

Risk of Status Epilepticus in Southern Europe

a report by

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The epidemiological features of status epilepticus (SE) are in the course of definition.¹ In northern and central Europe, an incidence of 10.3 and 17.1/100,000/year and a mortality rate of 7.6 and 9.3% have been reported, respectively.^{2,3} In southern Europe, an incidence of 10.7 and 11.6/100,000/year and a mortality rate of 7 and 39% have been estimated.^{1,4} In the US, a higher incidence of 18.3 and 41/100,000/year^{5,6} and a mortality rate of 19 and 22%^{6,7} have been observed. Given the limited data available in southern Europe,^{1,4} in 2003 we carried out an intensive survey of multiple sources of case material of SE in the Health District (HD) of Ferrara (Fe) in Italy.⁸

Methods

The study population was the resident population (in 2003, an average of 148,128 inhabitants; 46.9% men) of the HD of Fe, a well-defined area of 724km² in the province of Ferrara, Italy, which is the primary service area of the University Hospital (UH) of Fe (the only general hospital in this HD). The study period was from 1 January 2003 to 31 December 2003. In the HD of Fe, neurological patients are routinely referred to the UH of Fe,⁹⁻¹¹ where an on-call neurologist is available 24 hours a day, seven days a week. The HD territorial emergency service protocol for SE management recommends administering benzodiazepines intravenously (IV) and moving the patient as soon as possible to the UH emergency room. The purpose of the study was to identify SE cases in the study population in 2003 through an intensive survey of multiple sources of cases. All hospital ICD-9 discharge codes in 2003 concerning epilepsy in all positions were abstracted, and the clinical files were obtained from each hospital ward. Other sources were the UH electroencephalography (EEG) and paediatric EEG services archives. Further sources were the emergency room unit and the territorial emergency service computerised archives. The neurologists, the physicians in the paediatric neurological service and the physicians in the emergency room unit and the intensive care units of the UH of Fe were interviewed.

SE was defined as a single seizure lasting for more than 30 minutes or repeated seizures lasting for a period of more than 30 minutes without intervening recovery between seizures.¹² Charts of any possible SE case in 2003 selected through the above sources were carefully reviewed to identify those with SE and to classify SE by seizure type, duration and aetiology. SE seizure type was classified as: generalised from onset (no indication of anatomical localisation and no clinical evidence of focal onset), with the subgroups convulsive (tonic-clonic, tonic, clonic), non-convulsive (absence status) and myoclonic; partial, without generalisation, with the subgroups simple (no consciousness impairment) and complex (consciousness impairment); secondarily generalised; and unclassified.¹² The physicians involved in the management of SE patients were interviewed. Only the first SE episode was taken into account.^{3,5} Each SE case was reviewed according to the Hauser criteria¹³ to determine whether it was acute symptomatic (in close association – within a week – with an

acute brain insult) or unprovoked (no association with an acute brain insult); the latter cases were further categorised as progressive symptomatic (in association with a non-static progressive brain lesion), remote symptomatic (in association with a prior brain insult resulting in a static brain lesion; time between SE and the prior brain insult >1 week) or idiopathic/cryptogenic (no acute precipitating factor and no brain lesion), concerning SE of no clear aetiology – idiopathic was reserved for certain partial or generalised epileptic syndromes with particular clinical and EEG characteristics, while cryptogenic referred to cases where no factor associated with increased risk of seizures was identified. The only case of febrile SE (a special class of acute symptomatic SE occurring during a febrile illness among children in the absence of another acute symptomatic cause, such as central nervous system [CNS] infection)^{2,5} was not excluded from the statistical analysis.

