Epidemiology of Status Epilepticus

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Summary

Status epilepticus (SE) is one of the most common neurological emergencies. There is a wide variation in reports regarding clinical presentation, underlying etiology and prognosis. Variation across different studies relates to differences in the definition of SE, the etiological classification of SE, definition of outcomes, and to the study of heterogeneous populations. The most important cause of variation is the source of cases that is an indirect measure of disease severity and etiology. Most of epidemiological studies on SE have been conducted only recently, in the last twenty years. In this review four topics will be considered: definition, incidence, prognosis, and time trends. Yearly incidence ranges around 20/100,000 in US and around 10/100,000 in Europe. Case fatality at thirty days is about 20% in US studies while it appears lower in Europe (lower than 10%). Children have the lowest mortality. Age and the underlying etiology are the main prognostic factors that drive the outcome. When patients with myoclonic SE after cerebral anoxia are excluded, in view of their dismal prognosis, the survivorship after incident SE has been probably improving in recent years, especially among children.

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Key words: Status epilepticus, mortality, prognosis, epidemiology, incidence

Epidemiologie des Status epilepticus

Der Status epilepticus (SE) gehört zu den häufigsten neurologischen Notfällen. Es bestehen grosse Unterschiede in der Beschreibung der klinischen Symptome, der zugrunde liegenden Ätiologie und der Prognose. Die beträchtlichen Variationen in den verschiedenen Studien beruhen auf unterschiedlichen Definitionen des SE, Unterschieden bei der ätiologischen Klassifikation von SE und bei der Definition des Outcomes, sowie Heterogenität der untersuchten Populationen. Der wichtigste Grund für solche Abweichungen ist die Herkunft der Fälle: sie dient sozusagen als indirekter Indikator des Schweregrads und der Ätiologie. Die meisten epidemiologischen Studien wurden erst in jüngster Zeit, genauer gesagt in den letzten zwanzig Jahren durchgeführt. In diesem Beitrag werden vier Themenkreise behandelt, nämlich die Definition, die Inzidenz, die Prognose und Zeittrends. Die jährliche Inzidenzrate bewegt sich in den USA um 20/100'000 und liegt in Europa bei 10/100'000. Die Mortalität erreicht in den USA nach dreissig Tagen etwa 20%, in Europa liegt sie deutlich tiefer, nämlich unter 10%. Die tiefste Mortalität wurde bei Kindern registriert. Das Alter und die zugrunde liegende Ätiologie sind die ausschlaggebenden Prognosefaktoren für das Outcome. Abgesehen von den Patienten mit einem myoklonischen SE nach einer zerebralen Anoxie, deren Prognose sehr schlecht ist, hat sich die Überlebensrate nach einem SE-Zwischenfall in den letzten Jahren wohl verbessert, insbesondere bei Kindern.

Schlüsselwörter: Status epilepticus, Mortalität, Prognose, Epidemiologie, Auftreten

Epidémiologie du statut épileptique

Le statut épileptique (SE) est une des urgences neurologiques les plus répandues. Les descriptions des symptômes cliniques, de l'étiologie sous-tendue et du pronostic diffèrent largement. Ce manque d'unité dans les études s'explique par les différences dans la définition du SE, le classement étiologique du SE et la définition de l'issue (outcome), ainsi que par l'hétérogénéité des populations étudiées. Le facteur majeur de variations est celui de la provenance des cas qui est un indicateur indirect de la gravité des cas et de l'étiologie. La plupart des études épidémiologiques sur le SE ne remontent pas très loin dans le temps puisqu'elles ont été menées dans les 20 dernières années. Dans cet exposé, quatre thèmes sont appréhendés : la définition, l'incidence, le pronostic et les tendances au fil du temps. L'incidence annuelle tourne autour de 20/100,000 aux Etats-Unis et environ 10/100,000 en Europe. Aux Etats-Unis, environ 20% des cas ont une issue fatale dans les trente jours, un chiffre qui est nettement inférieur en Europe avec moins de 10%. La mortalité la plus faible a été constatée chez les enfants. L'âge et l'étiologie sous-tendante sont les principaux facteurs pronostiques qui vont influencer l'issue. Sans compter les patients avec un SE myoclonique suite à une anoxie cérébrale dont le pronostic est très défavorable, le taux de survie après un incident SE s'est probablement amélioré dans les années récentes, surtout chez les enfants.

