Unprovoked Status Epilepticus: The Prognosis for Otherwise Normal Children With Focal Epilepsy

WHAT'S KNOWN ON THIS SUBJECT: The outcome of status epilepticus in children depends on the etiology. In otherwise normal children who have ≥1 episodes of unprovoked status epilepticus as part of the evolution of their epilepsy, the seizure and intellectual outcome is unclear.

WHAT THIS STUDY ADDS: Based on population-based data and 20 to 30 years' follow-up of normal children with focal epilepsy, one-third with status epilepticus had recurrence of status. Reassuringly, intelligence, seizure control, and rate of remission were not altered compared with those without status epilepticus.

abstract

OBJECTIVE: To document the effect of unprovoked status epilepticus (SE) on the prognosis for otherwise normal children with focal epilepsy.

METHODS: From the Nova Scotia Childhood Epilepsy Study (population-based), we identified patients with focal epilepsy, normal intelligence, and neurologic examination and follow-up ≥10 years. We compared those with and without unprovoked SE.

RESULTS: One hundred eighty-eight cases had a mean follow-up of 27 ± 5 years with no deaths from SE. Thirty-nine (20%) had SE, 19 of whom experienced their first seizure. The number of episodes of SE was 1 in 27 patients (69%) and 2 to 10 in 12 patients. At onset 9 of 39 (23%) SE patients and 35 of 149 (23%) no-SE patients had specific learning disorders. At follow-up, 11 (28%) SE and 49 (33%) no-SE patients had learning disorders (P = not statistically different [ns]). Grades repeated, high school graduation, and advanced education did not differ. The number of antiepileptic drug (AED) used throughout the clinical course was the same: 22/39 (56%). SE patients used ≤2 AEDs versus 99 of 149 (64%) no-SE patients (P = .2). The distribution of patients using 3 to 11 AEDs was similar. The remission rate (seizure-free without AEDs at the end of follow-up) for SE patients was 24 of 39 (61%) versus 99 of 149 (66%) in no-SE (P = .5). Intractable epilepsy occurred in 15% SE and 11% of no-SE cases.

CONCLUSIONS: SE often recurs but apparently has little influence on long-term intellectual and seizure outcome in normally intelligent children with focal epilepsy. Pediatrics 2012;130:e501–e506
There is an abundant literature that documents the adverse effects of convulsive status epilepticus (SE), although clinical evidence indicates that most children with an episode of SE recover unchanged after an episode of treated SE. SE is considered to be a medical emergency with a quick response deemed critical, even though the cause of the SE is by far the most important predictor of outcome. Acute symptomatic SE from disorders such as encephalitis or head injury is often followed by serious, permanent neurologic deficits. Children with epilepsy may have unprovoked SE. In a sense, the SE is just a long one of their seizures. It is less certain how much influence SE has on the clinical outcome in these children because of the confounding effects of different epilepsy syndromes and degrees of preexisting neurologic comorbidities. However, in our experience, parents are typically extremely upset because convulsive SE treatment in a child with epilepsy implies ambulance transport and emergency care. After the SE has stopped, there are 4 main issues regarding prognosis: the recurrence risk, the possibility of brain injury from the SE, the risk of less successful seizure control, and the influence of SE on long-term remission.

In this article, we have attempted to answer these issues about prognosis with data from the Nova Scotia Childhood Epilepsy population-based cohort. For clarity, we have elected to study the largest, easily recognized group children with epilepsy: otherwise normal children with focal epilepsy. Our study is restricted to convulsive SE.

METHODS

Cases of SE were selected from the Nova Scotia Childhood Epilepsy population-based cohort. SE was defined in the conventional way: ≥30 minutes of unconsciousness with a continuous convulsive seizure or repeated shorter convulsive seizures without return of consciousness between seizures for >30 minutes. Consciousness was determined by parents and physicians in the clinical setting and was without a rigorous definition. All of the episodes of SE were unprovoked, and none were acute symptomatic or febrile.