SE duration was categorised as 30 minutes to two hours, two to 24 hours or 24 hours or longer.^{1,5} All patients with incomplete or unclear medical history or medical charts were excluded, as were non-resident patients and all patients with uncertain seizure duration. Anoxic myoclonic encephalopathy cases without a clear EEG seizure pattern were not included.² In the anoxic myoclonic encephalopathy cases in 2003, a clear EEG seizure pattern was not identified. Controversial EEG activity cases were finally evaluated and judged by an EEG expert (VCM, EF). History of epilepsy was defined as two or more seizures in a lifetime.^{1,5} Mortality was assessed at the end of hospitalisation.²

The SE incidence in the whole resident population of the HD of Fe in 2003 was calculated. Crude rates were directly age-adjusted using the European population as standard.¹⁴ The 95% confidence intervals (CIs) of the rates were calculated assuming a Poisson's distribution.¹⁵ To compare two incidence rates, the difference in rates and the 95% CI associated with the rate difference were calculated according to the Poisson's distribution.¹⁶ Age-adjusted incidence estimates were compared by constructing the 95% CI for each estimate.⁵ The Student t-test was used to compare two means and the χ^2 test to compare two frequencies. The case and data collection were performed in 2004.⁸



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Table 1: Age- and Sex-specific Annual Incidence of Status Epilepticus in the Health District of Ferrara in 2003

Age Group (years)	Both Sexes		Men		Women	
	Cases, Population (n)	Rate/100,000 (95% CI)	Cases, Population (n)	Rate/100,000 (95% CI)	Cases, Population (n)	Rate/100,000 (95% CI)
0–19	9, 18,318	49.1 (22.5–93.3)	8, 9,450	84.6 (36.5–166.7)	1, 8,868	11.3(0.3–62.9)
20–29	2, 14,451	13.8 (1.7–4.9.8)	1, 7,272	13.7 (0.3–76.3)	1, 7,179	13.9 (0.3–77.4)
30–39	3, 23,579	12.7 (2.6–37.1)	2, 11,886	16.8 (2.0–60.6)	1, 11,693	8.5 (0.2–47.3)
40–49	2, 22,090	9.0 (1.1–32.5)	1, 10,882	9.2 (0.2–51.2)	1, 11,208	8.9 (0.2–49.5)
50–59	5, 21,216	23.6 (7.6–54.9)	3, 10,227	29.3 (6.0–85.5)	2, 10,989	18.2 (2.2–65.7)
60–74	9, 30,036	29.9 (13.7–56.8)	6, 13,443	44.6 (16.4–97.2)	3, 16,593	18.1 (3.7–52.8)
75+	10, 18,438	54.1 (26.0–99.5)	4, 6,367	62.8 (17.1–160.7)	6, 12,071	49.7 (18.2–108.3)
Total	40, 148,128	27.0 (19.3–36.7)	25, 69,527	36.0 (23.3–53.2)	15, 78,601	19.1 (10.7–31.5)

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Table 2: Status Epilepticus Aetiology in the Health District of Ferrara in 2003

Aetiology	Cases (n)	Frequency (%)
Acute symptomatic	10	25
Remote symptomatic	18	45
Progressive symptomatic	6	15
Idiopathic/cryptogenic	6	15
Total	40	100

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Results

We identified 91 possible SE cases, of which 51 were excluded (eight non-resident, 21 incomplete and unclear medical history or medical charts and 22 uncertain seizure duration), so 40 incident SE cases (25 men and 15 women) were identified. This gave a crude incidence of 27.0/100,000/year (95% CI 19.3–36.7), with a higher incidence in men (36.0/100,000, 95% CI 23.3–53.2) than in women (19.1/100,000, 95% CI 10.7–31.5; difference in rates = 16.9, 95% CI associated with the rate difference 16.8–17.0). The age-adjusted incidence was 27.2/100,000/year (95% CI 19.4–36.9), and again was higher in men (41.7/100,000, 95% CI 26.9–61.7) than in women (12.3/100,000, 95% CI 6.9–20.4). The mean age was 50.6 years (standard deviation [SD] 27.9 years, range one to 85 years), with no significant difference between sexes (62.8 years, 20.5 SD in women; 43.2 years, 29.5 SD in men; $t=1.17$). The age-specific incidence showed a bimodal distribution (see Table 1), with a first peak in the youngest age group and a second peak in the oldest age group. In the 0–19 years age group the highest incidence was in the youngest subgroup (0–4 years), with four cases (subgroup population 4,704, incidence 85.0/100,000/year, 95% CI 23.2–217.2). In the adult population (≥ 20 years of age) the incidence was 24.0/100,000/year (95% CI 16.2–33.9), and was higher in the elderly (≥ 60 years of age: 39.2/100,000, 95% CI 23.6–61.1) than in the 20–59 years age group (14.7/100,000, 95% CI 7.6–25.7; difference in rates = 24.5, 95% CI associated with the rate difference 24.4–24.6).

