

Time Trends in Incidence, Mortality, and Case-Fatality after First Episode of Status Epilepticus

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Summary: *Purpose:* Status epilepticus (SE) is a medical emergency associated with a high mortality. Clinical series have suggested that mortality after SE has decreased. No studies have systematically examined trends in incidence, mortality, and case fatality after SE in a well-defined population.

Methods: All first episodes of SE receiving medical attention between January 1, 1935, and December 31, 1984, were ascertained through the Rochester Epidemiology Project Records-Linkage System and followed up until death or study termination (February 1, 1996). We calculated incidence rates in the 50-year period (1935–1984), while we considered mortality and case-fatality in the last 30-year period (1955–1984).

Results: Incidence of SE increased over time to 18.1/100,000 (1975 through 1984). The increase was related to an increased incidence in the elderly and to the advent of myoclonic SE after cardiac arrest, a condition not seen in the early decades. In the

last decade, ~16% of the incidence was due to myoclonic SE. The mortality rates increased from 3.6 per year in the decade 1955–1965 to 4.0/100,000 per year between 1975 and 1984. The 30-day case-fatality (CF) was unchanged, although a trend toward improvement was shown after excluding myoclonic SE.

Conclusions: Incidence and mortality rates of SE have increased in the last 30 years. Case fatality remained the same. The increased incidence and mortality are due to the occurrence in the last decade of myoclonic SE after cardiac arrest. The mortality in the elderly was twice that of the youngest age group, across all study periods. Changes in the age and cause distribution of SE over time are responsible for the stable survivorship. There is improvement in survivorship in the last decade when myoclonic SE is excluded. **Key Words:** Status epilepticus—Mortality—Prognosis—Incidence—Case-fatality.

Status epilepticus (SE) has been defined as a seizure or series of seizures lasting >30 min without intervening lucidity (1). SE is a common medical emergency associated with a high mortality (2–4). There are no published studies on time trends of incidence or mortality of SE. There is a perception that survivorship after SE has improved because of improved medical therapy. In clinical series, the reported mortality after SE has decreased over the past 50 years (2,5). Mortality has decreased in recent clinical series of children (5).

We used the medical records linkage system of the Rochester Epidemiology Project to compare changes in incidence, case-fatality, and mortality after a first episode of SE by using data from five sequential 10-year periods from 1935 through 1984.

METHODS

The records of the Rochester Epidemiologic Project index all medical contacts for Rochester residents at the Mayo Clinic and at other medical facilities at which Rochester residents are likely to seek medical care. Mayo Clinic facilities have been the center of referral for medical care in Rochester, Minnesota, since the beginning of this century. The register includes inpatient, outpatient, and home visits. We reviewed all records with a diagnosis of acute symptomatic seizure, single unprovoked seizure, or epilepsy between January 1, 1935, and December 31, 1984 (6). Moreover, we reviewed all records indicating a medical condition potentially linked to SE or seizure occurrence (stroke, metabolic encephalopathy, brain tumors, encephalitis, anoxic encephalopathy after cardiac arrest). This process permitted us to identify most first SE cases that came to medical attention among Rochester residents during the study period, all after 1955.

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Charts of each patient were reviewed by three of us (G.C., W.A.H., G.L.) to identify the occurrence of SE and to classify SE seizure type, duration, etiology, and to review the response to therapy.

Status epilepticus seizure type

Seizure type was categorized following criteria of the International League against Epilepsy (ILAE), and SE was identified as previously described (7,8). For the present analysis, we distinguished between motor (including generalized, secondarily generalized, and partial motor SE), nonmotor SE (including complex partial and absence SE), and myoclonic SE. The aim of this categorization was to group together SE cases with a similar likelihood of ascertainment. Motor SE is much easier to identify and is more likely to come to medical attention than is nonmotor SE. Myoclonic SE is characterized by minor motor activity but was considered separately from motor and nonmotor SE because of the subtle characteristics of this seizure activity. In our classification, myoclonic SE is probably equivalent to "subtle SE" described by other authors (9).

Etiology

Etiology was assigned into two broad categories based on our previous work and ILAE recommendations: acute symptomatic and unprovoked (including progressive symptomatic, remote symptomatic and idiopathic/cryptogenic) (5,7,8).

