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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 ».

Correspondance

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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   - Renvoi à la littérature dans l'ordre d'apparition dans le texte, numérotation arabe apparaissant dans le texte dans des parenthèses carrées.
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4. **Ordre:** 1. Page de titre (incluant le cas échéant, les remerciements aux personnes et/ou institutions qui ont contribués 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 ainsi 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.
   - **Références:** Les références à la littérature doivent être citées à la fin du travail dans l'ordre d'apparition dans le texte et citées suivant le modèle ci-dessous. Les communications personnelles, les résultats non publiés et/ou les manuscrits adressés à la publication ne sont pas acceptés, mais doivent être mentionnés de façon appropriée dans le texte. Les citations « à l'impression » resp. « in press » ne se rapportent qu'aux travaux qui ont été acceptés (en ajoutant le nom du journal, le numéro et l'année de parution, si connus). La citation de travaux « en préparation » n'est pas autorisée. Les communications de congrès ne seront prises en considération que sous forme d'abstract ou d'article de « Proceedings-Journal ».
   - **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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Tous les manuscrits doivent être envoyés en trois exemplaires, y compris les illustrations et tableaux. L'envoi de fichiers électroniques (MS Word) est préférable, comme alternative, l'envoi de trois exemplaires imprimés et d'une CDRom (pour les illustrations et les tableaux mentionner le programme utilisé) est possible.

Dr Andrea O. Rossetti, PD et MER

Questa edizione di Epileptologie è dedicata all'interfaccia tra epilettologia e cure intensive. Grazie all'apporto sempre più accessibile delle registrazioni digitali, che permettono non solo una correlazione ottimale con le imagini video, ma pure lo stoccaggio di importanti quantità di dati relativi ai lunghi tracciati e perfino un'analisi quantitativa del segnale in tempo praticamente reale, negli ultimi anni questo ambito sta vivendo uno sviluppo senza precedenti. Uno degli "effetti collaterali" interessanti e stimolanti è stato quello di avvicinare l'epilettologo ospedaliero a delle situazioni e problematiche acute, in rapida evoluzione, che necessitano un approccio interdisciplinare.

Questo numero riflette le conoscenze e l'attività clinica e di ricerca di esperti svizzeri e internazionali, nonché fruttuose collaborazioni transatlantiche. Gli articoli toccano le problematiche più frequenti in questo ambito: una sintesi dettagliata sull'approccio relativo allo stato di male epilettico refrattario precede un riassunto sui più importanti farmaci antiepilettici utilizzati in questo contesto. Quindi, le analisi dei tipi di tracciato e dei grafoelementi elettroenecefalografici relativamente specifici alle cure intensive, con la discussione delle relative ripercussioni a livello terapeutico, precedono una visione neurologica della prognosi dei pazienti dopo arresto cardiaco.

Ringrazio in modo particolare gli amici e colleghi che hanno contribuito alla risuscita di questo numero, che permette di esplorare un tasello relativamente nuovo e impegnativo della nostra attività, ed è stato concepito interamente in inglese, sorta di lingua franca nazionale in ambito scientifico, alfine di raggiungere una audience la più vasta possibile.

Auguro a tutti un'interessante e istruttiva lettura!

Andrea O. Rossetti

Dr Andrea O. Rossetti, PD et MER

This Epileptologie issue focuses on the interplay between epileptology and intensive care unit. Thanks to the progressive development of digital recording machines, allowing not only a reliable video correlation but also the stocking of impressive amounts of data and even real-time quantitative analyses of the signal, this field is experiencing an unprecedented development in the last years. The familiarization of the hospital-based epileptologist with acute, fast changing medical issues requiring an interdisciplinary approach represents one of the interesting "collateral effects".

This issue reflects the knowledge, clinical and scientific activities, and the fruitful collaborations of Swiss and international experts. The articles target the most frequent aspects in this field: a detailed review of the management of refractory status epilepticus precedes an overview of the most commonly used antiepileptic compounds in the ICU. Then, an analysis of the electroencephalographic patterns and transients commonly found in an intensive care setting, including the therapeutic implications, are followed by the description of the neurological approach to the prognostication of patients surviving a cardiac arrest.

I would like to thank warmly the friends and colleagues that contributed to the achievement of this issue, which reflects a relatively new and challenging aspect of our activity. This has been entirely edited in English in order to be enjoyed by the widest possible readership.

I wish you an interesting and instructive reading!

Andrea O. Rossetti

Dr Andrea O. Rossetti, PD et MER

Diese Ausgabe der Zeitschrift „Epileptologie“ ist dem Zusammenspiel von Epileptologie und Intensivpflege gewidmet. Dank der immer verbreiteter zugänglichen digitalen Übertragung, die nicht nur eine optimale Korrelation mit den Videobildern, sondern auch das Aufbewahren von einer riesigen Datenmenge, ja sogar die quantitative Analyse eines Signals in der realen Zeitspanne ermöglicht, hat dieses Gebiet in den letzten Jahren eine unglaubliche Entwicklung erfahren. Die wachsende Vertrautheit des im Spital tätigen Epileptologen mit akuten, sich rasch verändernden medizinischen Situationen, die ein interdisziplinäres Vorgehen erfordern, ist einer der interessanten kollateralen Effekte.

„Epileptologie“ 4-12 widerspiegelt die Kenntnisse, die klinischen und wissenschaftlichen Aktivitäten und die fruchtbare Zusammenarbeit von Schweizer und internationalen Experten. Die Beiträge beziehen sich auf die häufigsten Aspekte des oben genannten Themas: Ein detaillierter Überblick über das Management von refraktärem Status epilepticus wird gefolgt von einem Bericht über die am häufigsten angewandten Antiepileptika auf der Intensivpflegestation. Der dritte Artikel befasst sich mit der Analyse von elektroenzephalographischen Mustern und im Rahmen der Intensivpflege häufig vorgefundenen Potenziale, therapeutische Implikationen mit inbegriffen. Es folgt die Beschreibung des neurologischen Gesichtspunkt im Bereich der Prognose von Patienten, welche einen Herzstillstand überleben.

Ich möchte meinen Freunden und Kollegen, die zur Realisation dieser Nummer über diese relativ neuen und herausfordernden Aspekte unserer Tätigkeit beigetragen haben, ganz herzlich danken. Diese Ausgabe wurde ganz auf Englisch realisiert, damit sie in unserem mehrsprachigen Land möglichst viele Leserinnen und Leser erreicht.

Ich wünsche Ihnen eine interessante und instruktive Lektüre!

Dr Andrea O. Rossetti, PD et MER

Refractory Status Epilepticus: Epidemiology, Clinical Aspects and Management of a Persistent Epileptic Storm

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Summary

Refractory status epilepticus (RSE) is a life-threatening state of persisting seizure activity despite initiation of first- and second-line anticonvulsive treatment. Serious outcomes are considered mainly related to the etiology of RSE. Notwithstanding its high morbidity and mortality, large randomized multicenter trials of promising treatment options are lacking and management as well as prognostication often hold unresolved challenges. Neurointensive care of patients with RSE consist of a step-wise regimen tailored to the change or persistence of electrographic seizure activity best followed with continuous video-EEG monitoring. Further extent of patient support has to be adapted to the degree of altered consciousness and impairment of vital functions. Potential interactions of several anticonvulsive drugs with other medication are often complex and challenging.

This review encompasses epidemiologic, clinical, and prognostic aspects of RSE and delineates strategies for acute pharmacologic management.

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Key words: Refractory status epilepticus, mortality, recovery, etiology, neurocritical care

Refraktärer Status epilepticus: Epidemiologie, klinische Aspekte und Management eines persistierenden epileptischen Sturms

Der refraktäre Status epilepticus (RSE) ist ein lebensbedrohlicher Zustand mit einer anhaltenden epileptischen Aktivität trotz einer initiierten Erst- und Zweitlinien-Behandlung. Es wird angenommen, dass ernste Prognosen vor allem durch die zu Grunde liegenden Ursachen des RSE begründet sind. Trotz der hohen Morbidität und Mortalität fehlen randomisierte multizentrische Studien von vielversprechenden Therapieoptionen, womit die Behandlung und Prognose ungelöste Herausforderungen darstellen. Neurointensives Management von Patienten mit RSE beinhaltet ein Behandlungskonzept, angepasst an die ständig sich verändernde oder anhaltende elektroenzephalographische Anfallsaktivität, welche am besten mit einem kontinuierlichen Video-EEG-Monitoring überwacht wird. Weitere Massnahmen richten sich nach dem Ausmass der Vigilanzminderung und der Einschränkung der Vitalfunktionen. Potenzielle Interaktionen von verschiedenen Antikonvulsiva mit anderen Medikamenten sind oft komplex und stellen eine weitere Herausforderung in der Akutbehandlung von RSE-Patienten dar.

Diese Übersichtsarbeit erläutert kurz zusammengefasst epidemiologische, klinische, diagnostische und prognostische Aspekte des RSE und zeigt medikamentöse Behandlungsstrategien auf.

Schlüsselwörter: Refraktärer Status epilepticus, Mortalität, Erholung, Aetiologie, Neuro-Intensivpflege

Etat épileptique réfractaire : épidémiologie, aspects cliniques et gestion d'une tempête épileptique persistante

L'état de mal épileptique réfractaire (EME) est un état qui compromet le pronostic vital par une activité épileptique persistante malgré le déploiement d'une prise en charge de première et de deuxième ligne. On pense que les pronostics sérieux sont avant tout fondés par les motifs sous-tendant l'EME. Malgré la morbidité et la mortalité élevées, les études randomisées multicentriques d'options thérapeutiques prometteuses font défaut, de sorte que la prise en charge et le pronostic posent des défis jusqu'ici irrésolus. La prise en charge neuro-intensive des patients avec un EME comprend

un concept thérapeutique adapté à l'activité de crise électro-encéphalique changeante ou persistante qui sera de préférence surveillée par monitorage EEG-vidéo de longue durée. Les autres mesures dépendront de l'étendue de la baisse de vigilance et de la restriction des fonctions vitales. Les interactions potentielles de divers anticonvulsifs avec d'autres médicaments sont souvent complexes et constituent une difficulté supplémentaire dans les soins aigus aux patients EME.

Ce travail de synthèse présente un bref survol des aspects épidémiologiques, cliniques, diagnostiques et pronostiques de l'EME et met en évidence des stratégies thérapeutiques médicamenteuses.

Mots clés : état de mal épileptique réfractaire, mortalité, rétablissement, étiologie, soins neuro-intensifs

Introduction

Refractory status epilepticus (RSE) is a common and life-threatening neurologic emergency in intensive care units (ICUs), characterized by high morbidity and mortality. It heralds a prolonged hospitalization and worse prognosis than treatment-responsive status epilepticus (SE) [1 - 3]. A globally accepted definition of RSE has not yet been evolved, although it is widely recognized and discussed as an entity. The proposed criteria vary in the number of antiepileptic drugs (AEDs) failed – ranging from 2 [4 - 7] to 3 [8 - 10] agents and in the duration of SE proposed between less than 1 hour [4, 10, 11] to 2 hours [5, 7]. However, RSE is mostly defined as a persistent seizure activity after initiation of a first-line (i.v. benzodiazepines) and one second-line AED (mostly phenytoin, valproate, levetiracetam, or phenobarbital), while others suggest a duration of SE of more than 60 minutes [3, 6]. In addition, the most severe form of RSE was defined by Holtkamp et al. as a persistent seizure activity after high dose i.v. anesthetics (i.e., "malignant SE") [1]. Despite the clinical and socioeconomic impact of RSE, knowledge regarding diagnosis and management relies mostly on expert opinions, small case series, and few retrospective studies [1 - 3, 12 - 14]. These reports suggest an incidence of RSE among patients with SE of up to 43%, with the need of neurocritical care and pharmacologic coma induction in almost all RSE patients. In the Veteran Administrative Cooperative study, first antiepileptic treatment regimen was successful in 56% of patients with "overt" SE, but in only 15% of those with more "subtle" SE [15]. Refractory SE is associated with increased length of hospital stay and functional disability and morbidity [3]. One recent prospective study on 29 RSE episodes in a tertiary clinical setting reported a 40% case fatality rate [16].

Incidence and prevalence

Recurrent SE and RSE are frequent neurologic problems in emergency departments and ICUs. In a study of Rossetti et al. RSE was more prevalent and incident than recurrent SE [2]. In the United States the estimated incidence of SE is reported as 41/100'000 in a mixed Caucasian and Afroamerican population [17] while in an almost exclusively white population it yielded the same 15 to 20/100,000 per year as reported in studies from central Europe [18 - 21]. With estimates of the frequency of RSE in patients with SE ranging from 30% to 45% [1, 3], the annual incidence lies between 5 and 9/100,000 RSE in Europe.

Clinical aspects

Etiology

The majority of episodes of SE are thought to develop without a prior history of epilepsy, and they are almost always secondary to an underlying structural or metabolic-toxic pathology [22]. The etiology of RSE remains more obscure. The presumed etiologies described in literature vary; however, extensive investigations on the underlying causes commonly fail to identify them. In a recent study from Novy et al., potentially fatal etiologies (i.e., causes that per se may lead to death) were highly related to RSE development [16]. Anoxia (most likely with hypoxic-ischemic encephalopathy) and infections were predominant in another study on detection and treatment of 29 RSE patients [23]. In two other studies, encephalitis and toxic/metabolic problems were the predominant etiologies [1, 24]. Mayer et al. identified NCSE and focal motor seizures at onset to be independent risk factors for RSE in a retrospective cohort study [3] and Holtkamp and colleagues identified encephalitis as a risk factor for "malignant SE" typically in young patients [1]. In most cases of new onset RSE, the preceding febrile status suggests a possible infectious or inflammatory etiology [25]. However, there are also cases without signs of inflammation with normal cytokines, acute phase proteins, and no signs of pleocytosis in the serum and the cerebrospinal fluid as well as lacking evidence of inflammation in brain autopsies. In addition, in some patients the lack of response to probatory application of IVIG questions this hypothesis [25]. The frequently observed mild CSF pleocytosis also has to be questioned, as it can be observed in patients with different types of SE that are treatment responsive [26]. Immune mechanisms are increasingly recognized as important factors contributing to refractory epileptic activity. Cytokines released during seizures include IL-1beta, IL-6, and TNF-alpha which enhance excitatory mechanisms. Chemotaxins and adhesion molecules may attack the blood-brain barrier which upon opening

increases permeability for ions and proteins as well as facilitated transmigration of inflammatory cells reinforcing sustained epileptic activity [27 - 29]. RSE associated with intrathecally produced anti-glutamic acid decarboxylase antibodies may serve as a clinical example how autoimmune reactions of the adaptive immune system can result in treatment refractory seizure activity [30]. Similarly, recent animal models on RSE demonstrated a reduction of seizures and drug resistance after inhibiting the biosynthesis of interleukin-1beta by blocking of caspase-1 [31]. Furthermore, experimental studies of RSE in animal models and clinical experiences in humans identified selective overexpression of transmembranous proteins (like P-glycoprotein) in cells at the blood-brain barrier that extrude xenobiotics like AEDs and cytostatic drugs leading to insufficient AED levels in the brain despite correct dosage and eventually may prolong epileptic activity [32, 33]. In some cases, inhibition of P-glycoprotein by verapamil successfully terminated otherwise uncontrolled RSE [34 - 36].

