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Inhalt

Editorial	53
Epidemiology of Status Epilepticus <i>Giancarlo Logroscino</i>	54 – 58
Pathophysiology of Status Epilepticus <i>Martin Holtkamp</i>	59 – 64
Classification of Nonconvulsive Status Epilepticus (NCSE) <i>Stephan Rüegg</i>	65 – 77
Pseudo-états de mal épileptiques psychogènes <i>Nicolas Gomez et Pierre Thomas</i>	78 – 83
Treatment of Status Epilepticus <i>Andrea O. Rossetti</i>	84 – 89
Prognosis of Status Epilepticus <i>Peter Kaplan</i>	90 – 93
Epilepsie-Liga-Mitteilungen Informations de la Ligue Suisse contre l'Epilepsie	94 – 101
Kongresskalender	102 – 104

Instructions aux auteurs

Généralités

Le journal « Epileptologie » publie des articles adressés au journal, commandés ou non, se rapportant à tous les thèmes de l'épileptologie. Dans la règle, seuls les articles qui n'ont pas encore été publiés sont acceptés. Les articles, ou parties intégrantes d'articles, ne doivent pas avoir été soumis parallèlement à d'autres éditeurs, ni avoir été déjà acceptés par d'autres éditeurs. Tous les manuscrits feront l'objet de deux expertises. Il n'y aura pas de tirages à part des articles, par contre ils seront publiés sur la page web de la Ligue (www.epi.ch) et disponibles pour téléchargement sous forme de fichier « pdf ».

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Les manuscrits non commandés (ainsi que la correspondance à l'éditeur) doivent être envoyés à: **Madame M. Becker, Rédaction Epileptologie, Ligue Suisse contre l'Epilepsie, Seefeldstrasse 84, Case postale 1084, 8034 Zurich. Tél. 043/488 67 79, fax 043/488 67 78, e-mail: becker@epi.ch.**

Indications pour la rédaction des manuscrits

Seuls les manuscrits correspondant aux critères suivants seront acceptés. Les manuscrits qui ne seront pas rédigés correctement seront renvoyés avant l'expertise.

1. **Langue:** En plus de l'allemand, les articles en français et en anglais sont acceptés.
2. **Style:** En allemand, les formes alémaniques avec « z » et « k » (par exemple « Karzinom ») sont valables, les termes spécialisés en latin conservent leur orthographe (par ex. arteria carotis).
3. **Format:** L'ensemble du texte, y compris les références littéraires, les tableaux et légendes, doit être dactylographié et formaté de la façon suivante:
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 - Les tableaux et illustrations doivent être numérotés consécutivement par des chiffres arabes.
4. **Ordre:** 1. Page de titre (inclusant le cas échéant, les remerciements aux personnes et/ou institutions qui ont contribué au travail), 2. Résumé en allemand, français et abstract en anglais. Mots clés des trois langues. 3. Texte. 4. Littérature. 5. Tableaux. 6. Légendes des illustrations. 7. Illustrations.
- La page de garde contient le titre entier du travail (français et anglais), les noms et titres des auteurs, les institutions pour lesquelles les auteurs travaillent ain-

si que les coordonnées complètes de l'auteur principal, avec numéro de téléphone, fax et e-mail.

- Résumé et abstract en anglais (avec le titre du travail): Sans référence, ni acronyme, ni abréviation inhabituelle (maximum 250 mots).
- 3 à 6 mots clés.
- **Texte:** Disposition dans les travaux originaux : Introduction, méthodes (y compris matériel d'examen, patients, animaux de laboratoire, le cas échéant les autorisations, resp. respect de la Déclaration d'Helsinki, y compris le vote du comité d'éthique), résultats et discussion. Les abréviations doivent être écrites en entier à leur première apparition dans le texte.
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- **Tableau :** Chaque tableau doit apparaître sur une nouvelle page avec un titre explicatif court. Les abréviations et les signes doivent être expliqués en pied de page.
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- **Modèle de citation :** Article de journal : Daoud AS, Batieha A, Abu-Ekteish F et al. Iron status: a possible risk factor for the first febrile seizure. Epilepsia 2002; 43: 740-743 (nommer les 4 premiers auteurs; abréviation des journaux selon la « List of Journals indexed in Index Medicus »); Livres: Shorvon S. Status Epilepticus. Its Clinical Features and Treatment in Children and Adults. Cambridge: Cambridge University Press, 1994; Chapitres de livres: Holthausen H, Tuxhorn I, Pieper T et al. Hemispherectomy in the treatment of neuronal migrational disorders. In: Kotagal P, Lüders HO (eds): The Epilepsies. Etiologies and Prevention. San Diego, London, Boston et al: Academic Press, 1999: 93-102

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L'état de mal épileptique et ses frontières

**Dr Giovanni B. Foletti, MER
Dr Andrea O. Rossetti, PD et MER**



lance, précède un article détaillant plus en détail les imitateurs de l'EME, y compris les aspect psychogènes. Le traitement et ses défis, qui frôlent de près la pharmacologie clinique et les soins intensifs, ainsi qu'un regard sur le pronostic (le retour à l'épidémiologie) concluent les contributions.

Nous espérons vivement que ce numéro puisse contribuer à répondre à des questions, ainsi qu'à réveiller chez les lecteurs l'intérêt de la quête du...mal connu.

Avec nos meilleurs souhaits de bonne lecture,

Andrea O. Rossetti

Giovanni Battista Foletti

Ces dernières années, l'état de mal épileptique (EME) connaît un important retour en vogue, avec l'organisation de congrès internationaux, l'édition de monographies, et la publication toujours plus fréquente d'articles scientifiques. Vraisemblablement, cela reflète la fascination évoquée par une condition décrite déjà depuis plusieurs siècles avant notre ère, qui reste certes plutôt hétérogène et un peu floue (il n'y a pas encore de définition claire reconnue unanimement), mais qui implique une approche multidisciplinaire et collaborative avec des spécialités tant différentes que complémentaires. Quand on aperçoit les limites d'une discipline, ou des propres connaissances, on reste souvent intrigué par ce qui reste au-delà, à moitié connu, un peu convoité, entouré d'une certaine sensation d'incompréhension séduisante.

C'est justement pour souligner ces aspects que ce numéro d'Epileptologie est consacré à l'EME, en mettant l'accent sur ses « frontières », avec la contribution de plusieurs experts suisses, européens et américains reconnus dans le domaine. Le premier article se centre sur la définition et l'épidémiologie, afin de permettre de cadrer l'entité en question. Suit une contribution consacrée aux bases pathophysiologiques, indispensables pour la compréhension des implications cliniques. La caractérisation de l'EME non-convulsif, qui ouvre le diagnostic différentiel avec toute sorte de manifestation paroxystique et/ou impliquant des troubles de la vigi-



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-tendant 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 socio-economical 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 idio-

pathic/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 into 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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Pathophysiology of Status Epilepticus

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Summary

Status epilepticus is refractory to initial intravenous anticonvulsants in every third patient and at least the generalised convulsive form is commonly associated with neuronal long-term consequences. The understanding of pathophysiological mechanisms underlying development and maintenance of status epilepticus and its sequelae is therefore of uttermost importance. Spontaneous seizure termination seems to be an active energy-demanding inhibitory process aiming at restoration of impaired Na^+/K^+ -pump function. Lack of sufficient energy supply by mitochondrial ATP synthesis may result in ongoing seizure activity and the development of status epilepticus. Continuing epileptic activity itself induces a cascade of pathological alterations in the brain that contribute to maintenance of the condition. Decrease of inhibitory GABA_A receptors and increase of excitatory NMDA receptors at the postsynaptic membrane facilitate sustained epileptic activity. Furthermore, these key adaptions impact pharmacology of status epilepticus with progressive pharmacoresistance to GABAergic anticonvulsants and an increased anticonvulsant effect of NMDA receptor antagonists in advanced stages of status epilepticus. Long-term consequences such as development of chronic epilepsy have been studied extensively in experimental animals but in patients status epilepticus is epileptogenic as well. Neuronal circuit modifications such as mossy fiber sprouting and loss of GABAergic interneurons may contribute to epileptogenesis, other mechanisms comprise long-term changes in gene expression and disruption of the blood-brain-barrier. The proper identification of molecular targets is the prerequisite to develop effective antiepileptogenic treatment strategies in conditions such as status epilepticus and other severe brain injuries.

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Key words: epileptogenesis, GABA receptor, loss of inhibition, mitochondrial energy failure, neuronal loss, NMDA receptor

Pathophysiologie des Status epilepticus

Ein Status epilepticus ist bei jedem dritten Patienten refraktär gegenüber den initial applizierten intravenösen Antikonvulsiva und ist zumindest in seiner generalisiert konvulsiven Form häufig mit neuronalen Langzeit-

Schädigungen assoziiert. Ein vertieftes Verständnis der pathophysiologischen Mechanismen, die der Entstehung und Aufrechterhaltung des Status epilepticus und dessen Folgeschäden zugrunde liegen, ist daher von entscheidender Bedeutung. Die spontane Beendigung von epileptischen Anfällen scheint ein energieabhängiger inhibitorischer Prozess zu sein, der letztendlich die Wiederherstellung der zuvor eingeschränkten Na^+/K^+ -Pumpfunktion zum Ziel hat. Ein Mangel an ausreichender Energieversorgung durch mitochondriale ATP-Synthese kann zu anhaltender Anfallsaktivität und zur Entwicklung eines Status epilepticus führen. Die kontinuierliche epileptische Aktivität selbst induziert eine Kaskade an pathologischen Änderungen im Gehirn, die zur Aufrechterhaltung des Status epilepticus beitragen. Eine Abnahme der inhibitorischen GABA_A -Rezeptoren und eine Zunahme der exzitatorischen NMDA-Rezeptoren an der postsynaptischen Membran ermöglichen und fördern das Anhalten der epileptischen Aktivität. Darüber hinaus haben diese Adaptationsvorgänge Einfluss auf die Pharmakologie des Status epilepticus, einerseits hinsichtlich der progredienten Pharmakoresistenz gegenüber GABAerg wirkenden Antikonvulsiva und andererseits hinsichtlich eines mit der Dauer des Status epilepticus zunehmenden Wirkeffekts von NMDA-Rezeptor-Antagonisten. Langzeit-Schäden wie die Entwicklung einer chronischen Epilepsie sind ausführlich in Tiermodellen aufgezeigt worden, aber bei Menschen ist ein Status epilepticus ebenfalls epileptogen. Modifikationen neuronaler Netzwerke wie die aberrante Moosfaserprossierung und ein Verlust GABAerger Interneurone tragen wahrscheinlich zur Epileptogense bei, andere Mechanismen beinhalten langfristige Änderungen der Genexpression und die Ruptur der Blut-Hirn-Schranke. Die eindeutige Identifikation von molekularen Zielstrukturen ist die Grundvoraussetzung für die Entwicklung effizienter antiepileptogener Therapiestrategien beim Status epilepticus oder anderen schweren Hirnschädigungen.

Schlüsselwörter: Epileptogenese, GABA -Rezeptoren, Inhibitionenverlust, mitochondrialer Energieverlust, Neuronenverlust, NMDA-Rezeptoren

Pathophysiologie du statut épileptique

Chez une personne sur trois, un statut épileptique (status epilepticus) est réfractaire aux administrations initiales d'anticonvulsifs intraveineux ; et en tout cas dans sa forme convulsive généralisée, il est fréquem-



ment associé à des lésions sur le long cours. D'où l'importance capitale d'une compréhension approfondie des mécanismes pathophysiologiques qui régissent l'apparition et la persistance du statut épileptique et de ses séquelles. La terminaison spontanée de crises épileptiques semble être un processus inhibiteur énergétoco-dépendant ayant pour objectif le rétablissement de la fonction de pompage de Na^+/K^+ précédemment restreinte. Un approvisionnement énergétique déficient par synthèse ATP mitochondriale peut conduire à une activité de crise durable et au développement d'un statut épileptique. L'activité épileptique, lorsqu'elle est continue, induit elle-même une cascade d'altérations pathologiques dans le cerveau qui contribuent au maintien du statut épileptique. Une diminution des récepteurs GABA_A et une augmentation des récepteurs excitateurs NMDA sur la membrane post-synaptique permettent et favorisent la persistance de l'activité épileptique. Ces processus d'adaptation ont en outre une influence sur la pharmacologie du statut épileptique sous forme d'une pharmacorésistance progrédiente aux anticonvulsifs à action GABAergique et d'un impact grandissant des antagonistes de récepteurs NMDA à mesure que la durée du statut épileptique se prolonge. Les lésions en résultant sur le long terme, par exemple le développement d'une épilepsie chronique, ont été montrées en détail par modélisation animale, mais un statut épileptique est également épileptogène chez l'homme. Les modifications de réseaux neuronaux tels que la prolifération aberrante d'axones et une perte d'interneurones GABAergiques contribuent probablement à l'épileptogénèse, d'autres mécanismes entraînent à long terme des modifications de l'expression génique et la rupture de la barrière sang-cerveau. L'identification claire de structures moléculaires cibles est un prérequis pour le développement de stratégies thérapeutiques anti-épileptogènes efficaces dans la lutte contre le statut épileptique ou d'autres lésions cérébrales graves.

Mots clés : Epileptogénèse, récepteurs GABA, perte d'inhibition, perte d'énergie mitochondriale, perte de neurones, récepteurs NMDA

Some 150 years ago, Armand Trousseau from Paris recognised that during "status epilepticus, something happens [in the brain] that requires an explanation" [1]. Though we have seen some progress in our understanding of what is happening, we are far from being at the end of the road. Treatment success is still limited, more than one in three patients develops refractory status epilepticus (SE). Neuronal and clinical sequelae are commonly seen. Therefore, a better understanding of pathophysiological mechanisms underlying the development, maintenance and consequences of status epilepticus is urgently required.

Animal models resembling status epilepticus

Though EEG and MRI (functional and structural) may offer the chance to get insight into some pathophysiological aspects of SE in patients *in vivo*, the vast majority of work in this field has been performed on animals. However, experimental findings from animal model systems of SE have to be discussed critically regarding their translational relevance.

There are two commonly used approaches to induce SE in living animals, one is local or systemic administration of a proconvulsant drug, the other is electrical stimulation of susceptible brain structures. One of the most frequently used chemoconvulsants is pilocarpine that is a cholinergic substance acting on muscarinic acetylcholine receptors. Eventually, secondary release of the excitatory neurotransmitter glutamate acts proconvulsantly [2]. Turski was one of the first to develop this model system and he described a stereotypical sequence of electro-clinical alterations [3]. Twenty to 30 min following intraperitoneal administration of pilocarpine, intracranial recordings demonstrate isolated high voltage spikes in the hippocampal region that after another 20 min occur in neocortical structures as well. These electrophysiological alterations are accompanied by behavioural changes such as initial oral automatisms and eye blinking. After 30 min, the rats exhibit first partial motor seizures that progress to frequent generalised motor activity. After approximately 90 to 120 min, convulsions cease, and the rat is in a state termed limbic SE. This condition is characterised by staring, chewing and other stereotypical subtle movements, the EEG demonstrates continuous ictal discharges that occur predominantly in limbic structures. The electro-clinical features of experimental limbic SE resemble complex partial SE in patients. The main difference is the extent of continuous excitatory seizure activity, that is less severe and more fluctuating in patients compared to the animal models. This issue is of particular relevance in regard of consequences of SE such as neuronal loss and the development of chronic epilepsy and is discussed in more detail below.

The other frequently used chemoconvulsant is kainic acid that binds to a subtype of the ionotropic excita-

tory glutamate receptor which is termed kainate receptor [4, 5]. Nowadays less commonly used substances include picrotoxin, bicuculline, and penicilline [6]. Besides systemic administration, chemoconvulsants can be given intrahippocampally or intraventricularly.

Electrical stimulation of limbic structures such as the amygdala, the ventral hippocampus and the perforant path results in high-amplitude spontaneous discharges that occur continuously for hours even after the end of stimulation [7-10]. Therefore, in this model system, SE persisting beyond electrical stimulation is clearly *self-sustaining*. Behavioural changes are similar to those in the pilocarpine model, SE is predominantly limbic but motor features may be seen.

Most animal studies do not focus on pathophysiology of SE itself, but employ SE to induce brain injury subsequently resulting in the development of chronic epilepsy. The behavioural, electrophysiological and neuro-pathological features of this form of experimental epilepsy resemble temporal lobe epilepsy in patients [11]. The research interest is to elucidate the pathophysiological alterations underlying epileptogenesis, to identify possible molecular targets and to develop antiepileptic treatment strategies [12]. SE is the most commonly used model system to study subsequent epileptogenesis, and – depending on the specific model used – 70 to 100 % of rats develop chronic epilepsy within 2 to 8 weeks [10, 13-15].

Advantageous and disadvantageous features of chemoconvulsant SE animal models are contrasted with those of electrical stimulation models in **table 1**.

Development and maintenance of status epilepticus

Status epilepticus is the consequence of failure of spontaneous seizure termination. While seizure initiation has widely been studied, the underlying mechanisms of seizure termination still have to be elucidated. One hypothesis currently discussed is based on failure and restoration of mitochondrial energy supply. Following a stimulus, mitochondrial ATP synthesis is diminished and subsequently the energy-dependent Na^+/K^+ -pump function is impaired. Increased extracellular K^+ concentration facilitates neuronal excitability [16, 17]. The clinical response may be an epileptic seizure. This evokes marked cerebral vasodilatation, allowing increased cerebral perfusion that renews the access to oxygen. Mitochondrial ATP synthesis and Na^+/K^+ -pump function are restored, neuronal excitability is reduced and the epileptic seizure may terminate. This model suggests that epileptic seizures should inherently be self-limiting [18]. However, if seizure-associated hyperperfusion is unable to override the hypoxic stimulus, mitochondrial ATP synthesis can not be restored and ictal discharges persist. Clinically, the patient may develop SE. Other mechanisms contributing to seizure ter-

mination that – if impaired – may explain its failure are discussed in detail in an excellent recent review by Lado and Moshé [19].

Epileptic activity itself induces a cascade of pathophysiological alterations in the brain that contribute to the development and eventually maintenance of SE. Within the frame of milliseconds to seconds, neurotransmitters and modulators are released, ion channels become activated and inactivated, and receptors are phosphorylated and desensitised. In the range of seconds to minutes, receptor trafficking affecting GABA and glutamate receptors is responsible for some key adaptation. In the framework of minutes to hours, inhibitory peptides such as dynorphin, galanin and somatostatin are depleted, and the expression of the proconvulsant tachykinins substance P and neurokinin B is increased [20]. In the following, the focus is on receptor trafficking that may have direct implications for treatment approaches tailored to the specific stage of SE.

Following the current “receptor trafficking” hypothesis, ongoing epileptic activity results in gradual reduction in the number of inhibitory GABA_A receptors at the synaptic membrane following receptor internalisation into endocytic vesicles and subsequent degradation. Experimental *in vitro* findings have demonstrated that pilocarpine-induced SE of 1 h duration significantly diminishes the number of GABA_A receptors compared to control rats [21]. This process results in erosion of endogenous GABAergic inhibition that on the one hand majorly contributes to sustained epileptic activity and thus facilitates and maintains SE. On the other hand, loss of postsynaptic GABA_A receptors constitutes the pathophysiological basis for progressive pharmacoresistance of GABAergic drugs such as benzodiazepines, barbiturates and propofol with ongoing seizure activity. In an experimental *in vivo* model, the diazepam dose required to terminate SE was 10fold increased when administered 45 min compared to 10 min after onset of epileptic activity [22]. Analogously, clinical data indicate that treatment success of SE is dramatically reduced from 80% when initiated 30 min after seizure onset to 40% after 120 min [23].

