Prognosis of Status Epilepticus

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Summary

Prognosis in SE is vulnerable to ascertainment bias, treatment modalities and incorrect diagnosis. It is difficult to differentiate cause of SE as an independent risk factor. Convulsive status epilepticus (CSE – tonic-clonic status epilepticus) in early literature reported mortalities of 14-50%; more contemporary aggregate data suggest 18% largely due to SE cause and not SE itself. In 89%, death was attributable to cause, and in 2% due to SE proper. Mortality was 11% with cerebral pathology versus 3% with cryptogenic cases. The elderly have a higher mortality (~35%). Major adverse risk factors are represented by etiology (severe metabolic abnormalities, anoxia, organ failure), older age and duration of SE. In children, mortality (in those < 5 years) can be ~50%, attributable to duration of SE. More recently, older children with early treatment had mortalities of 3-6%; 20% of children may develop motor deficits; 17% may have repeated SE.

For NCSE, typical absence status has no sequelae; with de novo absence status in the elderly there are minor sequelae. In atypical absence status in Lennox-Gastaut syndrome, Landau-Kleffner, and electrical status epilepticus in sleep, it is difficult to differentiate progressive decline with the syndrome from the effects of SE – patients decline at variable rates with mortalities rising towards 50%. Complex partial status epilepticus (CPSE) occasionally induces sequelae: 3% in patients with epilepsy; 27% in patients with acute morbid medical problems. SE in anoxic coma is fatal without hypothermia treatment.

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Key words: Convulsive status epilepticus, nonconvulsive status epilepticus, prognosis, morbidity, mortality, refractory status

Pronostic d'un status epilpeticus

Le pronostic d'un SE peut être faussé par des idées préconçues, les modalités de traitement ou un diagnostic erroné. Il est difficile d'isoler un facteur de risque précis ayant pu être la cause d'un SE. Un taux de mortalité de 14-50% était jadis indiqué dans la littérature pour un statut épileptique convulsif (CSE – statut épileptique tonico-clonique) ; les données plus récentes suggèrent cependant que 18% des décès seraient imputables à la cause d'un SE plutôt qu'au SE lui-même. Dans 89% des cas, le décès était dû à la cause, contre 2% de décès seulement induits par le SE lui-même. La mortalité atteignait 11% en présence d'une pathologie cérébrale et 3% pour les cas cryptogènes. La mortalité est plus élevée chez les personnes âgées (~35%). Parmi les facteurs de risque majeurs, il faut retenir l'étiologie (anomalies métaboliques graves, anoxie, défaillances organiques), un âge avancé, ainsi que la durée du SE. Chez les enfants en bas âge (< 5 ans), la mortalité atteint ~50% en cas de durée prolongée. Chez les enfants plus âgés qui avaient été traités à temps, la mortalité se situait autour de 3 à 6% dans un passé plus récent; 20% des enfants ont gardé des séquelles motrices ; dans 17% des cas, des SE à répétition ont été constatés.

En cas de NCSE, les absences typiques restent sans séquelles ; des séquelles légères ont été enregistrées chez les patients âgés avec des absences de novo. Lors d'absences atypiques liées au syndrome de Lennox-Gastaut ou de Landau-Kleffner, ainsi que lors du statut épileptique électrique du sommeil, il est difficile de faire la part des choses entre le déclin progressif dû au syndrome et les répercussions d'un SE – l'état des patients se dégrade plus ou moins rapidement, le taux de mortalité avoisine 50%. Lors du statut épileptique partiel complexe (CPSE), des séquelles ont été observées pour une partie des patients : 3% chez les patients épileptiques ; 27% chez les patients avec des problèmes médicaux d'une morbidité aiguë. L'issue d'un SE dans le coma anoxique sera fatale sans traitement hypothermique.

