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First seizure definitions and worldwide incidence and mortality

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SUMMARY

While all patients with epilepsy experience seizures, not all individuals with seizures have epilepsy. Seizures may be acute symptomatic or unprovoked. Acute symptomatic seizures are seizures occurring at the time of a systemic insult or in close temporal association with a documented brain insult. Unprovoked seizures are seizures occurring in the absence of precipitating factors and may be caused by a static injury (remote symptomatic seizures) or a progressing injury (progressive symptomatic seizures). Unprovoked seizures may be single or recurrent (epilepsy). The incidence of acute symptomatic seizures is 29–39 per 100,000 per year. These predominate in men, in the youngest age class, and in the elderly. Traumatic brain injury, cerebrovascular disease, drug withdrawal, infarction, and metabolic insults are the commonest causes. The incidence of single unprovoked seizures is 23–61 per 100,000 person-years. As with epilepsy, single unprovoked seizures predominate in men and in patients less than 12 months and older than 65 years. Studies on the mortality of acute symptomatic seizures are lacking. A standardized mortality ratio (SMR) of 2.3 has been reported in patients experiencing a single unprovoked seizure. The SMR in patients with a newly diagnosed unprovoked seizure ranges from 2.5 to 4.1 according to the study population and design. The SMR is highest in the youngest patients and in those with symptomatic seizures.

KEY WORDS: First seizure, Definition, Incidence, Mortality.

While all patients with epilepsy experience seizures, not all individuals with seizures have epilepsy. One or more epileptic seizures may occur in the context of a brain insult (systemic, toxic, or metabolic). These events (defined acute symptomatic seizures, provoked seizures, or situation-related seizures) are presumed to be an acute manifestation of the insult and may not recur when the underlying cause has been removed or the acute phase has elapsed. Acute symptomatic seizure is a term used for seizures occurring at the time of a systemic insult or in close temporal association with a documented brain insult (Commission, 1993). Acute symptomatic seizures differ from epilepsy in several important aspects. First, unlike epilepsy, the proximate cause of these seizures is clearly identifiable. The close temporal sequence makes causality likely for conditions such as uremia, head injury, anoxia, or stroke, which all immediately precede or are concurrent with the seizure. Biologic plausibility also supports causality when there is an acute disruption of brain integrity or of metabolic homeostasis in association with the insult. In many cases, there is also a dose effect with more severe injury leading to a higher risk of seizures. Second, unlike epilepsy, acute symptomatic seizures are not necessarily characterized by a tendency for recurrence unless there is recurrence of the underlying acute causal condition (Hesdorffer et al., 1998). Third, although acute symptomatic seizures are an undisputable risk factor for epilepsy, they cannot be included in the definition of epilepsy, which is intended as the occurrence of two or more unprovoked seizures (Commission, 1993). An unprovoked seizure is a seizure or a cluster of seizures occurring within 24 h in a person older than 1 month of age, occurring in the absence of precipitating factors. Unprovoked seizures are defined as convulsive episodes occurring in the absence

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of a potentially responsible clinical condition or beyond the interval estimated for the occurrence of acute symptomatic seizures. The latter may be caused by a static injury (e.g., head trauma or stroke) and are referred to as remote symptomatic seizures or by a progressing injury (e.g., tumor or a degenerative disorder) and are referred to as progressive symptomatic seizures. Unprovoked seizures differ from acute symptomatic seizures in risk for seizure recurrence and mortality for several etiologies.

Unprovoked seizures may be single or recurrent. Although all patients with single unprovoked seizures may have "potential" epilepsy, seizure recurrence can be observed only in about one-half of cases (Berg and Shinnar, 1991). Population-based studies provide a 36–37% relapse rate at 1 year and 43–45% relapse rate at 2 years (Annegers et al., 1986; Hart et al., 1990). After a second unprovoked seizure, the risk of a third seizure has been estimated as 73% and the risk of a fourth seizure as 76% (Hauser et al., 1998). The difference between provoked and unprovoked seizures and between isolated and recurrent seizures is relevant to the definition of epilepsy and to the prognostic counseling in clinical practice. Proper distinction between acute symptomatic seizures and unprovoked seizures is useful for treatment decisions, prognostic determination, and epidemiological studies.