Mots-clés : Status epilepticus, mortalité, pronostic, épidémiologie, manifestation

In 1959 Richard Hunter published the first complete review on Status Epilepticus (SE) [1]. In his paper, he reported the first population-based data on SE as a cause of death. Death from SE was indexed by the Registrar General as an independent cause of death in England and Wales for the first time in 1949. According to these data deaths from SE were responsible for 37% to 51% of all deaths due to epilepsy in the period 1949-1956 in England and Wales. Hunter emphasized the poor prognosis of SE and commented that both Todd and Gowers were wrong when they described death in subjects with epilepsy as generally due to other diseases and SE as a rare event. After many years the main question in clinical research on SE is still the same: is the presence of SE per se an additional risk factor for a negative prognosis in subjects who experience SE in the course of another medical disease or event or during epilepsy? Most of epidemiological studies on SE have been conducted only recently, mostly in the last twenty years. In this review four topics of the epidemiology of SE will be considered: definition, incidence, prognosis, and time trends.

Definition of Status Epilepticus

According to the Dictionary of Epilepsy of the World Health Organization, SE is defined as a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition [2]. This definition based on the original work by Gastaut is vague, arbitrary and fails to provide objective criteria to separate SE from other seizure disorders. The definition was updated in the early nineties by a working group on SE and the new criteria established a new cut point with a precise time window: "a seizure persisting for 30 min or two or more seizures without recovery of consciousness over 30 minutes" [3]. This definition was chosen as the working definition of SE in epidemiological studies. The choice of a cut point of 30 minutes was based on the experimental work in baboons [4]. In the early phase of experimentally induced seizures, acidosis and increased osmotic pressure decrease neuronal excitability; later, systemic phenomena such as hyperpyrexia and hyperventilation increase the excitability. In this original work animals in SE for 50-120 min had no obvious brain injury. These physiological changes can be the basis of the observed distribution of seizure duration in clinical practice.

More recently Lowenstein [5] has proposed a new definition of generalized, convulsive SE based on practical considerations of patient management. The definition proposed is the following: "Generalized, convulsive status epilepticus in adults and older children (> 5 years old) refers to a 5 min of (a) continuous seizure(s) or two or more discrete seizures between which there is incomplete recovery of consciousness". The authors state that rarely the typical, generalized tonic-clonic seizure (GTCS) in adults appears to last > 5 min. In a recent study based on video-EEG analysis of 120 secondarily GTCSs in 47 hospitalized patients [6] the mean duration of GTCSs was 62 s, with a range of 16-108. Primarily generalized convulsive seizures (i.e., arising synchronously in the whole brain) last for a median time of 66 seconds (range 59-76 seconds) [7]. GTCSs in adults that do not terminate within 5 min are extremely variable in duration from few minutes to several hours or days. According to Lowenstein [5], this new definition is based on the approach of most of neurologists in clinical practice. A patient who is having continuous seizures is generally promptly treated and most clinicians do not wait 15 or 30 minutes before starting the AED administration. Numerous clinical studies suggested a relation between seizure duration and patient mortality but generally a clear increase in mortality has been observed following SE of at least 30 minutes duration. In a study using both prospective and retrospective data on seizures lasting between 10 and 29 minutes DeLorenzo et al. found that 43% of all SE subsided spontaneously, whereas the other patients needed antiepileptic drugs (AED); mortality was 0% in the first group and 4% in the latter [8]. Therefore based on data on prognosis, the cut point at 5 minutes does not seem appropriate. The obvious conclusion is that studies on seizure of duration between 1-2 minutes and 30 minutes (probably the critical time window) are lacking while they are key to establish the optimal interval for the definition of SE. Based on the available published work, the duration of 30 minutes seem the more appropriate to use in future studies.

Incidence of Status Epilepticus

After the report by Hunter [1] there was a gap of almost thirty years before the next population-based studies on SE were published. Extrapolating from incidence data from Rochester, MN, Hauser estimated that in 1990 50,000 to 60,000 individuals experience SE in the US annually and about two thirds of these individuals have no history of epilepsy [9, 10]. In a population-based study in Richmond, Virginia, DeLorenzo estimated an annual incidence of 41/100,000. The frequency of total SE episodes was 50 per year per 100,000 of the population. The mortality rate by 30 days for the population was 22%, 3% for children and 26% for adults [11]. Based on these data about 150,000 individuals will experience 200,000 episodes of SE per year in the US. The overall number of deaths in the US related to SE would be between 22,000 and 42,000 per year. In a more recent study conducted in Rochester [12], the incidence SE was determined by ascertaining all first episodes of SE (incident) in Rochester, Minnesota through the Rochester Epidemiology Project's records-linkage system between January 1, 1965 and December 31, 1984. The