All of the incident SE cases underwent at least one ictal and one interictal EEG according to the clinical practice in the study area. In 20% of the patients the SE ended within two hours, in 60% the SE lasted for two to 24 hours and in 20% the SE lasted for more than 24 hours. The frequency of SE duration longer than 24 hours was higher in women (26.6%) than in men (16%), a non-significant difference ($\chi^2 = 1.305$), and also was higher in the elderly (20%) and in the 0–19 years age group (25%) than in the 20–59 years age group (16.6%) – again non-significant differences ($\chi^2 = 0.055$ and $\chi^2 = 0.013$, respectively).

The SE was acute symptomatic in 25% and remote symptomatic in 45% (see Table 2). The SE was partial in 57.5%, partial secondarily generalised in 32.5% and generalised in 10%. Complex partial SE accounted for 27.5% of the patients, giving an incidence of 7.4/100,000/year (95% CI 3.7–13.2), with a higher incidence in the elderly (five cases, population 48,474, incidence rate 10.3/100,000/year, 95% CI 3.3–24.0) than in younger adults (three cases, population 81,336, incidence rate 3.7/100,000/year, 95% CI 0.7–10.8; difference in rates = 6.6, 95% CI associated with the rate difference 6.5–6.7).

The case fatality was 5% (two patients): both were acute symptomatic SE cases (one brain haemorrhage and one brain aspergillosis). Therefore, mortality was 20% in the acute symptomatic group. A history of epilepsy was found in 16 patients (40%); the epilepsy was symptomatic in 75% of these cases. In the 16 epileptic patients, the frequency of antiepileptic drug non-compliance as a risk factor for SE was 19%, while the overall frequency of antiepileptic drug non-compliance as a risk factor for SE in the total number of incident cases (epileptic and non-epileptic patients) was 7.5%. Cerebrovascular disease was the most frequent aetiology, accounting for 45% of the incident patients (60% of acute symptomatic cases and 66.6% of remote symptomatic cases), and remote strokes were the most frequent aetiology (30%). A brain tumour was the etiology in 12.5%, pre/peri-natal risk factors in 12.5% and a brain infection in 7.5%.

All of the patients received pharmacological treatment. The first treatment was lorazepam in 62.5%, diazepam in 32.5% and midazolam in 5%; 52.5% of the patients needed a second treatment, which was phenytoin in 52.4%, and 22.5% of the patients needed propofol-induced therapeutic coma. In 23 patients (57.5%) onset of SE occurred outside the hospital and in 17 patients (42.5%) onset of SE occurred inside the hospital. Of the 23 outpatients, 61% received the specific treatment before hospital admission; the ward of admission was the neurological ward in 69.6% and an intensive care unit in 30.4%. The mean duration of hospitalisation was 16 days.

Discussion

The study showed that the incidence of SE in the HD of Fe, a well-defined population in southern Europe, is 27.2/100,000/year – higher than that reported in the previous European studies,^{1–4} showing that the SE risk in southern Europe is more similar to that estimated in the US.^{5,6} The SE incidence in the adult population (24.0/100,000/year), as estimated in other European studies,^{1,3,4} is still the highest reported in Europe.^{1–4} Most of the current findings are consistent with the other European and American studies.^{2–6}



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A bimodal distribution of the age-specific incidence confirmed that the SE risk is highest in the youngest and in the oldest individuals of the population. The incidence was higher in men than in women, as in the US^{5,6} and in northern and central Europe,^{2,3} but in contrast to the previous South-European studies.^{1,4} The incidence was higher in the elderly than in younger adults, showing that the SE risk is age- and sex-dependent in southern Europe too.^{2,3,5,6} Although case underestimation by this study is unlikely,^{9–11} in SE studies there may be several sources of underestimation,^{3,17} so the current incidence should be regarded as a minimal SE incidence.³