New onset refractory status epilepticus

New onset RSE (NORSE) is a syndrome described in adult patients who present with severe generalized seizures of unclear etiology [25, 37 - 41]. In children and adolesecents, a similar condition exists which is additionally associated with a prodromal febrile illness, called fever-induced refractory epileptic encephalopathy syndrome (FIRES) [42 - 44]. These forms of RSE are known to have poor response to AEDs leading to high morbidity and mortality and morbidity. Little is known on the incidence and prevalence of this subgroup of RSE, as there exist only few case reports.

Acute management

In general, the development of RSE can be prevented best by early termination of SE – achieved with rapid treatment escalation. Despite the deleterious outcome of RSE in the vast majority of cases, there are no randomized controlled trials. Most experience derives from treatment with coma-inducing drugs such as pentobarbital, midazolam and propofol [7, 11, 24, 45 - 48]. Recent studies suggest a possible role of newer AEDs such as topiramate given by percutaneous gastrostomy [49 - 58] and i.v.-lacosamide [59 - 64]. In the early Veteran Administrative Cooperative study patients with refractoriness to first-line AEDs had an aggregate response rate of 7% to second-line AEDs and only 2% to third-line agents [15]. Only 5% of patients with SE who did not respond to lorazepam and phenytoin therapy, responded to phenobarbital administration [15, 65]. Besides pharmacologic treatment with AEDs and anesthetic drugs, general supportive management is important.

General management

The main goal is to stop seizure activity with a stepwise regimen tailored to the change or persistence of electrographic seizure activity [66]. Therefore, continuous video-EEG monitoring is essential. Underlying disorders should be addressed and side effects related to the treatment monitored frequently, and managed immediately.

Supportive management has to be adapted to the different clinical presentations of RSE. The extent of patient support should be adapted to the degree of altered consciousness and impairment of vital functions. Control of the airway is vital as apnea can occur with generalized seizures, and intubation may be required. Furthermore, potential interactions of several anticonvulsive drugs with other medication are often complex and challenging [67, 68].

Pharmacological treatment

After failure of benzodiazepines (i.e., first-line drugs) and a first second-line AED (e.g., valproic acid, phenytoin, levetiracetam) that will not be discussed here, third-line treatment is administered [69]. The use of third-line drugs such as pentobarbital, midazolam, propofol, and phenobarbital usually results in iatrogenic coma, which necessitates protection of the airways by intubation and mechanical ventilation. Complications, such as cardiotoxicity from phenobarbital and pentobarbital, severe hypotension from thiopental, or hepatotoxicity and metabolic acidosis with rhabdomyolysis and cardiac failure (i.e., propofol infusion syndrome [70 - 72]) from propofol represent additional hazards. In case series where barbiturates were used, mortality of RSE was 20% [73] to 55% [74]. Treatment with propofol yielded a mortality ranging from 7% [75] to 26% [24] and 88% [5]; and in patients receiving continuous drips with midazolam, mortality was 17% [7] to 69% [11]. However, the cohorts are relatively small, treatment monitoring and distribution of etiologies inhomogenous, limiting the generalizability of these results. A systematic review evaluated the efficacy of pentobarbital, midazolam, and propofol for RSE treatment [48]. Regarding short-term treatment failure, pentobarbital was more effective (failure in only 8%) than midazolam or propofol (failure in 23%; $p<0.01$). Breakthrough seizures and the need for additional continuous i.v. AEDs occured less often on pentobarbital than in the two others. The single prospective, randomized trial that tried to compare propofol with thiopental (European centers) or pentobarbital (US centers) calculated to include 150 patients for sufficient statistical power to detect a significant difference between the two drugs; however it had to be stopped after 3 years because of difficult recruitment (24 patients only) [76]. In a retrospective investigation on the effects of various combi-

nations of i.v. anesthetic drugs, no significant difference in outcomes were identified among single or combined regimens [2]. As a consequence, there are no clear guidelines as to which agent should be used first and how long and to which effect i.v. anesthetics should be titrated (burst-suppression versus complete seizure reduction).

Rescue therapy

There is no standard treatment of super-refractory or "malignant" SE. Ketamine has occasionally been successfully used in RSE [77 - 80]. It was effective in RSE when midazolam, propofol, and phenobarbital failed [80] and when midazolam, propofol, and thiopental where insufficient [77]. In addition, ketamine induces hypertension, which may be helpful when third-line treatment led to severe hypotension [78, 79].

New promising treatment options

In a small case series, RSE stopped after the administration of lacosamide in all 7 patients in the first 24 hours [59], while in another study RSE could be terminated after lacosamide in 17 patients, while 22 patients required further treatment escalation [81]. In contrast, Goodwin et al. reported a complete lack of response to lacosamide in 9 patients [82].

Topiramate is another promising treatment option for RSE. Besides several reports on topiramate in pediatric RSE [51-54] there are only few case series of adult patients [49, 50, 57]. In a recent report of Synowiec et al. on 35 RSE patients with adjunctive treatment with topiramate, the cumulative cessation of RSE was 11% at one day, 29% at two days, and 40% at three days. A less similar response rate was reported by Stojanova and colleagues where RSE stopped after adjunctive treatment with oral topiramate in 36% of 11 patients [57]. In a recent study on topiramate as an adjunctive treatment of RSE, its response rate after administration as the third AED was 86%, and 67% after administration as the fourth, fifth, sixth or seventh AED when the groups of successfully and probably successfully treated patients were pooled [58]. RSE was terminated in 71% of patients within 72 hours after first administration of topiramate.

Recently some promising treatment regimens for RSE, such as inhaled anesthetics [83] (which yet should be used with caution [84]), surgery [85], electroconvulsive therapy [86], hypothermia [87], vagus nerve stimulation [88], and the ketogenic diet [89] have been reviewed. A very recent and comprehensive overview is presented by Shorvon and Ferlisi [90].

Outcome

Mortality

In a systematic review, RSE was associated with high mortality of almost 50% and a significant morbidity [48] with only up to one third of patients returning to their pre-morbid condition. Mortality ranges from 16% to [3] to 88% in the literature [5]. The Veteran Administrative Cooperative study showed that short-term outcomes at 30 days post treatment were worse for patients with "subtle" SE compared to patients with "overt" SE [15]. Overall, at 30 days after treatment, 8.8% of patients were discharged, 26.5% were still in the hospital, and 64.7% had died. Other studies observed less high mortality rates between 16 to 20% [1-3]. In a study of Rossetti et al., short-term outcome was independent of specific coma inducing agents used and the extent of electrographic burst suppression, suggesting that the underlying cause represents its main determinant [2].

The effect of treatment delay

One of the most important and modifiable factors that are associated with RSE outcome is the delay of treatment initiation. However, it is challenging to determine the impact of treatment delay on outcome of RSE because it is confounded by the etiology of SE. Nevertheless, there are few pediatric studies devoted to this question. Treatment delay of less than 30 minutes did not affect the response rate in a study of 157 children with RSE, while treatment initiation beyond 30 minutes was associated with delayed seizure control [91]. In another study of 27 children treated with benzodiazepines as first-line AED and phenytoin or phenobarbital as second-line AEDs, termination of RSE could be achieved in 86% of patients when SE duration was less than 20 minutes, and only in 15% when seizure duration exceeded 30 minutes [92]. One early study in the 1980s on 154 adults with SE showed similar results [10]. Response to the initial treatment occurred in 80% of patients when treatment was initiated within the first 30 minutes, but in only 40% when treatment began more than 2 hours after SE onset.

Influence of different types of status epilepticus

Evidence for the influence of SE types on RSE cessation and outcome is limited. In one of our recently reported studies on 111 patients with SE and RSE of various severity and duration, those patients with CSE had a more favorable outcome than patients with other types of SE [93]. However, this association was no longer present when the comparison of SE types was per-

formed in the subgroup of patients with RSE.

Influence of different etiologies

Hypoxic-ischemic encephalopathy after cardiac arrest is known for having a substantial and deleterious influence on mortality [94 - 100]. However, in most of the studies it remains unclear to what extent RSE, hypoxic-ischemic brain damage, and early discontinuation of life-support in the light of the patient's and/or relative's preference with regard to end-of-life decisions, have contributed to this poor outcome [101]. In a recent study by Swisher et al. on 23 middle- to old-aged RSE patients (mean age 57) with metastatic brain tumors, cessation of RSE was 70% and mortality 0%. Although their AED regimen was intentionally chosen to minimize the need for intubation, complications, and short-term mortality, the yet high rate of successfully stopped RSE is surprising [102]. These results contrast with those of other studies; possibly because in most studies size and localization of brain tumors are often not provided despite their major impact on epileptogenesis and outcome [103, 104].

To conclude, diagnosis and therapeutic monitoring of RSE are essentially dependent on clinical examination and continuous or repeated intermittent EEG recordings. The treatment of RSE itself remains challenging due to the mostly underlying severe cause in an already critically ill patient, important co-morbidities, co-medications, and the risks associated with further interventions (i.e., intubation, mechanical ventilation, prolonged coma). Additionally, the current data on treatment are very inhomogeneous, often derived from small, retrospective single-center cohorts and therefore of low class of evidence. In this situation, most caregivers decide on the bases of individualized therapeutic plan, although guidance by informal recommendations may be helpful as recently emphasized by Shorvon et al. [90]. The management of RSE should include seizure suppression, treatment of underlying causes, the avoidance of iatrogenic complications through co-morbidities and co-medications, and sound neurointensive care.

Conflicts of interest

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Antiepileptic Medication in the ICU: Which Compounds Do We Need?

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Summary

The aim of this contribution is to offer an overview of the main antiepileptic treatment options used in the intensive care unit (ICU). Benzodiazepines (BDZ) are gamma-amino-butyric-acid (GABA) receptor agonists, improving the inhibition of signal transmission. Commonly used intravenous (IV) BZD include diazepam (DZP), midazolam (MDZ), lorazepam (LZP) or clonazepam (CLZ). The main problem with BZD is the phenomenon of tachyphylaxia, which may result in breakthrough seizures. Classical AED such as phenytoin (PHT), valproate (VPA), phenobarbital (PB), and more recently newer AED such as levetiracetam (LEV) and lacosamide (LCM), are also available in IV formulations. At times, the antiepileptic management includes administration of general anesthetics, mostly thiopental/pentobarbital (THP), propofol (PRO), or midazolam (MDZ). Further pharmacological, such as other anesthetics, as well as topiramate (TPM) or pregabaline (PGB) by nasogastric tube, or non-pharmacological treatments may also come at play in selected situations. Despite all these therapeutic options, the management seizures and status epilepticus in the ICU has a low level of evidence, and there is a lack of randomized controlled trials comparing the different options.

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Key words: Epilepsy, seizure, status epilepticus, treatment, intensive care unit

Antiepileptische Medikation in der Intensivpflege: Welche Antiepileptika brauchen wir?

Das Ziel dieses Beitrags ist es, einen Überblick über die wichtigsten antiepileptischen Therapiemöglichkeiten in der Intensivpflege zu geben. Benzodiazepine sind GABA-Rezeptor-Agonisten, welche die Hemmung der Signalübertragung verbessern. Die am häufigsten intravenös verwendeten Benzodiazepine sind Diazepam, Midazolam, Lorazepam oder Clonazepam. Das Hauptproblem mit Benzodiazepinen ist das Phänomen der Habituation, welche manchmal zur Dosiserhöhung führt. Klassische Antiepileptika wie Phenytoin, Valproat, Phenobarbital, und seit kurzem auch neuere wie Levetiracetam und Lacosamid, sind ebenfalls in intravenöser Form erhältlich. Manchmal müssen zusammen mit den Antiepileptika auch allgemeine Anaesthetika verabreicht werden, dann meistens Thiopental/Pentobarbital, Propofol oder Midazolam. In speziellen Situationen kommen ausserdem weitere, nichtsedierende Antiepileptika wie auch Topiramat oder Pregabalin durch einen nasogastrischen Zugang zum Einsatz. Trotz all dieser therapeutischen Optionen ist die optimale Behandlung von Anfällen und Status epilepticus in der Intensivpflege noch wenig erforscht, und es besteht ein Mangel an randomisierten kontrollierten Studien, welche diese verschiedenen Massnahmen vergleichen.

Schlüsselwörter: Epilepsie, Anfall, Status epilepticus, Behandlung, Intensivstation

Médicaments antiépileptiques dans l'Unité de Soins Intensifs : Quels composés avons-nous besoin?

L'objectif de cette contribution est d'offrir une vue d'ensemble des principales options de traitement antiépileptique utilisées dans l'unité de soins intensifs (USI). Les benzodiazépines (BDZ) sont des agonistes des récepteurs de l'acide gamma-amino-butyrique (GABA), contribuant à l'inhibition neuronale. Les BDZ plus couramment utilisés par voie intraveineuse (IV) comprennent le diazépam (DZP), le midazolam (MDZ), le lorazépam (LZP) ou le clonazépam (CLZ). Le principal problème avec les BZD est le phénomène de tachyphylaxie. Les AED classiques tels que la phénytoïne (PHT), le valproate de sodium (VPA), le phénobarbital (PB), et plus récemment des nouveaux AED tels que le lévétiracétam (LEV) et la lacosamide (LCM), sont également disponibles dans des formulations IV. En outre, la thérapie antiépileptique comprend parfois l'administration d'anesthésiques généraux, principalement le thiopental/pentobarbital (THP), le propofol (PRO), ou le midazolam (MDZ). D'autres approches pharmacologiques, comme d'autres anesthésiques, ainsi que le topiramate (TPM) ou prégabaline (PGB) par sonde naso-gastrique, peuvent se rendre utiles dans quelques situations particulières. En dépit de toutes ces options thérapeutiques, le traitement des crises et de l'état de mal épileptique à l'USI a un très faible niveau d'évidence.

Mots clés : Epilepsie, crise, status epilepticus, traitement, unité de soins intensifs

Introduction

Seizures represent a common complication in patients treated in the ICU, not only with neurological, but also with other medical or surgical problems, and may range up to 50% for selected groups of patients; most events are nonconvulsive (reviewed in [1] and in the contribution of JW Lee in this *Epileptologie* issue). Status epilepticus (SE) represents a frequent challenge in the Intensive Care Unit (ICU), with an estimated short-term mortality varying between 3.45% to 22% in different assessments, depending basically on the age and the underlying etiology [2, 3]. The optimal treatment in this setting involves both the acute cessation of ictal activity and preventing seizure recurrence, ideally by removing or correcting the trigger and providing pharmacological prophylaxis [4]. The aim of this article is to review the main antiepileptic drugs (AEDs) used in the ICU.

The treatment of the different phases of repeated seizures and SE has been extensively reported in the literature [5 - 8], and there are several (mostly similar) protocols advocating the initial use of benzodiazepines (BZD), followed by classical AEDs administration, and finally by anesthetic agents, in successive phases as follows:

– **Early-established status (<30-60min)**
- First line: IV BDZ (mostly midazolam, lorazepam, or clonazepam)
- Second line: IV classical AED (such as phenytoin, valproate, phenobarbital), or more recently levetiracetam and lacosamide

– **Refractory status (>30-60 min)**
- Third line: IV drips of thiopental/pentobarbital, propofol, or midazolam
- Further pharmacological (such as other anesthetics, topiramate or pregabaline by nasogastric tube) or non-pharmacological treatments

First line treatment: Benzodiazepines

These compounds penetrate rapidly into the brain, are potent gamma-aminobutyric acid (GABA) receptor agonists, and thus improve local inhibition of signal transmission. They represent the drugs of first choice for SE and seizures associated with post-anoxic insult or alcohol withdrawal. The main problem with BZD is the phenomenon of tachyphylaxis, resulting in possible breakthrough seizures after an initial response [9]. Commonly used BZD include diazepam, midazolam, lorazepam or clonazepam, each compound having its pharmacokinetic profile.