While with ongoing seizure activity the number of GABA_A receptors is significantly reduced, AMPA and NMDA receptors are progressively transported to the synaptic membrane [24]. This facilitates neuronal excitability and sustained SE. However, the enhanced expression of glutamate receptors may be useful in the therapeutic management of advanced stages of SE. In the electrical stimulation model of SE, the NMDA receptor antagonist ketamine did not have any effect when administered 15 min after onset of seizure activity while SE was terminated in all four rats when given after 60 min [25].

Furthermore, experimental data suggest that NMDA receptor activation regulates SE refractoriness to benzodiazepines, as receptor blockade reverses GABAergic pharmacoresistance [26]. This interrelation may

**Table 1****Characteristics of chemoconvulsant and electrical stimulation animal models of status epilepticus**

	chemoconvulsants	electrical stimulation of limbic structures
technical requirements to induce SE	(+)	++
acute fatality during SE	++*	(+) [27]
rate of successful SE (%)	40 – 100 [3, 28]	70 – 90 [10, 29]
self-sustaining character of SE	Δ	+++
neurotoxicity of the SE inducing methodological approach	++	Δ
rate of animals developing chronic epilepsy (%)	60 – 100 [13, 14]	50 – 100 [30, 31]

SE, status epilepticus; * fatality following systemic administration of pilocarpine was significantly reduced by coadministration of methylscopolamine [32]

have therapeutic relevance. Ketamine coadministered with diazepam in rats has recently been demonstrated to have strong synergistic anticonvulsant effects while each substance given alone did not have any effect at all [33]. In a patient with difficult-to-treat SE refractory to barbiturates and propofol, ketamine coadministered to midazolam eventually was successful [34].

Consequences of status epilepticus

Generalised convulsive SE is accompanied and complicated by a plethora of systemic alterations that manifest early in the course and that significantly contribute to morbidity and mortality. Generalised continuous epileptic activity results in excitation of hypothalamic and subsequently brain stem structures that eventually lead to massive release of endogenous catecholamines. The clinical consequences are – occasionally massive – arterial hypertension, tachycardia and potentially lethal tachyarrhythmia. In addition, severe hyperthermia up to 41°C that is due to ongoing convulsions is commonly observed. Furthermore, acid-base-dysbalance due to metabolic and respiratory acidosis and pulmonary oedema often occur [35]. Beyond any discussion on long-term neuronal consequences, these severe systemic complications of generalised convulsive SE require an early and aggressive anticonvulsant treatment approach. In non-convulsive forms of SE such as complex partial SE, these systemic consequences do not occur at

all or at most subtly. Therefore, the aggressiveness of anticonvulsant treatment has to be balanced against the risk of neuronal consequences and corresponding clinical sequelae [36].

In landmark experiments by Meldrum and colleagues, generalised convulsive SE induced by bicuculline in baboons lasting 1.5 to 5 h caused neuronal damage in cerebellar, hippocampal and neocortical structures [37]. If convulsions were avoided by complete muscle relaxation, neuronal cell loss was less severe but not completely prevented indicating the deleterious effects of continuing epileptic activity itself [38]. This argues to treat subtle SE (late stage of previously overt generalised convulsive SE [39]) as aggressively as the overt convulsive form [40]. Self-sustaining SE induced by electrical stimulation of limbic structures in rats results in a phenomenological spectrum ranging from continuous limbic, partial motor to generalised convulsive SE [41]. Comparing animals with partial motor SE to those with generalised convulsive SE, neuronal damage and development of chronic epilepsy were significantly less severe but still present. In summary, animal data on SE indicate that the severity of brain structural consequences depends on the extent of convulsive activity. However, non-convulsive epileptic activity has the potential to damage neurons as well. Translation of these experimental findings to human forms of non-convulsive SE should be made with caution for the following reasons. SE in animal models is often associated with extensive continuous excitatory seizure activity while – most no-

tably complex partial – SE in humans generally is interrupted by periods of less severe activity. Duration and frequency of epileptic activity have been shown to correlate with the extent of neuronal damage [42], and therefore experimental SE can not indiscriminately be compared with the human condition.

Neuronal consequences of non-convulsive forms of SE in humans may be assessed methodologically in postmortem autopsies or in vivo by neuroimaging. Commonly, non-convulsive SE is a condition that does not result in patients' death unless the underlying causative medical condition is lethal. Since in such cases allocation of the origin of neuronal cell loss can not be made with certainty, there are no reliable reports on structural consequences of non-convulsive SE as shown by histology, as yet.

Structural neuroimaging has also been used to search for cerebral consequences of status epilepticus. Indeed, a single case with temporal lobe epilepsy was reported who developed hippocampal atrophy after complex partial SE [43]. This report contrasts to another MRI volumetry study that assessed nine patients up to 12 months after generalised convulsive status epilepticus and did not reveal atrophy in limbic structures [44].

Non-convulsive SE occurring in patients with pre-existing epilepsy allows to clearly assess isolated clinical effects of continuing epileptic activity. Outcome is reported to be good to excellent for complex partial SE [45-47]. Advanced analysis of neuropsychological functions in patients with pre-existing epilepsy and at least one episode of complex partial SE showed an excellent intellectual prognosis in adults [48].

As mentioned above, 70 - 100% of animals develop chronic epilepsy with spontaneous recurrent seizures within 2 - 8 weeks after SE [10, 13-15]. The exact pathophysiological mechanisms underlying epileptogenesis still have to be elucidated. In mesial temporal lobe structures, mossy fiber sprouting [49] and transient impairment of inhibition possibly due to loss of GABAergic interneurons [10, 15] currently are discussed to facilitate the development of chronic epilepsy. Both alterations are NMDA receptor regulated [50, 51] that may display a molecular target for antiepileptogenic treatment strategies [12]. In patients, it may be difficult to discern whether epileptogenesis is the consequence of SE or of the underlying brain disease. The 10-year risk of developing epilepsy after acute symptomatic SE has been reported to be 41% and thus 3.3 fold higher than after a single epileptic seizure with comparable aetiology [52], giving evidence for the major impact of SE itself on epileptogenesis in humans. Perspectively, clinical research on consequences of SE and on prevention strategies should be further emphasised. This requires follow-up studies for years or even better for decades.

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Classification of Nonconvulsive Status Epilepticus (NCSE)

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Abbreviations:

AC:	aura continua
AS:	absence status
BZD:	benzodiazepines
BSMEI:	borderline severe myoclonic epilepsy of infancy
CISE:	critical illness status epilepticus
CPSE:	complex-partial status epilepticus
CT:	computer tomography
DSE:	dyscognitive status epilepticus
DWI:	diffusion-weighted imaging
EEG:	electroencephalography
ESES:	electric status epilepticus in slow-wave sleep
GCSE:	generalized convulsive status epilepticus
GPED:	generalized periodic epileptiform discharges
ICU:	intensive care unit
IGE:	idiopathic generalized epilepsy
ILAE:	International League Against Epilepsy
LEV:	levetiracetam
LTG:	lamotrigine
LZP:	lorazepam
MDL:	midazolam
MSE:	myoclonic status epilepticus
MRI:	magnetic resonance imaging
NCSE:	non-convulsive status epilepticus
PLED:	periodic lateralized epileptiform discharges
PSE:	postanoxic (myoclonic) status epilepticus
SE:	status epilepticus
SMEI:	severe myoclonic epilepsy in infancy
SSE:	subtle status epilepticus
TPW:	triphasic waves
VPA:	valproic acid

Summary

There is no widely accepted classification of nonconvulsive status epilepticus (NCSE) and any classification has its own strengths and flaws. The following article incorporates the two main proposals of the International League against Epilepsy (ILAE) and Shorvon for the classification of NCSE. In general, NCSE may be subdivided into the focal and (primary) generalized forms, and in those types occurring in critically ill patients with focal or generalized electroencephalographic patterns. In addition, there are age-specific forms of NCSE in the neonatal, early infancy and childhood periods. The generalized forms include typical and atypical absence status, de novo absence status of late onset and the myoclonic SE in idiopathic generalized epilepsies. The focal forms are split into those forms without impairment of consciousness, called "aura continua" (corresponding to the former "simple partial NCSE") and those with impaired consciousness, called "dyscognitive SE" (corresponding to the former "complex-partial" or "psychomotor" SE). The latter is further subdivided into the "mesial temporal" ("limbic") and the "neocortical" forms.

The neonatal, early infancy and childhood forms of NCSE are only briefly discussed and listed in a table. A concise electroclinical case vignette may illustrate the principal features of each type of NCSE in adults.

Epileptologie 2009; 26: 65 – 77

Key words: non-convulsive status epilepticus, classification, absence status, aura continua dyscognitive status epilepticus, subtle status epilepticus, postanoxic myoclonic status epilepticus, electroencephalography

Classification du statut épileptique non convulsif

Il n'existe toujours pas de classification généralement acceptée du status epilepticus non convulsif (NCSE). Toute solution proposée jusqu'à ce jour présente ses avantages et ses inconvénients spécifiques. L'article ci-après se réfère à deux schémas actuels de classification du NCSE : celui de la Ligue Internationale contre l'Epilepsie (ILAE) et celui de Shorvon. De manière générale, on peut scinder le NCSE en formes focales et en formes (primaires) généralisées, plus les pathologies très lourdes avec un bilan encéphalographique focal ou générat-



lisé. A cela s'ajoutent encore les types de NCSE âge-dépendants tels que la période néonatale, la première enfance et l'enfance préadolescente. Les formes primaires généralisées englobent l'état d'absence typique et atypique, l'état d'absence « de novo » à début tardif, ainsi que le SE myoclonique dans le cadre des syndromes d'une épilepsie généralisée idiopathique. Les NCSE focaux sont subdivisés en formes sans perte de connaissance, celles à facultés cognitives restreintes, aujourd'hui « aura continua » (anciennement « NCSE partielle simple ») et en « mal épileptique dyscognitif » (autrefois appelé SE « partiel complexe » ou « psychomoteur »). Pour ce dernier état, la distinction se fait toujours entre les formes « mésio-temporales » (jadis aussi « limbiques ») et les formes « néo-corticales ». Les différents types de NCSE de la période néonatale, de la petite enfance et de la préadolescence ne sont mentionnés qu'en marge et inclus dans la synopsis. Une courte vignette électroclinique de cas représentant chaque forme importante de NCSE doit illustrer la discussion.

Mots clés : Statut épileptique non convulsif, état d'absence, aura continua, statut épileptique dyscognitif, statut épileptique « subtil », statut épileptique myoclonique post-anoxique, électroencéphalographie

Klassifikation des nicht-konvulsiven Status epilepticus

Zurzeit besteht nach wie vor keine allgemein akzeptierte Klassifikation des nicht-konvulsiven Status epilepticus (NCSE). Jeder bisherige Vorschlag weist seine spezifischen Vor- und Nachteile auf. Im nachfolgenden Artikel wird auf zwei aktuelle Klassifikations-Schemata für den NCSE, eines der Internationalen Liga gegen Epilepsie (ILAE) und dasjenige von Shorvon, zurückgegriffen. Generell kann der NCSE in die fokalen und (primär) generalisierten Formen unterteilt werden sowie zusätzlich in diejenigen, welche bei schwerst erkrankten Patienten mit fokalem oder generalisiertem elektroenzephalographischem Bild auftreten. Darüber hinaus bestehen altersgebundene Typen des NCSE in der Neugeborenenperiode, im Kleinkindalter sowie in der späteren Kindheit. Die primär generalisierten Formen umfassen den typischen sowie atypischen Absencenstatus, den „de novo“ spät beginnenden Absencenstatus sowie den myoklonischen SE im Rahmen der idiopathischen generalisierten Epilepsiesyndrome. Die fokalen NCSE werden unterteilt in diejenigen Formen mit erhaltenem und in diejenigen mit eingeschränktem Bewusstsein und heutzutage „aura continua“ („früher einfach-partieller NCSE“) beziehungsweise „dyskognitiver SE“ (früher „partiell-komplexer“ oder „psychomotorischer“ SE) genannt. Bei letzterem wird weiter zwischen den „mesial temporalen“ (früher auch „limbischen“) und den „neokortikalen“ Formen unterschieden. Die NCSE-Typen der Neonatalperiode, der Kleinkindphase und der

späteren Kindheit werden nur gestreift und tabellarisch aufgeführt. Eine kurze elektroklinische Fall-Vignette zu jeder wichtigen NCSE-Form soll mithelfen, das Besprochene zu veranschaulichen.

Schlüsselwörter: Nicht-konvulsive Status epilepticus, Klassifikation, Absence-Status, aura continua, dyskognitiver Status epilepticus, „subtle“ Status epilepticus, postanoxischer myoklonischer Status epilepticus, Elektroenzephalographie

Introduction

Any classification of a disorder relies on its definition. Nonconvulsive status epilepticus (NCSE) shares one of the most debated classifications because of the difficulty to define it. The most simple definition of NCSE may be the mathematical formula NCSE = all status epileptici (SE) minus the convulsive SE. Beyond the lack of convulsive signs and the therefore often intriguingly subtle or protean clinical manifestations of NCSE, NCSE essentially needs to be confirmed by electroencephalography (EEG). Thus, a definition of NCSE could read as proposed by Shorvon [1]: “nonconvulsive SE is a term used to denote a range of conditions in which electroencephalographic seizure activity is prolonged and results in nonconvulsive clinical symptoms”. This “range of conditions” was already evoked by Gastaut in 1962 when he stated “there may be as many forms of SE as seizure types exist” during the Xth Marseille Colloquium on Epilepsy [2]. Minimal duration of NCSE is another debated issue among epileptologists. While the former 30 minutes duration for SE was reasonably shortened to 5 minutes for generalized convulsive SE (GCSE) after the results of the large VA study on GCSE [3] and the proposal of Lowenstein [4], the minimal duration of NCSE was kept at a duration of 30 to 60 minutes, although Jordan proposed 15 to 30 minutes [5, 6]. The current Swiss guidelines for the treatment of SE insist on a duration of 5 minutes [7], since more than 90% of seizures stop after 3 minutes [8, 9] and those during longer than 10 minutes have only a minor tendency to stop spontaneously [10]. Also from a brain's perspective, it does not make a difference for a neuron whether it is involved in convulsive or nonconvulsive activity: prolonged hyperexcitation of both of them carries the risk of neuronal damage or death.

The various manifestations of NCSE and its electroclinically blurred margins leave many doors open to borderline conditions (like the postanoxic (myclonic) SE, the critical illness SE or the epileptic encephalopathies (discussed in this article) or even imitators of NCSE (discussed in the article of P. Thomas in this issue). The classification of NCSE can be based on age of manifestation [11], on localization and semiology, on focality, and on etiology; the latter may also be subdivided into the groups of symptomatic or idiopathic SE and into



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Kahn-Preis Epileptologie

Zur Unterstützung wissenschaftlicher Arbeiten von jüngeren Forschenden aus dem gesamten Gebiet der Epileptologie stellt die Jubiläumsstiftung der Bank Hugo Kahn für Epilepsieforschung einen Betrag von

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zur Verfügung. Der 1998 initiierte Preis kann sowohl zur Anerkennung bereits abgeschlossener Arbeiten als auch zur Unterstützung laufender Erfolg versprechender Projekte aus klinischen oder theoretischen Fachgebieten eingesetzt werden. Das Höchstalter für Gesuchstellende beträgt 45 Jahre.

Einzureichen bis: Ende Mai 2010.

Bewerbungen und Vorschläge sind **bis Ende Mai 2010** unter Beifügung der entsprechenden Unterlagen in dreifacher Ausfertigung einzureichen an:

Schweizerische Liga gegen Epilepsie

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A soumettre jusqu'à: fin mai 2010.

Les candidatures et les propositions de candidats accompagnées d'un dossier en trois exemplaires sont à soumettre **jusqu'à fin mai 2010** à :

Ligue Suisse contre l'Epilepsie
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To be submitted by: the end of May 2010.

Candidates and applications from candidates accompanied by three copies of their file should be submitted **by the end of May 2010** to:

Swiss League Against Epilepsy
Dr. Günter Krämer, Chairman
P.O. Box 1084
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Panel of Judges: Dr. Günter Krämer, Zurich (chairman), Prof. Dr. Paul-André Despland, Lausanne, and Prof. Dr. Theodor Landis, Geneva.

Table 1: Types of nonconvulsive status epilepticus (NCSE) in adults:**focal:****with maintained consciousness:****aura continua:**

- dysaesthetic
- painful
- epigastric
- fearful
- déjà-/ jamais-vu
- visual
- olfactory
- gustatory
- auditory
- pilomotor
- aphasic

with impaired consciousness:**dyscognitive SE:****mesial temporal:**

- emotional (fear, anger)
- amnestic
- déjà-/ jamais-vu
- confusional
- olfactory
- gustatory
- epigastric
- psychotic

neocortical:

- dysaesthetic
- auditory
- visual
- aphasic
- pilomotor

primarily generalized:

- typical absence status
- atypical absence status
- de novo absence status of late onset
- myoclonic SE (in IGE)

in comatose patients (generalized & focal):

- postanoxic (myoclonic) SE
- subtle SE (after overt convulsive SE)
- critical illness SE

whether an epileptic disorder is already known or absent. Most classifications cannot stringently rely on solely one of these criteria and therefore they were almost always an intermingled conglomerate of all of these factors.

Classification

The most early classification used the terms “absence status” (AS) for generalized NCSE and “complex partial SE” (CPSE) for the focal forms of NCSE. The advent of clinical EEG [12] allowed for better differentiation of the clinically almost indistinguishable states of purely postictal alterations and non-convulsive status epilepticus (NCSE). The typical EEG picture of absence status (AS) was discovered by Lennox and co-workers [13]; Penfield and Jaspers reported the existence of continuous somato-sensory SE which they labelled “aura continua” [14]. Landolt emphasized the usefulness of EEG for the discrimination between AS and complex partial SE (CPSE) which often are clinically hardly to distinguish [15]. The Xth Marseille Colloquium on Epilepsy held in 1962 was the first conference devoted to classify the various forms of SE. This classification, however, submerged in a babylonian use of terms for both conditions given the countless manifestations of NCSE on the one hand and the clinically often very similar nature of AS and “classical, psychomotor” CPSE on the other hand; accordingly, there were more than 20 different expressions for this disorder [1]. This eventually resulted in complete confusion and substantial difficulties to perform (epidemiological) studies. The most recent proposal of an expert panel of the ILAE from 2006 slightly modified and enlarged the subtypes and incorporated them into their classification. They kept the term AS for primarily generalized NCSE, but correctly refined focal NCSE by the terms “aura continua” (AC) [14] for simple partial NCSE and “dyscognitive SE” (DSE) for CPSE properly [16]. However, more recent results of basic science and the progress of modern medicine led to the surge of new forms of NCSE, like the “subtle” SE (SSE) [17] or postanoxic myoclonic SE (PSE) and “critical illness” SE (CISE) [18, 19] which should be incorporated in contemporary classifications. Such a classification is presented in **table 1**. In addition, this article will only briefly touch on those types of NCSE which exclusively occur in the neonatal and early childhood period. The latter form a unique continuum of paroxysmal episodes of NCSE often developing into a more chronic encephalopathic state [20].