age-adjusted incidence of SE was 18.3 per 100,000 population. SE incidence was U-shaped, peaking under 1 year and over 60 years of age. The incidence of SE was greater for males than for females, for acute symptomatic etiology than any other etiology, and for partial SE that did not generalize than any other seizure type. SE of long duration (at least 2 hours) occurred more frequently among infants and the elderly than among persons aged 1 to 65 years. Cumulative incidence was 4 per 1,000 to age 75 and showed the greatest increase after age 60. More recent studies in Europe suggest a lower incidence with the lowest incidence reported in Geneva, Switzerland, (9.9/100,000) [13] and in Bologna, Italy, (10.7/100,000) [14]. In these studies myoclonic SE were not included. A study conducted in California using hospital discharge database, estimated an incidence of generalized convulsive SE being 6.2/100,000 with a decreasing trend over time from 1991 to 1998 [15]. This estimate is lower than the incidence of generalized convulsive SE obtained in community studies and suggests that reliance of epidemiological studies on diagnostic registries will miss a considerable number of cases. Two other studies conducted in Europe, one in Hessen, Germany, and one in a French-Speaking Canton, Switzerland, reported a higher incidence around 15/100,000) [13, 16].

All population-based studies suggest a J-shaped age-incidence curve of SE: the incidence is highest among children, especially under 1 year of age, and in the elderly of age 65 and above. The high incidence of SE among infants has been attributed to a greater susceptibility of developing brain to seizures [17]. The physiological basis of the increased susceptibility of child's brain may include incomplete development of the substantia nigra, insufficient synthesis of GABA, or inadequate proliferation of glial cells. This increase in susceptibility in children when compared to adults might explain the occurrence of SE in children due to conditions like fever that are not causes of SE among adults. The elderly (over 65) also have a high incidence of SE. The incidence among the elderly is up to 10 times higher than in young adults. Incident SE among the elderly is characterized by high mortality that is mainly related to the high proportion of SE attributed to serious conditions such as anoxic encephalopathy or cerebrovascular diseases. These conditions are more than 50% of all episodes of SE among the elderly. The incidence of SE is therefore expected to increase considering the aging of the general population. Finally, the incidence of SE has been shown to vary across ethnic groups. The incidence among blacks was almost three times that of white in Richmond, Virginia. The authors state that there was no clear evidence of differences in the distribution of causes between races. The same trend was present in a study on convulsive SE conducted in California by Wu with double the risk among black and half of the risk among Hispanic and Asian subjects [15]. Differences in access to medical care with subsequent delay in the treatment of seizure, or difference in compliance to the antiepileptic therapy across ethnic groups could explain a higher frequency of SE in non whites associated with medical conditions that have a good prognosis (low AED levels). It is also possible that African-Americans have a specific vulnerability to develop seizures of longer duration even in presence of similar causes or treatments.

Mortality

There have been many other published studies regarding mortality after SE, most of which are based on clinical series from tertiary centers. The mortality estimated from these studies varies widely: from 6% to 25% among children and from 11% to 43% in adults [10, 18, 19]. This variability of SE prognosis is related to methodological issues including differing definitions of SE, differing distributions of SE etiology, and variable length of follow-up. In population-based studies the short-term mortality is quite uniform: about 20% in studies from US [20, 21] while in Europe it is generally lower than 10% [13, 16, 22], with one exception with very high mortality of about 39% reported in a study conducted in urban setting (39%; [14]. The authors explain the worse outcome of their study with inaccurate management of some patients in their series. Etiology and age are the most important determinant of prognosis: The prognosis is much better in children (3% mortality in population-based studies, [23, 25], severe in elderly subjects compared to adults [20, 21]. Hypoxia, CNS infections and cerebrovascular disease have the worst prognosis with the highest case-fatality. Among hypoxic encephalopathy associated with cardiac arrest, with myoclonic SE, the mortality is as high as 80% [21, 25]. Inadequate AED levels and fever, and traumatic brain injuries have lower mortality in all series. The lowest short term mortality is present among idiopathic SE where no deaths were present in the Rochester series in the first 30 days [21].

Long term mortality after incident SE has been investigated only in one study [26]. Long term mortality at ten years among subjects who survived thirty days after an episode of incident SE was 3 times higher than in the general population. The long term mortality at ten years was higher in subjects with acute symptomatic SE and myoclonic status after anoxic encephalopathy.

An additive effect of SE on the prognosis of subjects with cerebrovascular disease has been reported in at least one study [19]. The effective role of SE as additional prognostic factor or a simple marker of the underlying severity of the disease is still to be studied as we will address more specifically in the paragraph of long-term prognosis of idiopathic SE.