- **Diazepam (DZP)** is a highly lipophilic drug, which rapidly redistributes from the serum into fat tissue. The anticonvulsant duration lasts less than 30 minutes, whereas its elimination takes many hours. Such kinetics may result in brief seizure control, yet a prolonged sedative effect if large dosages are administered. DZP is rarely used in our environment because of the above mentioned issue, the recommended loading doses range from 0.1 to 0.25 mg/kg.

- **Midazolam (MDZ)** is also a highly lipophilic and short acting drug (2 to 4 hours), and is cleared by the liver – via CYP 3A4 – much more rapidly than DZP, resulting in better correlation between drug effect and clearance [10]. However, MDZ exhibits use-dependent pharmacokinetic changes that may be important clinically in situations that require prolonged therapy, raising the elimination half-life to 50 hours [11]. The efficacy of intramuscular (IM) MDZ versus intravenous (IV) lorazepam as a first-line treatment in the pre-hospital setting has been recently demonstrated in a randomized non-inferiority clinical trial. It adds the advantage of its ease of administration and practicality for paramedic use [12]. Therefore, MDZ 0.15 mg/kg IM is one of the drugs of choice for immediate seizure control, especially in the pre-hospital setting, with a maintenance dose of 0.1–0.4 mg/kg/h.

- **Lorazepam (LZP)**, a compound with greater water solubility that prolongs its serum half-life, is clinically effective for 6-8 hours, and has an elimination half-life of about 20 hours. In a randomized controlled trial, LZP was found to be superior to DZP, phenytoin, and phenobarbital alone in terminating clinical and EEG seizures [13]. The duration of effect reflects LZP low hepatic clearance, small volume of distribution, and absence of active metabolites (unlike DZP and MDZ), with a low risk of drug interactions [14].

- **Clonazepam (CLZ)** is extensively metabolized in the liver into pharmacologically inactive metabolites. It has an elimination half-life of 19 - 60 hours, is largely bound to plasma proteins and it passes easily through the blood-brain barrier, with levels in the brain corresponding with levels of unbound CLZ in the serum. However, plasma levels seem very unreliable, as they can vary as much as tenfold between different patients [15]. The optimal loading dose for the initial treatment of seizures is 0.015 mg/kg IV. This compound is basically used in Europe, especially in French-speaking countries, and is unavailable as intravenous formulation in the US.

Second line treatment: Antiepileptic drugs

If patients are not responsive to BZD, the next step is adding first, second or even third generation AEDs available in IV formulations. Only the oldest drugs have a consensual approval for the second-line treatment of SE; however, the more recent AEDs may offer the advantage of a better tolerance and ease of administration.

- **Phenobarbital (PB)** is the oldest AEDs still in use, as it was commercialized exactly one century ago. It binds to the $GABA_A$ receptor, extending the duration of GABA-mediated chloride channel openings. An IV PB bolus remains an effective second-line drug option, although this drug is used less frequently in recent years due to adverse effects, including respiratory depression, sedation, and hypotension (especially with rapid infusion rates and previous treatment with IV BZD). Nevertheless, the prolonged effect may be advantageous. The loading dose is 15 to 20 mg/kg IV and the recommended target serum level is 30-40 mg/L. PB dosage range from 40 to 140 mg/kg/day. A number of drugs can influence the serum concentration of PB, and on its turn PB is a potent enzyme inducer, which does not make it recommendable in polymedicated patients [16].

- **Phenytoin (PHT)** mostly acts by blocking voltage-dependent neuronal sodium channels. Its metabolism takes place in the liver through a non-linear kinetics enzyme. Both PHT and the pro-drug fosphenytoin (which has the advantage of better local tolerability but not available in Switzerland) can be administered intravenously with doses roughly equivalent to the oral route, usually pursuing plasma concentrations between 12 to 20 mg/L. In the ICU, the loading dose is 20 mg/kg (maximal dript rate, 50 mg/min), and it is mandatory to perform a continuous hemodynamic monitoring due to the risk of significant bradyarrhythmias or hypotension. A great number of drugs can influence the serum concentration of PHT, which also is a potent enzyme inducer and has a high protein-binding. Renal failure impairs the protein-binding of PHT and so the pharmacologically active free concentration may increase relative to the total concentration. The major systemic side effects include gingival hypertrophy, hypertrichosis, rash, Stevens-Johnson syndrome, lymphadenopathy and neurotoxic side effects. It is important to remember that PHT may also aggravate absence and myoclonic seizures in Idiopathic Generalized Epilepsy (IGE).

- **Valproate (VPA)** is a broad-spectrum AED with multiple mechanisms of action, including blockage of voltage-dependent sodium channels, increase of GABA concentrations, and suppression of T-type calcium currents. As PHT, VPA is tightly protein-bound and is metabolized in the liver. Therapeutic concentrations are usually in the 50 to 100 mg/L range. Accumulating evidence suggests that IV VPA can be safely infused at rates up to 10 mg/kg per minute and doses of up to 30 mg/kg [17]. A large number of drugs affect the serum level of VPA, which is an enzyme inhibitor. Side effects of VPA include nausea, vomiting, hair loss, tremor, weight gain, obesity, insulin resistance, thrombocytopenia or other coagulation disturbances, subclinical hypothyroidism, pancreatitis and polycystic ovarian syndrome. Indeed, VPA-exposure in utero is associated with major malformations and cognitive impairment; thus, it should be avoided when possible in women of childbearing age and pregnancy. Finally, VPA-related hyperammonemic encephalopathy causes lethargy, increased seizures, and rarely coma and death.

- **Levetiracetam (LEV)** is a more recently developed broad spectrum AED whose mechanism of action includes the binding to the synaptic vesicle protein SV2A, modulating synaptic transmission through alteration of vesicle fusion. Its catabolism (renal excretion and hydrolysis) is independent of the cytochrome CYP450 system, avoiding the potential pharmacokinetic interactions with AEDs or other compounds. However, the dosage must be adjusted for patients with renal impairment. IV formulation confers a relatively rapid onset of action [18], at a loading dose of 30 mg/kg, administered in 5-10 minutes. LEV does not require a titration period, and the IV formulation is bioequivalent to oral tablets; nor recommended serum level known for the ICU setting. There is a lack of randomized controlled trials (RCT) comparing the efficacy of the different AEDs for second line treatment of SE; nevertheless, a tendency to a lower responder rate with LEV compared to PHT or VPA (used as second-line compounds) has been described [19]. Otherwise, a recent randomized pilot study has shown that LEV is comparable to LZP for the first line treatment of SE [20], offering an alternative in patients with respiratory compromise and hypotension. Most adverse events associated with LEV are mild to moderate in intensity and include fatigue, somnolence, dizziness, while psychiatric complaints may be significant, especially (but not only!) in intellectually disabled patients or subjects with baseline behavioral problems [21].

- **Lacosamide (LCM)** has become available as the second IV formulation of a new AED based on bioequivalence to the oral formulation, with also a low potential of drug interactions. More than 100 patients who received IV LCM for a SE or repeated seizures have been reported, mostly using loading doses of 200-400mg, with an overall success rate of 67% [22]; this very high proportion may nevertheless

represent a publication bias. As for LEV, there is a lack of prospective studies or RCT, and target serum levels are not known.

Third line treatment: General anesthetics

When the patient does not respond to the first and second line treatment, a refractory status epilepticus (RSE) is considered, and, especially in cases of generalized-convulsive SE, the therapeutic management requires rapid admission to the ICU and administration of general anesthetics under continuous EEG monitoring and mechanical ventilation [5 - 8] (**Tables 1 and 2**). The prevalence of RSE – compared to all those in SE – varies from 23% to 43%, in prospective and retrospective cohorts respectively [23, 24]. Despite the high mortality (16 - 39%) and morbidity, the adequate management is not evidence-based, and the treatment is limited by the different side effects, especially regarding hypotension.

- **Propofol (PRO, 2,6-diisopropylphenol)** is a frequently used compound, in alternative to barbiturates, for the management of patients with RSE. In our institution, PRO is considered the first option at a loading dose of 2 mg/kg and a maintenance of <5 mg/kg/h, administered together with MDZ (which is described in the above section) at 0.2 mg/kg/h in order to reduce its toxicity (which correlates with the total dose). Its mechanism of action includes a modulation of $GABA_A$ receptors at a site different from that targeted by BZDs and barbiturates, a subcortical dopamine agonism (which explains its occasional association with the appearance of dystonia or other abnormal movements) and a glycine antagonism, while its anti-glutamate properties are debated. Metabolized in the liver, it is highly lipid soluble and has very short distribution and elimination half-lives (2-4 min and 30-60 min, respectively). It is important to avoid prolonged infusions (>48 h) for the risk of the so-called propofol-infusion syndrome (PRIS),

Table 1: Pharmacokinetic and outcome of main anesthetic agents (Rossetti 2007 [33], Shorvon & Ferlisi 2012 [4], Claassen 2002 [7]).

	THP	PRO	MDZ
Mechanism of action	$GABA_A$>NMDA> Ca channels	$GABA_A$ >> NMDA, Ca and Na channels	$GABA_A$
t ½ (Half life)	< 36h	0.5-2h	1.5-50h
Cumulation	+++	±	++
Tachyphylaxis	-	±	+++
Hypotension	+++	++	+
Loading dose	2 mg/kg	2 mg/kg	0.2 mg/kg
Maintenance	3-5 mg/kg/h	2-10 mg/kg/h	0.05-0.6 mg/kg/h
Control of seizures (SE)	64%	68%	78%
Breakthrough seizures (SE)	0-12%	1-15%	3-51%
Withdrawal seizures (SE)	9-43%	6-46%	<1-63%
Therapy failure because of side-effects (SE)	3%	6%	<1%
Mortality (SE)	19-48%	8-52%	2-46%

SE=status epilepticus

Table 2: Advantages and disadvantages of anesthetics used in SE (Modified after Shorvon & Ferlisi 2012 [4])

	Advantages	Disadvantages
Thiopental/pentobarbital	• Strong antiepileptic action • Long clinical experience • Theoretical neuroprotective effects	• Significant accumulation, long recovery time, hepatic metabolism, autoinduction, drug-drug interactions • Cardiovascular and respiratory depression resulting in hypotension, apnea and airway obstruction • Pancreatic and hepatic toxicity • Possible immunological inhibition
Midazolam	• Antiepileptic action • Only BZD with pharmacokinetic properties suitable for prolonged infusion without accumulation	• May be less effective than other anesthetics • Hypotension, cardio-respiratory depression • Risk of hepatic and renal impairment • Risk of tolerance and breakthrough seizures • Use-dependent pharmacokinetic changes • IM MDZ suitable for first-line treatment of SE
Propofol	• Good pharmacokinetic properties • No drug interactions • Less hypotension and cardio-respiratory depression	• Propofol infusion syndrome (PRIS) • Occasional appearance of involuntary movements
Ketamine	• No cardiodepressant or hypotensive action • Anti-glutaminergic action	• Very limited published experience • Possible neurotoxicity

a potentially fatal complication characterized by hyperlipidemia, rhabdomyolysis (including sever myocardial dysfunction), and lactic acidosis, particularly described in young children, patients with severe brain-injury, and under co-medication with steroids or catecholamines [25].

- **Tiopental (THP)** is now mostly considered in very severe SE cases. As a barbiturate, THP is a non-selective agent that binds to an entire superfamily of ligand-gated ion channels, of which $GABA_A$ receptor agonism represents the most significant, but also displays glutamate antagonism. It is a highly lipophilic molecule which rapidly crosses the blood brain barrier, with a significant sequestration in fat tissue, leading to marked accumulation. Once redistributed, the free fraction in the blood is metabolized in the liver, mainly to pentobarbital. THP causes cardiovascular and respiratory depression resulting in hypotension, apnea and airway obstruction; paralytic ileus may represent a severe problem, and immunological inhibition is also discussed [26].

The recommended loading dose is 2-3 mg/kg and the maintenance dose is 3-5 mg/kg/h. It is contraindicated in hepatic disease, myasthenia gravis, porphyria, severe hemorrhage or burns, severe cardiovascular disease and adreno-cortical insufficiency.

- **Inhalational anesthetic agents (isoflurane and desflurane)**: The antiepileptic effects are likely due to potentiation of inhibitory postsynaptic $GABA_A$ receptor-mediated currents, and a modulation in thalamocortical pathways. The pharmacokinetic and pharmacodynamic properties (rapid onset of action and elimination) make them effective and easy-to-titrate agents [27]. However, there is a list of potential complications including hypotension, apart from the challenges of providing a tight environment on the patient, to prevent inhalation of the compounds by the caregivers. It has been occasionally reported in refractory SE.

- **Ketamine:** The progressive loss of gabaergic inhibition with ongoing seizure activity together with the increase of N-methyl-D-aspartate (NMDA) expression may limit the efficacy of agents with predominantly GABAergic mechanisms of action. Ketamine, an NMDA antagonist, has therefore been used to terminate seizure activity in highly refractory cases and, due to its sympathomimetic properties, hypotension associated with other anesthetic agents is prevented [28]. The loading dose is 1-3 mg/kg and the maintenance dose is up to 5-10 mg/kg/h, administered together with BDZ in order to prevent neurotoxic effects. There are surprisingly limited data regarding its use in SE.

Oral AEDs may represent further add-on treatment options for patients not responding to conventional IV AEDs. In particular, topiramate (TPM) and pregabaline (PGB), two second-generation AEDs with good oral bioavailability and fast titration, may be safely administered via nasogastric tube. However, the reported rate of efficacy seems to be low [29 - 31]. There are also several other possible non-pharmacological treatments, such as hypothermia, magnesium, pyridoxine (especially in infants), immunotherapy, ketogenic diet, emergency neurosurgery, electroconvulsive therapy, cerebrospinal fluid drainage, vagal nerve stimulation and deep brain stimulation, but in all cases the efficacy has been described only in individual patients [5 - 7].

In conclusion, despite all the different therapeutic approaches, the adequate management of repeated seizures, SE and RSE in the ICU remains at a low level of evidence [4 - 7, 32]. It is therefore important to address this issue in future by well-designed clinical trials.

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Electroencephalographic Patterns in Coma: When Things Slow Down

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Summary

Electroencephalography (EEG) has long been used in evaluating comatose patients, and is being increasingly found to uncover patterns of prognostic significance, reveal subclinical seizure activity and provide data during treatment in which patients are paralyzed. Some EEG patterns reveal increasing degrees of cerebral compromise with progressive slowing of the background frequencies, while others can be explored for reactivity to external stimuli for prognostic purposes. With some etiologies, particular patterns carry grave import such as flat or highly suppressed patterns, or unreactive alpha, delta or burst-suppression patterns. Others including beta and triphasic patterns may herald a good prognosis, depending on cause. A working knowledge of these EEG patterns with their extenuating features can supplement the imaging and clinical examination information available to the treating physician.