The methodology for the Nova Scotia Childhood Epilepsy population-based cohort has been described in several previous articles. In Nova Scotia, physicians reported that they always request an EEG when a child presents to the health care system with an unexplained seizure. Therefore, the initial case finding method was clinical reports from a central EEG reading facility for the Province of Nova Scotia. Medical records were then reviewed, and nearly every child had been seen by a pediatric neurologist. When there was doubt about the diagnosis, we contacted the family directly for more details. In this fashion, we were able to identify all children with newly diagnosed epilepsy (≥2 unprovoked seizures) in Nova Scotia between 1977 and 1985. We have had intermittent contact with these families and patients since that time. In 2009–2011, we recontacted patients and often their parents to gather data for this article.

Eligible patients were 1 month to 16 years of age at the time of their second unprovoked seizure and residents of Nova Scotia for at least the first 2 seizures. SE could have occurred as the first unprovoked seizure or at any time in the subsequent course. For this study, all patients experienced only focal seizures (includes focal with secondary generalization) through their entire clinical course. Patients were included if their overall intelligence was judged to be normal and their neurologic examination did not reveal any problems sufficient to interfere with activities of daily living. Follow-up had to be at least 10 years from the date of their first seizure. Patients were excluded if they had generalized seizure types or mental handicap. Specific learning disorders with preserved overall intelligence (IQ >70) were permitted. More than 90% of those with specific learning disorders had this impression confirmed with standard psychometric testing. A wide variety of psychometric testing was carried out at many ages by different psychologists, particularly in the school system and less often by tertiary-level neuropsychologists. Therefore, we have not provided details.

Data were analyzed by using that statistical package SPSS version 15.0. χ² was used for nonparametric comparisons and t tests for parametric data with 1-tailed tests on the grounds that it is unlikely that SE improves outcome. Statistical significance was defined as P ≤ .05.

RESULTS

In the overall cohort, 254 patients were potentially eligible for study; however, 66 had a follow-up <10 years and were excluded. The remaining 188 (74%) met all of the eligibility criteria and had a follow-up of >10 years and are the subjects for this report. There were 107 male and 81 female patients with an average follow-up of 27.8 ± 5 (SD) years. For all cases, we reviewed the medical records. Additional information came from the patient only (21%), a parent only (8%), the patient plus a parent (62%), other sources such as spouse (4%), and chart only (13%). One patient in the original cohort died of SE, but his death occurred only 14 months after the onset of epilepsy, and therefore, he was not eligible for this study. There were no additional deaths from SE.

There were 39 eligible patients with SE (17 male and 22 female patients) and 149 without SE. SE occurred for the first time at an average age of 112 ± 93 months (range 4–340) and was the first seizure in 20 (51%) patients. For those with SE that was not at onset,
the interval from onset of epilepsy to SE averaged 71 months (range 2–212 months). All patients came to a hospital emergency department for treatment of their SE; although in many, the SE was over by the time of assessment. All 20 patients with SE as their first seizure were hospitalized. When SE occurred later in the clinical course, 15 of 19 were hospitalized. Nearly all patients were treated with benzodiazepines, some received intravenous phenytoin or phenobarbital. No patient had refractory SE status to the point of requiring anesthesia or barbiturate coma.

Table 1 shows the demographic characteristics for the SE and non-SE groups and details of their seizure and intellectual outcome. Using all of the information available through the clinical course, the cause of epilepsy remained unknown in 53% of those with SE and 68% in those without SE (P = .2).

### Number of Episodes of SE

Overall, 27 (69%) had a single episode of SE and 12 (31%) had more: 7 had 2 episodes of SE, 3 had between 3 and 5, and 2 had 10. Four of the 20 (20%) with SE as their first seizure had ≥1 recurrence of SE as did 8 of the 19 (50%) with a first episode of SE occurring later in the course of their epilepsy (P = .25).

### Brain Injury

Details of cognitive function are shown in Table 2. Based on our inclusion criteria, all patients were judged to be of normal intelligence at seizure onset. Between the onset and the end of follow-up, no patient developed mental retardation or neurologic deficits sufficient to interfere with activities of daily living. At onset, the proportion diagnosed with a specific learning disorder was 23% in both the SE and non-SE groups (formal psychometric testing unavailable in only 1 case). By the end of follow-up, learning disorder was noted in 28% of the SE group and 33% of the non-SE group (P = ns). Rates of repeated school grades, special schooling arrangements, high school graduation, and technical/community college and university graduation were the same in both groups. Earned income at the end of follow-up (a possible reflection of cognitive abilities) was the same in both groups.