Ethnicity seems also to influence prognosis. The prognosis is much better among African Americans (overall mortality: African Americans 17%, whites 31%) in the

Richmond study [20]. This study did not report any clear differences in the distribution of causes between the races. Similarly, a higher incidence of SE with a better prognosis was recently reported in London among children of Indian immigrants [24]. On the other hand some studies from developing countries seem to indicate that the prognosis in other ethnic groups do not differ substantially from SE prognosis among caucasians within the same etiological strata [27]. Differences in distribution and prognosis across different ethnic groups, as reported by DeLorenzo [20], may indicate different genetic susceptibilities to develop seizures of longer duration, though possibly with a better prognosis. Addressing this question may require more multiethnic studies conducted in the same area, where possible issues related to different referral or treatment because of socioeconomical status may be also excluded.

The specific role of SE on the increased risk of death both short and long term is still an open question. The seriousness of the underlying medical conditions associated with most cases of SE, especially in adults and in the elderly, makes it impossible to determine the independent impact of prolonged seizure on mortality. Demonstration of an independent contribution of SE on mortality may further support the need for aggressive treatment to reduce the duration of prolonged seizures. A possible way to study this question is to evaluate the prognosis of subjects with idiopathic/cryptogenic SE in whom the confounding effect of other causes is absent. In a study conducted in Rochester, Logroscino et al. tested the hypothesis by comparing mortality of subjects with incident idiopathic/cryptogenic SE as a first seizure (SE group) with an incident cohort of subjects with first idiopathic/cryptogenic unprovoked seizure that was not SE (seizure group) and with that expected in the general population [28]. In this study, subjects with idiopathic/cryptogenic SE as their first unprovoked seizure had a non significant 2.4-fold increased risk of death compared with subjects who had briefer unprovoked seizures at 10 years. There was also a 2.6-fold increased risk of death when compared with the general population. Previous studies of mortality following SE had several limitations, including a short follow-up (1 year) and the inclusion of cases with multiple causes. This is the first study to show an independent association between SE without an underlying cause and reduced life expectancy, although the worse prognosis in presence of SE was restricted to subjects who later developed epilepsy and to elderly subjects. Therefore subjects older than 65 years with SE experience a higher risk of death than subjects older than 65 years with a briefer seizure. A prolonged seizure might be more dangerous among elderly persons because any damage induced by SE might be more extensive in the aging brain. An alternative explanation may be that some elderly subjects may have underlying vascular or neurodegenerative disease without clinical manifestations and, therefore, are incorrectly classified as having idiopathic/cryptogenic SE. On the other hand, several hypotheses may explain why mortality is increased in subjects with a first idiopathic/cryptogenic SE who develop epilepsy during follow-up. SE may induce neuronal damage in vulnerable areas of the central nervous system, leading to a permanent dysregulation of neurovegetative activities. Alternatively, SE may be a clinical marker of severity of idiopathic/cryptogenic epilepsy when it occurs as the first unprovoked seizure. An additional hypothesis relates to the basic underlying mechanism of SE: SE is effectively the result of a failure of inhibitory mechanisms. The main limitation of this study was the limited sample size with only 16 incident idiopathic SE and 5 deaths during follow-up of ten years after incident idiopathic SE. In addition the underlying etiology of SE was established without the support of imaging techniques (magnetic resonance).

Time trends in status epilepticus mortality

Although no studies have specifically examined the question, there is a general perception that mortality after SE has decreased in recent years. This has been attributed to better recognition and thus more rapid treatment of SE, and to better management of those with SE [29]. Logroscino et al. using data from Rochester Epidemiologic project failed to support this perception, and in fact find trends in the opposite direction [30]. Mortality following SE has increased over the fifty-year study period (1935-84). The increased mortality was caused by an increase in incidence and an unchanged summary case-fatality rate. The increase in incidence and mortality were due to the occurrence in the last decade of that study of myoclonic SE after cardiac arrest. The mortality in the elderly was twice that of the youngest across all the study period. Mortality had decreased in pediatric cases, particularly in those under 1 year of age. Overall the Rochester study shows that there is improvement in survivorship in the last decade when myoclonic SE was excluded. Changes in causes of SE over time, particularly the high frequency of SE associated with anoxic encephalopathy following cardiac arrest in recent years suggest that overall mortality and case fatality can be expected to increase in the future. This will occur especially if the number of survivors after cardiac arrest will increase as expected because of the better management of these conditions in the intensive care unit [25].

Conclusions

SE is one of the most common neurological emergencies. Many clinicians and researchers view SE as a condition with a well-defined clinical presentation that is quite uniform in its core features, with a simple and precise diagnostic and therapeutic protocol. Most of the

studies show that SE is indeed quite heterogeneous in clinical presentation, with a wide range of underlying causes, and prognosis. Age and the underlying etiology are the main prognostic factors that drive the outcome [31]. The additional risk of negative prognosis due to SE itself is probably minimal and restricted to older subjects and subjects who will later develop epilepsy [28]. This should be clearly taken in to account when considering the appropriate therapy and management of the patients and the planning of future trials for new therapeutic agents of SE.

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