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Key words: Alpha coma, beta coma, theta coma, continuous high-voltage delta coma, spindle coma, burst-suppression, low-voltage, slow and nonreactive coma, electro-cerebral inactivity, periodic EEG coma patterns, electroencephalography, neurocritical care

EEG-Muster im Koma: Wenn alles langsamer wird

Elektroenzephalographie (EEG) wird seit geraumer Zeit zur Evaluation von komatösen Patienten eingesetzt. Zunehmend werden prognostisch relevante EEG-Muster, subklinische epileptische Anfälle und therapierelevante informationen in paralysierten Patienten identifiziert. Einige Muster weisen mit einer zunehmenden Verlangsamung auf eine progrediente zerebrale Kompromittierung hin, während andere Muster besonders durch deren Reaktivität auf externe Stimuli einen prognostischen Wert haben. Einige EEG-Veränderungen haben eine gravierende Bedeutung in Zusammenhang mit bestimmten Ätiologien, wie beispielsweise eine deutliche Kurvenabflachung, eine ausgeprägte Supprimierung, ein areagibles Alpha-, ein Delta- oder „burst-suppression"-Muster. In Abhängigkeit von der zu Grunde liegenden Ursache stehen andere EEG-Veränderungen meist in Zusammenhang mit einer eher günstigen Prognose, so zum Beispiel eine Betaaktivität und das Auftreten von triphasischen Wellen. Ein fundiertes Wissen über diese EEG-Muster und deren zusätzliche Merkmale kann eine wichtige Ergänzung zu klinischen und bildgebenden Untersuchungsbefunden für den behandelnden Kliniker sein.

Schlüsselwörter: Alpha-Koma, Beta-Koma, Theta-Koma

Les tracés EEG à l'état comateux : quand tout ralentit

L'électroencéphalographie (EEG) est utilisée depuis pas mal de temps pour évaluer les patients comateux. De plus en plus de tracés EEG importants pour le pronostic, révélateurs de crises épileptiques subcliniques et indicateurs de pistes thérapeutiques sont identifiés chez les patients paralysés. Certains tracés permettent de conclure à une compromission cérébrale progrédiente en raison d'un ralentissement progressif, tandis que d'autres tracés ont une valeur pronostique, en particulier à cause de la réactivité aux stimuli externes. Certaines modifications de l'EEG sont significatives en relation avec des étiologies déterminées, par exemple un aplatissement net de la courbe, une suppression marquée, un tracé alpha non réactionnel, un tracé delta ou de burst suppression. Selon la cause sous-tendante, d'autres modifications de l'EEG seront des indices pronostiques plutôt favorables, par exemple un tracé bêta ou l'apparition d'ondes triphasiques. Une connaissance approfondie de ces tracés EEG et de leurs caractéristiques supplémentaires peut apporter aux cliniciens un complément d'informations précieuses pour étayer les résultats d'un examen clinique ou d'imagerie.

Mots clés : Coma de niveau alpha, coma de niveau bêta, coma de niveau thêta, coma de niveau delta à haut vol-

tage en continu, coma de spindles, burst suppression, bas voltage, coma lent et non réactionnel, inactivité électro-cérébrale, tracés EEG des activités périodiques à l'état comateux, électroencéphalographie, soins neurocritiques.

Introduction

Coma is an eyes-closed state of unresponsiveness with severely impaired arousal and cognition. It represents a failure of neurologic function resulting from damage of a critical number of brainstem and diencephalic pathways, which regulate the overall level of cortical function. Coma has been identified as a major predictor of death and poor neurofunctional outcomes in patients with a variety of critical illnesses, including ischemic strokes [1], intracerebral hemorrhage [2], traumatic brain injury [3, 4], hypoxic encephalopathy after cardiac arrest [1, 5, 6], and metabolic derangements or sepsis [1]. Besides ventilator dependency and infectious complications, coma is one of the major critical conditions leading to prolonged intensive care and increased mortality [7]. Cerebral electrographic patterns allow distinction of coma from normal sleep and other causes of confusion or unresponsiveness. Some EEG patterns reflect a deepening or lightening of mental status, though progression of coma through various EEG patterns is inconsistent. Several EEG patterns indicate the type of cerebral impairment, while others may suggest favorable or unfavorable prognoses.

This review presents different abnormalities of EEG patterns and background activity seen in coma, along with those that indicate deepening coma and have particular prognostic significance.

Early insights

Early studies on stupor and coma [8] have correlated decreases in mental status and deepening levels of coma with particular EEG patterns and suppression of EEG reactivity. Initial case studies have reported EEG features associated with toxic, metabolic, ischemic, anoxic and endocrine disorders. Patterns recognized early on included predominant delta patterns, diffuse severe suppression, intermittent rhythmic delta activity, including frontal varieties (FIRDA) [9 - 14], triphasic waves [15 - 20], alpha frequency patterns in coma [21 - 33], and spindle-like sleep patterns in coma [33 - 41]. With worsening metabolic encephalopathies, EEG background amplitudes were seen to increase while dominant frequencies of background activity decreased. In the early 1960s, investigators noted the association between slowing of EEG activity and clinical evidence of cerebral cortical neuronal activity [42]. Comparable findings were noted by Stockard and Bickford, who found progressive EEG frequency slowing with progressive anesthesia [43] (**Figure 1**).

Clinical importance of EEG in comatose patients

Although EEG was increasingly looked at to provide objective evidence of brain dysfunction, it became evident that it provided little in the way of diagnostic specificity to an underlying cause. From another perspective, however, when used in specific etiologies of coma encountered in the intensive care unit, EEG has been progressively seen as providing a helpful tool in prognosis [44], revealing subclinical seizure activity, and tracking brain activity while patients are paralyzed [45 - 49]. To date, EEG is of greatest value in prognostication following closed traumatic brain injury [50] and cardio-respiratory arrest (CRA) with consequent hypoxic-ischemic encephalopathy [51, 52]. Recently, good outcome in comatose patients after CRA was shown to correlate well with EEG background variability and reactivity to stimulation during or after mild therapeutic hypothermia (MTH), or conversely herald poor outcome when evidence of reactivity to noxious stimuli was absent (**Table 1**). Advances in quantitative EEG during MTH after CRA recently identified subgroups of patients with distinct evolutions of qEEG "burst-suppression ratios" that were likely to have good neurofunctional recovery [53]. Several studies reported associations of a range of etiologies with particular EEG patterns in coma, providing some prognostic significance and guidance for prognosis that are presented below and summarized in **Table 2**.

Electroencephalographic frequency patterns in coma and their clinical context

Frequencies of background activity, such as alpha, theta, delta, or beta may predominate in different encephalopathies in coma, along with varying EEG background reactivity (changes in frequency, spatial distribution or amplitude) to external noxious stimuli. An excellent approach to EEG patterns and their associations with outcome in conjunction with background activity and reactivity in coma can be found in the work of Husain [54], with a similar approach used here.

Beta coma

Generalized 12-16 Hz background activity is maximally seen over the frontal regions in patients with beta coma [55]. This activity can be intermixed with or without sleep spindle-like activity, alpha, or even delta activity (**Figure 2 A**). Background reactivity to noxious stimulation can be preserved. However, there may be no EEG reactivity in deep coma [54, 56].

Beta coma can be seen in patients with intoxication

Table 1: Predictive value of EEG background reactivity in comatose patients following cardiac arrest

Reference	Study design	Number of patients	Time of examination	EEG background reactivity*	Results
Rossetti et al., 2010	Prospective study	34 patients	After CPR and during therapeutic hypothermia	Absent	False-positive rate 0% during hypothermia for poor outcome
Rossetti et al., 2010	Prospective study	111 patients	In the first 3 days after CPR and therapeutic hypothermia	Absent	False-positive rate 7% for poor outcome
Thenayan et al., 2010	Prospective study	29 patients	After CPR and with or without therapeutic hypothermia	Preserved	10/11 patients with reactivity regained awareness
Rossetti et al., 2012	Prospective study	61 patients	After CPR and during therapeutic hypothermia	Absent	False-positive rate 0% during and after hypothermia for poor outcome
Howard et al., 2012	Prospective study	39 patients	At a mean of 5 days after CPR	Absent or periodic generalized phenomenon	Significant association with poor outcome (False-positive rate not provided)

CPR = cardiopulmonary resuscitation; EEG = electroencephalography;
cEEG = continuous electroencephalography
* to external noxious stimulation

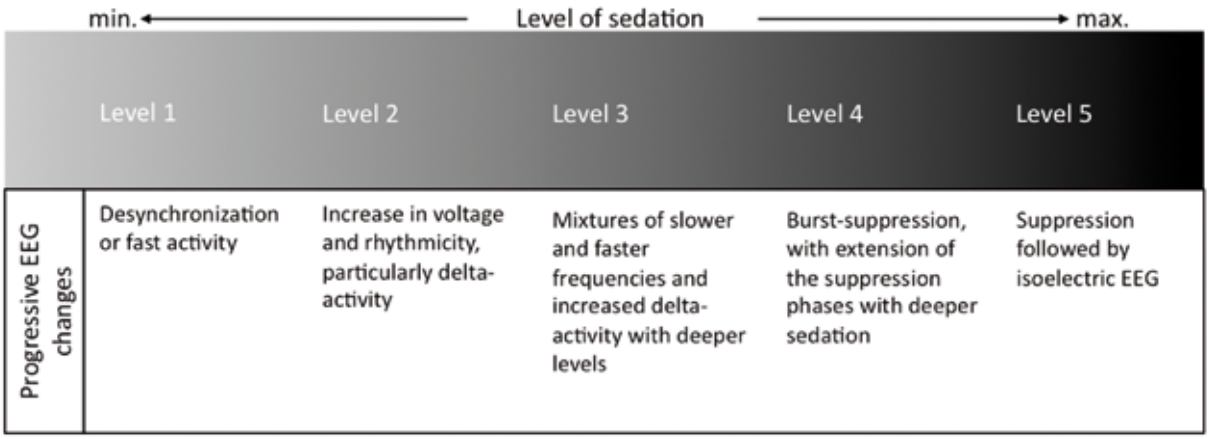

Figure 1: Progressive EEG changes with increasing level of sedation

Table 2: Etiologies and prognosis of different electroencephalographic coma patterns

Coma pattern	Etiologies	EEG background reactivity*	Most frequent outcome
Beta coma			
Intermingled with alpha activity	Intoxications or withdrawal (barbiturates or benzodiazepines), severe hyperthyroidism	+ / -	favorable
Intermingled with delta activity	Brainstem lesions	-	unfavorable
Alpha coma			
More diffusely	Intoxication (barbiturates, benzodiazepines, anesthetic agents, meprobamate, imipramine)	+	favorable
Monomorphic posterior	Brainstem lesions, locked-in syndrome	+ / -	unfavorable
More diffusely	Hypoxic-ischemic encephalopathy	(+) / -	unfavorable
Theta coma	Hypoxic-ischemic encephalopathy, mild to moderate metabolic encephalopathies, severe systemic infections	(+) / -	unfavorable
High-voltage delta coma			
Anterior predominance or focal, unilateral	Metabolic encephalopathies, focal or unilateral white matter lesions	+	favorable
More diffusely	Severe metabolic encephalopathy, severe encephalitis, vasculitis, large white matter lesions, markedly increased intracranial pressure	(+) / -	unfavorable
Spindle coma			
Theta and delta activity with paroxysmal bursts of symmetric spindles	Traumatic brain injury, intracerebral hemorrhage, post-ictal states, intoxication	+	favorable
Theta and delta activity with paroxysmal bursts of symmetric spindles	Hypoxic-ischemic encephalopathy, severe traumatic brain injury, large intracerebral hemorrhage	(+) / -	unfavorable
Burst-suppression			
With interruptions	Intoxication (sedative drugs), anesthetic drug use, and hypothermia	+ / (-)	favorable
No interruption	Hypoxic-ischemic encephalopathy, severe intoxication	(+) / - (controversial for outcome)	unfavorable
Low-voltage delta coma			
Theta and delta activity with intrusions of alpha and beta activity	Traumatic brain injury, healthy individuals	+	favorable
Theta and delta activity without intrusions of higher frequency activity	Hypoxic-ischemic encephalopathy, severe traumatic brain injury	(+) / -	unfavorable
Electro-cerebral inactivity			
No spontaneous neuronal activity detectable	Marked hypothermia, severe intoxications (nervous system depressant drugs)	-	favorable
	Hypoxic-ischemic encephalopathy	-	unfavorable

+ = preserved EEG background activity, - = no EEG background activity EEG = electroencephalography, * to external noxious stimulation

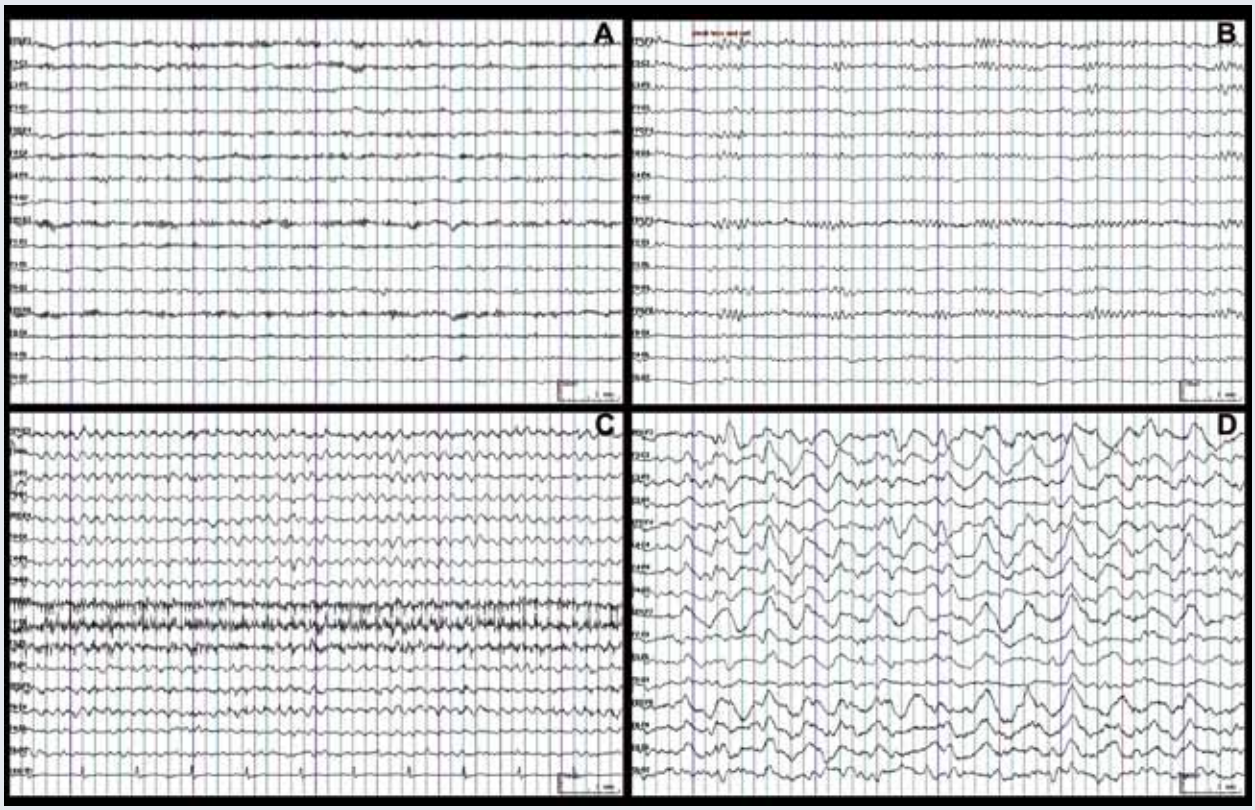

Figure 2: Electroencephalographic patterns in coma (part 1). A beta coma pattern; B alpha coma patterns; C theta coma pattern; D high-voltage delta coma pattern

or withdrawal from sedating drugs, such as barbiturates or benzodiazepines [57, 58] but can also occasionally occur with brainstem lesions [59]. Following medication, beta coma is largely reversible and hence has a good prognosis if patients can be medically supported during the acute intoxication [56].