Table 2: Types of NCSE and epileptic encephalopathies in children (modified from [1])**Types of NCSE shared between children and adults:**primarily generalized:

typical absence status

myoclonic SE (in IGE)

NCSE in Lennox Gastaut syndrome:

- atypical absence status
- tonic SE

NCSE in other symptomatic encephalopathies or in patients with learning disabilities

focal:

with maintained consciousness:

- aura continua (s. also **table 1**)

with impaired consciousness:

dyscognitive SE (s. also **table 1**):

- mesial temporal
- neocortical

in comatose patients (generalized & focal):

postanoxic (myoclonic) SE

subtle SE (after overt convulsive SE)

critical illness SE

Types of NCSE of exclusively childhood:

NCSE of early-onset benign occipital epilepsy of childhood (Panayiotopoulos syndrome)

NCSE of specific childhood epileptic syndromes (often with genetic background and progressive):

- ring chromosome 20 syndrome
- Angelman syndrome
- Rett syndrome
- myoclonic-astatic epilepsy (Doose syndrome)
- Lafora's disease

Electric status epilepticus in slow-wave sleep (ESES)

Landau-Kleffner syndrome

Types of NCSE confined to the neonatal and early infancy period:

- neonatal SE
- Ohtahara syndrome
- West syndrome
- severe myoclonic epilepsy of infancy (SMEI; Dravet syndrome); boundary/"benign" variant (BSMEI)
- NCSE in other forms of epilepsy during the neonatal and early infancy period

Absence status [AS]

Absence status may mainly occur in three different populations of patients. First and important, "typical" AS may develop in patients with an idiopathic generalized epilepsy (IGE) syndrome most frequently due to a medication error (dose-reduction, inadequate drug choice, etc.) [21]. "Atypical" AS occurs in patients with a cryptogenic or symptomatic (generalized) epilepsy syndrome, like in chromosomal disorders, non progressive encephalopathy, Lennox-Gastaut syndrome, etc. "De novo" AS is probably the rarest form of AS, most likely resulting from (un-)intentional benzodiazepine (BZD) withdrawal [22]. An impairment of consciousness, of concentration and of the ability to store and recall memory content is common to all these types of AS. The clinical signs may be susceptible only to the individual, but not to bystanders, to both of them or only to the bystanders, but not the patient itself (s. **case-1; figure 1**) and can impede the diagnosis if an EEG is not available. The EEG shows generalized spike-wave activity of 2.5 Hz or faster, usually no attenuation after the end of the generalized spike-wave activity, and occasionally focal single spike-wave activity. Interictal EEG tracings look out normally, but sometimes bi-temporal slowing may develop, especially in patients with seizures difficult to control. Atypical AS, as well as most forms of cryptogenic and symptomatic myoclonic SE (MSE) often manifest as a continuum of clinical absences, intermingled with positive or negative myoclonic manifestations and subtle other (even focal) motor signs. Pure MSE in patients with IGE, especially with juvenile myoclonic epilepsy, is rare and has to be considered as convulsive SE [23, 24].

De novo AS starts in later life and more than two thirds result from BZD withdrawal (s. **case-2; figure 2**).

Aura continua (AC)

Aura continua confers to the focal forms of NCSE without changes of consciousness, and may be also considered as the nonconvulsive forms of simple partial SE. The clinical manifestations of AC are dependent on the cerebral focal localization: those originating from the parietal lobe will display sensory symptoms (paresthesias, pain), those from occipital lobe visual phenomena, those of neocortical temporal lobe with auditory features, those from mesial temporal lobe with fear, epigastric, gustatory or olfactory sensations, and those from frontal lobe may imitate temporal lobe signs and symptoms, or pilomotor and other autonomic symptoms. The EEG shows continuous focal epileptiform discharges or – depending on the depth of origin of the epileptic activity – rhythmic delta activity (s. **case-3; figure 3**).

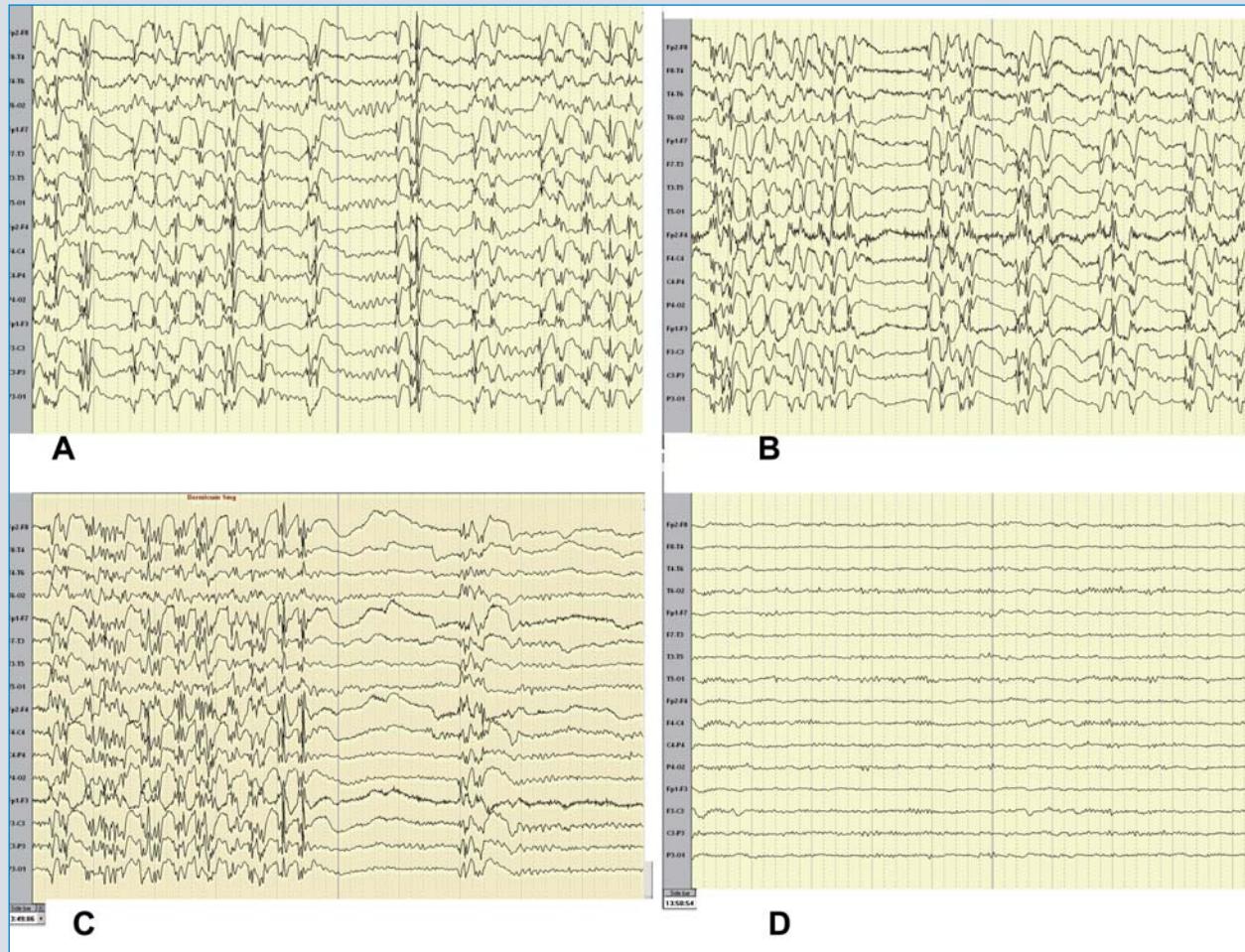


Figure 1: 47 year-old man with generalized tonic-clonic seizures and absences since age 17. Valproic acid (VPA) and primidone never completely controlled his seizures. He developed severe hyperammonemic encephalopathy and had to be switched to levetiracetam (LEV), lamotrigine (LTG), and topiramate. He then experienced several episodes of AS where he was walking around, but was confused. He could speak and responded to questions, but mimicked Ganser's syndromes in that his most answers were "near- correct" (October 17 instead of November 17, for example). The EEG showed almost permanent primary generalized (poly-)spike-wave discharges with short bouts of normal background activity (A). Absence status did not stop after i/v-administration of 8 mg of lorazepam (LZP), but the background activity became flattened and beta activity was increased (B). The subsequent i/v-administration of 1 mg of midazolam (MDL)(C) completely abolished the epileptic activity within 90 sec.(D).

Dyscognitive status (DSE)

Dyscognitive (formerly "psychomotor", "complex-partial") SE is further subdivided into the mesial temporal and the neocortical forms and includes all those forms of NCSE of focal origin with an alteration of consciousness. While limbic signs and symptoms (confusion, amnesia, fear, etc., "limbic" SE) dominate the clinical appearance of mesial DSE [25, 26], the neocortical forms of DSE may also display impairments of vision, language, hearing etc. [27, 28]. The EEG of mesial DSE shows either focal epileptiform discharges (s. case-4; figure 4) or prolonged rhythmic delta activity over the temporal regions, sometimes bilaterally.

Clinically, it may be often difficult if not impossible to differentiate AS from DSE, especially the confusional

forms; therefore, the role of the EEG and sometimes imaging is crucial for yielding the correct diagnosis.

Subtle status epilepticus (SSE)

Subtle status epilepticus is neither a syndromal nor an etiological type of NCSE, but denotes the clinical situation where focal motor or GCSE apparently stops, but epileptiform discharges continue in the EEG and the patient does not regain consciousness or return to his pre-ictal state (case-5; figure 5). The concept of SSE was established by the pivotal animal studies of Treiman et al. where they identified a relatively strictly evolving sequence of electroclinical events during SE [17], later clinically corroborated by DeLorenzo [29].

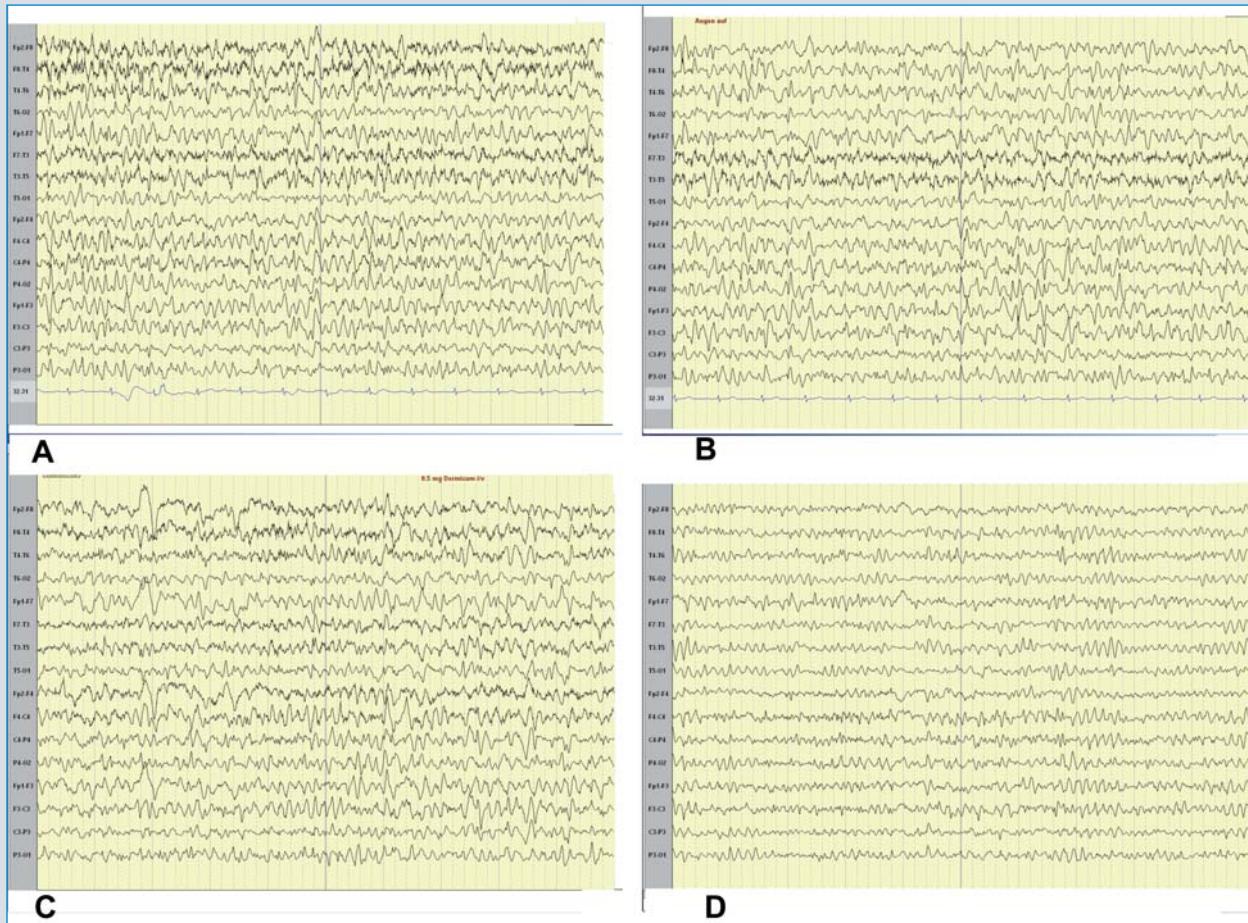


Figure 2: 84 year-old otherwise healthy woman who was found slightly confused in her apartment. A CT scan and the CSF were completely normal. Within 24 hours, she became comatose. The EEG showed diffuse, irregular, sharp-contoured, high-amplitude theta- and delta activity, intermingled with multifocal sharp waves (A). This activity did not change upon eye opening (B). The i/v-administration of 0.5 mg MDL (C) markedly reduced the epileptic activity and led to an accelerated, more regular background activity within 90 seconds (D). The patient opened her eyes and briefly talked. Extensive work-up did not reveal another cause than BZD intake for insomnia and an involuntary stop of this medication a few days before admission because of medication run-out.

Postanoxic (myoclonic) status epilepticus (PSE)

Hypoxia after cardiac arrest or prolonged cardiopulmonary resuscitation, severe asthmatic crisis, carbon monoxide poisoning, and near-missed drowning damage the brain, especially the cortex, basal ganglia, and the mesolimbic system resulting in postanoxic encephalopathy. Coma and often bursts or prolonged phases of spontaneous or stimulus-sensitive myoclonus, either subtle (periocular, facial or truncal), multifocal or generalized may be present [30-32]. The EEG is characterized by almost always lacking background activity (suppression) and either periodic lateralized or generalized epileptiform discharges (case-6; **figure 6**) or bursts of focal or generalized (poly-)spike-wave discharges (cases-7&8; **figure 7 and 8**). The myocloni may be epileptic from cortical islets of malfunctioning cerebral cortex (especially when multifocal), they may be of reticular origin (especially when generalized or bilateral), whereby they can be epileptic too by retrograde volleys to the

cortex, as well as they may represent a disinhibitive phenomenon of the reticular formation which seems to exert an important “gating” function with regard to seizure propagation [33]. Treatment of PSE is often disappointing and may influence only the EEG and probably reduce the frequency and intensity of myocloni, but not improve the patients comatose state. In addition, PSE has been shown to be an independent outcome predictor after cerebral anoxia in a retrospective study [34]. Some authors argue that PSE is not a form of SE, but the expression of a toxic-anoxic severest dysfunction of the brain.

Critical illness status epilepticus (CISE)

Life-threatening illness with multi-organ failure also influences brain functions and may provoke epileptic activity or unmask an otherwise not manifest propensity of the patient’s brain to seize up to build up SE.

According to recent reports, this results mainly from proconvulsive inflammatory cytokines, like IL-1 β and fever [35-38], but also from well known factors like hypotension, hypoxemia, and medications, like cefepime, carbopenems, etc.[19]. The EEG shows substantial alteration of background activity intermingled with epileptiform discharges and often also triphasic waves reflecting, for example, uremia and/or hepatic failure (case-9; **figure 9**); both, triphasic waves and epileptiform discharges may disappear upon administration of BZD [39].

Chronic static or progressive epileptic encephalopathies

During the neonatal period, SE exclusively occurs as NCSE, either in its neonatal specific form with a pleomorphic EEG signature (repetitive epileptic discharges of 10 seconds or more over at least one hour) [40] or some days to weeks later in the form of the Ohtahara syndrome, again with a typical EEG tracing (bursts with high-voltage slow-wave activity and multifocal spikes of 1-3 sec duration alternating with suppression of 3-5

sec) [41].

In childhood, NCSE may occur in the form of AS (typical and atypical), AC, DSE; and several progressive and non-progressive encephalopathies, (like ring chromosome 20-, West-, Rett-, Angelman-, Lennox-Gastaut-, and Landau-Kleffner syndrome, etc.), resulting from structural alterations and/or metabolic disturbances of an often genetic background may be associated with NCSE, frequently lasting for days, if not weeks and months. Thus, classifications were built upon these various, often age-dependent, syndromic encephalopathies (**s. table 2**) [1, 11, 20, 42].

Epileptic encephalopathies developing in adults only are rather uncommon and can reflect a non- or slowly progressive underlying disorder. Due to the often insidious, slow onset and the non-convulsive clinical appearance, the highly epileptic EEG activity – formally SE or often close to it – is detected only when clinical suspicion raises the need for an EEG (case-10; **figure 10**). The electroclinical response to treatment in these patients is very slow and may need several months.