### Seizure Control

The course of epilepsy was similar in the SE and non-SE groups (Table 1). Fifty-one percent of those with SE had complex partial seizures compared with 52% without SE. Forty-three percent of patients with SE and complex partial seizures had 21 to >100 partial complex seizures through their clinical course compared with 42% in the non-SE group. All 39 in the SE group had at least 1 secondarily generalized convolution compared with 105 (67%) in the non-SE group (P = .002). Forty-one percent of the SE group had ≥21 secondary generalized convulsions compared with 31% of those in the non-SE group who had secondary generalized convulsions (P = ns). The number of antiepileptic drugs (AEDs) used by the SE and non-SE groups throughout their clinical course was similar (Table 1). In the SE group, 56% used only 1 or 2 AEDs through the clinical course compared with 64% in the non-SE group (P = ns). At end of

### Table 1 Patient Demographics and Details About Their Epilepsy Course

<table>
<thead>
<tr>
<th>Age of epilepsy onset</th>
<th>SE (n = 39)</th>
<th>No SE (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5 ± 4.4 y (0.3–15.6)</td>
<td>7.4 ± 4.3 y (0.2–15.8)</td>
<td></td>
</tr>
<tr>
<td>Age at follow-up</td>
<td>33.8 ± 7.7 y (15–47.9)</td>
<td>35.4 ± 7 y (12.5–46.6)</td>
</tr>
<tr>
<td>Length of follow-up</td>
<td>27.8 ± 5.3 y (11.6–35.1)</td>
<td>28 ± 4.9 y (10.8–37.7)</td>
</tr>
<tr>
<td>Epilepsy syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign rolandic</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Other benign</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Focal not well localized</td>
<td>29 (74%)</td>
<td>105 (70%)</td>
</tr>
<tr>
<td>Temporal</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Other definite localization</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Partial complex seizures

<table>
<thead>
<tr>
<th>Number of AEDs used</th>
<th>0</th>
<th>19 (49%)</th>
<th>69 (49%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throughout clinical course</td>
<td></td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>44 (50%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12 (31%)</td>
<td>64 (43%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10 (26%)</td>
<td>32 (21%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>7–11</td>
<td>3</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Average longest time seizure-free

<table>
<thead>
<tr>
<th>Average longest time seizure-free on AEDs</th>
<th>SE (n = 149)</th>
<th>No SE (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 ± 10.5 y (range 0–31.7)</td>
<td>19.4 ± 10.3 y (range 0–36.4)</td>
<td></td>
</tr>
<tr>
<td>4.8 ± 6.6 y (range 0–30)</td>
<td>4.3 ± 5.1 y (range 0–25.8)</td>
<td></td>
</tr>
<tr>
<td>13.5 ± 15.3 y (range 0–31.3)</td>
<td>16 ± 10.4 y (range 0–32.4)</td>
<td></td>
</tr>
</tbody>
</table>

Remission at the end of follow-up

<table>
<thead>
<tr>
<th>Remission at the end of follow-up</th>
<th>SE (n = 39)</th>
<th>No SE (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off AEDs, seizure-free: 24</td>
<td>66</td>
<td>15 (38%)</td>
</tr>
<tr>
<td>Off AEDs, still having seizures: 2</td>
<td>20 (13%)</td>
<td></td>
</tr>
</tbody>
</table>

Intractable epilepsy at the end of follow-up

<table>
<thead>
<tr>
<th>Intractable epilepsy at the end of follow-up</th>
<th>SE (n = 149)</th>
<th>No SE (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off AEDs, seizure-free: 99</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Off AEDs, still having seizures: 7</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2  Cognitive Outcome