Alpha coma

Electroencephalographic patterns in unarousable patients that lie in the alpha frequency range (8-13 Hz) define alpha coma. Alpha activity is mostly seen over the frontal areas (**Figure 2 B**) [55]. However, the EEG alpha distribution and outcome depends largely on the etiology.

Reactive alpha patterns usually emerge after drug overdoses and lead to recovery in up to 90%. Alpha coma can also be seen in toxic encephalopathies [30, 57, 60, 61]. Intoxication is usually caused by barbiturates, benzodiazepines, anesthetic agents and anxiolytic agents [62]. EEG background reactivity is usually preserved and outcome tends to be good [61]. In contrast, posterior predominance is seen in comatose patients with brainstem lesions and varies often with external stimuli, but has a poor prognosis. Alpha frequency patterns appear more diffusely with hypoxic-ischemic encephalopathy after CRA and background reactivity to external stimuli is usually absent. Outcome is mostly poor with mortality exceeding 90% [31, 60, 61].

Theta coma

Theta coma refers to a diffuse background activity of 4-7 Hz in coma. This pattern may occur with or without intermixed alpha or delta activity (**Figure 2 C**) [31, 63].

Aside from "benign" theta dominant patterns in patients with cortical dysfunction, such as in dementia or mild to moderate encephalopathy [64], it can be seen in conjunction with hypoxic-ischemic brain injury and carries a poor prognosis [65]. Diffuse and unreactive theta activity appears most prominently over the anterior regions and usually carries a poor prognosis.

High-voltage delta coma

High-voltage delta activity in coma is defined as a background activity of 1-3 Hz with amplitudes that sometimes reach several 100 µV (**Figure 2 D**). Delta pattern coma may exhibit polymorphic shape or more rhythmic, blunted triphasic waves.

Although this pattern is usually seen in late stages of coma, reaction to noxious stimuli is mostly preserved. However, when coma further deepens, background reactivity to external stimuli decreases and becomes unreactive. These patterns usually arise with

more advanced states of encephalopathy as well as in coma, and are predominantly reflected over the anterior regions, but then tend to appear more diffusely as coma deepens. The predominant structural abnormalities involve large areas in the subcortical white matter; however, severe metabolic derangements may also produce similar patterns [54, 62, 66] and focal or unilateral delta activity usually is the expression of focal subcortical brain lesions. Overall, high-voltage delta activity is associated with a poor outcome [62].

Spindle coma

Spindle coma is defined as predominant theta and delta background activity with superimposed, frequent, paroxysmal spindle-shaped bursts. The spindles are usually bilateral, symmetric, synchronous, and have frequencies of up to 14 Hz (**Figure 3 A**). Intermittent elements of sleep architecture (i.e., K-complexes, vertex waves or slowing) may be triggered by external noxious stimuli [67, 68].

While spindle coma pattern is mainly seen in patients with injury to the pontomesencephalic junction below the thalamus [34, 56], it may also follow hypoxic-ischemic brain damage [68], traumatic brain injury [34, 69, 70], intracerebral hemorrhage [34], post-ictal states [71], intoxication [35, 36], encephalitis [37, 38], and other diffuse cerebral insults [67]. This is why the prognosis largely depends on the underlying cause. Overall, preserved background reactivity to noxious stimuli and lack of evidence of severe intracerebral, parenchymal lesions or signs of hypoxic-ischemic brain injury is associated with good prognosis [72].

Burst-suppression

Burst-suppression patterns are generalized, synchronous bursts of high-voltage, irregular activity and/or epileptic elements of different frequencies (e.g., such as spikes, sharp waves) that interrupt EEG suppression (**Figure 3 B**). Both bursts and periods of suppression may vary in duration. With deeper coma, the proportion of bursts decreases while suppression increases and sometimes persists without interruption [54].

Hypoxic-ischemic encephalopathy, intoxication with sedative drugs, anesthetics, and hypothermia are the major underlying etiologies that determine outcome [62, 73 - 77]. It remains unclear whether a reactive burst-suppression pattern to external stimuli (i.e., an interruption by stimulation) is predictive of better outcome.

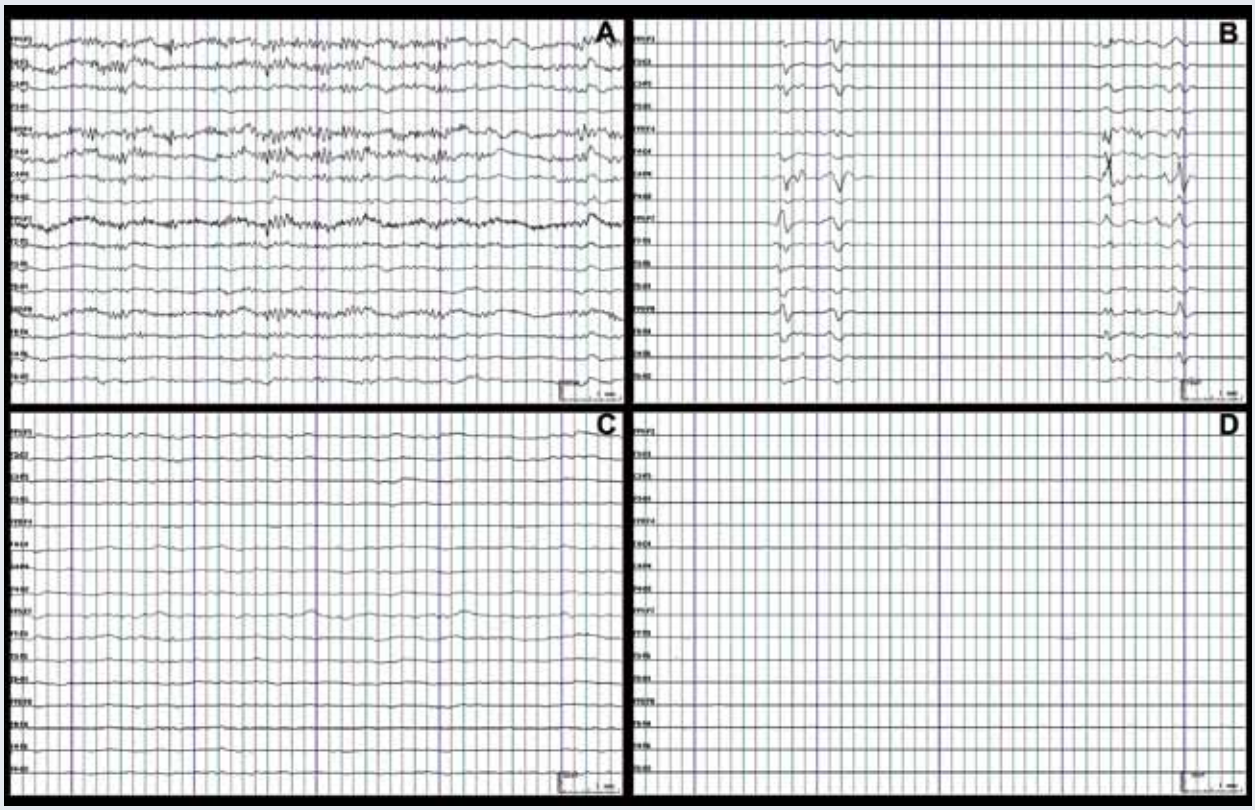

Figure 3: Electroencephalographic patterns in coma (part 2). A spindle coma pattern; B burst-suppression; C low-voltage delta coma; D electro-cerebral inactivity

Low-voltage delta coma

This coma pattern consists of persistent theta and delta activity with small amplitude (usually < 20 µV; **Figure 3 C**) [62]. This low-voltage activity may also be present in healthy individuals but usually with preserved background reactivity to external stimulation and intrusions of alpha and beta activity. A low-voltage, slow and unreactive EEG pattern is associated with large and severe brain damage (i.e., hypoxic-ischemic encephalopathy and severe traumatic brain injury) [56, 64, 78], and poor outcome.

Electro-cerebral inactivity

Electro-cerebral inactivity, also described as isoelectric, nonreactive EEG, flat EEG or electro-cerebral silence, is the expression of severe and widespread cerebral dysfunction in which EEG activity is undetectable (i.e., amplitudes of < 2 µV) with conventional scalp electrodes placed at double the routine international 10-20 electrode distances with body core temperature above 34 degrees centigrade, and with at least 30 minutes of continuous recording (**Figure 3 D**). Artifacts from electrocardiograph, respiration, and intravenous drips must be differentiated from brain activity and the term should only be used in the global absence of electrical activity, even after intense sensory stimulation [54]. In addition, marked hypothermia must be excluded, as it may result in potentially reversible electro-cerebral inactivity. Most common etiologies are diffuse hypoxic-ischemic brain injury and severe intoxication with nervous system depressant drugs. As the clinical impact of electro-cerebral inactivity is grave, the standard protocols for obtaining "brain death" recordings must be followed, such as proposed by the American Clinical Neurophysiology Society [79]; of note, however, a brain death diagnosis does not require EEG in Switzerland. Patients with electro-cerebral inactivity on the EEG either die or remain in a persistent vegetative state [54, 79].

Periodic EEG coma patterns

Aside from changes in background activity in coma, periodic patterns are also frequently seen with altered mental status. Such recurring EEG elements usually consist of waves or complexes that repeat with a variety of intervals, ranging from 0.3 to several seconds, and which occupy most of at least a 20 minute standard recording. Different types of periodic discharges have been described, such as periodic lateralized epileptiform discharges (PLEDs), bilateral independent periodic lateralized epileptiform discharges (BIPLEDs), generalized periodic epileptiform discharges (GPEDs) [80]. Among different metabolic and toxic derangements, periodic patterns in coma are mostly seen in patients with hypoxic-ischemic insult, nervous system infections, and multi-focal brain trauma.

Periodic non-epileptic patterns are often difficult to differentiate from clinical states of coma with EEG ictal activity. The latter consist of complexes of spike, spike waves, or sharp waves. In these states of nonconvulsive status epilepticus, the periodic epileptic discharges usually occur at higher frequencies. In addition, there are often subtle clinical correlates, such as facial, perioral, eyelid, and limb myoclonias, staring or rigidity [81]. With ongoing seizure activity, the interposed background activity may slow down and not be identified as the frequency of epileptic discharges increases.

Conclusion

The EEG provides objective electrophysiological measurements of cerebral dysfunction, and complements clinical and neuroimaging assessment of comatose patients. Aside from the detection of epileptic activity seen in subclinical seizures or occult status epilepticus, EEG frequency, amplitude and distribution patterns may indicate diffuse, cortical, subcortical or arousal dysfunction. EEG patterns and background reactivity may provide information on prognosis and may suggest specific causes for coma.

Conflicts of interest

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EEG in the ICU: What Should One Treat, What Not?

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Summary

Paroxysmal and periodic patterns on continuously recorded EEG are commonly seen in the neurocritical care setting. As these patterns span the non-epileptic, interictal, and ictal continuum, accurate identification and appropriate management of these patterns present challenges. This review will survey the most commonly seen patterns, including sharp waveforms, lateralized and generalized periodic discharges, and subclinical seizures. Evidence based guidelines for management of these patterns are lacking; reasonable approaches to their management will be presented. Where continuous monitoring is available, a measured approach with close follow-up of these uncertain patterns may be reasonable in a large number of these cases.

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Key words: EEG, seizure, intensive care unit, periodic epileptiform discharges

EEG in der Intensivpflegestation: Was sollte man behandeln, was nicht?

Paroxysmale und periodische Muster im kontinuierlich aufgenommenen EEG treten häufig auf in der Neuro-Intensivpflege. Die genaue Identifikation und das angemessene Management dieser Muster stellen häufig eine Herausforderung dar. Dieser Artikel bietet einen Überblick über die häufigsten EEG-Muster. Leider fehlen „Evidence based"-Richtlinien für den Umgang damit; hier werden praktische Vorschläge präsentiert.

Schlüsselwörter: EEG, Anfall, Intensivpflegestation, periodische epileptiforme Entladungen

L'EEG au service des soins intensifs : quand faut-il traiter et quand non ?

Les tracés paroxysmaux et périodiques se rencontrent souvent lors de l'enregistrement en continu de l'EEG aux soins neuro-intensifs. L'identification précise et la gestion adéquate de ces tracés posent souvent un défi. Le présent article offre une vue d'ensemble des tracés EEG les plus courants. Malheureusement, il manque des directives basées sur l'évidence concernant leur maniement : le texte présente des suggestions pratiques.

Mots clés : EEG, crise épileptique, soins intensifs, tracés périodiques épileptiformes

Introduction

The proliferation of the use of continuous EEG monitoring in the intensive care unit has led to the discovery that paroxysmal and periodic patterns are very common. These EEG patterns encompass a spectrum between non-epileptic, interictal, and ictal. Management of such patterns is particularly challenging; delayed treatment of an ictal pattern may result in difficulty in ultimately controlling a seizure or may result in further brain damage. Overly aggressive treatment with antiepileptic drugs (AEDs) may result in iatrogenic complications, such as drug reaction, drug interaction, and increased sedation resulting in further morbidity in an already compromised patient.

In this review the most common patterns encountered in the neurocritical care setting will be discussed. Two important caveats should be noted. Treatment decisions should be tailored to take account of the patient's comorbidities and severity of illness; with a similar brain injury and EEG pattern, one patient may be a candidate for aggressive intravenously infused anesthetic treatment whereas another patient should not be treated with such. In addition, similar paroxysmal discharges in one particular underlying condition may not confer the same risk for seizures as compared to another condition; PLEDs seen in metabolic dysfunction likely confer smaller risk for impending seizures as compared to PLEDs seen in brain tumors or other conditions with structural brain injury [1]. These caveats inherently limit the ability to give all-encompassing

guidelines for management for EEG patterns. Nonetheless, reasonable generalizable approaches to their treatment can be made.

Sharp waveforms

In patients undergoing evaluation for epilepsy, isolated focal spikes or sharp waves have high specificity for impending clinical seizures. The existence of such discharges in a population with a reasonably high pretest probability for seizures translates into very high positive predictive value for seizures, and is an indication for starting an AED. Although it may seem reasonable to presume focal spikes or sharp waves have similar specificity in the neurocritically ill population as well, there are few formal studies that have examined this systematically. The mere existence of a sharp waveform that morphologically qualifies as a spike or sharp wave may not necessarily indicate similarly high risk for seizures. For example, in patients with acute ischemic strokes, focal spikes or sharp waves occur in 14% of patients, whereas seizures occur only in 2% [2].

The determination of a truly epileptiform focal spike/sharp wave is also challenging. Patients who have undergone a neurosurgical procedure may exhibit a "breach" rhythm. These waves consist of a wide variety of EEG changes, including predominantly a high voltage 6 to 11 Hz mu-like rhythm in the centrotemporal areas, as well as other sharp waveforms [3]. Discharges that markedly disrupt the background and are associated with a field spanning more than 2 electrodes are particularly concerning for cortical irritability; positive sharp waves should also be considered potentially epileptiform [4]. However, breach patterns mimic features of, and may indeed be virtually impossible to distinguish from epileptic sharp waves. Overly aggressive treatment of sharp waveforms is therefore not indicated, though patients are generally already on a conventional AED after neurosurgical procedures.