The period of follow-up was terminated by death or the end of the study period (February 1996). We calculated incidence for each of five 10-year intervals from 1935 through 1984. There were several sources of medical care in the community for whom records were not included in the record-linkage system prior to 1952. Because this could have led to a systematic bias in case identification before that time for conditions such as SE, we calculated the age-specific mortality and CF only for the three 10-year intervals between 1955 and 1984. These are the decades used for analytic assessment in other studies of seizure disorders (10–13).

Statistical methods

We calculated the age-specific mortality rates as the number of deaths divided by the person-years at risk in the population. We used census data stratified by age and gender to determine the person-years at risk for each decade (14). Mortality and incidence rates were adjusted to the age and gender distribution of 1980 U.S. white population, using the direct method (15). We used proportional hazards modeling to calculate the crude and gender- and age-adjusted relative risk for mortality in the last two decades, using the 1955–1964 interval as decade of reference (16,17).

Because more prompt medical treatment with antiseizure medication (AED) could be responsible for changes

in mortality (18), we compared the distribution of interval with use of AEDs of SE across decades.

RESULTS

During the period 1935–1984, we identified 356 first episodes of SE. We excluded from the analysis 47 cases younger than 5 years with fever and with no other apparent cause of SE (febrile SE). Febrile SE is an age-limited benign condition with no associated mortality (1). Therefore 309 episodes of incident afebrile SE were identified in the population of Rochester, Minnesota. Demographics, distribution of etiologies, and crude and adjusted incidence are shown in Table 1.

Time trends in incidence

We calculated the age-adjusted incidence of SE over each 10-year interval for the 50-year period (Table 1 and Fig. 1). In the first decade, there is probably underascertainment of cases. Therefore the incidence comparison with this decade would be misleading. Between 1945 and 1954, the annual age-adjusted incidence of afebrile SE was 14.1/100,000. The adjusted incidence increased to 18.1/100,000 in the last decade of the study (1975 through 1984).

Etiology

The overall age-adjusted incidence of acute symptomatic SE increased from 6.3/100,000 in the 1945–1954 interval to 9.8/100,000 in the last decade (1975 through 1984) (Fig. 1). For unprovoked SE, the adjusted incidence was stable: 7.9/100,000 in the 1945–1954 period and 8.3/100,000 in the 1975–1984 period.

Age

The age distribution of those affected by SE has changed over time: between 1945 and 1954, only 17% of subjects with SE were older than 65 years, whereas individuals in this age range accounted for 50% of cases between 1975 and 1984. There was a threefold increase in incidence of SE in those 65 and older (Table 1).

Seizure type

Important changes occurred for seizure type. Better recognition of more subtle forms of SE could in part account for the increase in incidence. The incidence of motor SE almost doubled, increasing from 7.4 in the first decade (1935 through 1944) to 11.1 in the last decade (1975 through 1984). Nonmotor SE accounted for 3% of all cases identified between 1935 and 1944, 13% between 1945 and 1954, 11% between 1955 and 1964, 15% between 1965 and 1974, and 13% between 1975 and 1984 ($\chi^2 = 32$; $p = 0.001$). The incidence rate of nonmotor SE increased fivefold from 0.4/100,000 in the first time interval (1935–1944) to 2.2/100,000 in the second (1945–1954) interval. The increase in incidence after

TABLE 1. Age distribution of the Rochester population, crude incidence, and cases of status epilepticus (SE) by decade

Age by decade	Incidence/100,000 (crude)	Rochester population n (%)	All SE n (%)	Acute SE n	Unprovoked SE n
1935–1944					
<65 yr	6.5	230,063 (94)	15 (83)	8	7
>65	18.9	15,906 (6)	3 (17)	0	3
Total	7.3	245,969	18	8	10
Adj I	8.0			3.5	4.5
1945–1954					
<65 yr	13.1	258,452 (91)	34 (83)	19	15
>65	29.2	24,000 (9)	7 (17)	2	5
Total	14.4	285,452	41	21	20
Adj I	14.1			6.3	7.9
1955–1964					
<65 yr	11.7	349,530 (94)	41 (61)	25	16
>65	73.5	35,351 (9)	26 (39)	14	12
Total	17.4	384,881	67	39	28
Adj I	15.2			8.5	6.7
1965–1974					
<65 yr	8.6	466,694 (90)	40 (62)	21	19
>65	47.8	50,209 (10)	24 (38)	14	10
Total	12.4	516,903	64	35	29
Adj I	11.0			5.9	5.1
1975–1984					
<65 yr	11.7	510,952 (89)	60 (83)	37	23
>65	96.1	61,374 (11)	59 (50)	27	32
Total	21	572,326	119	64	55
Adj I	18.1			9.8	8.3

Adj I, Sex- and age-adjusted incidence in the U.S. white population, census 1980.