Mots clés : statut épileptique convulsif, statut épileptique non convulsif, pronostic, morbidité, mortalité, statut réfractaire

Prognose beim Status epilepticus

Die Prognose beim SE kann verfälscht werden durch voreilige Trugschlüsse, Behandlungsmodalitäten oder eine fehlerhafte Diagnose. Es ist schwierig einen einzelnen Risikofaktor als Ursache eines SE auszumachen. In der Literatur wurde die Mortalitätsrate bei einem konvulsiven Status epilepticus (KSE – tonisch-klonischer Status epileticus) früher mit 14-50 % angegeben; in der jüngeren Vergangenheit gesammelte Daten weisen jedoch darauf hin, dass 18 % davon eher der Ursache eines SE als dem eigentlichen SE zuzuschreiben sind. In 89 % aller Fälle war ein tödlicher Ausgang der Ursache zuzuschreiben und nur in 2 % der Fälle verursachte effektiv ein SE den Tod. Die Mortalität erreichte bei zerebralen Pathologien 11 %, bei kryptogenen Fällen jedoch

nur 3 %. Bei älteren Patienten ist die Mortalität höher (~35 %). Zu den Hauptrisiken zählen ätiologische Faktoren (schwerwiegende metabolische Abnormalitäten, Anoxie, organisches Versagen), ein fortgeschrittenes Alter und die Dauer eines SE. Bei Kleinkindern (unter 5 Jahren) besteht eine Mortalität von ~50 % bei längerem Anhalten. Bei älteren, rechtzeitig behandelten Kindern betrug die Mortalität in der jüngeren Vergangenheit 3-6 %; bei 20 % der Kinder bleiben motorische Schäden bestehen; bei 17 % tritt ein SE wiederholt auf.

Bei einem NKSE bleiben typische Absenzen ohne Folgen; bei älteren Patienten mit de-novo-Absenzen sind leichtere Folgeschäden feststellbar. Bei atypischen Absenzen im Zusammenhang mit einem Lennox-Gastaut- oder Landau-Kleffner-Syndrom und beim elektrischen Status epilepticus im Schlaf ist es schwierig, den durch das Syndrom hervorgerufenen progressiven Verfall von den Auswirkungen eines SE zu unterscheiden – der Zustand der Patienten verschlechtert sich mehr oder weniger schnell, die Todesrate beträgt nahezu 50 %. Beim komplexen partiellen Status epilepticus (KPSE) sind teilweise Folgeschäden zu beobachten: 3 % bei epileptischen Patienten; 27 % bei Patienten mit akut morbiden medizinischen Problemen. Bei einem SE im anoxischen Koma ist der Verlauf ohne hypothermische Behandlung tödlich.

Schlüsselwörter: Konvulsiver Status epilepticus, nichtkonvulsiver Status epilepticus, Prognose, Morbidität, Mortalität, refraktärer Statuts

Convulsive status epilepticus

Most early observations on status epilepticus referred to the convulsive form, namely that of tonic-clonic status epilepticus (SE). As with most observational studies, ascertainment bias was significant and must color our present understanding of any conclusions derived from these early times. Binswanger (in Turner) noted a 50% death rate, Lorenz a 45% mortality (cited by Clarke and Prout); and Clarke and Prout a 14% fatality [1-3]. More recent data reflect the improvement in case controls and ascertainment which lean against a bias towards worse cases, as well as the improvement in treatment, with the advent of benzodiazepines and other parenteral antiepileptic drugs. An aggregate of 12 more recent case series yields a fatality of 18% of 1686 episodes, but 89% were thought to be attributable to the underlying cause of status, with death attributable to status itself in only 2% of cases [1]. Oxbury and Whitty noted that although 11% of their 54 patients died in status when they had cerebral pathology, only one of 32 patients without known pathology died. Of those who died acutely, all had progressive diseases such as subarachnoid hemorrhage, glioblastoma, pulmonary embolus, meningitis or alcoholism [4]. More recently, investigators found that of 98 adults, in only 2/16 was death attributable to SE. In the other patients, death was caused by the underlying cause, or ensuing medical complications [5]. Similarly 35% of 31 patients over age 60 years died [6]. In a recent study, 100/235 patients (25%) died from status largely from the underlying causes and complications, with only 2 patients dying from SE itself [7].