In rare instances, one may encounter incontrovertible sharp waves from the hemisphere contralateral to a given lesion. The etiology of such patterns is unclear, but may be due to subtle mass effect or possibly a result of previous, possibly silent, compromise of the contralateral hemisphere, for example, due to a scarring nidus from a previous silent ischemic process. In the absence of other clinical or electrographic indications, such patterns do not warrant treatment with an AED.

Periodic discharges

Periodic discharges are seen commonly in the neurocritically ill population. The gamut of periodic activity runs from manifestations of encephalopathy without any proclivity towards epileptic activity, to instances where distinguishing from frank status epilepticus is difficult. As such, the American Clinical Neurophysiology Society position paper on nomenclature subdivides these into lateralized periodic discharges (LPDs), bilateral independent periodic discharges (BIPDs), multifocal periodic discharges, and generalized periodic discharges (GPD), replacing the frequently utilized terms periodic lateralized epileptiform discharges (PLEDs), bi-PLEDs, and generalized periodic epileptiform discharges (GPEDs). However, the latter terms are still widely employed in both the clinical and research arenas.

PLEDs/LPDs (**Figure 1**) have been long recognized as abnormal findings on EEGs although their clinical significance has not been clear. They are associated with nearly any type of structural abnormalities, including infectious, neoplastic, ischemic, hemorrhagic, and anoxic etiologies. They are generally associated with poor prognosis, particularly in patients with neoplasms [5, 6]. Clinical seizures are seen up to 70% of patients [1]. It is unclear whether PLEDs present an ictal phenomenon, an interictal pattern, or an epiphenomenon of brain injury. PLEDs are associated with increase in glucose metabolism [7] and blood flow [8, 9], suggesting that at least some of them are definitely ictal phenomenon requiring aggressive treatment with AEDs [10]. PLEDs have been reported as a definite electrographic correlate to clinically apparent seizures [11]. On the other hand, patients with chronic PLEDs have been reported; in patients who experienced seizures, ictal discharges in the EEGs were distinct from the PLEDs, and during this time the PLEDs disappeared [12], suggesting PLEDs to be an interictal phenomenon. As such, other authors have advised against routinely treating patients with these patterns unless it can be established that they represent a true ictal phenomenon rather than merely an interictal pattern [13]. As depressed mental status is extremely prevalent in patients with PLEDs, determining whether PLEDs are ictal or not is challenging. It seems reasonable starting or maintaining a conventional AED in all patients with PLEDs without escalating treatment unless clear ictal electrographic or clinical semiology is observed. To distinguish electrographic characterization of PLEDs more likely associated with seizures, distinction of PLEDs into PLEDs proper versus PLEDs plus has been made [14] (**Figure 2**). PLEDs plus are associated with brief focal rhythmic discharges, and are more frequently associated with seizures than PLEDs proper. Care must be taken not to overtreat patients in whom pseudo-PLEDs appear because severe pathology in one hemisphere suppresses what otherwise would have been generalized periodic discharges, resulting in PLED-like patterns over an intact hemisphere.

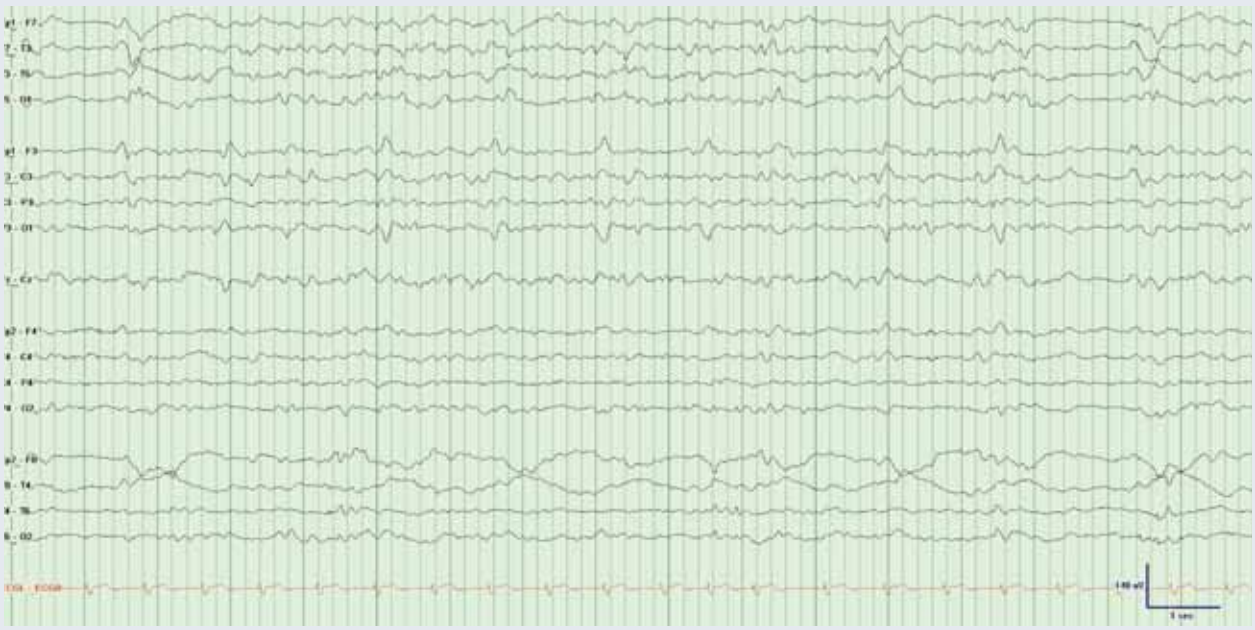

Figure 1: An 84-year-old man with herpes simplex virus encephalitis. The EEG demonstrates lateralized periodic discharges PLEDs.

BiPLEDs defined as periodic discharges are independently and simultaneously present in both hemispheres. They are far less common than PLEDs and are associated with higher risk for seizures, depressed consciousness, and mortality than PLEDs [15]. As such, greater vigilance regarding epileptic activity is required than in PLEDs, though the approach to AED management is the same.

GPDs are perhaps the most challenging pattern to analyze, as they commonly span the gamut from the nonepileptic to the interictal to status epilepticus, potentially within a short period of time. The most common etiology are anoxic/metabolic or infectious [16, 17], although GPDs are nonspecific and may be seen in nearly any cause of depressed mental status. There is decreased risk for seizures in patients whose GPDs exhibit a triphasic morphology [18] (**Figure 3**), defined as surface negative triphasic complexes discharging every 1-2 Hz, and often with an antero-posterior or postero-anterior phase lag. GPDs discharging greater

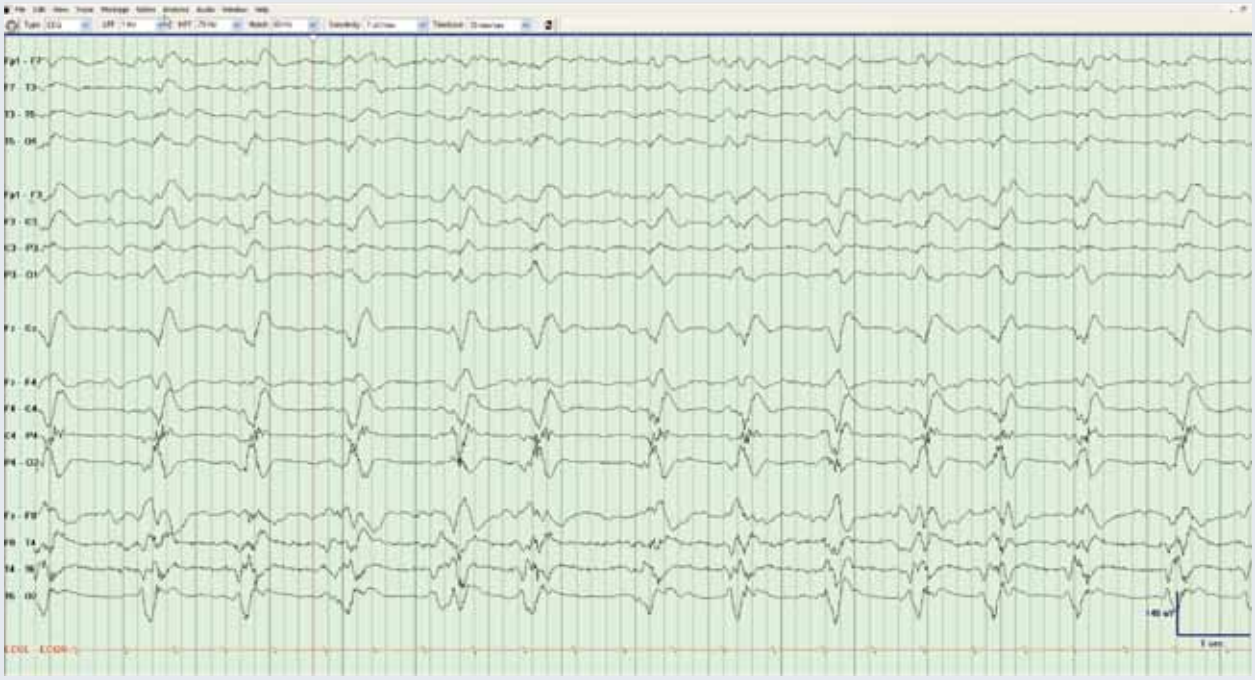

Figure 2: A 78-year-old man with history of stroke, seizures. The EEG demonstrates PLEDs and focal rhythmic discharges, consistent with PLEDs plus.

than 3Hz are generally considered to be ictal in nature [19, 20] (**Figure 4**). AED management of these patterns must truly be done in conjunction with careful clinical and pathophysiological assessment. For example, GPDs with a triphasic morphology due to purely metabolic etiology without clinical correlation should not be treated with AEDs whereas other GPDs are clearly manifestations of status epilepticus [17].

The differentiation between ictal GPDs and nonictal metabolic triphasic waves often cannot be made reliably. It has been suggested that a challenge dose of intravenous benzodiazepine be given, and determine whether there is clinical or incontrovertible electrographic improvement [21], which would suggest an ictal phenomenon. In reality, this procedure is rarely useful; benzodiazepines will electrographically resolve both ictal and nonictal GPDs. Observing clinical improvement is nearly impossible as benzodiazepines will depress mental status in both scenarios.

SIRPIDs

Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) are found in approximately 20% of patients undergoing continuous EEG monitoring. They are considered to fall somewhere along the ictal-interictal continuum. Clinical or subclinical/electrographic seizures are found in about half of these patients; status epilepticus is found more frequently in focal or ictal appearing SIRPIDs [22]. As such, treatment with a conventional antiepileptic drug is advisable. Other studies have shown no increase in regional cerebral blood flow, and as a result have advocated against aggressive treatment [23]. Experience in our own center indicates that SIRPIDs are a transitional, unstable pattern that either will devolve into more definitively ictal pattern, or more commonly, dissipate in time, in either case, losing the stimulus induced character. The recommendation of the author is to start a conventional antiepileptic drug; if already on an AED, escalation of treatment is not recommended. Although evidence for such is lacking, it seems reasonable to minimize stimulating the patient any more than medically necessary. After cardiac arrest, SIRPIDs are associated with poor outcome [24], especially during hypothermia, but in other instances, outcome is yet to be defined.

Nonconvulsive seizures

Nonconvulsive seizures (NCS) are commonly found in the neurocritical care setting, present between 18 and 35% of patients [25, 26]. Of these, up to 75% of patients are in nonconvulsive status epilepticus (NCSE) [27]. The determination of NCS can be challenging due to the fact that many of the observed waveforms lie in the interictal-ictal continuum. The Young criteria [19] (**Table 1**) provides a reasonable guideline in determining whether a pattern is consistent with NCS. This has been modified by other groups which emphasized the importance of frequency/locational evolution and de-emphasized amplitude changes [28] (**Figure 5**).

It has yet to be definitely determined whether

Figure 3: A 61-year-old man with hepatic encephalopathy. The generalized periodic discharges have a triphasic morphology; this pattern would not be considered ictal.

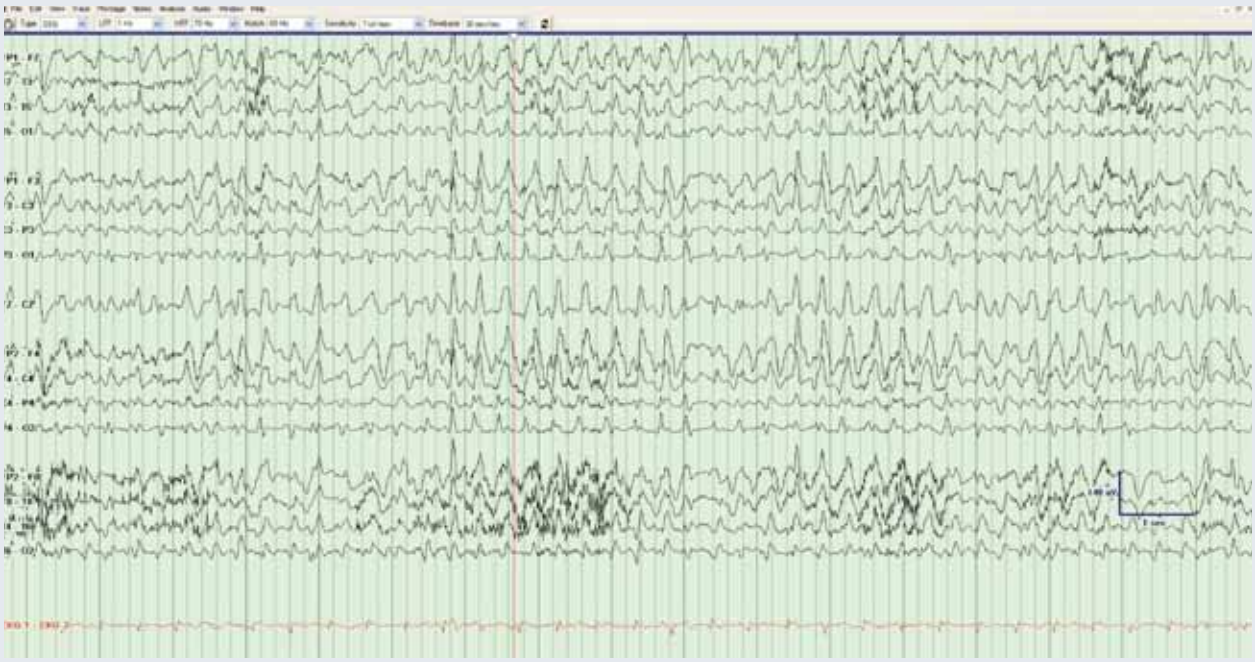

Figure 4: A 64-year-old female after cardiac arrest. Generalized periodic discharges are synchronous with subtle corresponding eye movements, consistent with an ictal phenomenon.

NCS or NCSE independently cause neuronal injury or are mere epiphenomena of the underlying insult. The mortality of NCSE is high, and most of the morbidity from NCS is likely due to the underlying condition rather than seizures themselves [29, 30]. Some studies have not shown neurocognitive deterioration after status epilepticus after eliminating progressive illness [31]. Aggressive treatment is likely to incur iatrogenic morbidities. However, other studies have shown deleterious effects associated with NCS. For instance, in patients with intracerebral hemorrhage, expansion of hemorrhage size has been demonstrated in patients with NCS [32]. In patients with traumatic brain injury, increase in intracranial pressure and lactate-pyruvate ratio [33] as well as hippocampal atrophy [34] has been observed in patients with NCS. However, the nature of the causality still remains unclear, e.g. whether seizures were the causes or effects of these changes.