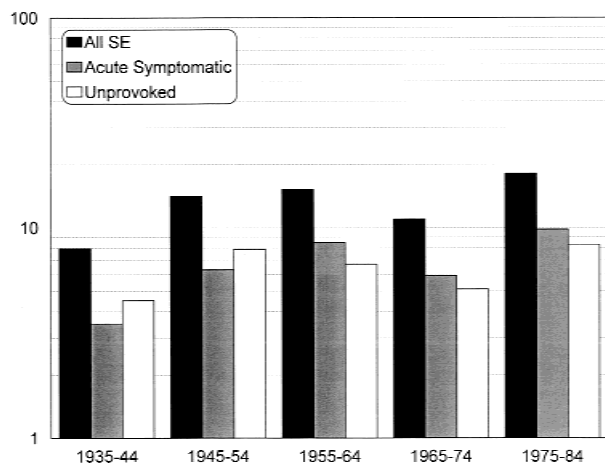
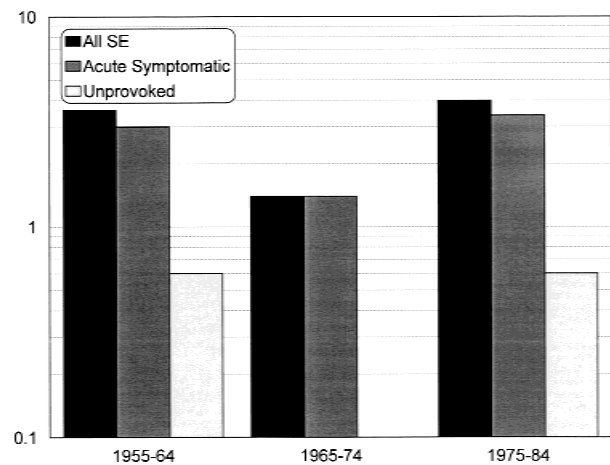
1945 was modest, reaching 2.7/100,000 in the last decade.

The most relevant change over time was the advent of myoclonic SE, a SE subtype that was not present in the earliest decades. We identified no case of myoclonic SE before 1965, two cases in the 1965–1974 interval, and 18 cases in the last decade (1975 through 1984). Myoclonic SE represented 16% of all cases during the 1975–1984 interval. The adjusted incidence for myoclonic SE was 4.3/100,000 in the last decade. The crude incidence of SE

decreased from 20.8 to 17.6/100,000 after exclusion of myoclonic SE.

Time trends in mortality

We measured the 30-day age- and gender-adjusted mortality rate after an incident episode of SE for the last three decades (1955–1984) where ascertainment was probably thought to be homogeneous for all SE subtypes (Fig. 2). The mortality rate increased 10% in the 30-year interval from 3.6/100,000 between 1955 and 1964 to 4.0/100,000 between 1975 and 1984 (Fig. 2).

Incidence (n/100000)**FIG. 1.** Age-adjusted incidence of all status epilepticus, unprovoked and acute symptomatic, during the period 1935–1984.**Mortality(n/100000)****FIG. 2.** Age-adjusted mortality rates of all status epilepticus, unprovoked and acute symptomatic, during the period 1955–1984.

30-day case fatality

The CF was high for those with acute symptomatic and low for those with unprovoked SE across all decades (Table 2). A Cox proportional hazard model, with age and time period included as covariates, showed no difference when the CF in the decade 1975–1984 was compared with the decade 1955–1964 (RR = 1.3; 95% CI, 0.8–2.2).

30-day case fatality and myoclonic SE

CF in people with myoclonic status was 65%, more than twice the CF of the remaining subtypes of SE. Because myoclonic SE did not exist in the community in earlier decades, we calculated CF of SE excluding the myoclonic cases. We thought this would provide a more appropriate comparison of the CF across time. After exclusion of myoclonic SE among the acute symptomatic cases, SE 30-day CF decreased from 37% in 1955–1964 to 26% in the 1975–1984 decade (Table 2 and Fig. 3). In those older than 65 years, exclusion of myoclonic cases in the last decade reduced CF from 58% to 38% (Table 2 and Fig. 4). Thus CF has decreased over time when we exclude myoclonic SE.