Worldwide Incidence of Acute Symptomatic and Isolated Unprovoked Seizures (Table 1)

There are few epidemiologic studies on the incidence of acute symptomatic seizures. This is in part because such seizures are seldom indexed as a diagnosis. A diagnosis of the underlying condition is in fact more likely to be coded making medical record review guided by ICD codes for seizures inadequate. Further, patients with acute symptomatic seizures are seldom referred to neurologists for long-term follow-up and, given the acute nature of the underlying insult, an electroencephalographic evaluation may not be warranted. In addition, studies relying on field surveys frequently fail to distinguish acute symptomatic seizures from unprovoked seizures. Thus, even though the causation and prognosis of acute symptomatic seizures are quite different from epilepsy, some epidemiologic studies included individuals with such seizures as "epilepsy" (Placencia et al., 1992), or failed to distinguish between unprovoked and acute symptomatic seizures (Luhdorf et al., 1986).

The incidence of acute symptomatic seizures (isolated or recurrent) is 29–39 per 100,000 per year (Loiseau et al., 1990; Annegers et al., 1995). Acute symptomatic seizures represent about 40% of all cases of afebrile seizures in developed countries and more than half in some geographic areas, for example, where cystercosis is endemic (Pal et al., 2000). Men seem at higher risk than women depending on the differing distribution of the underlying epileptogenic conditions in the two sexes. Acute symptomatic seizures predominate in the youngest age class (less than 1 year of age) and, to a lesser extent, in the elderly. Traumatic brain injury, cerebrovascular disease, drug withdrawal, infection, and metabolic insults represent the commonest causes.

The incidence of *isolated* unprovoked seizures can be only estimated from studies with prolonged (virtually lifetime) follow-up. In one of these studies (Hauser et al., 1993), which explored a 50-year period, the age-adjusted incidence of a first unprovoked seizure was 61 per 100,000 person-years, which was approximately 33% higher than the incidence of epilepsy in the same community.

In the Rochester, Minnesota population, the cumulative incidence of single and recurrent epileptic seizures by the age of 80 years was approximately 8% (Hauser et al., 1996). The incidence was close to 10% when acute symptomatic seizures were also included.

In Iceland, the incidence of all unprovoked seizures was 56.8 per 100,000 person-years and the incidence of single unprovoked seizures was 23.5 per 100,000 person-years (Olafsson et al., 2005). After adjustment to the European population, the incidence was 55.2 and 22.8, respectively. The incidence of single unprovoked seizures was 24.4 in men (age-adjusted 24.1) and 22.5 in women (age-adjusted 21.8). As expected, the age-specific incidence of all

Table 1. Incidence (per 100,000 population per year) of seizures by type

				Incidence				
Author (year)	Area (country)	Population	N. cases	All	Acute symptomatic	Unprovoked	Single	Design
Loiseau et al. (1990)	Gironde (France)	1,128,164	804	71.3	29.0	42.3	18.3	Prospective
Hauser et al. (1993) Annegers et al. (1995)	Rochester (U.S.A.)	2,003,357[a]	1,572	100.0	39.0	61.0	NA	Retrospective
Forsgren et al. (1996)	Umea (Sweden)	101,583	218	76.0	20.0	56.0	NA	Prospective, adults
Jallon et al. (1997)	Geneva (Switzerland)	384,657	273	70.8	25.2	45.6	NA	Prospective
MacDonald et al. (2000)	London (U.K.)	100,230	NA	NA	NA	57.0	11.0	Prospective
Olafsson et al. (2005)	(Iceland)	882,151	501	NA	NA	56.8	23.5	Prospective

[a]Person-years (50-year period).
NA, not available.

unprovoked seizures was 130.2 in patients less than 12 months and 110.5 in patients 65 years and older. The incidence of single unprovoked seizures was similar to that of epilepsy up to 64 years of age. After age 64, the incidence of epilepsy exceeded that of single unprovoked seizures.