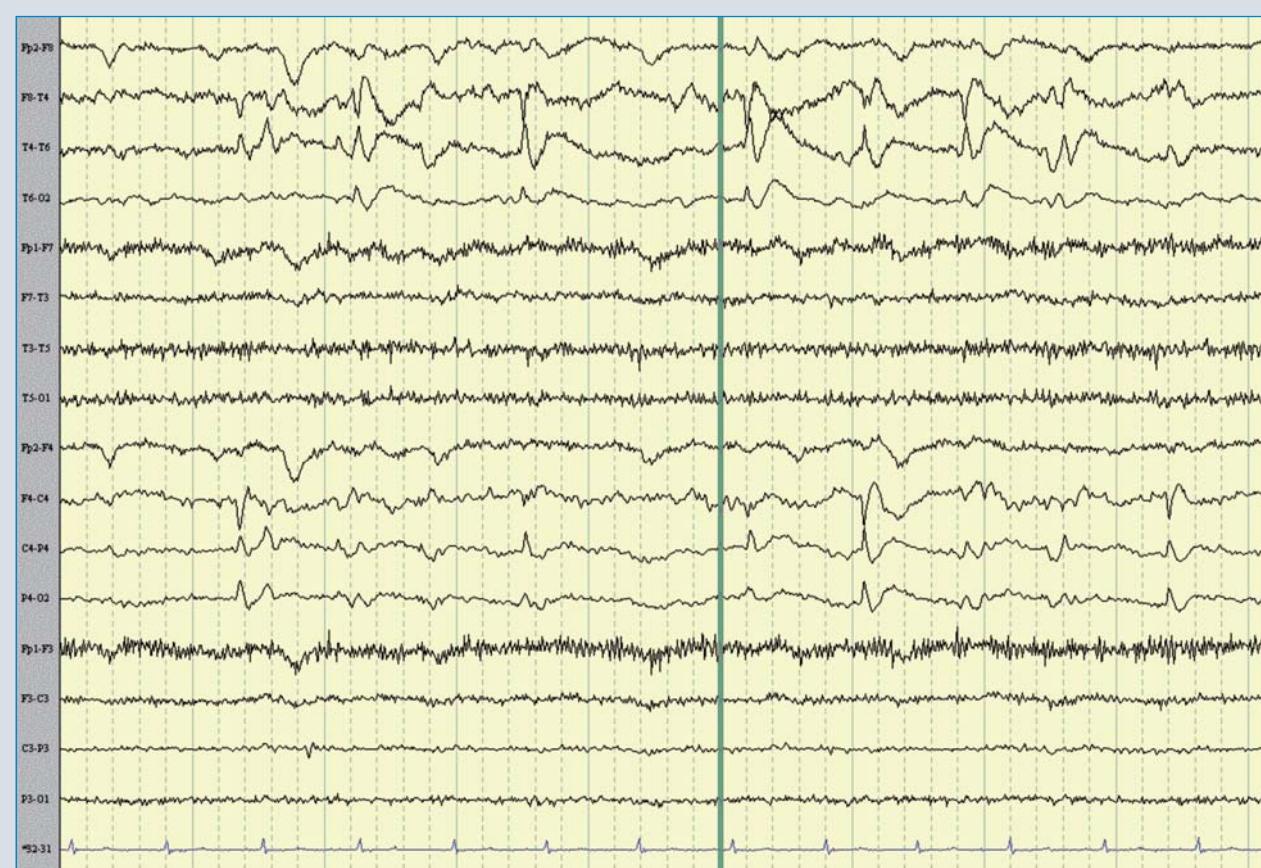


Figure 3: 52 year-old woman with a history of right-sided temporal, parietal and occipital bleeding due to an arteriovenous malformation three years ago. The patient then underwent embolisation of the malformation and experienced no seizures thereafter. Without preceding tonic-clonic movements, she experienced weakness of her left arm and face, but responded well to questions. MRI did not indicate recurrent bleeding, tumor or ischemia (diffusion-weighted imaging inclusively(DWI)). The EEG showed continuous pseudoperiodic right-sided epileptic discharges over the central and temporal regions. Symptoms completely resolved after control of the epileptic activity upon administration of i/v-MDL (inhibitory SE).

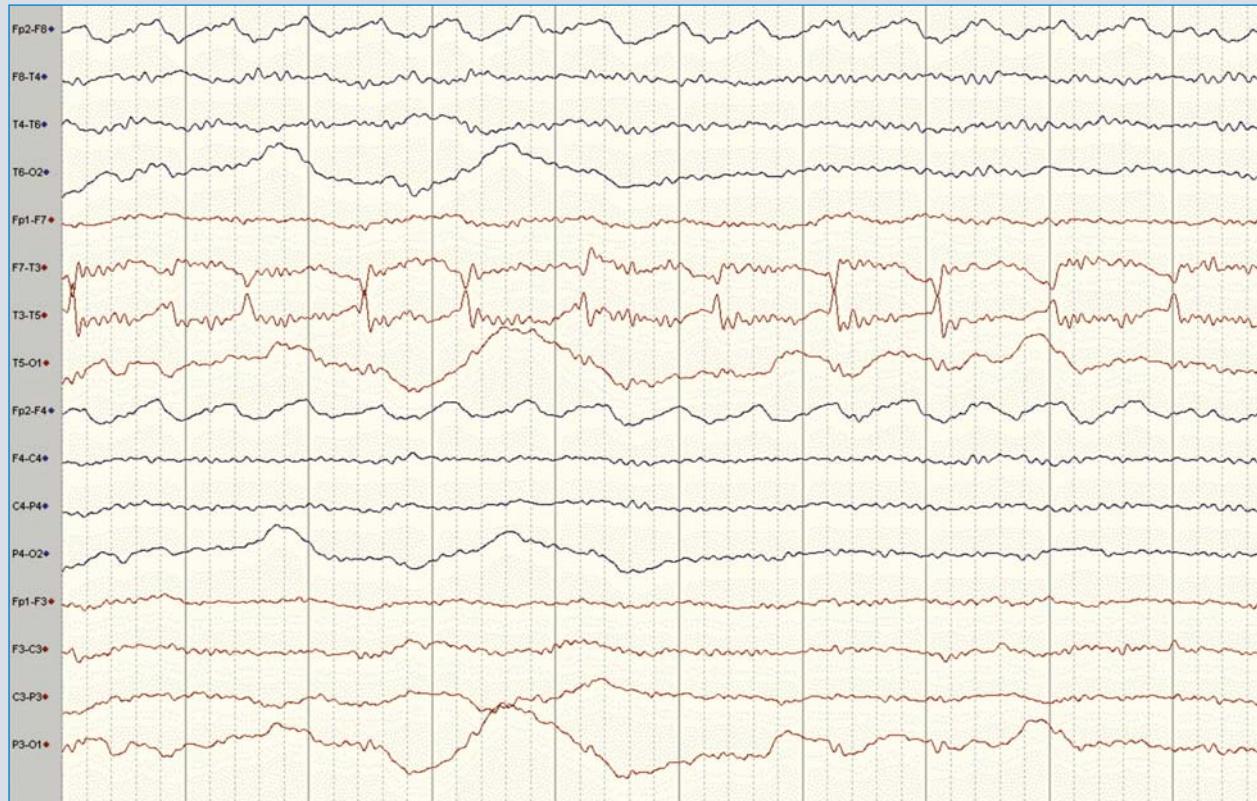


Figure 4: 84 year-old man with a long history of hypertension and depression. He suddenly stopped talking while an appointment with his family doctor. He had no right-sided hemiparesis, but seemed confused and apractic. Cerebral MRI revealed no acute lesion (DWI inclusively), but signs of cerebral microangiopathy; intracranial vessels were without stenosis or occlusion on MR-angiography. The EEG showed periodic lateralized epileptic discharges in the left frontal and temporal region which soon resolved upon the i/v-administration of 3 mg of MDL. The patient had amnesia for the period from entering the family doctor's office until the recovery on the intensive care unit (ICU).

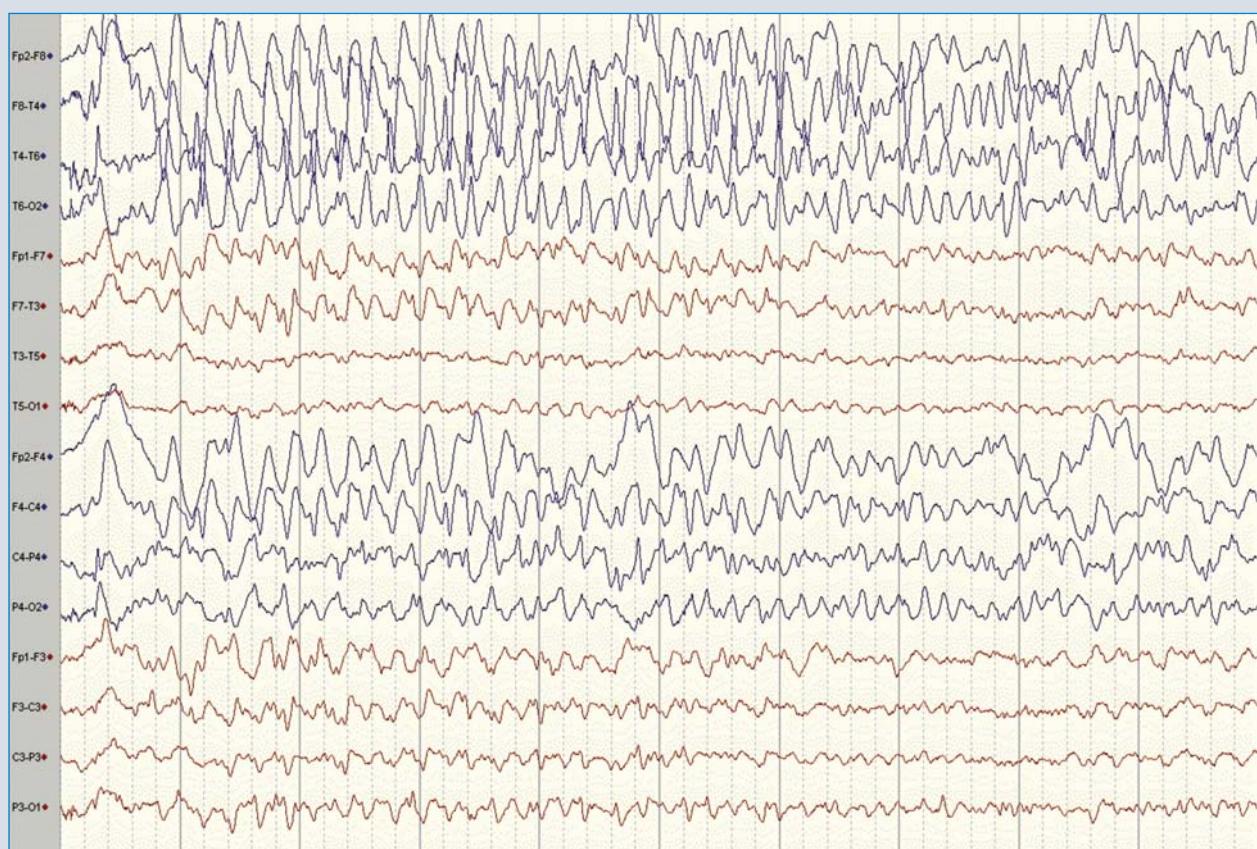




Figure 5: 52 year-old man with large meningioma of the sphenoidal plane, operated four years ago. No postoperative seizures. On admission he had a series of focal motor seizures with swift secondary generalization. He remained comatose, had minimal perioral twitching, and was transferred to the ICU. The EEG showed continuous epileptic activity over almost the whole right hemisphere with spike-waves in the right frontal, central and temporal regions and propagation of rhythmic theta/delta activity to the left hemisphere. He subsequently experienced highly refractory subtle SE.

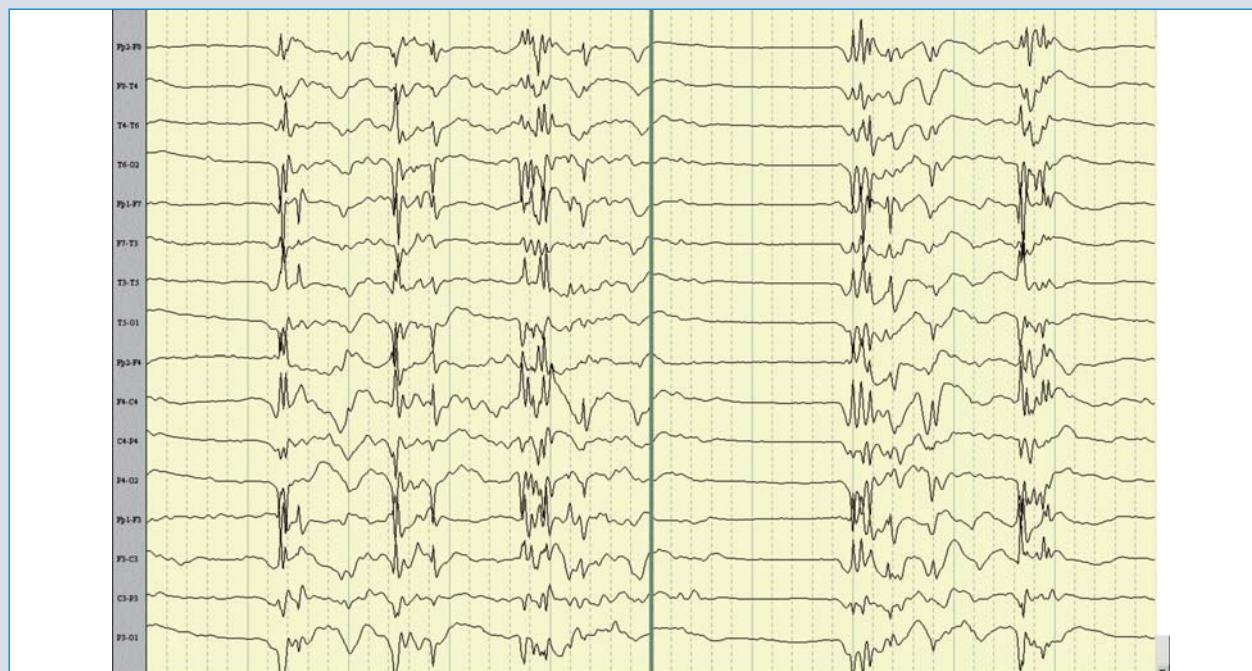


Figure 6: 82 year-old man after prolonged cardiopulmonary resuscitation (CPR) following pulseless electrical activity. He experienced severe postanoxic encephalopathy and had recurrent bouts of generalized myocloni. The EEG showed almost absent/flat background activity, interrupted by bursts of generalized poly-spike wave activity, clinically manifesting as myocloni.



Figure 7: 70 year-old man after successful outdoor CPR in the context of known severe coronary heart disease and ventricular fibrillation. Stenting and revascularization failed. He was treated by hypothermia for 24 hours, but remained comatose. The EEG 72 hours after stopping sedation showed generalized periodic epileptiform discharges (GPED) which were not responsive to external stimuli. The patient developed fulminant pneumonia and died from septic shock with multi-organ failure.

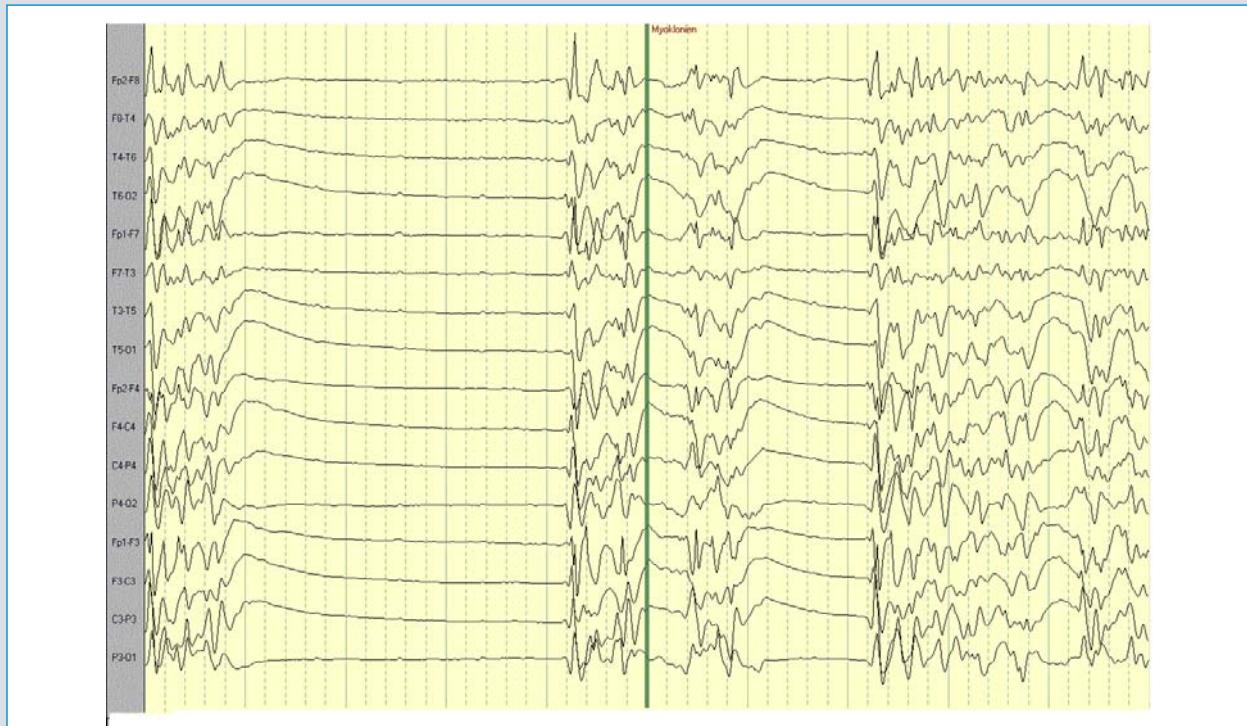


Figure 8: 53 year-old woman with acute respiratory exhaustion after left ventricular decompensation and subsequent pulseless electric activity. Successful outdoor reanimation after an estimated time of hypoxia of 35 minutes. She was treated by hypothermia for 24 h. EEG after rewarming without sedative drugs showed a spontaneous burst-suppression pattern with spike-slow- and sharp-slow-waves with clinical myocloni. She remained deeply comatose and somatosensory evoked potentials 48 h later showed absence of cortical responses.



Figure 9: 81 year-old patient with sepsis caused by *E. coli*, prosthetic hip infection and multiple retroperitoneal abscesses was treated with rifampicin and cefepime; two days later, acute renal failure occurred and the patient was comatose despite immediate dialysis. The EEG (A) showed periodic triphasic waves (TPW) (*left box) with fronto-occipital shift (**); additionally, multifocal epileptic discharges (***, boxes in the middle and at the right) were observed in both paracentral regions and over the right temporal region. Intravenous administration of 1 mg of LZP (B) led to complete abolition of both the TPW and the epileptic discharges.

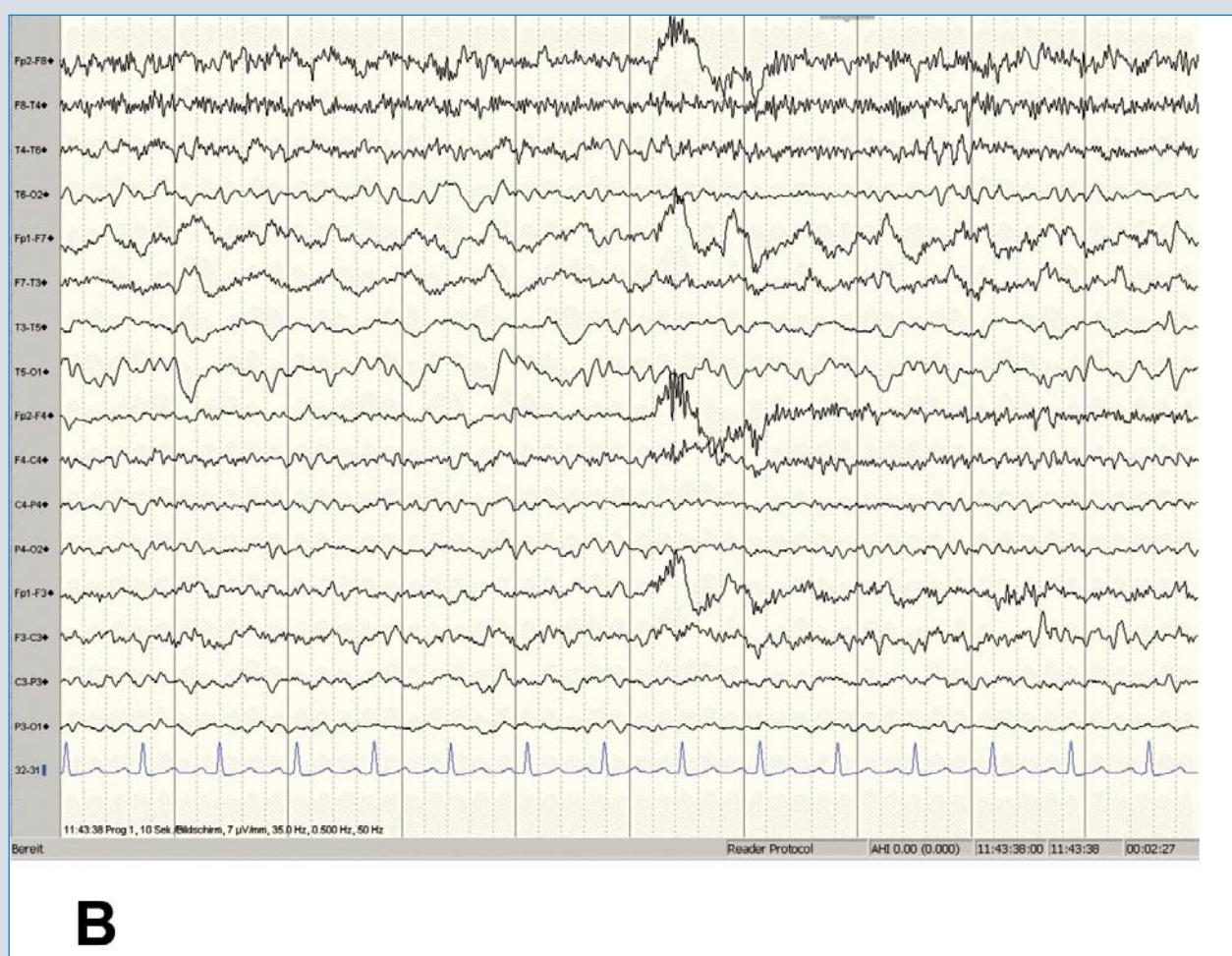
**A****B**

Figure 10:56 year-old woman with a history of multi-drug addiction (BZD, tramadol, alcohol). One year before admission, she insidiously became demented with bursts of frantic behaviour, where she tried twice to inflame her house. A giant aneurysm of the left middle cerebral artery was detected and the EEG showed substantial slowing of background activity and severe focal slowing over the left frontal and temporal regions often becoming rhythmic and with propagation also to the right. Epileptiform discharges frequently appeared over the left temporal region (**A**). Because of a lack of observation of episodic changes indicating overt seizures, epileptic and symptomatic encephalopathy resulting was suspected. She was started on an intensive antiepileptic regimen (VPA, LTG, and LEV) without BZD. Six months later, her cognitive and behavioural state had improved despite a further increase in size of the aneurysm. The EEG revealed an acceleration of background activity and a decrease of epileptic activity (**B**).