In children, the situation regarding convulsive status reflects a higher incidence and severity of the condition. In 239 infants and children [85% < 5 years of age], 10 died acutely and 17 over the ensuing months to years, but in only 50% was death attributable to the status itself [8], largely related to the duration of SE. In contrast others found only a 3% fatality in 66 children [9]; and 7 deaths in 193 children [10], possibly due to earlier and improved treatment [11]. In 218 incidents of SE there was a 6% mortality even with ICU management; but among those with idiopathic SE, only 1% died [12].

Once the early studies had delineated mortality, differentiating cause and duration as risk factors for death, other studies helped determine neurological sequelae short of death. Of 154 cases of whom 22 died, 15 (10%) had severe deficits warranting supportive care and prolonged stays [13]. In children also, prolonged morbidity short of mortality has been noted, but rarely due to SE itself. Deficits appear to arise from the cause of SE, such as trauma, stroke or encephalitis [1]. Younger children are particularly vulnerable, with 20% developing motor deficits and a third, mental impairment [8]. It remains unresolved in many cases whether epilepsy subsequently arises from SE or from the cause of status.

SE may recur. Seventeen percent of 95 children had a second, and 5% had further attacks of SE [14]. The lowest recurrence was seen with neurologically normal children at SE onset [8, 9, 11, 14]. Cerebral atrophy may follow SE proper [15].

The most morbid etiologies of SE are acute vascular damage, encephalitis, trauma and expanding mass lesions. In the Lowenstein and Alldredge series (1993) 90% of SE from alcohol, drugs or trauma did well, while only a third with anoxia, stroke or metabolic problems survived without major sequelae [13]. A second clear risk factor for outcome is duration of SE. Barois et al. (1985) found 4% mortality for short-duration SE, contrasting with almost 50% dying or remaining with severe deficits after SE [16].

Furthermore, severe metabolic disturbances, anoxia, and multi-organ system failure all adversely affect prognosis. Studies on the effect of old age (independent of complicating co-morbidities or etiology) provide a mixed picture, in part because of the difficulty of separating risk factors from age, but increasing age above 60 appears to increase mortality. In the other direction, infants and neonates have a high mortality (29%), compared with ages 1 to 3 years [11, 15]; 6% above 3 years [10]. Yager et al. noted that of 52 children in SE, duration > 1 hour produced a 5.5 OR of bad outcome; and for epilepsy as a risk versus acute or chronic encephalopa-

thy: OR 0.12 versus OR 5.6 and 9.2 [17].

More recent studies have centered on a subgroup of convulsive SE – that of patients refractory to 2 AEDs. Mayer and colleagues noted that almost a third failed to improve within an hour on 2 AEDs, with a mortality of 23% [18]. Others found a morality of 61% in 33 patients [19].

Other forms of status epilepticus

As noted by Gastaut, there are as many forms of status epilepticus as there are types of seizures. Although many forms of seizures rarely occur as SE, this review will cover the principal types. Contemporary classifications of SE now incorporate an approach that segregates SE types according to levels of brain development, presence of encephalopathy, epilepsy syndrome and anatomical location of the epileptic activity. Hence newer approaches categorize according to age.

Determination of prognosis in other forms of SE is vulnerable to ascertainment bias, treatment modalities and appropriate diagnosis of status type. Even when determining the effect of status duration, it is difficult to tease out the effect of cause as an independent risk factor. In patients with mental retardation (who constitute a group vulnerable to SE), it appears challenging to differentiate the chronic mental deficits from possible cognitive neurological sequelae from SE, if any. In non-convulsive forms, the EEG is key in diagnosing NCSE, and hence over- or under-interpretation of SE on EEG affect the equation.