<table>
<thead>
<tr>
<th></th>
<th>SE (n = 39)</th>
<th>No SE (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal intelligence</td>
<td>39 (100%)</td>
<td>149 (100%)</td>
</tr>
<tr>
<td>Learning disorder</td>
<td>9 (23%)</td>
<td>35 (23%)</td>
</tr>
<tr>
<td>Formal psychometric testing</td>
<td>11 (28%)</td>
<td>49 (33%)</td>
</tr>
<tr>
<td>School grade repeated</td>
<td>14 (36%)</td>
<td>70 (47%)</td>
</tr>
<tr>
<td>Extra help at school, resource</td>
<td>15 (39%)</td>
<td>73 (49%)</td>
</tr>
<tr>
<td>Work/study program at school</td>
<td>4 (10%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Stimulant medication</td>
<td>4 (10%)</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>High school graduation</td>
<td>28 (72%)</td>
<td>104 (70%)</td>
</tr>
<tr>
<td>University education</td>
<td>12 (31%)</td>
<td>36 (24%)</td>
</tr>
<tr>
<td>Technical school or community college</td>
<td>13 (33%)</td>
<td>48 (31%)</td>
</tr>
<tr>
<td>Lowest income*</td>
<td>10 (26%)</td>
<td>49 (33%)</td>
</tr>
<tr>
<td>Highest income</td>
<td>11 (28%)</td>
<td>51 (34%)</td>
</tr>
</tbody>
</table>

* For patients no longer in school, total family income (patient or partner) at the end follow-up was assigned to 1 of 3 groups: low (at or below the poverty line), medium (between the poverty line and the upper 25th percentile), high (>25th percentile), based on Statistics Canada estimates for Nova Scotia.

follow-up, 27, no longer received AED treatment, 8 received monotherapy, and 4 received 2 AEDs.

The average longest time seizure-free through the entire clinical course was also similar between the 2 groups (SE 17 ± 10.5 years and non-SE 19.4 ± 10.3 years). Table 1 shows that during this period of seizure-freedom the average time with and without AED treatment did not differ between the groups.

During follow-up, epilepsy surgery was undertaken in 3 (8%) of the SE group and 9 (6%) of those without SE. At the end of follow-up, the proportion of patients with intractable epilepsy (a seizure at least every 3 months and trials of ≥3 AEDs at maximum tolerated dose) was the same in both groups: 6 of 39 (15%) in the SE group versus 17 of 149 (11%) in the non-SE group.9

Long-term Remission

Remission was defined as seizure-free and no longer receiving AEDs. At the end of follow-up, 24 (61%) of the SE group and 99 (66%) of the non-SE group were in remission (P = ns). The length of terminal remission after successfully discontinuing AED treatment was 13.5 ± 15.3 years in the SE group and 16 ± 10.4 years in those without SE (P = ns).

Because there is concern that SE in children <2 years of age may have a more sinister outcome, we selected children with epilepsy onset ≤2 years for additional analysis. There were only 3 patients with an episode of SE before age 2 years (4, 14, and 16 months). None of these patients had recurrent SE, and their intellectual and seizure outcomes were similar to those whose seizure onset was ≥2 years but never had an episode SE.

DISCUSSION

For otherwise normal children with epilepsy characterized by focal seizures, ≥1 episodes of convulsive SE did not have a significant effect on their long-term seizure or intellectual outcome compared with those without status. Those with SE were more likely to have at least 1 secondarily generalized seizure. However, large numbers of this seizure type were the same in both groups. Our patients should be clearly distinguished from those with acute symptomatic SE in which the etiology is the major determinant of the outcome.6,7 We do not have data about what might have precipitated SE in our patients, such as sleep deprivation or poor medication adherence.

Others have noted that SE in children with epilepsy has a recurrence risk of ~10% to 20%.6,13 The effect of these episodes of SE on seizure outcome has generally been noted to be minor. A careful systematic review of the literature suggested that “The effect of an episode of convulsive SE on the course of epilepsy is unclear.”76 Details of the effect of SE on intellectual outcome in otherwise normal patients with focal epilepsy have not been extensively reported. A well-known population-based Finnish epilepsy cohort followed for many years only included 11 patients with SE and no other neurologic problems.15 These 11 children had similar educational outcomes to those without SE. Most previous studies have either focused on SE as a first seizure and the risk of subsequent epilepsy or the influence of SE in children with epilepsy.15–18 Unprovoked SE as a first seizure does not increase the risk of recurrent seizures (epilepsy) more than a short first seizure.14,15 In a study of children in Connecticut who had developed a wide spectrum of epilepsy syndromes and then an episode of SE, there was a slight increase in the risk of intractability.16

Our study is of similar size but focused on a more homogenous group of children with epilepsy (otherwise normal with focal seizures). Even with a longer follow-up, we did not find an increase in intractable epilepsy after SE.