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Pseudo-états de mal épileptiques psychogènes

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Résumé

Les pseudo-états de mal épileptiques de nature psychogène (PEMEPs) sont des événements factices, le plus souvent de nature conversive, qui miment de près un état de mal épileptique tonico-clonique (EMETC). Ces événements retiennent depuis peu l'attention des épileptologues et des urgentistes car ils peuvent conduire à des thérapeutiques inopportunes et agressives, thérapeutiques qui représentent paradoxalement le principal facteur de morbidité d'une affection dont les complications systémiques spontanées sont nulles ou très bénignes. Cette revue de la littérature rappelle les principales caractéristiques cliniques ou paracliniques des PEMEPs : événements paroxystiques récidivants chez des patients souvent traités antérieurement à tort pour épilepsie, non-réponse au traitement antiépileptique IV, occlusion palpébrale forcée, résistance à l'ouverture oculaire, mouvements de dénégation du chef, dosage veineux normal des CPK et de la prolactine, EEG d'urgence dépourvu de toute anomalie paroxystique. Lorsque le diagnostic n'est pas établi, le non-respect des différentes séquences des protocoles standardisés de traitement de l'EMTC apparaît comme un des facteurs principaux d'aggravation de la iatrogénicité. Ces éléments plaident en faveur d'une meilleure collaboration entre neurologues et urgentistes dans le diagnostic précoce de cette entité déroutante dont la fréquence est probablement sous-estimée.

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Mots clés : Pseudo-état de mal épileptique psychogène, état de mal épileptique factice, crises pseudo-épileptiques, état de mal épileptique

Psychogener Pseudostatus epilepticus

Ein psychogener Pseudostatus epilepticus (PSE) ist ein meist nach konversivem Muster ablaufender Vorfall, welcher einen tonisch-klonischen Status (TKS) täuschend ähnlich mimt. Solche Vorfälle haben in jüngster Zeit das Interesse der Epileptologen und Notfallärzte geweckt, weil sie zu unangebrachten und aggressiven Behandlungsmethoden führen können, die paradoxe Weise an oberster Stelle stehen als Morbiditätsfaktoren einer Krankheit, die eigentlich keine oder nur ganz harmlose systemische Komplikationen mit sich bringt.

In dieser literarischen Übersicht werden die klinischen oder paraklinischen Hauptmerkmale des PSE zusammengefasst: wiederkehrende, paroxysmale Störungen, oft bei früher bereits fälschlicherweise gegen Epilepsie behandelten Patienten, refraktär gegen intravenös applizierte Antiepileptika, zwanghafte palpebrale Okklusion, Widerstand gegen Augenöffnen, verneinende Kopfbewegungen, CPK- und Prolaktinspiegel venös normal, Notfall-EEG ohne paroxysmale Auffälligkeiten. Wurde keine gesicherte Diagnose gestellt, so erscheint das Nichtbeachten der verschiedenen standardisierten Vorgehensprotokolle bei PSE als einer der Hauptfaktoren für eine Verschlimmerung der Iatrogenität. Diese Tatsachen sprechen klar für eine bessere Zusammenarbeit zwischen Neurologen und Notfallärzten bei der Frühdiagnose dieses verwirrenden Phänomens, das wohl häufiger ist als allgemein angenommen.

Schlüsselwörter: Psychogener Pseudostatus epilepticus, Pseudostatus epilepticus, pseudo-epileptische Anfälle, Status epilepticus

Psychogenic Nonepileptic Seizure Status

Psychogenic nonepileptic seizure status (PNES-s) is a factitious condition more often of conversive nature, mimicking closely status epilepticus with generalised motor features. This condition has been recently drawing the attention of epileptologists, emergency and intensive care physicians as patients with PNES-s are likely to be misdiagnosed and therefore receive inappropriate and aggressive emergency treatments while paradoxically their condition doesn't involve any significant spontaneous systemic risk.

This review of literature reminds us of the principal characteristics of patients with PNES-s : repeated emergency presentation, convulsions refractory towards anticonvulsant, eye resistance to examination, side to side rolling head movements, normal CK and/or prolactin serum level after generalized motor features and normal postictal EEG's.

These elements associated with the probable underestimation of PNES-s frequency suggest the need of a better collaboration between neurologists, emergency and intensive care physicians to rapidly assess a correct diagnosis and therefore avoid iatrogenic harm.

Key words: Psychogenic nonepileptic seizure status, nonepileptic seizure status, nonepileptic seizures, status epilepticus

Introduction

Le pseudo état de mal épileptique psychogène (PEMEP) ou « psychogenic non epileptic seizure status » des anglo-saxons (PNES-status) est un état caractérisé par une ou plusieurs crises pseudo-épileptiques (CPE) qui s'organisent en état de mal épileptique (EME) factice. Ces épisodes ne sont pas associés à des signes électroencéphalographiques (EEG) de la série paroxystique, et relèvent de mécanismes non organiques. Ils sont une complication fréquente et récurrente des CPE et ne posent aucun problème de pronostic vital et/ou fonctionnel immédiat si un diagnostic correct est posé précocelement [1]. Néanmoins, dans de nombreux cas, les PEMEP ne sont pas reconnus comme tels et aboutissent à des traitements agressifs, prolongés, injustifiés, et à fort potentiel iatrogénique [2]. De ce fait, ils sont un facteur certain de morbidité et dans certains cas de mortalité [3]. Cet article propose une revue générale sur le sujet.

Généralités

Malgré l'importance du problème et sa fréquence, les données de la littérature restent relativement pauvres, avec quelques séries rétrospectives comportant un nombre relativement réduit de patients. Les caractéristiques de ces travaux sont résumées (**tableau 1**).

Les PEMEP sont des événements fréquents chez les patients porteurs de CPE. D'après Howell et al. [4], ce taux est calculé à 36% (13 patients sur 36). Dans la série de Reuber et al. [5], 20% des patients porteurs d'un diagnostic exclusif de CPE ont présenté un antécédent de PEMEP. Dans l'étude de Dworetzky et al. [1], 18,4% des patients (9 patients sur 49) présentent cet antécédent.

La moyenne d'âge au moment du diagnostic est de 26,7 ans avec des extrêmes compris entre 18 et 54 ans [2, 4, 6]. Une surreprésentation du sexe féminin est retrouvée dans de nombreux travaux : 67% [1, 7], 78% [2], 84,8% [5], 95% [6], 100% [8].

La majorité des patients est sans profession au moment du diagnostic [8, 3]. Dans d'autres travaux, la profession n'est pas toujours mentionnée [2, 1, 9, 6, 4].

Les PEMEP sont des événements récidivants dans la majorité des cas. On note 60% de récidives dans l'étude de Reuber et al. [8], 75% dans l'étude de Reuber et Elger [10], et 100% dans l'étude d'Howell et al. [4]. Le nombre moyen de récurrence par patient est compris entre 3 (soit 69 PEMEP identifiés chez 13 patients) dans le travail d'Howell et al. [4], et 14 [8]. En comparaison, les EME récidivent plus rarement [4, 2].

Dans l'étude de Dworetzky et al. [1], 67% des pa-

tients inclus, soit 6 patients sur 9, présentent un délai diagnostique moyen, mesuré par la date du diagnostic de certitude apporté par enregistrement vidéo-EEG soustrait de la date du premier PEMEP, inférieur à un an. Reuber et Elger [10] ont souligné l'importance de ce type d'antécédent dans le diagnostic différentiel. Ils identifient comme arguments principaux d'une part le caractère récidivant des épisodes initialement diagnostiqués comme organiques (récidives fréquentes en cas de PEMEP et plus rares en cas d'EME), d'autre part la présence d'antécédents psychiatriques, plus fréquents en cas de CPE et de PEMEPs qu'en cas d'EME.

Antécédents psychiatriques

Le profil psychiatrique des patients porteurs d'un diagnostic de CPE ne diffère pas de celui des patients porteurs d'un diagnostic de PEMEP, à l'exception des manifestations d'auto-agressivité, plus fréquemment constatée en cas de PEMEP [5].

Les données de la littérature révèlent un pourcentage élevé d'antécédents psychiatriques chez les patients ayant présenté un PEMEP : 80% dans la série de Pakalnis et al. [6], 75% pour Howell et al. [4]. Un antécédent d'abus sexuel est retrouvé chez 60% des patients de Reuber et al. [8] et chez 30% des patients de Pakalnis [6]. Des troubles de la personnalité sont fréquents : 30% pour Howell et al. [4], 50% pour Pakalnis et al. [6].

Phénoménologie

Les PEMEP miment le plus souvent des EME convulsifs [4, 6, 2, 8, 5, 3, 9]. Les caractéristiques cliniques suggestives d'anorganicité sont listées dans le **tableau 2** [5, 11 - 13].

La présence d'une occlusion palpébrale lors des manifestations pseudo-épileptiques est hautement suggestive de CPE et de PEMEP. C'est également le cas des mouvements de dénégation du chef.

Chung et al. [14] ont constaté une occlusion palpébrale dans 96% des cas de CPE, soit chez 50 patients sur 52, et une ouverture oculaire dans 97% des crises épileptiques (152 patients étudiés). Dans le travail d'Alhalabi et Verma [15], une occlusion palpébrale est constatée dans 75% des cas de CPE, soit chez 36 patients sur 48, tandis qu'une ouverture oculaire est notée chez tous les patients épileptiques (191 patients).

La fréquence des mouvements de dénégation du chef est variable selon les séries : 15% dans la série de Leis et al. [16], 20% dans celle de Pierelli et al. [17].

Une cyanose et/ou un stertor sont fréquemment constatés en cas d'EME et sont exceptionnels dans les PEMEP [4, 8].

Parmi les autres signes cliniques, certains tels les mouvements rythmiques du bassin (MRB) ne présentent pas de réelle spécificité. En effet, les MRB consti-

Tableau 1: Caractéristiques des principales études sur les PEMEP

	Reuber et al., 2003 [5]	Pakalnis et al., 1991 [6]	Howell et al., 1989 [4]	Dworetzky et al., 2006 [1]	Holkamp et al., 2006 [2]	Reuber et al., 2000 [8]	Taliansky et al., 2000 [21]	Hassan et al., 1990 [22]	Toone et Roberts, 1979 [7]	Reuber et al., 2004 [3]	Wilner et Bream, 1993 [9]	Savard et al., 1988 [23]
Type d'étude	Comparative Rétrospective	Série de cas	Comparative Rétrospective	Comparative Rétrospective	Comparative Rétrospective	Série de cas	Série de cas	Série de cas	Série de cas	Cas clinique	Cas clinique	Cas clinique
Nombre de patients	33	20	13	9	8	5	4	4	3	1	1	1
Nombre de PEMEP	Non précisée, au moins 2 par patient	Non précisée, au moins 20	69	9	9	5	4	4	4	1	1	3
Antiépileptique IV	Oui, sans détail	Au moins 1	Oui, sans détail	Non précisée	Au moins 2	Oui, neuro-sédation	Oui, neuro-sédation	Oui, sans détail	Oui, sans détail	Propofol	non	Oui, neuro-sédation (21 jours)
Complications	?	11 DR	8 DR 2 PNP 3 lymphangites 2 sepsis	?	3 DR	2 DR	?	1 DR	4 DR 1 DH 2 AC 1 sepsis	Décès sur CA au curare	Non	Décès par suicide
Mesures potentiellement iatrogéniques	17 adm. en USI	11 IOT	5 IOT	?	2 IOT 3 DVI	2 IOT	4 IOT	1 IOT	4 adm. en USI	1 IOT	Non	3 IOT

DR= défaillance respiratoire, PNP= pneumopathie, adm.=admission, USI= unité de soins intensifs, AC=arrêt cardiaque, DVI= dispositif veineux implantable, DH= défaillance hémodynamique, CA= choc anaphylactique, IOT= intubation orotrachéale, IV= intraveineux, NA=non applicable

tuent un symptôme classique des crises épileptiques désorganisant les régions frontales médiales dans certaines formes topographiques d'épilepsie frontale [18]. Plusieurs études [19, 20] retrouvent un pourcentage comparable de MRB chez les patients porteurs d'une épilepsie du lobe frontal et chez les patients présentant des CPE.

Caractéristiques paracliniques

Les EEG des patients porteurs d'un PEMEP (**figure 1**) sont bien sûr dépourvus d'anomalie épileptique [1, 8, 6, 4], contrairement à la grande majorité des EEG réalisés chez les patients porteurs d'un EME [1, 4]. Cependant, la disponibilité de l'examen n'est pas toujours immédiate en service d'accueil des urgences [2].

Un dosage normal des créatines-phosphokinases (CPK) après un épisode initialement diagnostiqué comme un EME devrait alerter le clinicien et l'amener à reconsiderer le diagnostic d'EME en faveur d'un PEMEP [2].

De même, le dosage veineux de la prolactine 15 à 20 minutes après un évènement paroxystique est élevé en cas d'EME convulsif ou d'EME partiel complexe. La normalité de ce dosage pourrait constituer un argument intéressant en faveur d'évènements psychogènes [24].

Reuber et al. [25] font état d'une imagerie cérébrale anormale chez 27% de leurs patients avec diagnostic

exclusif de CPE, soit 20 cas sur 74. Dworetzky et al. [1] retrouvent cette donnée chez 44% de leurs patients, soit 4 IRM anormales sur 9.

Diagnostic

Howell et al. [4] relèvent des doutes sur l'organicité dès l'admission dans 18,8% des leurs cas, soit 13 PEMEP sur 69. Cependant, aucune de ces réserves diagnostiques n'a pu éviter l'escalade thérapeutique chez ces patients.

Sinon, les neurologues paraissent plus aptes à diagnostiquer cliniquement les CPE que les urgentistes, mais ils sont loin d'être infaillibles, et sont d'ailleurs supplantés par les techniciens des unités d'épileptologie [26]. De toutes façons, l'accès à un avis neurologique en urgence n'est pas toujours possible selon les centres [2].

Prise en charge et complications

La majorité des patients présentant des PEMEP ont été admis et traités en service d'accueil des urgences [5]. Cette donnée est aussi retrouvée dans les travaux d'Holtkamp et al. [2] et de Taliinsky et al. [21], avec la réserve cependant que l'étape intubation-neuroscédatrice a été pratiquée en unité de soins intensifs. Dans un

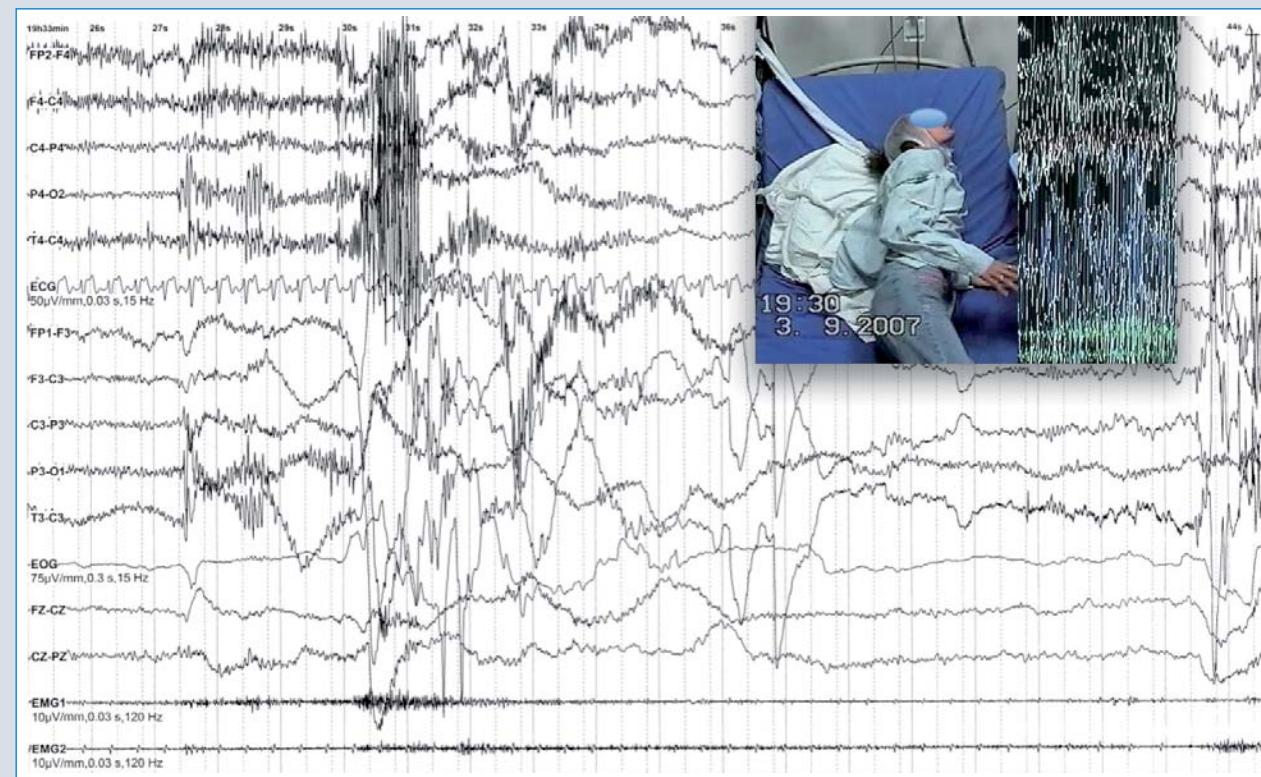


Fig. 1: Crise pseudo-épileptique spontanée chez une patiente âgée de 27 ans présentant des pseudo-états de mal épileptiques psychogènes. L'EEG ne montre que des artefacts myogènes.