The other findings were also similar to those of other studies,^{2,3,5,6} such as cerebrovascular disease being the main aetiology in both acute and remote symptomatic cases, a history of epilepsy being present in fewer than 50% of the incident patients, partial SE and partial secondarily generalised SE being the most common seizure types and the majority of SE cases lasting for less than 24 hours.^{1,2,5} We captured a good share of complex partial SE (27.5%) – greater than other population studies with an optimal surveillance system.^{1,2,6} This is an indirect indicator of good case ascertainment, since non-convulsive SE is the most difficult type to diagnose.^{3,17} The study confirmed that complex partial SE should always be considered in the differential diagnosis of consciousness disorders,¹⁷ especially in the elderly, in which it reaches the not negligible incidence of 10.3/100,000/year.

The study showed that in southern Europe, SE is a frequent neurological emergency and confirmed that case ascertainment depends on the presence of specialised medical personnel with an interest and expertise in SE, such as an on-call neurologist available 24 hours a day, seven days a week.^{2,3} The case fatality was lower than that reported in previous population studies in southern Europe.^{1,4} Several factors related to SE management could have positively influenced the outcome: the presence in the UH of Fe of an on-call neurologist 24 hours a day, seven days a week, the high proportion (69.6%) of SE outpatients admitted into the neurological ward, the high proportion (61%) of SE outpatients who received the specific treatment before hospital admission and the favoured use of lorazepam as first treatment (62.5%) rather than diazepam (32.5%). In a previous study in southern Europe¹ that reported a high case fatality (39%), the neurologist was not on call for about two-thirds of the week and the proportion of SE outpatients admitted into the neurological ward was low (10%), as the proportion of outpatients who received the specific treatment before hospital

admission (15%) and the choice of drug for the first treatment favoured the use of diazepam (78%). Interestingly, in the other available population study in southern Europe,⁴ which found a case fatality of 7% (similar to that in the HD of Fe), these factors were more similar to those we found in the HD of Fe, such as an on-call neurologist being available six days a week, 44.4% of SE outpatients being admitted into the neurological ward and lorazepam being favoured as the choice of drug for the first treatment rather than diazepam (46 and 33%, respectively). In a population study in central Europe² that reported a similar case fatality rate to the HD of Fe (7.6%), the specific treatment before hospital admission was administered in 59% of the SE outpatients, similar to the proportion observed in the HD of Fe. Moreover, evidence of a probable enhanced effectiveness of lorazepam alone rather than diazepam alone is available.^{18,19} As in other studies^{1,6,7} the case fatality was higher in acute symptomatic SE patients. The proportions of partial SE and partial secondarily generalised SE were the highest.^{2,3,5,6} This was probably influenced by the high proportion of individuals over 50 years of age in the study population (47%). In fact, as in other studies,^{3,5,6} the partial SE frequency was lower in young incident patients (37.5%) than in adult patients (62.5%), showing that also in southern Europe age correlates not only with SE incidence, but also with SE type.^{3,5} Given the methods, no cases of anoxic myoclonic encephalopathy were included, which contributed to the observed low case fatality rate. In fact, in other studies anoxic myoclonic encephalopathy accounted for 7–16% of the incident cases.^{1,4,5,6} The higher incidence in men and in the older population likely relates to the higher frequency of cerebrovascular disease in these subpopulations.^{3,5}

The current study showed that also in southern Europe men experienced a significantly higher SE risk than women. In these findings, the gender difference could have been influenced by differing distributions of SE aetiology. Men are at higher risk of cerebrovascular disease than women and, consequently, men had a greater incidence of acute symptomatic SE (61.5 versus 38.5%) and remote symptomatic SE (59 versus 41%) than women. Given the progressive ageing of the population, SE will become an increasingly important health problem in southern Europe.^{3,5} Indirect evidence suggests that some factors related to SE management could have positively influenced the outcome. ■

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