It is reasonable to treat all patients with NCS with at least one conventional antiepileptic drug. Escalation of treatment must be decided on a case-by-case basis. In general, there are few, if any, scenarios where de novo intubation and administration of an intravenous anesthetic is indicated solely for the purpose of the treatment of an EEG pattern.

General guidelines

Sharp, rhythmic, or periodic appearing discharges are all extremely common in the neurocritical care setting, and in many instances, the delineation between nonepileptic, interictal, and ictal patterns is difficult. Although rapid treatment of status epilepticus has universally been advocated as it increases chance of seizure control, in patients with uncertain patterns, it is advisable to temper treatment. Firstly, the potential drawbacks of anticonvulsants in critically ill patients have been demonstrated [35]. Secondly, it is uncertain whether aggressive treatment of NCS or even NCSE will result in improved outcome, as it has been postulated that nonconvulsive epileptic activity may be an epiphenomenon of an injured brain [36]. Given the availability of medications that are easily administered with relatively low toxicity, a conventional AED at a relatively low dose can be administered in patients with uncertain rhythms. Thereafter, careful monitoring without escalation of therapy until an uncertain pattern declares itself to be a malignant rhythm may be a superior strategy rather than early escalation of treatment of such patterns; a large portion of the uncertain patterns will revert to clearly nonepileptic patterns. Further research is needed to determine the characteristics of patterns that will devolve into ictal patterns requiring escalation of treatment.

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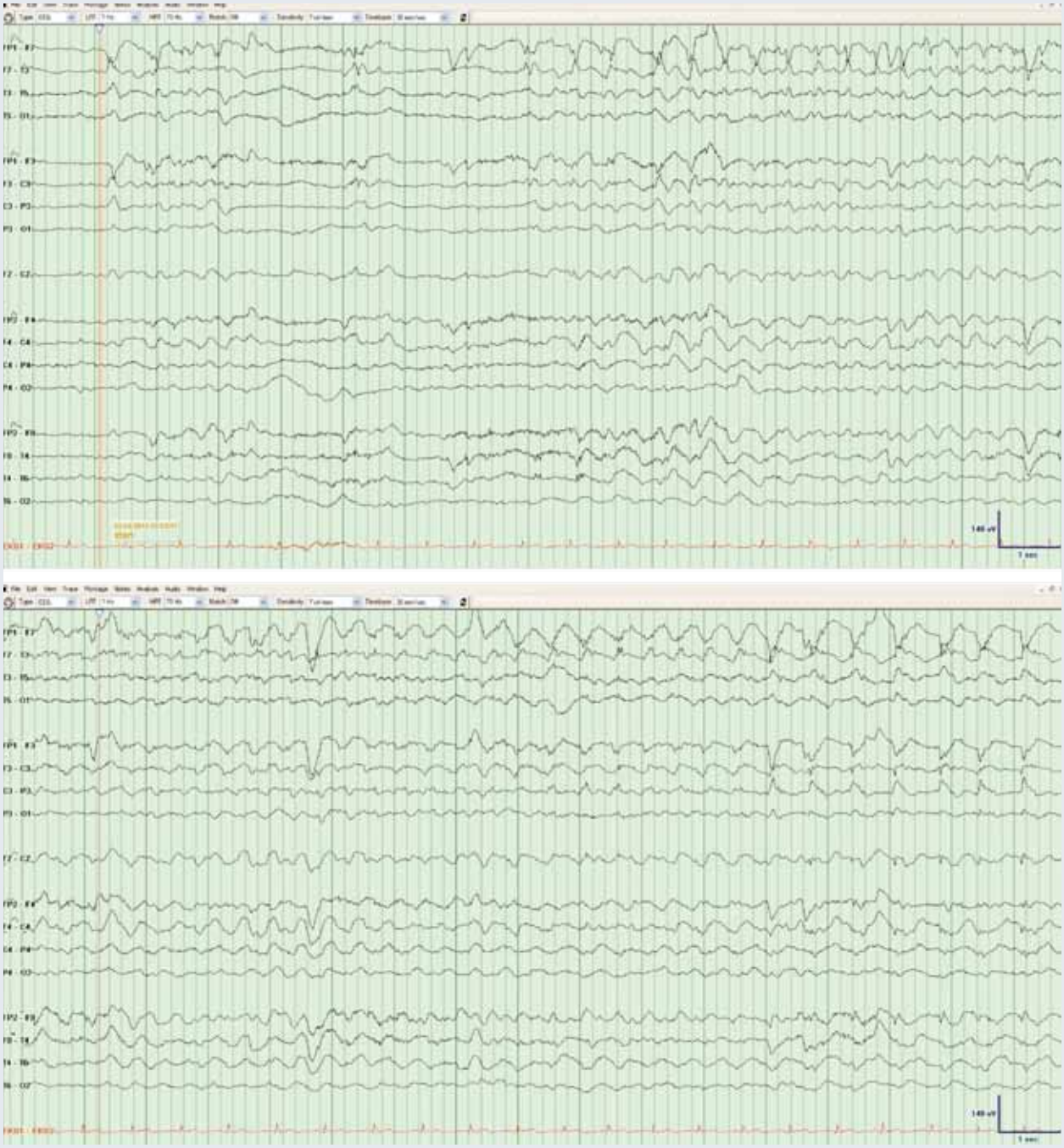

Figure 5: A 63-year-old man after meningioma resection. The evolution of morphology and frequency that defines this nonconvulsive seizure.

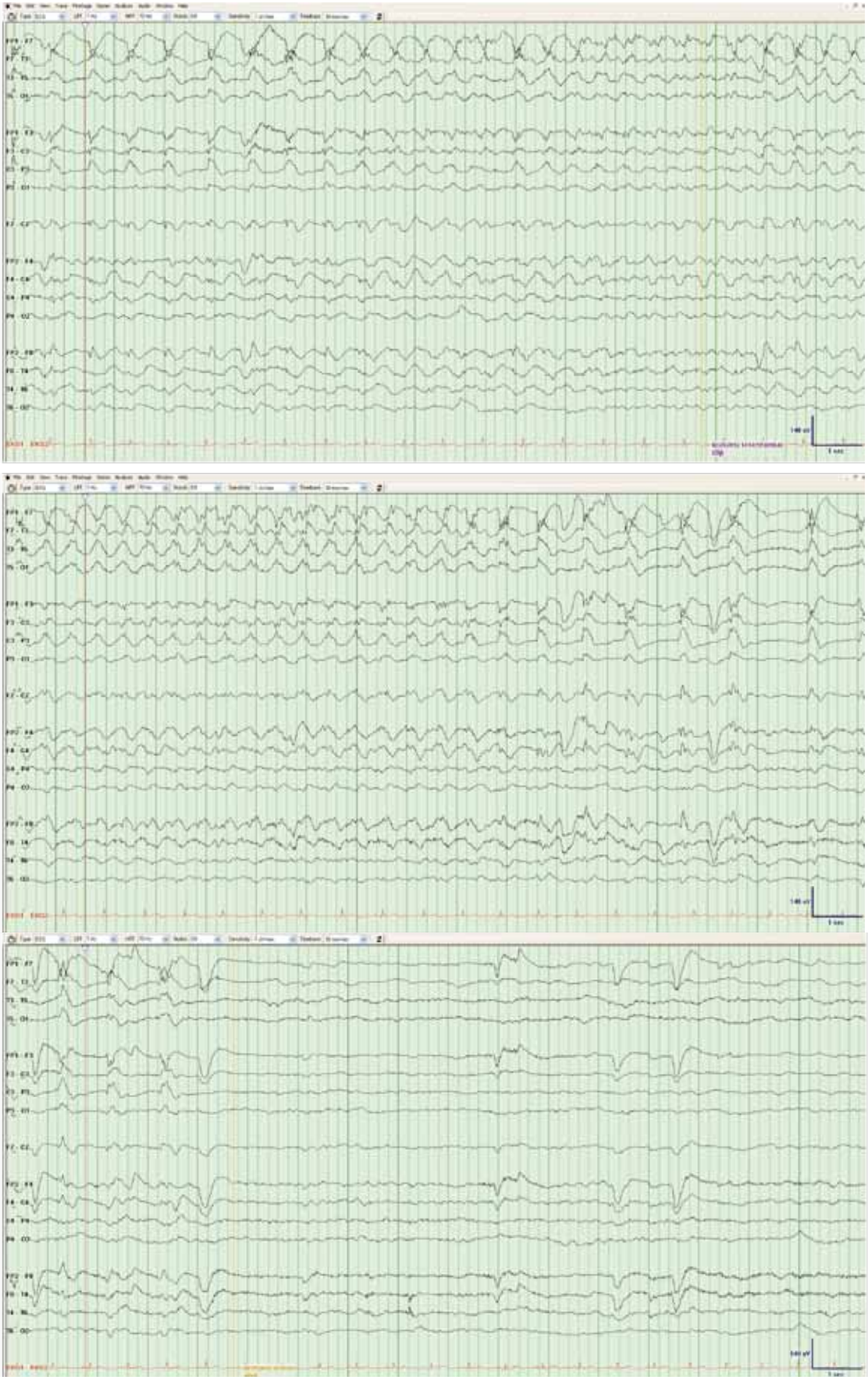

Figure 5: A 63-year-old man after meningioma resection. The evolution of morphology and frequency that defines this nonconvulsive seizure.

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Prognosis after Cerebral Anoxia in Adults: What's the Role of EEG Specialist?

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Summary

Anoxic/hypoxic encephalopathy is a severe neurological condition associated with a poor outcome. Neurologists, and particularly electroencephalographers, are often implicated in the assessment of comatose survivors of cardiac arrest. Therapeutic hypothermia has been increasingly implemented in the intensive care units starting less than a decade ago; in this new context, some outcome predictors previously known as reliable, such as the clinical examination, seem no more robust to decide on life support discontinuation. Conversely, the role of electroencephalography has gained in consideration, with converging new data pointing to its reliability in both hypothermic and normothermic conditions.

This article will review the EEG role in the evaluation of comatose survivor of cardiac arrest, important technical parameters and also the essential EEG patterns of this setting.

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Key words: Neurocritical care, hypoxic brain injury, prognosis, cardiac arrest, hypothermia, outcome

Prognose nach einer zerebralen Anoxie bei Erwachsenen: Welche Rolle spielt der EEG-Spezialist?

Die anoxische-hypoxische Enzephalopathie ist eine schwerste neurologische Beeinträchtigung mit einer schlechten Prognose. Die Neurologen, ganz besonders die Elektroenzephalographie-Spezialisten, sind hierzulande oft gefragt bei der Beurteilung von komatösen Patienten nach Herzstillstand. Seit etwa zehn Jahren wird die therapeutische Hypothermie auf den Intensivpflegestationen mehr und mehr eingesetzt. Seither scheinen vorher zuverlässige Kriterien, insbesondere die klinische Untersuchung, nicht mehr so stichhaltig, wenn es um die Frage der Weiterführung von lebenserhaltenden Massnahmen geht. Hingegen hat die Elektroenzephalographie an Bedeutung gewonnen mit neuen Daten, die zunehmend Informationen über hypothermische und normothermische Zustände liefern.

Dieser Artikel gibt einen Überblick über die Rolle des EEGs bei der Beurteilung von komatösen Überlebenden eines Herzstillstands, über wichtige technische Parameter und auch über die wesentlichsten EEG-Muster in dieser Situation.

Schlüsselwörter: Neuro-Intensivpflege, anoxische-hypoxische Enzephalopathie, Prognose, Herzstillstand, Hypothermie

Pronostique après une anoxie cérébrale chez l'adulte : quel est le rôle du spécialiste en EEG ?

L'encéphalopathie anoxique / hypoxique est une condition neurologique grave

associée à un mauvais pronostic. Les neurologues, et en particulier les spécialistes en électroencéphalographie sont souvent impliqués dans l'évaluation de ces patients. Cela fait environ dix ans que l'hypothermie thérapeutique est de plus en plus pratiquée dans les unités des soins intensifs. Depuis lors, certains éléments pronostiques tels que l'examen clinique, précédemment reconnus comme robustes, semblent beaucoup moins fiables quant la décision de l'arrêt de la réanimation. A l'inverse, le rôle de l'électroencéphalographie a gagné en importance, avec de nouvelles données montrant sa fiabilité tant durant l'hypothermie que durant la normothermie.

Cet article va examiner le rôle de l'EEG dans l'évaluation des survivants à un arrêt cardiaque restant dans le coma, les paramètres techniques importants, ainsi que les patterns EEG essentiels à connaître dans ce contexte.

Mots clés : soins intensifs neurologiques, encéphalopathie anoxique, pronostique, arrêt cardiaque, hypothermie

Introduction

Anoxic/hypoxic encephalopathy is a severe neurological condition associated with a dismal outcome. In recent years, therapeutic hypothermia (TH) has been progressively implemented [1, 2], leading to an improvement of functional outcome; its impact is illustrated by the relatively low number needed to treat

(NNT=7). Neurologists and electroencephalographers are often involved in the assessment of comatose survivors of cardiac arrest, in order to distinguish as reliably and rapidly as possible between patients who will benefit from maximal care, and those who will not recover. In this context, neurological examination, EEG and somatosensory evoked potential (SSEP) have been extensively studied and shown to be useful and reliable in outcome prediction [3]; however, those findings and related guidelines are based on data obtained essentially before the TH era. Indeed some recent data show that those recommendations have to be reconsidered in patients undergoing TH [4]: clinical examination, in particular regarding motor response to pain, seems considerably less reliable than the EEG evaluation. Of note, the EEG has also an important role in the pediatric population suffering from brain anoxia [5], but this is beyond the field of this brief review, which will focus on the prognostic role, technical parameters and important EEG patterns in adults.

EEG in the assessment of adult survivors of cardiac arrest

Outcome prediction

According to a meta-analysis performed by the American Academy of Neurology (AAN) [3], clinical examination appeared a reliable parameter in outcome prediction of comatose survivors of cardiac arrest. Indeed, absence of brainstem reflexes and of motor response to painful stimuli was considered as strong and reliable predictors of bad outcome with a false positive rate (FPR) of 0% (95% CI: 0-3%). This information was mainly based on class II studies performed before the TH implementation [6, 7]; however, recent data challenge these findings [4, 8]. Indeed a recent study of 111 survivors of cardiac arrest, performed in Lausanne [9], showed that those clinical predictors are no more precise enough after TH. For example, motor reaction to pain no better than extension assessed within the third day after cardiac arrest showed an FPR of poor outcome prediction as high as 24% (95% CI: 14-49%). This appears clearly suboptimal and dangerous when one has to decide on life support discontinuation. In the same study, absent brainstem (pupillary, oculocephalic, or corneal) reflexes (FPR: 4%; 95% CI: 1-15%) and early myoclonus (FPR: 3%; 95% CI: 0-11%) resulted as better clinical predictors.