Tableau 2 : Caractéristiques cliniques suggestives d'anorganicité [d'après 5, 11, 13 modifié]

- Occlusion palpébrale, résistance à l'ouverture oculaire**
- Mouvements de dénégation du chef**
- Sensibilité aux manœuvres de suggestion**
- Mouvements anarchiques, asynchrones des membres**
- Attitude oppositioniste lors des manifestations « critiques »**
- Gémissements et pleurs lors des manifestations « critiques »**
- Postures dystoniques (dont opisthotonus)**
- Facteurs déclenchant émotionnels ou situationnels**
- Caractère non latéralisé d'une éventuelle morsure de langue.**
- Secousses du bassin**
- Crises motrices prolongées (> 2 minutes)**

autre travail [8], tous les patients ont présenté un PEMEP au décours d'une anesthésie générale.

A l'admission, Howell et al. [4] constatent que de la prise chronique d'antiépileptiques, habituelle chez un patient considéré comme porteur d'une épilepsie, peut conforter le médecin dans une hypothèse diagnostique erronée d'organicité, ne l'encourageant pas à envisager un diagnostic différentiel de manifestations comportementales.

Des complications iatrogéniques graves sont constatées : choc anaphylactique au curare ayant entraîné le décès [3], arrêts cardiaques [7], défaillances respiratoires chez 11 patients de Pakalnis et al. [6], 8 patients de Howell et al. [4], 4 patients de Toone et al. [7], 3 patients de Holtkamp et al. [2], 2 patients de Reuber et al. [8] et 1 patient de Hassan et al. [22]. Parmi les complications moins sérieuses, Howell et al. [4] mentionnent 7 complications infectieuses, dont 2 pneumopathies bactériennes. Un sepsis généralisé est enfin noté dans la série de Toone et al. [7].

Parmi les mesures médicales agressives non médicamenteuses, l'intubation oro- ou naso-trachéale est la principale procédure iatrogénique, retrouvée chez 10 patients sur 20 dans l'étude de Pakalnis et al. [6], 5 patients sur 13 dans la série d'Howell et al. [4], 4 patients sur 5 dans la série de Talansky et al. [21], 2 patients sur 8 dans l'étude d'Holtkamp et al. [2], 2 patients sur 5 dans la série de Reuber et al. [3], 1 patient sur 4 dans la série de Hassan et al. [22] ainsi que dans l'observation de Wilner et Bream [9]. Ainsi, en moyenne 43% des patients vont être « victimes » d'une procédure instrumentale potentiellement agressive et de toutes façons inadaptée.

Décès

Le syndrome de Münchhausen est défini par la simulation délibérée de troubles amenant à des explorations ou à des traitements dangereux, l'unique bénéfice secondaire étant la mise en échec du corps médical. Reuber et al. [3], rapportent le cas d'un patient admis en service d'accueil des urgences à 37 reprises dans 11 hôpitaux différents. Le patient présenta un choc anaphylactique dans les suites immédiates d'une curarisation avant intubation, au décours d'un PEMEP initialement diagnostiqué comme un EME. Lors de la trente septième et dernière admission le patient présenta un nouvel épisode qui fut à nouveau considéré comme organique. Le patient alléguait alors de faux antécédents d'allergie à la phénytoïne, au valproate et au phénobarbital. Devant la persistance des manifestations motrices après traitement par benzodiazépines, une intubation fut pratiquée après injection d'atracurium, 40 mg IV, qui entraîna un décès immédiat par arrêt cardio-respiratoire. L'antécédent connu de pathomimie n'était pas disponible en urgence, le patient ayant été admis dans un hôpital d'une région différente. Un cas similaire, n'ayant pas conduit au décès a également été rapporté [27].

Evolution et pronostic

Howell et al. [4] dans leur étude sur les PEMEP mentionnent un taux de rémission de 23% à 2 ans. Nous n'avons pas retrouvé d'autres données pronostiques.

Conclusions

Le PEMEP suscite actuellement un intérêt certain auprès des médecins impliqués dans la prise en charge de l'EME. De nouvelles recommandations formalisées d'experts sur la prise en charge des EME ont été publiées début 2009 sous l'égide de la Société de Réanimation de Langue Française [28]. Le PEMEP est mentionné dans le Champ 2 concernant le diagnostic différentiel de l'EME. « Face à des manifestations motrices prolongées atypiques suggérant un EME convulsif, il convient systématiquement d'évoquer un pseudo-état de mal (origine psychogène). Les éléments cliniques faisant évoquer ce diagnostic doivent être connus de tout médecin prenant en charge un EME tonico-clonique : fermeture des yeux, résistance à l'ouverture des yeux, atypie des mouvements et contact possible avec le patient ». Les autres arguments sont les suivants : événements paroxystiques récidivants, dosage veineux des CPK normal devant des manifestations convulsives bilatérales, non-réponse au traitement antiépileptique intraveineux, EEG d'urgence dépourvu de toute anomalie paroxystique. Ces éléments diagnostiques devraient prévenir le principal risque qui est l'escalade thérapeutique, source de complications iatrogéniques graves, voire de décès.

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Treatment of Status Epilepticus

Summary

Status epilepticus treatment involves the use of several pharmacological compounds, which are conceptually divided in three successive and additional lines of action. Benzodiazepines represent the first approach, due to their rapid onset of action; these are followed by classical AED that are administered IV. In refractory episodes, pharmacological coma induction with an appropriate anesthetic agent is advocated. Apart from the first-line, the level of evidence is limited.

It is important to specifically address etiology in order to maximize the impact of the antiepileptic therapy. Furthermore, the fine tuning of the treatment strategy, including mainly the decision regarding coma induction, should be performed balancing benefits of a rapid SE control with the risks of side effects. While each status epilepticus episode should be treated as rapidly as possible, it appears advisable to reserve coma induction for the forms that have been shown to bear a consistent risk of neurological sequelae, i.e., generalized convulsive status.

Epileptologie 2009; 26: 84 – 89

Key words: Benzodiazepines, phenytoin, valproate, levetiracetam, anesthetic agents

Le traitement du statut épileptique

Le traitement du statut épileptique suppose le déploiement d'un arsenal pharmacologique qui se scinde en trois vecteurs d'action conceptuels successifs se complétant. Les benzodiazépines sont engagées en première ligne du fait de leur action rapide ; suivent les anti-épileptiques classiques par application IV. Dans les épisodes réfractaires, l'induction d'un coma pharmacologique au moyen d'un anesthésique approprié est préconisée. Mise à part la première ligne d'action, il manque cependant encore une documentation suffisante pour les autres.

Il est important de définir l'étiologie exacte afin de maximiser l'impact de la thérapie anti-épileptique. De plus, le réglage fin de la stratégie thérapeutique, et notamment de la décision d'induire un coma ou non, devrait se faire en pondérant soigneusement les bénéfices d'un contrôle rapide du statut épileptique versus le risque d'effets indésirables. Car si chaque épisode d'état de mal épileptique nécessite bien une intervention aussi rapide que possible, l'induction d'un coma devrait être réservée aux formes où un risque consistant de séquelles neurologiques, p.ex. un statut convulsif généralisé, a été avéré.

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Mots clés : benzodiazépines, phénytoïne, valproate, lévétiracétam, agents anesthésiques

Behandlung des Status epilepticus

Zur Behandlung des Status epilepticus stehen verschiedene pharmakologische Waffen zur Verfügung, die sich in drei sukzessive und sich vervollständigende Handlungsstrategien unterteilen. Erste Priorität haben ihrer raschen Wirkungsweise wegen die Benzodiazepine, gefolgt von den klassischen, IV verabreichten Antiepileptika. Schliesslich wird bei refraktären Episoden eine Koma-induktion mit geeigneten Anästhetika vertreten. Wirklich gut bekannt ist dabei nur das erste Behandlungskonzept, die beiden anderen sind noch nicht ausreichend dokumentiert.

Es ist wichtig, die Ätiologie genau zu kennen, um mit der antiepileptischen Therapie das bestmögliche Resultat zu erzielen. Zudem sollten bei der Feinregulierung der Behandlungsstrategie, und insbesondere bei einem Entscheid für oder gegen ein induziertes Koma, die Vorteile einer raschen Kontrolle des SE sorgfältig abgewogen werden gegen das Risiko unerwünschter Nebeneffekte. Natürlich sollte jeder Status epilepticus so rasch als möglich behandelt werden, trotzdem scheint es ratsam, die Koma-induktion jenen Formen von SE vorzubehalten, bei welchen ein konsistentes Risiko neurologischer Folgen, z.B. in Form eines generellen convulsiven Status zu befürchten sind.

Schlüsselwörter: Benzodiazepin, Phenytoin, Valproat, Levetiracetam, anästhetische Wirkstoffe

Pharmacological background and general outline

There is a general consensus on the need to treat status epilepticus (SE) as soon as possible, in order to prevent potentially deleterious sequelae [1 - 4]. The pathophysiological mechanisms occurring during an episode of SE are characterized, at the beginning, by an imbalance between inhibitory (mostly GABA_A) and excitatory (predominantly glutamate-mediated, kainate and AMPA) inputs [1, 5-12]. This represents the rationale to start SE treatment with benzodiazepines, rapidly acting GABA-ergic agents. GABA resistance then develops progressively following receptor trafficking and subunit changes; afterwards, a shift towards self-sustaining glutamate-mediated excitotoxicity occurs, resulting pri-

marily from the activation of NMDA receptors. These changes may explain both refractoriness to benzodiazepines and excitotoxic neuronal damage.

SE treatment aims at stopping seizure activity, and controlling complications [2]. Pulmonary and cardiac function need to be secured; in parallel, a targeted examination and history taking should be performed to detect SE imitators, such as movement disorders (e.g., shivering in the ICU) and psychogenic seizures [13]. Laboratory and neuroradiological work-ups are paramount to address SE etiology, since its specific treatment may greatly influence the success of AED prescription. In general, SE treatment should be performed under EEG control.

Pharmacological SE treatment may be categorized into three phases of antiepileptic drug (AED) administration, generally intravenously: 1. benzodiazepines aiming at rapid SE control; 2. classical AEDs targeting

early resistant forms and long term coverage following anticipated control of SE; 3. general anesthetics for refractory SE. This approach should be sequential and additional. A simple protocol with corresponding timing is proposed in the figure. Awareness of a protocol greatly facilitates this practical approach, and allows a smooth interplay between the different providers (paramedics, emergency or ICU team, neurologists).

First line

The first-line SE treatment has been better investigated than second- and third-line. A small study in 1983 found a nonsignificant trend toward better response to lorazepam (LZP) as compared to diazepam (DZP) [14]. A pre-hospital trial found that LZP had a nonsignificant superiority over DZP, whereas both treatments were

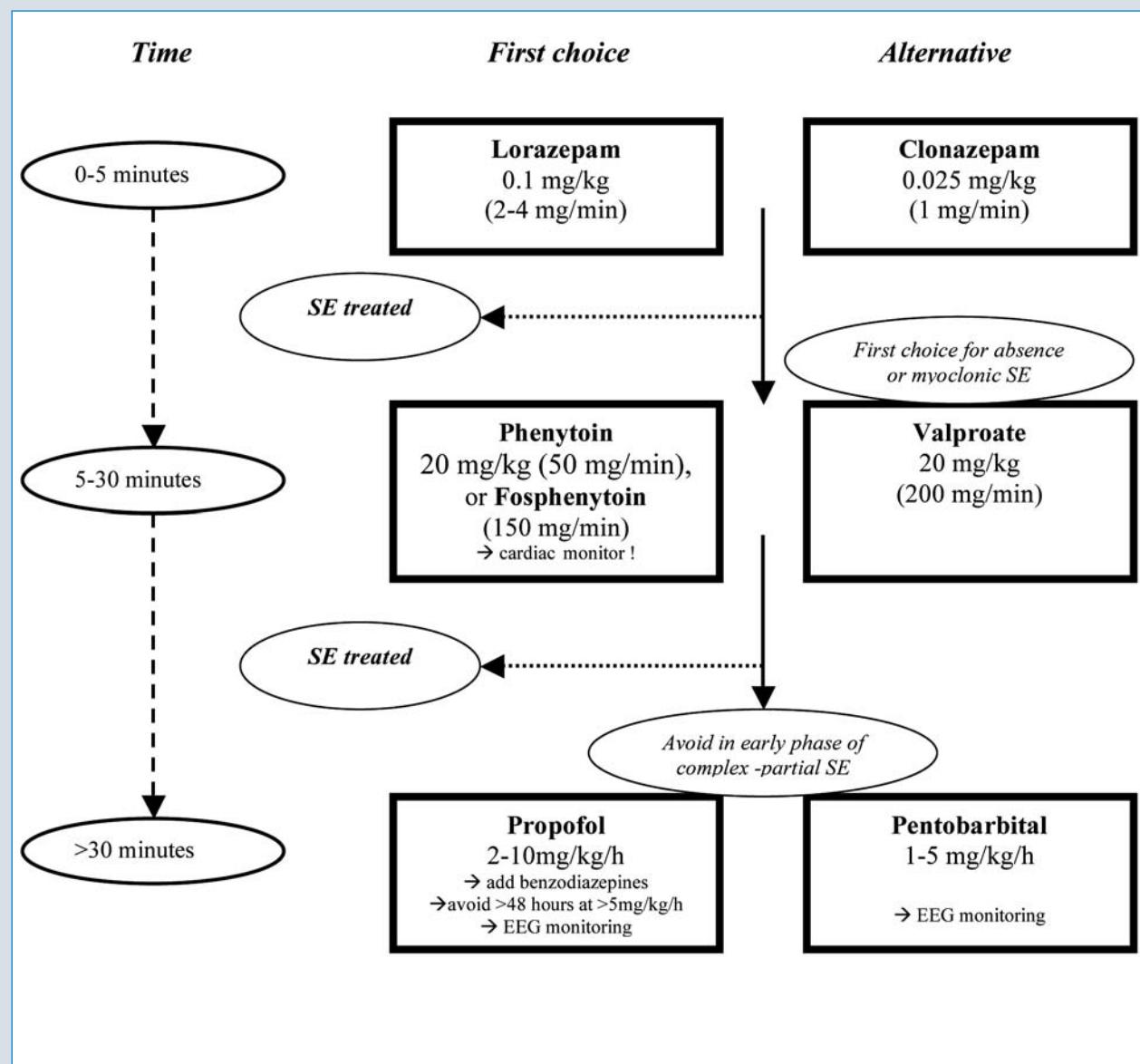


Figure: Pharmacological SE treatment

significantly better than placebo; cardiovascular and respiratory complications did not differ among groups [15]. A large VA trial, focusing on generalized convulsive SE and assessing the efficacy of LZP, phenobarbital (PB), diazepam (DZP) followed by phenytoin (PHT), and PHT alone, disclosed better efficacy of LZP as compared to PHT alone, but not to the other arms [16]. The overall response in overt SE was higher than in subtle SE (about 60% vs. 20%). Nevertheless, as SE becomes more refractory to treatment with time [7], and the first treatment has a far better chance of success than the second or third, regardless of the drug (55% vs. 7% vs. 2%) [17], it is important to administer IV drugs that act quickly. Therefore, benzodiazepines represent the better option over PB and PHT, although there is usually no contraindication to giving both at essentially the same time. Compounds with a long CNS elimination half-life are desirable, since this avoids rebound seizures as drug levels decline. Note that tonic SE in patients with developmental delay may be aggravated by benzodiazepines.

– *Lorazepam (LZP)* is administered in a slow bolus of 0.1 mg/kg (2mg/min); it enters the brain in less than 2-3 minutes [18] and has a long duration of action (at least 12 h), as it is far less prone to redistribute in the tissue than diazepam [19]. Its elimination half-life is 8-25 h [18, 19].

– *Diazepam (DZP)* is administered at 0.2 mg/kg (5mg/min), it enters readily the brain (less than 10 sec), but its free fraction redistributes in the fat tissue accordingly to its high lipophilicity and protein given rectally.

– *Clonazepam (CLZ)* is relatively widely used in Europe. It is administered at a bolus of 0.025 mg/kg. It reaches the brain within 1 min [18], and despite its lipophilicity has stable action over time. It has a long half-life (up to 38 h) and moderate protein binding (less than LZP: 65% vs. 90%) [18, 20].

– *Midazolam (MDZ)* has a short half-life (about 2 h), but represents a valuable alternative when IV lines are not available or in children (intranasal or buccal administration). The usual dosage is 0.1-0.2 mg/kg, but doses up to 0.5 mg/kg have been reported [21].

The administration of a benzodiazepine bolus may induce respiratory and circulatory collapse (about 10-26%) [15, 16], thus, monitoring of these functions is mandatory.

Second line

To date, there have not been any large-scale, prospective comparative assessments among AED used as second- or third-line SE treatment. The VA study included a PHT (which acts principally through sodium channel modulation) and a PB (mainly a GABA_A agonist) arm as initial SE treatment, and found a nonsignificant trend toward a better efficacy of PB (58% vs. 44% [16]). Intravenous valproate has been repeatedly reported to

be efficacious for several SE types [22, 23], without cardiovascular adverse reactions, therefore there is no need of concurrent monitoring. Levetiracetam has also been employed in SE treatment [24]; recent availability of an intravenous formulation makes it even a more promising option [25, 26].

– *Phenytoin (PHT)* is the most widely used agent in this context, administered at 20mg/kg (maximal infusion rate, 50mg/min). Maximal concentrations in the CNS are reached after 20 min [19]. The elimination half-life is about 24 h, but is longer at high serum levels. Some rare but serious local reactions (purple glove syndrome) are induced by the alkaline solution, whereas PHT itself is associated with hypotension and bradycardia (27% and 7% in the VA study group [16]). A slower infusion rate is especially advisable in elderly subjects. Cardiac monitoring should always be available during intravenous PHT administration.

– *Phosphenytoin (PPHT)* is a water-soluble PHT prodrug lacking propylene glycol and therefore safer regarding local reactions. It is administered in PHT-equivalents. Although it can be infused at a much faster rate (150mg PHT equivalents/min), it is questionable whether effective CNS concentrations are reached before PHT administered at optimal rates [27].

– *Phenobarbital (PB)* is administered at 15 mg/kg (100mg/min). It reaches the brain after 20-40 min. Its half-life is around 100 h. It also bears a consistent risk of hypotension (34% in the VA study [16]).

– *Valproic acid (VPA)* is loaded at 20mg/kg, up to 200 mg/min [22, 28], and its elimination half-life is about 15 h. VPA enters the CNS rapidly through active transport [29]. Clinical experience in SE suggests that effective CNS concentrations are reached within 30 min [28, 30]. Its main advantage is the lack of cardio-depressive reactions.

– *Levetiracetam (LEV)* may be loaded up to 20 mg/kg [25]; its plasma half life is about 7 hours, but the bioavailability within the blood-brain barrier is probably longer [31]. It is unclear how fast LEV reaches the brain, but personal observations suggest that an effect occurs within 15 to 30 minutes of IV administration. The most frequent adverse event is mild sedation; no cardiovascular reactions have been reported.