30-Day case fatality and age

The CF in the elderly was double that of young across the last three decades (Table 2).

Therapy

Information on interval to first treatment was available for 200 (91%) of the 220 subjects treated with AEDs. There appeared to be little change in the promptness of medical treatment over time for both motor and nonmotor SE across all the study period ($\chi^2 = 3.2$; $p = 0.19$).

DISCUSSION

It has been suggested that mortality after SE has declined over time, but there have been no studies of change in mortality rates after SE in a well-defined population. Disease-specific mortality rates are determined by

TABLE 2. Case-fatality rate (%) after status epilepticus by etiology across three decades (1955–1984)

Decades	1955–1964	1965–1974	1975–1984	χ^2 (p)
All status	25	14	24	NS
<65 yr	17	7	17	NS
>65 yr	38	25	32	NS
Unprovoked	10	0	7	NS
<65 yr	0	0	4	NS
>65 yr	21	0	9	NS
Acute symptomatic	37	24	38	NS
<65 yr	27	13	24	NS
>65 yr	58	42	59	NS
Acute symptomatic w/out MS	37	25	26	NS
<65 yr	28	14	18	NS
>65 yr	58	42	38	NS

NS, not significant; MS, myoclonic status epilepticus.

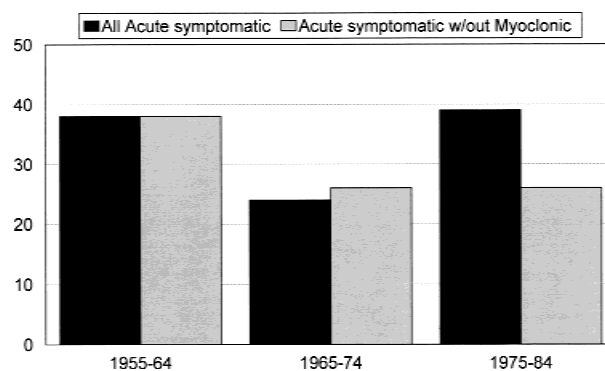


FIG. 3. Case fatality (%) after acute symptomatic status epilepticus (SE) in the period 1955–1984, with and without myoclonic SE after anoxic encephalopathy.

incidence and CF. Our study suggests that there has been a modest increase in SE mortality rates in the study period. This increase is related to an increase in incidence of SE with a stable CF. The increase in incidence of SE occurred in all age groups but was most pronounced among those older than 65 years and was particularly evident during the period from 1975 through 1984. The increased incidence is due to a true overall increase of the incidence of SE among the elderly and related to the occurrence of a new condition, “myoclonic” SE, associated with anoxic encephalopathy among survivors of cardiac arrest after 1965. The apparent change in incidence could be attributed, in part, to underascertainment of SE, particularly in the first decade. Even in 1935, a case of generalized SE would have come to medical attention. A case of nonmotor SE would have been less likely to be recognized as such and thus be less likely to receive prompt medical intervention. This is true for the entire study period but may have been a more important reason for underascertainment in the 1935–1944 interval, but less so in the last two decades. Accuracy of diagnosis could have improved over time because of EEG moni-

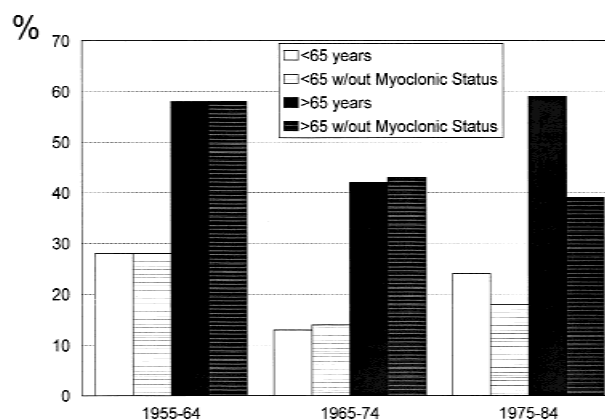


FIG. 4. Age-specific (older and younger than 65 years) case fatality (%) after acute symptomatic status epilepticus (SE) in the period 1955–1984, with and without myoclonic SE after anoxic encephalopathy.

toring; this could be relevant especially for nonmotor SE, as reflected by their differential increase over time.