In London, U.K., the incidence of all unprovoked seizures was 57 per 100,000 population per year (single unprovoked seizures 11 per 100,000 per year) (MacDonald et al., 2000). The incidence of all unprovoked seizures was 60 per 100,000 per year in Sweden (Sidenvall et al., 1993; Forsgren et al., 1996) and 46 per 100,000 per year in Geneva, Switzerland (Jallon et al., 1997).

In summary, the incidence of (single) acute symptomatic seizures tends to vary across studies but is generally lower than that of epilepsy. Acute symptomatic seizures predominate in men, in the youngest age class and in the elderly. The incidence of single unprovoked seizures is also variable. As with epilepsy, single unprovoked seizures predominate in men, in patients younger than 12 months, and in those older than 65 years. This is in contrast to the incidence of all unprovoked seizures, which is fairly similar in countries with satisfactory case ascertainment. Given the homogeneous baseline characteristics of the populations at risk, this observation may better reflect differences in the study design and methods for case ascertainment. As well, the differing incidence of acute symptomatic seizures may be explained by the definitions used, the intensity of case ascertainment, and the distribution of the immediate causes. A better insight into the incidence of acute symptomatic seizures might come from prospective population-based cohort studies using the same definitions for seizures and epilepsy and focused on the principal epileptogenic conditions (e.g., head trauma, stroke, and CNS infections).

Worldwide Mortality of a First Seizure (Table 2)

Studies on the mortality of acute symptomatic seizures are rare (for the same reasons given for incidence) and studies on the mortality of a first unprovoked seizure have been reported in limited numbers.

In a retrospective U.S. cohort study of 618 children and adults with first diagnosis of epilepsy (Hauser et al., 1980), 159 patients were identified as having experienced a single unprovoked seizure, 26 of whom died during a 8,233 person-year period of follow-up, giving a standardized mortality ratio (SMR) of 2.3 (95% CI 1.5–3.3). Of these, 13 deaths occurred during the first 2 years (SMR 4.2).

In a retrospective population-based cohort study done in Iceland including 224 children and adults diagnosed with single or recurrent seizures followed for 6,308 person-years (Olafsson et al., 1998), there was no increase in SMR

Table 2. Mortality of seizures in population-based studies by type

Author (year)	Area (country)	Person-years	N. cases	SMR (95% CI)				Design
				All	Acute symptomatic	Unprovoked	Single	
Hauser et al. (1980)	Rochester (U.S.A.)	8,233	618	2.3 (1.9–2.6)	NA	2.3 (1.9–2.6)	2.3 (1.5–3.3)	Retrospective
Olafsson et al. (1998)	(Iceland)	6,308	224	1.6 (1.2–2.2)	NA	1.6 (1.2–2.2)	1.2 (0.1–4.0)	Retrospective
Loiseau et al. (1999)	Gironde (France)	804	804	9.3 (7.9–10.9)	10.3 (8.3–12.7)	4.1 (2.5–6.2)	NA	Prospective
Lindsten et al. (2000)	Vasterbotten (Sweden)	850	107	2.5 (1.2–3.2)	NA	2.5 (1.2–3.2)	NA	Prospective, adults
Beghi et al. (2005)*	(Italy)	3,098	323	2.8 (1.6–4.6)	NA	2.8 (1.6–4.6)	NA	Prospective, adults
Hesdorffer and D'Amelio (2005)	Rochester (U.S.A.)	35.7	428	149.1 (119.0–184.7)		NA	NA	Retrospective

NA, not available; SMR, standardized mortality ratio; 95% CI, 95% confidence interval.
*Randomized pragmatic trial.

at any time among patients with a single seizure (all of whom being of unknown cause).