Third line

In generalized convulsive SE, the earliest administered treatment has the greatest chance to be effective [11, 17], therefore the sequential administration of second-line treatments does not appear to have a good rationale, and it seems reasonable to proceed straight to 3rd-line treatment once the 2nd-line (which takes at least 20-30 min to be effective) has failed [2, 32]. An important caveat concerns SE episodes in which patients are at least partly conscious, including absence and several forms of complex partial SE. Indeed, it is unclear



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* American Psychiatric Association 2002. Practice Guideline For The Treatment of Patients With Bipolar Disorder.



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Wirkstoff: Natriumvalproat, 1 Ampulle 3 ml zu 300 mg Natrii valproas. 1 Ampulle 10 ml zu 1000 mg Natrii valproas. **Dosierung:** mittlere Tagesdosis: 20-30 mg/kg KG. Tagesdosis kann auf 2 - 4 Einzeldosen verteilt werden. Bei Status epilepticus: Initialbolus von 15 - 20 mg/kg innerhalb von 5 - 10 Minuten. Nach der Initialdosis kontinuierliche Infusion mit 1 - 2 mg/kg/h während mind. 24 h (bei Co-Medikation mit Lamotrigin oder Felbamat maximal 1 mg/kg/h). **Indikationen:** Petit-Mal/Absenzen, massive bilaterale Myoklonien, Grand-Mal mit oder ohne Myoklonien, photosensible Epilepsie, sekundäre, generalisierte Epilepsien, vor allem beim West- und beim Lennox-Gastaut Syndrom; epileptische Äquivalente mit einfacher oder komplexer Symptomatologie (psychoseanale und psychomotorische Formen); Epilepsie mit sekundärer Generalisierung, Mischformen (generalisierte und äquivalente). Orfiril® Injektionslösung wird dann angewendet, wenn eine orale Natriumvalproattherapie nicht möglich ist. Im Rahmen definierter Therapiepläne beim Erwachsenen ausserdem: als Mittel der 2. Wahl im Status convulsivus, konvulsive Krämpfe, alle Mittel der 1. Wahl sind versagt. **Hinweise:** Status und als Mittel der 2. Wahl beim Status convulsivus, nicht chronisch-einnahmefähig und hochdosiert für Anfall. **Unerwünschte Wirkungen:** Hypotonie, Hypotonie, Pannerit, Blutbildveränderungen, Granulozytopenie, Eosinophilie bei Säuglingen und Kleinkindern; Hyperammonämie, Paroxysmale Blutdrucksteigerungen, Sondererscheinungen: Encephalopathie bei Langzeitkombination mit anderen Antiepileptika; Gichtzusammenfassung: Überaktivität, Dys- und Aminonikrose, veränderte Geschmackskampfindung, Amblyopie, Timinitus, Gehörverlust, Haarsausfall, Fancier-Syndrom; Vasculitis; Hautreaktionen; Lysyl-Syndrom; Stevens-Johnson-Syndrom; polymorphe Erytheme. **Interaktionen:** Acetylcholinesterase, Carbamazepin, Cimetidin, Erythromycin, Felbamat, Lamotrigin, Mefloquin, Meropenem, Neuroleptika, Phenobarbital, Phenytin, Primidon, Warfarin, Zidovudin. **Kontraindikationen:** Überempfindlichkeit auf valproinsäurehaltige Arzneimittel; Leber- und Pankreasfunktionsstörungen; schweren Hepatitis in der Familieneranamnese; hämorrhagische Diathese; Anwendung bei Kleinkindern bei gleichzeitiger Behandlung mit mehreren Antiepileptika. **Abgabekategorie:** B. **Zulassungsinhaberin:** Desitin Pharma GmbH, 4410 Liestal, E-Mail: info@desitin.ch, www.desitin.ch. *ausführliche Informationen entnehmen Sie bitte dem Arzneimittelkompendium der Schweiz* (www.kompendium.ch)

whether prolonged complex partial seizures in humans induce permanent structural neurological damage [33-37], as opposed to generalized convulsive SE, in which damage of limbic structures has been confirmed both pathologically and radiologically [38, 39]. It is thus debatable whether and when coma induction, which may predispose to several complications (e.g., pneumonia, deep vein thrombosis, pulmonary embolism, neuropathy, myopathy, ileus), is warranted in SE forms other than generalized convulsive SE. A recently validated severity score (STESS) may help to orient early treatment strategy in unclear situations [40]. In some instances, it appears advisable to attempt avoiding coma induction by administering non-sedating AED sequentially. SE episodes in patients with idiopathic generalized epilepsy (absence or myoclonic SE) readily respond to benzodiazepines and VPA and should not be intubated. Conversely, postanoxic SE, the expression of a severe underlying encephalopathy, is often refractory to standard treatments; in selected cases, however, after considering other prognostic factors, AED including anesthetics could be prescribed before reassessing the patient [41].

Existing studies on refractory SE are represented by case series. A meta-analysis of barbiturates, propofol, and midazolam [42] did not disclose any significant difference in short-term mortality among these three agents, although some variations were noted in both efficacy and tolerability. A retrospective analysis taking into account possible combinations of anesthetics did not show any notable difference in outcome among the agents, used alone or in association [43]. There is also considerable uncertainty regarding the optimal extent of EEG suppression [43, 44], and the optimal length of treatment. An EEG target of burst-suppression with an interburst interval of about 10 sec, maintained for 24-36 hours, followed by progressive tapering over 12-48 hours, represents a good practical option.

– *Barbiturates*, such as thiopental in Europe or its metabolite pentobarbital (PTB) in North America, show a long half-life after continuous administration (PTB: 15-22 hours) [45]. There is a considerable tendency of this drug to accumulate, prolonging the need for mechanical ventilation. Induction with PTB is performed with boluses of 5-15 mg/kg, and maintenance dose is 1-5 mg/kg/h.

– *Propofol* has a short half-life of about 1-2 hours [46], allowing rapid titration and withdrawal. It may induce the so-called “propofol infusion syndrome”, a potentially fatal cardio-circulatory collapse with lactic acidosis, hypertriglyceridaemia and rhabdomyolysis, especially in young children, which has been only exceptionally described in patients with SE [47, 48]. Concomitant benzodiazepines could lower the needed propofol dose, possibly reducing the risk of this complication [49]. Loading dose is 2 mg/kg, followed by maintenance at 2-10 mg/kg/h. Prolonged (over 48 h) administration of doses over 5 mg/kg/h should be avoided.

– *Midazolam (MDZ)* has a half-life of 6-40 hours af-

ter prolonged infusion [50], with marked tachyphylaxis developing within 24-48 h [51]. It is loaded at 0.2 mg/kg, then maintained at 0.05-0.6 mg/kg/h.

Other treatment approaches

Other anesthetics, such as ketamine, an NMDA antagonist [52, 53], or isoflurane [54], an inhalation anesthetic, represent alternatives for extremely refractory SE, which is classically encountered in young patients with documented or presumed encephalitis [55], but are not used routinely. Also high-dose oral topiramate may be beneficial at times [56]. Immunomodulatory approaches, such as steroids, IVIG, or plasma exchanges, are often tried those cases [57]. Regarding non-pharmacological treatments, vagal nerve stimulation [58] and hypothermia [59] should be mentioned.

Conclusion

Although several pharmacological options are used in the treatment of SE, there is substantial lack of comparative, high-level, evidence-based information. These issues need to be investigated in well-designed studies. It is paramount to continue SE treatment, together with supportive care, also in those episodes refractory to treatment for prolonged time, as long as clear evidence of irreversible neurological damage is not available [57, 60].

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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 epilepticus

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 epilepticus) 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 morbidem medizinischen Problemen. Bei einem SE im anoxischen Koma ist der Verlauf ohne hypothermische Behandlung tödlich.

Schlüsselwörter: Konvulsiver Status epilepticus, nicht-konvulsiver Status epilepticus, Prognose, Morbidität, Mortalität, refraktärer Status

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. Baroix 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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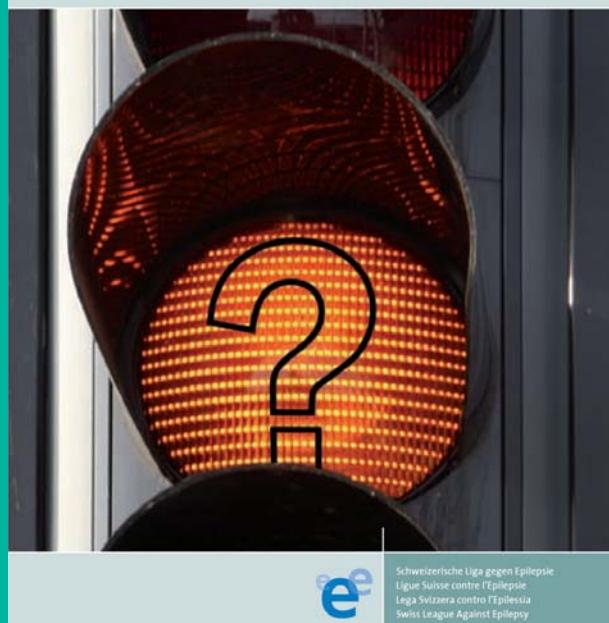


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Dieser Preis ist nach dem deutschen Neurologen und Psychiater Alfred Hauptmann (1881 – 1948) benannt. Er hatte u.a. schon 1912 – noch als Assistenzarzt – erstmals auf die antiepileptische Wirkung von Phenobarbital aufmerksam gemacht. 1935 wurde er aufgrund seiner jüdischen Abstammung von den Nationalsozialisten aus dem Dienst als Direktor der Psychiatrischen und Nervenklinik der Universität Halle/Saale entfernt und musste in die USA emigrieren.

Der Preis wurde von 1980 bis 2008 in der Regel alle zwei Jahre durch das Epilepsie-Kuratorium e.V. vergeben, ab 2009 ist es ein gemeinsamer Preis der Deutschen Gesellschaft für Epileptologie, der Österreichischen Sektion der Internationalen Liga gegen Epilepsie und der Schweizerischen Liga gegen Epilepsie mit Vergabe auf den alle zwei Jahre stattfindenden gemeinsamen Tagungen.

Ausgezeichnet wird die beste wissenschaftliche Arbeit aus dem deutschsprachigen Raum auf dem Gebiet der experimentellen und klinischen Epileptologie aus den beiden letzten, der Verleihung vorangegangenen Jahren.

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an den Vorsitzenden des Kollegiums zu senden:

Herrn Dr. med. Günter Krämer
Medizinischer Direktor
Schweizerisches Epilepsie-Zentrum
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Es können sowohl unveröffentlichte als auch publizierte Arbeiten eingereicht werden. Bei der Einreichung ist mitzuteilen, ob und wo die Arbeit zum ersten Mal veröffentlicht wurde. Die Arbeiten sollen in deutscher oder englischer Sprache verfasst sein. Dem Kollegium können auch Arbeiten zur Preisvergabe vorgeschlagen werden.

Preisrichterkollegium: Dr. med. Günter Krämer (Vorsitzender), Schweizerisches Epilepsie-Zentrum Zürich, Prof. Dr. med. Rudolf Korinthenberg, Universitätskinderklinik Freiburg, Prof. Dr. med. Wolfgang Löscher, Institut für Pharmakologie, Toxikologie und Pharmazie, Hannover, Univ.-Doz. Dr. med. Eugen Trinka, Neurologische Universitätsklinik, Innsbruck.



Epilepsie-Liga-Mitteilungen



Foto: Ursula Häne, Zürich

V. l. n. r.: Dr. Günter Krämer, Dr. Heidemarie Gast, Dr. Dr. Kaspar Schindler und Dr. Claude Kahn

Verleihung des Hugo Kahn-Preises

Anlässlich der Hugo Kahn-Preisverleihung vom 17. April 2009 in Zürich referierte der Preisträger Dr. med. Dr. sc. nat. Kaspar Schindler aus Bern über seine Forschungsarbeit betreffend die komplexen Netzwerke im Gehirn. Der Präsident der Epilepsie-Liga, Dr. med. Günter Krämer, Zürich, hielt die Laudatio.

„Sehr geehrter Herr Dr. Kahn
Sehr geehrte Mitglieder der Hugo Kahn & Co. AG Jubiläumsstiftung für Epilepsieforschung
Lieber Herr Schindler
Meine sehr geehrte Damen und Herren

Es ist mir eine grosse Freude, Ihnen auch im Namen von Herrn Professor Landis aus Genf und Herrn Professor Despland aus Montreux als den beiden anderen Mitgliedern des Preisrichterkollegiums den Preisträger des Hugo Kahn-Preises für Epileptologie 2008 vorstellen zu können.

Herr Dr. med. als auch Dr. sc. nat. oder scientiae naturalium Kaspar Anton Schindler wurde am 1.1.1970 in Bern geboren. Er legte seine Matura in mathematisch-naturwissenschaftlicher Richtung am Gymnasium Bern Neufeld ab. Anschliessend studierte er bis 1995 an der Universität Bern Medizin, 1996 besuchte er die Offiziersschule, der das Abverdienen als Militärarzt folgte. Von 1996 bis 1999 nahm er an einem M.D.-Ph.D.-Programm für Ärzte am Institut für Neuroinformatik der Universität und der ETH Zürich mit Hauptfach Neurophysiologie und Nebenfächern Mathematik und Elektrotechnik teil. 1999 promovierte er in Zürich sowohl an der Mathematisch-Naturwissenschaftlichen Fakultät zum Doktor scientiae naturalium (kurz: sc. nat.) als auch an der Medizinischen Fakultät zum Dr. med. Von 1999 bis 2001 war er Assistenzarzt an der Neurologischen Universitätsklinik Bern bei Herrn Professor Dr. Christian Hess. Neben der Tätigkeit an der Poliklinik und im Notfalldienst war er wissenschaftlicher Mitarbeiter in einem Nationalfondprojekt zur prächirurgischen Lokalisation epileptogener Zonen durch multimodale Bildgebung. 2002 war er Assistenzarzt für Innere Medi-



zin (so genanntes Fremdjahr für den Facharzt Neurologie) am Herzzentrum der Sonnenhofklinik in Bern, 2003 Assistenzarzt in der Neurologischen Klinik des Universitätsspitals Zürich bei Professor Klaus Hess und Professor Claudio Bassetti mit Tätigkeit in der Poliklinik, Stroke-Unit. In den Jahren 2004 und 2005 folgte eine Assistenzarztzeit in der Epileptologie und Elektroenzephalographie bei Professor Heinz-Gregor Wieser am Universitätsspital Zürich, ab 2005 war er dann Oberarzt in dieser Abteilung. Von 2006 bis März 2007 folgte ein Forschungsaufenthalt an der Klinik für Epileptologie der Universität Bonn bei Professor Christian Elger, im April 2007 ein Forschungsaufenthalt an der Naturwissenschaftlichen Fakultät der Universität Morelos in Mexiko. Seit Juli 2007 ist Herr Schindler Oberarzt in der Neurologie, speziell für Epileptologie und Elektroenzephalographie, an der Neurologischen Universitätsklinik Bern.

Der rote Faden seiner Forschungsarbeiten der letzten Jahre ist der Ansatz, epileptische Anfälle auf der Netzwerkebene zu verstehen. Die Motivation dazu beruht auf seiner Überzeugung, dass beim Versuch, die Mechanismen epileptischer Anfälle besser verstehen zu lernen, eine ausschliesslich reduktionistische Herangehensweise zwar zu einem grossen Informationsgewinn auf der Ebene einzelner Nervenzellen führen mag, dass man daraus aber nicht auf die selbst-organisierende Dynamik ausgedehnter Neuronenverbände rückschlussen kann. Diese, oft komplexen, funktionellen Verknüpfungen liegen aber letztlich klinisch manifesten epileptischen Anfällen zugrunde.

In einer ersten Studie konnte durch eine visuelle und quantitative Analyse von EEG-Ableitungen, also so genannten Hirnstromkurven, von Epilepsiepatienten nachgewiesen werden, dass bei rund einem Viertel klinisch sekundär generalisierter, also scheinbar das ganze Hirn beteiligender Anfälle, die Hirnrinde tatsächlich nur zum Teil epileptiforme Anfallsmuster generiert. In einer zweiten Studie wurden aus der statischen Physik stammende Methoden verwendet, um die Korrelationsstruktur intrakranieller iktaler EEG-Ableitungen zu analysieren. Das heisst, es wurde die Anfallsaktivität von Nervenzellen des Gehirns mit Hilfe von zuvor neurochirurgisch eingelegten EEG-Elektroden ausgewertet. Dabei zeigte sich, dass auf Netzwerkebene epileptische Anfälle keineswegs nur so genannte „hypersynchrone“, also abnorm regelmässig feuernde Nervenzellen oder Zustände sind, sondern dass sie eine typische innere Dynamik aufweisen. Insbesondere wurde nachgewiesen, dass die EEG-Korrelation vor dem Ende eines Anfalls immer signifikant ansteigt. Dies unterstützt die Hypothe-

se, dass eine zunehmende Korrelation ein über die rein zelluläre Aktivität hinausgehendes Phänomen zur Beendigung epileptischer Anfälle darstellt, was in einer Folgestudie bei Status epilepticus weiter untermauert werden konnte. Schliesslich konnte auch nachgewiesen werden, dass die EEG-Synchronisation durch elektrische Stimulation der Anfallsursprungszone beeinflusst wird, was hinsichtlich neuer, in der Entwicklung befindlicher Therapieansätze wichtig sein könnte.

Das Preisrichterkollegium war übereinstimmend der Auffassung, dass bei einer Reihe interessanter und prinzipiell preiswürdiger Bewerbungen derjenigen von Herrn Dr. Kaspar Schindler die Auszeichnung mit dem Hugo Kahn-Preis gebührt. Er wird Ihnen jetzt die wichtigsten Ergebnisse seiner Forschung in einem eigenen Referat mit dem Titel „Epileptische Anfälle als komplexe Netzwerk-Phänomene“ selbst vorstellen.

Lieber Herr Schindler, herzlichen Glückwunsch !“



Zweite DVD für Fachleute

Die zweite von der Epilepsie-Liga herausgegebene DVD in der Reihe für Fachleute ist dem Thema „Dissoziative Anfälle“ gewidmet. Sie wurde von Prof. Dr. Andreas Schulze-Bonhage verfasst. Die Schweizerische Liga gegen Epilepsie dankt ihm für die Erlaubnis zur Publikation.

In seinem Vorwort zum DVD-Booklet erläutert Liga-Präsident Dr. Günter Krämer die Aktualität dieser Thematik:

„Nichtepileptische psychogene Anfälle wurden in früheren Jahrhunderten auch als hysterische Anfälle bezeichnet. Dieser Terminus wurde zwischenzeitlich in erster Linie wegen negativer Assoziationen mit dem Hysteriebegriff fallengelassen, nach wie vor besteht aber eine terminologische Vielfalt, beziehungsweise Unklarheit. Am neutralsten ist die Bezeichnung psychogene nichtepileptische Anfälle (auch in Abgrenzung gegenüber organischen nichtepileptischen Anfällen, beispielsweise bei kardialen Störungen), daneben ist auch die Bezeichnung als dissoziative Anfälle weit verbreitet. Zwischen 10 und 20 % der mit einer vermeintlichen schwer behandelbaren Epilepsie an Epilepsie-Zentren zugewiesenen Patienten leiden an diesem Problem! Eine intensive Beschäftigung sowohl in diagnostischer als auch in therapeutischer Hinsicht ist also erforderlich und lohnenswert.“

Die DVD „Dissoziative Anfälle“ richtet sich an Fachleute. Sie ist auch als Lehrmittel zum Selbststudium geeignet. Sprache: Deutsch.