The increase in mortality rate has paralleled the increase in incidence of SE. In contrast, the survivorship as measured by CF in the last three decades was stable. Cardiac arrest was probably universally fatal in all but last intervals of this study (19). SE after anoxic encephalopathy due to cardiac arrest did not occur in the earliest decades in Rochester. Improved survivorship after cardiac arrest is responsible for all myoclonic SE in this series, but the prognosis of these cases remains grave: two thirds in this subgroup died in the next 30 days. During the 1975–1984 interval, myoclonic SE accounted for 28% of all acute symptomatic SE cases and 16% of all first SE cases. When CF is analyzed after exclusion of myoclonic SE, the CF improves over time.

Age was also an important determinant of mortality and incidence: the incidence of SE among those 65 and older increased threefold between 1945 and 1944 and 1975 and 1984. Because age is such an important predictor of survivorship, the increase of the overall CF in the last interval is affected by the increased proportion of older subjects. In the elderly for all time intervals, CF after an incident episode of acute symptomatic SE was double that of the younger group. After the exclusion of myoclonic SE, we observed a general improvement in CF both in the young and in the elderly.

The interval from onset of SE to initiation of AED treatment has not changed over time. Improvements in nonmyoclonic CF might be related to ancillary treatment and better management of respiratory and cardiac conditions.

This study shows that there is an increasing incidence of SE due to myoclonic SE and to SE in the elderly. The unchanged CF is related to a new distribution of age and etiology of SE in the last decade.

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REFERENCES

1. Hauser W.A. Status epilepticus: epidemiologic considerations. *Neurology* 1990;40(suppl 2):9–13.
2. Hesdorffer D, Logroscino G, Cascino G, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965–84. *Neurology* 1998;50:735–41.
3. DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective population-based epidemiological study of status epilepticus in Richmond, Virginia. *Neurology* 1996;46:1029–35.
4. Logroscino G, Hesdorffer DC, Cascino G, et al. Short-term mortality after a first episode of status epilepticus. *Epilepsia* 1997;38:1344–9.
5. Philips SA, Shanahan RJ. Etiology and mortality of status epilepticus in children: a recent update. *Arch Neurol* 1989;46:74–6.
6. Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota, 1940–1980. *Epilepsia* 1991;32:429–45.
7. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 1993;34:592–6.
8. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizure. *Epilepsia* 1981;22:489–501.
9. Treiman D. Generalized convulsive status epilepticus in the adult. *Epilepsia* 1993;34(suppl 1):S2–11.
10. Hesdorffer DC, Hauser WA, Annegers JF, et al. Severe uncontrolled hypertension and adult-onset seizures: a case study in Rochester, Minnesota. *Epilepsia* 1996;37:736–41.
11. Annegers JF, Hauser WA, Lee JR, et al. Incidence of acute symptomatic seizures in Rochester, Minnesota, 1935–1984. *Epilepsia* 1995;36:327–33.
12. Hesdorffer DC, Hauser WA, Annegers JF, et al. Dementia and adult onset unprovoked seizures. *Neurology* 1996;46:727–30.
13. Hesdorffer DC, Hauser WA, Annegers JF, et al. Major depression is a risk factor for seizures in older adults. *Ann Neurol* 2000;47:246–9.
14. Schroeder DJ, Offord KP. A SAS macro which utilizes local and reference population counts appropriate for incidence, prevalence, and mortality rate calculations in Rochester and Olmsted County, Minnesota. *Technical Report Series*, 20. Mayo Clinic, Rochester, MN: 1982;6.
15. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. New York: Van Nostrand Reinhold, 1982:122–30.
16. Rothman KJ. *Modern epidemiology*. New York: Little, Brown, 1986:38–40.
17. Vine M, Schoenbach V, Hulka B, et al. Atypical metaplasia and incidence of bronchogenic carcinoma. *Am J Epidemiol* 1990;131:781–92.
18. Collett D. *Modelling survival data in medical research*. New York: Chapman & Hall, 1994:15–85.
19. Goldberg RJ, Gore JM, Haffajee CI, et al. Outcome after cardiac arrest during acute myocardial infarction. *Am J Cardiol* 1987;59:251–5.