This dichotomy of opinion is evident by the fact that postanoxic SE cases were excluded from the Swiss study. In the population-based studies, hypoxia is the cause of SE in 8% to 13% of patients, with an associated mortality typically in the range of 60% to 80%, although mortality of 100% was reported in the Bologna study (4 patients). In this study, the 30-day case-fatality rates were calculated with (39%) and without (33%) postanoxic patients.

In a study of 166 postanoxic survivors of cardiac arrest treated with hypothermia, postanoxic SE was present in 24%, with mortality of 80% compared with overall mortality of 71% (P < .001). Postanoxic SE was associated with
a higher mortality rate regardless of the type of acute cardiac rhythm or hypothermia treatment. A retrospective study of mortality in CSE by Koubeissi and Alshekhlee, hypoxia–ischemic brain injury–associated SE was the strongest predictor of mortality, with an OR of 9.85 (95% CI, 6.63–14.6) and mortality of 69%, and was a significant risk factor for the need for mechanical ventilation (P < .001). In the study by Towne et al, anoxia-induced SE was responsible for 11.9% of cases, with mortality of 60%, and was associated with the highest OR for mortality (OR, 8.22; P < .001).

In a study of the outcomes of 114 patients after cardiopulmonary resuscitation, 50 patients (44%) had seizures or myoclonus. Of 36 patients (32%) with SE, 10 (9%) had SE other than myoclonic SE (MSE), only 1 (10%) of whom was alive at 3 months; 19 (17%) had MSE, 3 of whom (16%) were alive at discharge and none at 6 months; and 7 (6%) had status myoclonus other than MSE, none of whom were alive at discharge. When the subgroups with SE were considered individually, only MSE had significantly poorer survival (P < .01).

In a study of 147 admissions with SE, of which 20 (13.6%) were due to bacterial meningitis and 20 (13.6%) to encephalitis, both of which were associated with high morbidity and mortality. Infections of the CNS were the cause of SE in 10.6% of cases in the study by Sagduyu et al and were associated with 71.4% mortality (OR, 13.88; P = .01). The CNS infections causing SE were also predictive of a poor outcome in the study by Hui et al (adjusted OR, 30.27; P = .003). The refractory nature of SE induced by encephalitis and its rather poor outcome has been demonstrated in several hospital-based studies. In a review of 22 cases of refractory SE in children, presumed or agent-identified encephalitis was the underlying cause in 10 patients, of whom 4 died, 5 developed seizures, and 1 returned to baseline. Holkamp et al found that encephalitis was the cause of refractory SE in 22% of cases compared with only 4.3% of cases of nonrefractory SE (P < .02). In a case series of 17 cases of refractory GCSE treated with continuous infusion of midazolam, 4 cases were found to be due to viral encephalitis: 1 patient died, 2 had moderate to severe encephalopathy, and 1 made a full recovery. Lin et al reviewed all cases of SE related to presumed encephalitis in the pediatric intensive care unit during a 4-year period. Of 46 patients, 20 (43.4%) developed refractory SE, with 30% mortality. Of the survivors, all but 1 developed subsequent epilepsy or neurological deficits, and none returned to baseline. Of 26 patients with nonrefractory SE, 4 died, 16 developed epilepsy or neurological deficits, and only 6 returned to baseline.

Population-based studies tend to show a more favorable outcome, with a lower frequency of refractory cases. For example, in the California Encephalitis Project, which is an ongoing project aimed at determining the cause of encephalitis, all patients identified with encephalitis were subdivided into 3 categories: refractory SE (defined as SE that requires anesthetic coma for management) (4%), nonrefractory SE (40%), and patients without seizures (56%). Patients with refractory SE associated with encephalitis tended to be younger (median age, 10 years) and had a poor outcome, with 28% dying within 2 years and 56% being neurologically impaired or undergoing rehabilitation.

In a study of the clinical characteristics and factors of postencephalitic epilepsy in 44 children from Taiwan, SE occurring as the first seizure (P < .05) and herpes simplex encephalitis (P < .01) were associated with a poor prognosis and an increased risk of intractable epilepsy. There are cases reported in the literature of acute encephalitis associated with refractory repetitive partial seizures.

In resource-poor countries, cerebral infections play a much more prominent role in the causation of SE, especially in children but also in adults. Consideration of prognosis in SE due to tropical infection is beyond the scope of this article but was one of the topics covered at the recent Innsbruck Colloquium on Status Epilepticus in April 2009.