Our findings should not encourage a lackadaisical approach to the treatment of SE as the first seizure or in children with established epilepsy. Because of indisputable reports of children who have suffered irreversible brain damage from long SE, we continue to encourage prompt treatment to stop long seizures, particularly convulsive seizures. All of our patients had their episode of SE in the context of a health care system that permitted prompt access to emergency care in an era when the use of parenteral or rectal benzodiazepines was the norm. We were not able to document the total length of SE for most of our patients, although in all cases, we judged that the seizure duration was at least 30 minutes. Even when the medical record suggested a precise length of seizure, we suspect that there would be many errors. In our clinical experience, the exact time of the onset is often unclear, and the exact time when the seizure stopped is often difficult to determine unless there is simultaneous EEG
recently been discouraged.19 In the 2010 though the term cryptogenic has re-

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committee of the American Academy of

CONCLUSIONS

We conclude that the prognosis for
otherwise normal children with focal
epilepsy is apparently not significantly
altered by unprovoked SE. The risk of
recurrence of SE appears to be ~50%.
Significant brain injury is unlikely in
a geographic setting with good access to
prompt treatment of SE. The clinical
course (ease of seizure control and risk of intractable epilepsy) and chance of remission are unchanged.
The overall message to parents and
caretakers about SE should be one of reassurance.

recording. This clinical reality limits all
studies that might attempt to compare the
length of SE with the outcome. Nonetheless,
SE lasting several hours appears more
likely to injury the brain than shorter SE.17

Our study was limited to children
without intellectual or neurologic de-


city, the rates of specific learning
disorder in the status group. All chil-
dren had focal epilepsy, although only
13.3% had a recognized benign focal
epilepsy syndrome. Because MRI was
not available at the time that our cohort
was assembled, we do not know how
many of our patients had an identifi-
able brain lesion to explain the cause of
their epilepsy. Based on CT scanning
(available in 86% of our cases) and
clinical information (obtained through-
out follow-up), ~60% had no identifi-
able cause found for their epilepsy. These
patients would fall in the broad category
of cryptogenic partial epilepsy,18 al-

though the term cryptogenic has re-

cently been discouraged.19 In the 2010

proposed epilepsy classification scheme,
they would be identified as focal epi-
lepsy, cause unknown with the addi-
tional features of normal intelligence
and neurologic examination.19 We hope
that the group of patients who we have
studied are easily recognized. It may
be incorrect to extend our findings to
other epilepsy syndromes or catego-
ries of epilepsy.

The number of cases of SE in our study
was relatively modest so that rare poor
outcomes cannot be excluded. We lim-
ited our cases to children without global
intellectual deficits before their first
seizure. There have been few studies of
patients who have had psychometric
testing before and after seizures or SE.

The National Collaborative Perinatal
Project study did report standard psy-
chometric testing in a prospective study
of >50 000 newborns followed to age 7
years.20 There were 62 patients without
previous seizures when they under-
went psychometric testing at age 4
years. Between age 4 and 7 years, they
had ≥1 unprovoked seizures, although
it is unclear how many seizures they
had or how severe they were and if any
constituted SE.21 Psychometric testing
was repeated at age 7 years. The
results at age 4 and 7 were identical.
Dodrill described adults with chronic
epilepsy who had pre- and post-SE
psychometric testing.22 He did recog-
nize some new deficits, but the findings
were subtle, and it is not clear how
many other nonstatus seizures these
patients had between their psycho-
metric assessments. Roy et al reported
neuropsychological testing in a highly
selected group of infants who had a
prolonged febrile seizure. They were
found to have some problems with ex-
ecutive functioning compared with a
small number of controls. Unfortu-
nately, there was no preseizure test-
ing, and therefore it is not possible to
attribute a cause-and-effect relation-
ship between the febrile status
epilepticus.23


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