For typical absence status (TAS), there appear to be no residual sequelae attributable to the status itself, and most patients respond rapidly to benzodiazepines [20-22]. For de novo absence status in the elderly, all 11 responded without recurrence; others have noted recurrences in some patients [23, 24]. No series include reports of death or cognitive decline. Absence status with degenerative generalized epilepsies, progressive myoclonic epilepsies, and atypical absence status (AASE) with Lennox-Gastaut syndrome have a poorer overall prognosis, but it is difficult to separate the progressive nature of the disease, for whatever cause, from the particular effect of AASE. Marked progressive debility, retardation with AASE in case series by Doose et al., Bret, Ohtahara et al., Stores et al., Tomson et al. and Tassinari et al. in different age groups and different severe epileptic encephalopathies report episodes of prolonged, AED-resistant SE with morbidity usually exceeding 50% (reviewed by Kaplan [25]).

SE presentations may be age-dependent. Children may have convulsive and non-convulsive forms. Those with electrical status epilepticus during slow sleep (ESES) may temporarily improve in the mid-teens, but many relapse with intellectual decline [26, 27]. Similarly poor overall prognoses are seen in patients with acquired epileptic aphasia (Landau-Kleffner syndrome) and with ring chromosome 20 syndrome, but again, it is often not possible to separate syndrome progression from the effect of SE.

Conversely, simple partial status epilepticus rarely causes death, and cases are usually self-limited. However, some medication-resistant forms of epilepsia partialis continua (Kojewnikov's syndrome) may remain highly refractory to AEDs, and some cause progressive focal weakness. Data are in the form of individual case reports and hence are without epidemiological significance.

More commonly encountered types of NCSE are those with complex partial status epilepticus (CPSE), with mild to moderate obtundation and EEGs showing continuous or intermittent lateralized frontal, temporal or bifrontal seizure activity. When these patients with CPSE have SE due to low AED levels, or when NCSE occurs in patients with chronic epilepsy (without new neurological insult or metabolic/infectious problems), the morbidity and mortality are low. Shneker and Fountain reported a mortality of 3% in this group, contrasting with a mortality of 27% in patients with acute medical problems and 18% in those who were cryptogenic; 36% of those patients with acute complications and 7% in those without. In patients with severe mental status impairment, mortality was 39% versus 7% with mild impairment. Nonetheless, the cause of death was attributable to the underlying etiology or complications in 89% of patients [28]. Kaplan reported that the prognosis may be determined by the level of consciousness during NCSE, as well as by the etiology [29, 30]. In elderly patients with multi-system failure, prognosis is usually worse because of the concurrent disease [31]. In a series of patients in CPSE with uni-frontal versus bifrontal NCSE, patients were less obtunded and had a better outcome [32].

Finally, a frequent form of acquired NCSE with coma is that seen after anoxic insult with cardiac arrest. These patients may present with status myoclonicus, or more subtle facial twitches with electrographic status on EEG. In these subjects, SE usually forebodes death, but a few selected cases (if treated early after cardiac arrest with hypothermia) may have a relatively good outcome [33].

Conclusion

Prognosis can be looked at in terms of death and serious morbidity at one extreme, or in terms of refractoriness to treatment, or recurrence at the other. There is an increasing research into many of these aspects. Investigation is impaired by the largely retrospective nature of most studies that use an accumulation of cases, but also by ascertainment bias, problems of correct classification, categorization by management and comorbidity, and even by correct EEG diagnosis for cases of NCSE. Outcomes range from excellent (TAS) to grave

(refractory convulsive SE, post-anoxic SE) with intermediate results seen with the progressive degenerative CNS syndromes seen in infancy and childhood. With improved epidemiological approaches and standardization of classification of SE (particularly the NCSE forms), there should be an improved understanding and more accurate determination of prognosis.

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