In one population-based study reporting 1-year mortality in 804 children and adults with a first afebrile seizure in Gironde, France, the overall SMR was 9.3 (95% CI 7.9–10.9) (Loiseau et al., 1999). The SMR for unprovoked seizures was 4.1 (95% CI 2.5–6.2). Mortality was increased in patients with remote symptomatic seizures (SMR 6.4; 95% CI 3.6–10.3), acute symptomatic seizures (SMR 10.3; 95% CI 8.3–12.7), and progressive symptomatic seizures (SMR 19.8; 95% CI 14.0–27.3). By contrast, there were no deaths among patients with idiopathic seizures and mortality was not increased in patients with cryptogenic seizures (SMR 1.7; 95% CI 0.1–9.7).

In an adult Swedish population-based cohort, the SMR in patients with a newly diagnosed unprovoked seizure was 2.5 (95% CI 1.2–3.2), with a first peak (SMR 7.3; 95% CI 4.4–12.1) during the first 2 years after diagnosis and a second peak (SMR 5.4; 95% CI 2.70–11.2) at years 9–11 (Lindsten et al., 2000). SMR was higher for remote symptomatic seizures and age younger than 60. The Swedish study reported the higher SMR in the younger age groups and a progressive decrease with age.

In an Italian population including 419 children and adults who were enrolled in a randomized clinical trial comparing the effects of treatment of the first tonic–clonic seizure to treatment of the relapse, data on mortality were obtained in 323 patients, 15 of whom had died (SMR 2.8; 95% CI 1.6–4.6) (Beghi et al, 2005). The SMR was 2.1 in men (95% CI 1.0–4.0) and 5.4 in women (95% CI 2.0–11.7) and peaked in patients aged less than 19 years (SMR 7.7; 95% CI 2.1–19.7).

A study of mortality in the first 30 days after an acute symptomatic seizure was undertaken in the community of Rochester, Minnesota over a 20-year period (Hesdorffer and D'Amelio, 2005). Based on 428 patients with acute symptomatic seizures, the case-fatality ratio was 19.2% and the SMR was 149.1 (95% CI 119.9–184.7). Among patients aged 65 years or older, the SMR for seizures caused by anoxic encephalopathy was 1,357.1.

In a retrospective U.S. population-based cohort study, the 30-day mortality of a first episode of status epilepticus was 19% (Logroscino et al., 1997). In this population, 89% of deaths occurred with nonfebrile acute symptomatic status epilepticus. In the same population, 40% of patients surviving the first 30 days after the seizure died within the ensuing 10 years (Logroscino et al., 2002). The SMR was 2.8 (95% CI 2.1–3.5) and was significantly elevated in symptomatic status epilepticus. By contrast, patients with idiopathic/cryptogenic status epilepticus had no increased risk of death compared to the general population. Age, duration of status epilepticus, seizure type, and etiology contributed to mortality in the multivariate analysis.

In summary, a twofold SMR has been reported in patients experiencing a single unprovoked seizure in one study. However, the results of this study were not confirmed by another study with a similar design, in which no excess mortality was found in patients with a single seizure. Mortality is increased in the youngest patients and in those with symptomatic seizures. The greater mortality in women than in men with a first tonic–clonic seizure reported by the Italian trial is apparently unexplained and the possibility of a chance finding cannot be excluded. The short-term mortality is fairly high after an acute symptomatic seizure and a first episode of status epilepticus. The mortality of status epilepticus is affected by age and seizure type, duration, and etiology. Differences in the SMR across studies can be explained in part by the different populations at risk and by the study design and methodology, with special reference to the inclusion of acute symptomatic seizures and recurrent seizures. However, based on the published reports, seizure etiology is the single most important risk factor for the increased mortality in patients with a first seizure. The highest SMR in the youngest age groups can be interpreted in part in the light of the underlying epileptogenic conditions and of the lower number of competing causes of death.

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