Erhältlich bei der Epilepsie-Liga, info@epi.ch, Tel. 043 488 67 77.





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CHF 20'000.—

par an, la priorité étant accordée aux projets cherchant à élucider les causes et à mettre au point des traitements de l'épilepsie.

Aucune bourse ne sera octroyée pour la formation de base ou continue ou pour des séjours à l'étranger. En revanche, la prise en charge de frais de voyage et de séjour (sans salaire) est possible pour les séjours de courte durée (quelques semaines au maximum) lorsque ces séjours servent à apprendre des méthodes appliquées dans le cadre d'un projet bénéficiant de soutien en Suisse.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Délai de remise des demandes : 31 mars 2010

Les formulaires, ainsi que le guide pour les candidats peuvent être demandés à l'adresse suivante :

Ligue Suisse contre l'Epilepsie
Seefeldstrasse 84
Case postale 1084
8034 Zurich
Tél. 043 488 67 77
Fax 043 488 67 78
info@epi.ch

Mise au concours – Prix de promotion

La Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie) décerne chaque année un prix d'un montant de CHF 2'500.—

pour la meilleure dissertation dans le domaine de l'épileptologie.

Tous les domaines spécialisés et tous les groupes professionnels couvrant les disciplines fondamentales ou cliniques sont invités à soumettre leur candidature. Aucune limite d'âge n'a été fixée.

Le jury décernant le prix se compose de trois membres du comité directeur de la Ligue contre l'Epilepsie. Il peut être complété au besoin par des experts externes. La décision est prise par vote secret.

Si le requérant a déjà fait une demande de soutien ailleurs, il faut nous en informer en spécifiant où et avec quel résultat.

Le prix est toujours décerné l'année suivante dans le cadre de l'assemblée annuelle ou générale de la Ligue contre l'Epilepsie.

Les dossiers de candidature doivent parvenir au **Secrétariat de la Ligue contre l'Epilepsie (Seefeldstrasse 84, case postale 1084, 8034 Zurich) jusqu'au 31.12.2009** et comporter les pièces suivantes :

- trois exemplaires de la dissertation achevée et remise au décanat,
- trois exemplaires d'une prise de position du directeur de thèse (il peut par exemple s'agir de l'expertise concernant la dissertation).



Informations de la Ligue Suisse contre l'Epilepsie



D. g. à d. : Dr Günter Krämer, Dr Heidemarie Gast, Dr Dr Kaspar Schindler und Dr Claude Kahn

Remise du Prix Hugo Kahn

A l'occasion de la cérémonie de remise du Prix Hugo Kahn du 17 avril 2009 à Zurich, le Dr. méd. et ès sc. nat. Kaspar Schindler de Berne qui en est le lauréat a parlé de ses travaux de recherche sur les réseaux complexes dans le cerveau. Le discours élogieux qui accompagnait la remise a été prononcé par le Dr. Günter Krämer, Zurich.

« Cher Dr. Kahn
Chers membres de la Fondation Hugo Kahn & Cie SA pour la recherche sur l'épilepsie
Cher Monsieur Schindler
Mesdames, Messieurs

Au nom de tout le collège du jury formé par les professeurs Landis de Genève et Despland de Montreux en plus de ma propre personne, j'ai le grand plaisir de vous présenter le lauréat du Prix Hugo Kahn de l'épileptologie 2008.

Kaspar Anton Schindler, porteur du double titre de docteur en médecine et en sciences naturelles, a vu le jour le 1.1.1970 à Berne. Il a passé sa maturité à profil sciences naturelles au Gymnase Neufeld à Berne, puis a enchaîné avec des études de médecine à l'Université de Berne qu'il a terminées en 1995. En 1996, il a fait l'école d'officiers, puis a payé ses galons en tant que médecin militaire. De 1996 à 1999, il a participé à un programme M.D.-Ph.D. pour médecins à l'Institut de neuroinformatique de l'Université et de l'EPF à Zurich avec la neurophysiologie comme branche principale et les mathématiques et l'électrotechnique comme branches annexes. En 1999, il a soutenu sa thèse à la fois à la Faculté des mathématiques et des sciences naturelles pour un doctorat en sciences naturelles et à la Faculté de médecine pour un doctorat en médecine. De 1999 à 2001, il a été médecin hospitalier à la Clinique universitaire de neurologie à Berne auprès du Professeur Dr. Christian Hess, menant de front son activité à la Polyclinique et au service des urgences, ainsi qu'un travail de collaborateur scientifique dans un projet du Fonds national pour la localisation préopératoire de zones épileptogènes par



imagerie multimodale. En 2002, il a accompli un assistanat en médecin interne (un « stage extra-disciplinaire » pour ce spécialiste de la neurologie) au Centre cardiaque de la Clinique Sonnenhof à Berne, puis est devenu assistant en 2003 à la Clinique de neurologie du Centre hospitalier universitaire de Zurich sous le professeur Klaus Hess et le professeur Claudio Bassetti, son activité se centrant sur la « stroke unit » de la Polyclinique. Dans les années 2004 et 2005 a suivi un assistanat dans le service d'épileptologie et d'électroencéphalographie du Professeur Heinz-Gregor Wieser à l'Hôpital universitaire de Zurich où il est devenu chef de clinique en 2005. De 2006 à mars 2007, un séjour de recherche l'a conduit auprès du Professeur Christian Elger à la Clinique d'épileptologie de l'Université de Bonn et en avril 2007, il a mis le cap sur le Mexique pour un stage de recherche à la Faculté des sciences naturelles de l'Université de Morelos. Depuis juillet 2007, Monsieur Schindler est chef de clinique au Service de neurologie, et plus spécialement de l'épileptologie et de l'encéphalographie, à la Clinique universitaire de neurologie à Berne.

Le fil conducteur de ses travaux de recherche a été depuis quelques années la volonté de déchiffrer les crises épileptiques au niveau des réseaux, sa motivation venant de la conviction qu'une optique purement réductionniste dans la tentative de mieux comprendre les mécanismes des crises épileptiques pouvait certes apporter des connaissances précieuses au niveau de cellules nerveuses individuelles, mais qu'il n'en ressortirait aucun enseignement quant à la dynamique d'auto-organisation des vastes réseaux de neurones. Or, ces connexions fonctionnelles souvent complexes sous-tendent en fin de compte les manifestations cliniques des crises épileptiques.

Dans une première étude, il a été possible de démontrer à travers une analyse visuelle et quantitative de dérivations d'EEG, les dénommées courbes de courants cérébraux de patients épileptiques, que dans environ un quart des crises à généralisation secondaire du point de vue clinique, donc des crises intéressant apparemment tout le cerveau, le cortex cérébral ne générerait en réalité que partiellement des schémas de crise épileptiformes. Une deuxième étude a ensuite fait appel aux méthodes de la physique statique pour analyser la structure corrélationnelle de dérivations d'EEG intracrâniens ictaux. En d'autres termes, l'activité de cellules nerveuses du cerveau en phase ictale a été évaluée à l'aide d'électrodes EEG implantées au préalable par neurochirurgie. Il est apparu qu'au niveau des réseaux, les crises épileptiques ne sont pas du tout seulement des

états de décharge neuronale dite « hypersynchrone » ou d'une régularité anormale, mais qu'elles présentent une dynamique interne typique. Une progression significative de la corrélation EEG a notamment pu être établie avant la terminaison d'une crise. L'hypothèse qu'une corrélation progressive est un phénomène qui va au-delà de la simple activité cellulaire et a pour fonction de terminer une crise épileptique a ainsi été confortée, puis encore consolidée par une étude consécutive en phase de statut épileptique. Enfin, il a été possible de démontrer que la synchronisation EEG pouvait être influencée par stimulation électrique de la zone foyer de la crise, ce qui pourrait être important dans le développement de nouvelles pistes thérapeutiques actuellement en chantier.

Le jury collégial a été unanime dans son choix: placé devant une série de candidatures intéressantes et qui en principe méritaient toutes d'être récompensées, il a retenu les travaux du Dr. Kaspar Schindler comme particulièrement dignes du Prix Hugo Kahn. Le lauréat va maintenant vous présenter lui-même les résultats de ses recherches dans un exposé placé sous le titre « Les crises épileptiques en tant que phénomènes réticulaires complexes ».

Cher Monsieur Schindler, sincères félicitations !



Kongresskalender

2009

19.-20.6.2009 | Erlangen, Deutschland

5th Epilepsy Colloquium Erlangen, Networks and Epilepsies

Information: Claudia Saint-Lôt, Epilepsiezentrum, Schwabachanlage 6, 91054 Erlangen, Deutschland, Tel. 0049 / 9131 / 8539116, Fax 0049 / 931 / 8536460, e-mail: claudia.saint-lot@uk-erlangen.de, www.epilepsiezentrum-erlange.de

20.-24.6.2009 | Mailand, Italien

19th Meeting of the European Neurological Society (ENS)

Information: ENS Administrative Secretariat c/o Congrex Deutschland GmbH, Hauptstrasse 18, 79576 Weil am Rhein, Deutschland, Tel. 0049 / 7621 / 9833-0, Fax 0049 / 7621 / 78714, e-mail: ensinfo@akm.ch, www.ensinfo.com

28.6.-2.7.2009 | Budapest, Ungarn

28th International Epilepsy Congress (ILAE & IBE)

Information: ILAE / IBE Congress Secretariat, 7 Priory Hall, Dublin 18, Ireland, Tel. 00353 / 1 / 2056720, Fax 00353 / 1 / 2056156, e-mail: info@epilepsycongress.org., www.epilepsycongress.org

3.-5.7.2009 | Hamburg, Deutschland

Richard-Jung-Kolleg: Elektroenzephalografie (EEG) – Epilepsie Schlafstörungen

Information: Thieme.congress, in Georg Thieme Verlag KG, Rüdigerstr. 14, 70469 Stuttgart, Deutschland, Tel. 0049 / 711 / 8931554, Fax 0049 / 711 / 8931370, e-mail: info@richard-jung-kollge.de, www.richard-jung-kolleg.de

12.-17. Juli 2009 | Kiel, Deutschland

3rd Baltic Sea Summer School on Epilepsy

Information: www.epilepsy-academy.org

27.-30.8.2009 | München, Deutschland

1st International Congress on Clinical Neuroepidemiology (ICCN) 2009

Information: K.I.T. GmbH, Association & Conference Management Group & Co. KG, Kurfürstendamm 71, 10709 Berlin, Deutschland, Tel. 0049 / 30 / 24603261, Fax: 0049 / 30 / 24603200, e-mail: iccn2009info@kit-group.org, www.neuro2009.com

30.8.-4.9.2009 | Boston, MA, U.S.A.

XIV World Congress of Neurological Surgery

Information: CNS, 10 N Martingale Rd., Suite 190, Schaumburg, IL 60173, U.S.A.
Tel. 001 / 847 / 2402500, Fax 001 / 847 / 2400804, e-mail: info@1cns.org, www.neurosurgery.org

3.-5.9.2009 | Zürich

10th International Congress, European Society of Magnetic Resonance in Neuroradiology (ESMRN)

Information: Congress Secretariat, IMK Institut für Medizin und Kommunikation, Münsterberg 1, 4001 Basel, Tel. 0041 / 61 / 2713551, Fax 0041 / 61 / 2713338, e-mail: mail@imk.ch, www.imk.ch

6.-13.9.2009 | Eilat, Israel

3rd Eilat International Educational Course: Pharmacological Treatment of Epilepsy

Information: Target Conferences, P.O. Box 29041, Tel Aviv 61290, Israel, Tel. 00972 / 3 / 5175150, Fax 00972 / 3 / 5175155, e-mail: eilatedu@targetconf.com, www.eilat-aeds.com

12.-15.9.2009 | Florenz, Italien

13th Congress of the European Federation of Neurological Societies (EFNS)

Information: Kenes International, 17 Rue du Cendrier, PO Box 1726, 1211 Geneva 1, Tel. 0041 / 22 / 9080488, Fax 0041 / 22 / 7322850, e-mail: efns09@kenes.com, www.efns.org/efns2009

27.9.-2.10.2009 | Ascona

6th International Narcolepsy Symposium

Prof. Dr. Claudio Bassetti, Neurologische Klinik, Universitätsspital Zürich, e-mail: claudio.bassetti@usz.ch

30.9.-3.10.2009 | North Yorkshire, England

8th European Paediatric Neurology Society Conference (EPNS)

Information: Diane Rodie, EPNS 2009 Congress, c/o BPNA Secretariat, Bridge House, Harrow Road, Bolton, BL1 4NH, England, Tel: 0044 / 1204 / 492888, Fax: 0044 / 1204 / 493003, e-mail: epns2009@bpna.org.uk, www.bpna.org.uk/epns2009



Kongresskalender

1.-3.10.2009 | Schluchsee bei Freiburg, Deutschland

15. Tagung des Deutsch-Österreichisch-Schweizer Arbeitskreises für Epilepsie

Information: Prof. Dr. Bernhard Steinhoff, Ärztlicher Direktor, Epilepsiezentrums Kork, Landstrasse 1, 77694 Kehl-Kork, Deutschland,
Tel. 0049 / 7851 / 842250, Fax 0049 / 7851 / 842555,
e-mail: bsteinhoff@epilepsiezentrum.de, internet:
www.diakonie-kork.de

8.10.2009 | Lugano, Ospedale Civico, 17.00 Uhr

Manifestazione specialistica della Lega contro l'Epilessia

Information: Geschäftsstelle der Epilepsie-Liga, Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 488 / 6777, Fax 0041 / 43 / 488 / 6778,
e-mail: info@epi.ch, www.epi.ch

8.10.2009 | Lugano, Ospedale Civico, 19.30 Uhr

Manifestazione pubblica della Lega contro l'Epilessia

Information: Geschäftsstelle der Epilepsie-Liga, Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 488 / 6777, Fax 0041 / 43 / 488 / 6778,
e-mail: info@epi.ch, www.epi.ch

8.-11.10.2009 | Prag Tschechien

The Third World Congress on Controversies in Neurology

Information: Comtec Headquarters and Administration, 53 Sderot Rothschild, P.O. Box 68, Tel Aviv, 61000 Israel,
Tel. 00420 / 972 / 35666166,
Fax 00420 / 972 / 35666177,
e-mail: cony@comtecmed.com,
www.comtecmed.com/cony

11.-14.10.2009 | Baltimore, USA

Annual Meeting of the American Neurology Association (ANA)

Information: American Neurological Association, 5841 Cedar Lake Road, Suite 204, Minneapolis, MN 55416, USA,
Tel. 001 / 952 / 5456284, Fax 001 / 952 / 5456073,
e-mail: ana@lmsi.com

15.-18.10.2009 | Peking, China

3rd Beijing International Epilepsy Forum

Information: caae2008@sina.com

24.-29.10.2009 | New Orleans, LA, USA

Congress of Neurological Surgeons Annual Meeting

Information: Congress of Neurological Surgeons,
10 North Martingale Road, Suite 190, Schaumburg,
IL 60173 USA,
Tel. 001 / 847 / 2402500, Fax 001 / 847 / 2400804,
www.neurosurgeon.org/meetings/2009

24.-30.10.2009 | BITEC, Bangkok, Thailand

19th World Congress of Neurology

Information: WCN 2009 Secretariat,
c/o Congrex Sweden, P.O. Box 5619,
11486 Stockholm, Sweden,
Tel. 0046 / 8 / 4596600, Fax 0046 / 8 / 6619125,
e-mail: wcn2009@congrex.com,
www.wcn2009bangkok.com

5.-7.11.2009 | Aarau

Herbsttagung, Schweizerische Neurologische Gesellschaft (SNG)

Information: IMK Institut für Medizin und Kommunikation AG, Münsterberg 1, 4001 Basel,
Tel. 0041 / 61 / 2713551, Fax 0041 / 61 / 2173338,
e-mail: mail@imk.ch, www.imk.ch

5.-7.11.2009 | Marseille, France

12èmes Journées Françaises de l'Epilepsie

Information: Secrétariat de la LFCE,
Tél. 0033 / 467 / 109223,
e-mail: secretariat-lfce@ant-congres.com

12.-14.11.2009 | Leipzig, Deutschland

17. Jahrestagung der Deutschen Gesellschaft für Schlafforschung und Schlafmedizin (DGSM)

Information: Conventus Congressmanagement & Marketing GmbH, Jana Radoi, Markt 8, 07743 Jena, Deutschland,
Tel. 0049 / 3641 / 3533221, Fax 0049 / 3641 / 3533271,
e-mail: dgsm@conventus.de, www.conventus.de

14.11.2009 | Zürich, Schweiz. Epilepsie-Zentrum, 10 Uhr

Patiententag: Stress

Information: Geschäftsstelle der Epilepsie-Liga, Seefeldstrasse 84, Postfach 1084, 8034 Zürich,
Tel. 0041 / 43 / 488 / 6777, Fax 0041 / 43 / 488 / 6778,
e-mail: info@epi.ch, www.epi.ch



Kongresskalender

3.-5.12.2009 | Berlin, Deutschland

Gemeinsame Jahrestagung der Deutschen Gesellschaft für Neurorehabilitation (DGNR) und der Deutschen Gesellschaft für Neurotraumatologie und Klinische Neurorehabilitation (DGNKN): 20 Jahre moderne Neurorehabilitation - Von der Intensivstation bis zur Versorgung des chronischen Patienten zu Hause
Information: Karola Mannigel, Conventus Congressmanagement & Marketing GmbH, Markt 8, 07743 Jena, Deutschland, Tel. 0049 / 3641 / 3 / 533265, Fax 0049 / 3641 / 3 / 53321, e-mail: karola.mannigel@conventus.de, www.conventus.de/dgnkn

4.-8.12.2009 | Boston, Massachusetts, USA

63th Annual Meeting of the American Epilepsy Society (AES)

Information: Karan Murray, American Epilepsy Society, 638 Prospect Avenue, Hartford, CT 06195-4240, USA, Tel. 001 / 860 / 5867505, Fax 001 / 860 / 5867550, e-mail: info@aesnet.org, www.aesnet.org

2010

10.-17.4.2010 | Toronto, ON, Canada

62th Annual Meeting of the American Academy of Neurology

Information: American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116, USA, Tel. 001 / 651 / 6952717, Fax 001 / 651 / 6952791, e-mail: memberservice@aan.com, www.aan.com

25.-29.4.2010 | Eilat, Israel

10th Eilat Conference on New Antiepileptic Drugs (Eilat X)

Information: 10th Eilat Conference on New Antiepileptic Drugs, PO Box 29041, Tel Aviv 61290, Israel, Tel. 00972 / 3 / 5175150, Fax 00972 / 3 / 5175155, e-mail: eilatx@targetconf.com, www.eilat-aeds.com

28.4.-1.5.2010 | Halle, Deutschland

54. Jahrestagung der Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung (DGKN) mit Richard-Jung-Kolleg

Information: Congrex Deutschland GmbH, Hauptstrasse 18, 79576 Weil am Rhein, Deutschland, Tel. 0049 / 7621 / 9833-0, Fax 0049 / 7621 / 78714, e-mail: info@akmcongress.com



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