In summary, acute CNS infections are an important cause of SE in hospital studies and are associated with significant morbidity and mortality. Encephalitis is associated with a high proportion of refractory compared with nonrefractory cases, but many patients with encephalitis do not develop SE, and SE is by no means invariably refractory. However, for those who survive refractory or nonrefractory SE caused by encephalitis, there is a substantial risk of subsequent epilepsy.

CNS Infections, Encephalitis, and SE

Acute CNS infection and encephalitis are important causes of SE, particularly in children, typically accounting for approximately 1% to 12% of all cases in various series from the developed world, and are a more common cause of SE in children than in adults. In the California study, acute CNS infection was the cause of SE in 0.6% of patients, with a median age of 42 years and mortality of 32.6%. In the NLSTEPSS, 6% of children (n = 11) with SE had acute bacterial meningitis and 4% (n = 7) had a viral CNS infection. Moreover, 3 of the 7 children who died had acute bacterial meningitis. The mortality for CNS infections in the study by Koubeissi and Alshekhlee was 3%.

In a retrospective study of all admissions to a pediatric intensive care unit in Montreal over a 10-year period, there were 147 admissions with SE, of which 20 (13.6%) were due to bacterial meningitis and 20 (13.6%) to encephalitis, both of which were associated with high morbidity and mortality. Infections of the CNS were the

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Cerebral Tumor and SE

Brain tumors are an uncommon cause of SE, representing 2% to 5% of cases in most studies but 12% of cases in the Hessen study. The associated mortality is typically in the range of 0% to 20%.

One study specifically looked at the clinical implications of SE in patients with neoplasms. Thirty-five patients were retrospectively identified with cerebral neoplasms and SE. Twenty-five patients (71.4%) had a primary brain tumor, the most common of which was high-grade glioma (n = 11) followed by low-grade glioma (n = 6). Ten patients had systemic tumors with presumed or identified cerebral metastases. Fifteen patients (43%) had a history of seizures, and 20 (57%) were taking AEDs at the time of SE. Status epilepticus occurred at the time of diagnosis (10 patients; 29%), during tumor progression (23%), or while the tumor was stable (23%). Only 1 confirmed case occurred during a period of tumor regression. Thirty-day mortality was 23% (n = 8), with 50% dying during hospitalization for SE. The only significant factor in predicting 30-day mortality was tumor histologic features, with 3 patients (27%) with primary brain tumors dying compared with 5 patients (50%) with systemic tumors (P = .01). All cases of SE were controlled. In further follow-up, age was associated with higher mortality (5 patients [71%] >70 years and 15 patients [54%] ≤70 years died at a median of 44 and 154 days, respectively; P = .049).

In summary, primary brain tumors or cerebral tumors are an uncommon cause of SE, perhaps reflecting their subacute or chronic rather than acute nature, and the seemingly paradoxical benign prognosis of brain tumor–related SE is possibly due to their propensity (particularly frontal lobe lesions) to cause partial SE (simple focal motor, epilepsy partialis continua, or complex partial) rather than GCSE, with its associated better prognosis. Status epilepticus occurs more frequently with primary brain tumors and usually at the time of diagnosis or during a period of tumor progression. Based on evidence from 1 small study, systemic tumors (with cerebral metastases) with SE seem to be associated with a higher risk of death.

Trauma and SE

Trauma is also an uncommon cause of SE, typically accounting for 0% to 10% of cases in the major studies, with associated mortality of up to 25% (Table 4). Head trauma was associated with 0% mortality in the study by Koubeissi and Alshekhlee. In a series of 94 patients with moderate to severe traumatic brain injury (TBI) who underwent continuous electroencephalography, seizures were detected in 21 (22%), manifesting as focal motor twitching or atypical myoclonus in 6 and nonconvulsive in 2. All the patients with SE died: 2 as a result of sepsis after control of SE, 3 as a result of progressive neurological deterioration, and 1 as a result of respiratory arrest after discharge.

In a study of the impact of acute symptomatic seizures on mortality and risk of subsequent epilepsy, of 262 patients with acute symptomatic seizures, TBI was the cause in 91 (34.7%). Of the 148 patients with a first unprovoked seizure, 37 (25%) had a history of TBI. Ten patients (11%) with acute TBI had SE, which was significantly less than that seen with acute stroke (36.3%) and acute CNS infections (58.8%). Similarly, those with a history of TBI with a first unprovoked seizure were less likely to present with SE (16.2%) compared with those with a history of stroke (22.8%) or CNS infection (90%). Thirty-day mortality was 11% in those with acute symptomatic seizures due to TBI, and 10-year mortality was similar in those with acute symptomatic and unprovoked seizures with a history of TBI.

In summary, acute (or remote) trauma is an uncommon cause of SE and seems largely to result in a favorable outcome. How accurate a reflection this is of situations in which patients are artificially ventilated anyway after severe TBI and who have significant mortality and morbidity is unclear, and it is possible that ascertainment of such cases was not complete in the large reported series.

Metabolic Disorders and SE

Metabolic disorders are the cause of SE in 2% to 35% of cases in reported series, with associated mortality of up to 31%. Acute metabolic disturbance (electrolyte imbalance, hypoglycemia, hypocalemia, or hypomagnesemia) was the cause of SE in approximately 3% of children in the NLSTEPSS. In the San Francisco study, 4% of cases were due to metabolic causes, 50% of which failed to respond to first-line treatments, and were associated with poor outcome (severe neurological deficit requiring full supportive care or death) in 65%.

Acute metabolic causes were the origin of SE in 11.5% of patients, with mortality of 31%, in the study by Towne et al. Acute metabolic causes were responsible for 20%, 22%, and 26% (8 of 31) of refractory SE cases, with mortality of 25%. However, patients with metabolic disorders and GCSE were significantly more likely to require mechanical ventilation (P < .001), with a 3-fold increase in mortality for those who required mechanical ventilation compared with those who did not (7.43% vs 2.22%; OR, 2.79).

In summary, acute metabolic disorders are common causes of SE (5%–35%), with a significant mortality rate (10%-35%) and an increased risk of mechanical ventilation in acute metabolic disturbance–related SE, which is itself an independent risk factor for poorer outcome.

Cryptogenic SE

Despite investigations, the etiology of SE remains undetermined in many cases. In the Richmond study, approximately 3% of cases were classified as idiopathic, with mortality of 22%. In the Minnesota study, 17.5% of cases of SE were classified as idiopathic/cryptogenic, and the etiology of SE was unknown in 13 patients (8.7%), 1 (7.7%) of whom died, in the Hessen study. In the NLSTEPSS, 21 patients (11.9%) were classified as idiopathic or cryptogenic, with 0% mortality, and in the San Francisco study, the cause of SE was unknown in 8 patients (5.2%), and 5
(62.5%) had a good outcome. In the study by Sholtes et al,11 the etiology of SE was unknown in 110 patients (31.8%), 100 (91%) of whom had a good outcome, 7 (6.4%) of whom had associated morbidity, and 3 (2.7%) of whom died. In the study by Towne et al,14 14.2% of cases of SE were classified as idiopathic, with associated mortality of 19.4%. The cause of SE was unknown in 7 patients (8.4%) with SE in the study by Holtkamp et al,19 none of whom developed refractory SE (P = .02).

In a retrospective review of all cases of unprovoked seizure and SE in Rochester over a 30-year period, Logroscino et al30 identified 291 people with a first brief unprovoked seizure and 16 with SE. There were 5 deaths (all aged >65 years) in those with SE. Compared with people with seizures, the adjusted relative risk of death in those with SE was 2.4 over 10 years. This risk was more marked in those older than 65 years (relative risk, 5.1; 95% CI, 1.6-15.7) and in those with SE who later developed epilepsy (5 of 16, 31.2%) (6.3; 1.5-26.0). The standardized mortality ratio for SE was 2.6 (95% CI, 0.8-5.3).

In summary, the etiology of SE remains obscure in approximately 5% to 15% of patients. In these idiopathic or cryptogenic cases, SE is associated with a variable prognosis. Mortality rates are generally (but not always) low, but up to one-third of the patients will develop subsequent epilepsy, which is associated with a higher long-term mortality rate compared with the general population.

**IMPORTANCE OF ETIOLOGY ON OUTCOME**

In this review, we have demonstrated that the outcome of SE is strongly related to the nature of the underlying cause.59 Status epilepticus associated with causes such as low AED levels and alcohol abuse have a relatively good prognosis, with reported mortality in the case series of less than 10%, whereas causes such as metabolic disorders, cerebrovascular disease, and, particularly, anoxia/hypoxia are associated with much poorer outcomes (Table 4).

It is also clear that when SE occurs in the setting of an acute neurological insult, the prognosis is worse than in cases without, particularly in cases of stroke,27,32 meningitis,46 and postanoxic SE.44,55 Of course, this may not be a direct causal relationship because the occurrence of SE may itself also reflect the severity of the underlying pathology.

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