There are also some important updates regarding electroneurophysiological data since TH era. In the AAN recommendations, so-called "malignant" EEG patterns (such as generalized background suppression; burst-suppression with generalized epileptiform activity; periodic, or epileptiform complexes on a flat background) during the three first days after cardiac arrest were associated with poor outcome (death) with a FPR of 3% (95% CI: 0.9-11%). Since TH implementation, EEG background reactivity (assessed off sedation and after rewarming) has received increasing consideration [4, 9]. Reactivity has been shown to be a relatively reliable predictor of bad outcome in the cohort from Lausanne (FPR: 7%; 95% CI: 1-18%). Moreover, the same group evaluated the predictive performance of this parameter during hypothermia in 37 patients in a preliminary study [10], with very encouraging results showing a FPR of 0% (95% CI: 0-18%) for bad outcome (death) in patients without any background reactivity in the early phase of treatment. The predictive performance of hypothermic EEG resulted significantly higher than that of somatosensory evoked potentials during normothermia. Of note, "malignant" EEG patterns (see above) seem still associated with dismal outcome as it was before TH [9, 11]. These findings have been confirmed in an expanded assessment of 61 patients (FPR for lack of reactivity *during* TH: 0%, 95%CI: 0.15%) [12]. In the same direction, a score of prediction has been recently proposed [13]: age and the first EEG registration were the most robust variables whereas the Glasgow Coma Scale (traditional clinical examination of comatose patients) was much more unreliable.

In conclusion, the importance of EEG in the outcome prediction of survivors of cardiac arrest has received increasing attention after TH implementation, and seems to represent a robust predictor, especially as regards to the lack of reactivity during both hypo- and normothermia.

Seizures identification

Electrographic status epilepticus can occur in as much as 30% of patients suffering from brain hypoxia [11] and is considered as an independent factor predicting bad outcome. However a small subgroup of patients suffering from myoclonic post-anoxic status epilepticus may still experience a reasonable outcome and thus warrant an aggressive anti-epileptic treatment; in a recent study, all patients with a favorable outcome after an electrographic post-anoxic status epilepticus shared specific characteristics [14]: all brainstem reflexes were present, early cortical SSEP were recorded bilaterally, and the normothermic EEG background was reactive, within 3 days after cardiac arrest. This profile was found in about 10% of patients with electrographic seizure patterns (representing about 3% of the total studied cohort of postanoxic patients), thus helping in identifying those subjects with a potentially favorable prognosis.

Practical parameters

EEG recordings

The International Federation of Clinical Neurophysiology (IFCN) recommends that the usual technical EEG requirements should also been applied when assessing comatose patients [15]. The importance to rule out some confounding factors is emphasized. Indeed, drugs frequently used in Intensive Care Unit (ICU), body temperature and metabolic disturbances could massively influence the EEG and therefore should be carefully taken into account during interpretation. The international 10-20 system is recommended, with the use of 21 electrodes. A reduced electrode number could be applied in some particular situations; 11 electrodes are acceptable for neonates and for diagnosis of brain death if EEG is needed (of note, this particular application is not required nor recommended in Switzerland). EEG with ECG and video recordings are clearly preferred, due to the easiness of identifying potential artifacts and clinical manifestations.

It is generally recommended to assess EEG reactivity with auditory (hand clapping, taking care of avoiding air displacements near the electrodes) and noxious stimulations at bedside, under video recording. Because sternal rub often induces movement artifacts, and painful stimuli application to fingers or toes may be proven unreliable (reduced nerve conduction in cold conditions, ICU polyneuropathy) we recommended nipples quenching. Stimuli should be repeated at least twice, and be separated by at least 20 sec of recording, in order to identify reliably the baseline background.

EEG monitoring or routine EEG recordings?

This question is highly relevant, the subject of a lively debate, but still unresolved, and the IFCN recommendation does not answer it. On the one side, EEG monitoring is highly "resources-consuming", depending on the institutional availability of recording machines. Conversely, a continuous EEG undoubtedly appears appealing in this setting and may allow the follow-up of the evolution of the patient. As stated earlier, EEG background reactivity seems one of the most important aspects of the outcome prediction: several hours of recording without stimulations probably do not increase the precision of forecast, at least in our experience. Continuous EEG could possibly identify subclinical seizures that punctual EEG evaluation might miss, but this has not been shown convincingly in this particular clinical setting. It is also not clear if treatment of those seizures would change the patient's outcome [16]. Moreover, seizures are seldom isolated and mostly manifest as repetitive or continuous, defining status epilepticus, which should be caught with repetitive "standard" re-

Table 1: Synek Score (adapted from [17])

Grade 1	Dominant reactive alpha activity with some theta activity	REACTIVE PATTERN
Grade 2	Dominant theta activity, preservation of normal sleep features, and with frontal monorhythmic delta activity	
Grade 3	Small amplitude, diffuse, irregular, non reactive delta activity	INTERMEDIAT PATTERN
Grade 4	Burst suppression, epileptiform discharges, and low-output nonreactive activity or Alpha/theta coma	NON-REACTIVE PATTERN
Grade 5	Isoelectric	

cordings. It seems reasonable to recommend that two video-EEG evaluations of at least 20-30 min (one during hypothermia and one after rewarming, off sedation), with 21 electrodes, should represent the minimum standard, with repeated background reactivity testing performed by trained personnel.

Important EEG patterns

Background activity

As already illustrated above, the background reactivity represents one of the most important EEG parameter in outcome evaluation (**Figure 1**). EEG reactivity is mostly defined as a clear, reproducible change in background frequency (and mostly amplitude) following auditory or noxious stimulation. EEG background reactivity has the advantage to represent a simple, reproducible and dichotomous evaluation.

The EEG background activity has also been suggested to be a marker of the future cognitive status. A small study (15 patients) showed that chronic (mean delay between the EEG evaluation and the cardiac arrest: 48 days) EEG activity graded according to the Synek score (**Table 1**) [17] was correlated with cognitive function at three months [18]. Of note, the Synek scale implies that discontinuous patterns are not reactive, this at times proves incorrect in our experience.

"Malignant" patterns

So called "malignant" patterns include, according to the AAN recommendations: diffuse background suppression below 20µV, burst-suppression (**Figure 2**), alpha and theta coma, and generalized periodic complexes on an isoelectric backgound [3]. We observed also a sort of "seizure-suppression pattern", in which electrographic seizures alternate with flat background during TH [12]. These represent a grouping of EEG features, which have been showed to be clearly associated with poor outcome in patients without therapeutic hypothermia. Unfortunately, there are not enough data to assess every pattern independently, but a study [7] showed that generalized epileptiform activity or diffuse suppression lower than 20µV shows a stronger association with poor outcome than other patterns (e.g., alpha/theta-coma or burst-suppression pattern);

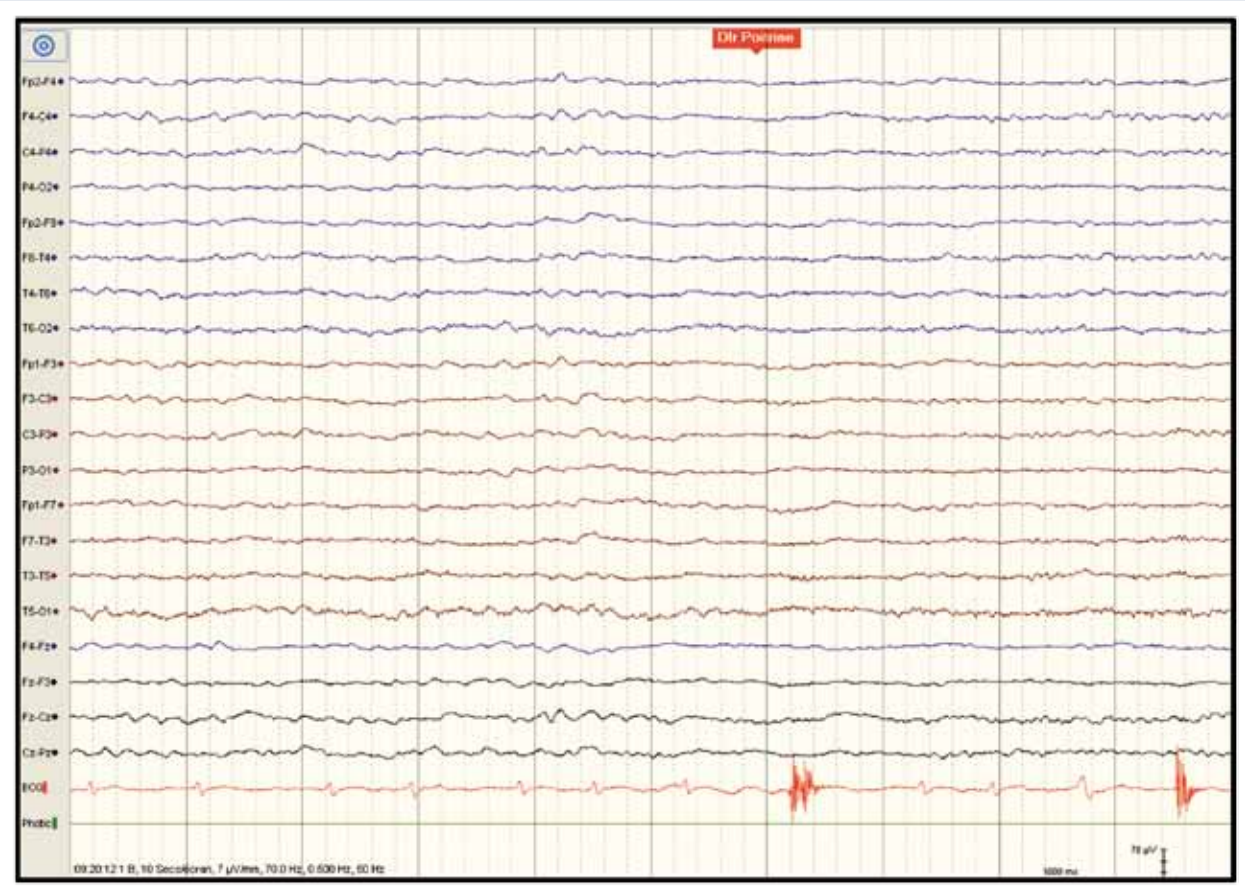

Figure 1: Background reactivity: clear change in background frequency (and mostly amplitude) following stimulation (red mark). Bipolar montage. Filter: highpass: 0.5 Hz / lowpass: 70 Hz / notch: 50

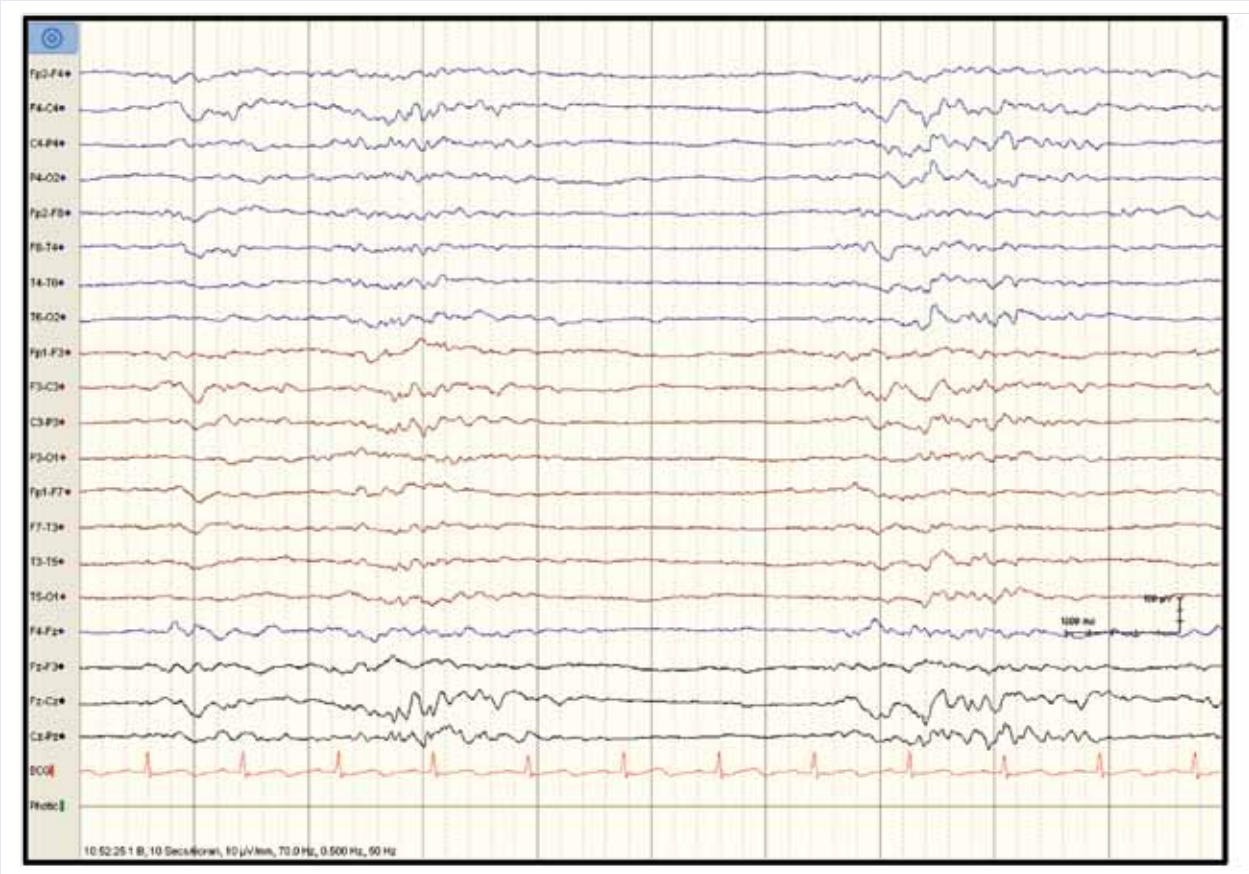

Figure 2: Burt-Suppression pattern: Bipolar montage. Filter: highpass: 0.5 Hz / lowpass: 70 Hz / notch: 50 Hz.

however, confidence intervals were too large to make these conclusions reliable. The "alpha coma pattern", a nonreactive trace with (slow) and poorly developed alpha frequencies, appears uncertain as regards outcome prediction. Regaining consciousness or dying during hospitalization did not differ significantly among unconscious patients with or without alpha frequencies in their EEGs [19]. Another work indicated a high mortality and morbidity associated with alpha coma, but patients with some EEG reactivity (which *strictu sensu* excludes the classical alpha coma pattern) could regain a reasonable functional outcome [20]. Of note in these two studies, "alpha coma" was defined as a comatose patient with alpha frequencies on EEG without any further detail on its reactivity.

Another pattern called "Stimulus Induced Rhythmic, Periodic or Ictal Discharges" (SIRPIDs) (**Figure 3**) is also important in comatose patients, albeit only few studies have been dedicated to it, probably because it has been described only recently [21]. Periodic, rhythmic, or ictal-appearing discharges were defined as consistently induced by alerting stimuli or patient care activities. The original report included only one patient suffering from post-anoxic coma. A recent analysis by our group [22] observed this pattern in 13.3% (14/105) comatose survivors of cardiac arrest. None of the patients with SIRPIDs during TH survived, whereas three survived when SIRPIDs occurred only after rewarming (one reaching a good functional outcome). In view of the relatively low numbers, this observation needs confirmation, but SIRPIDs, particularly if appearing during TH, seem to reflect a severe neuronal damage and thus suggest a tendency towards poor outcome.

In conclusion, the principal and cardinal parameter of the EEG of comatose survivors of cardiac arrest is background reactivity evaluation.

Conclusions

Outcome prediction of comatose survivors after cardiac arrest is a major challenge for the involved clinicians, as following their evaluation, life support can be withdrawn. Several studies have been performed in this field, and multiple prognostic tools are available. We have shown in this short review that the EEG represents one of the most important assessments, especially since the implementation of therapeutic hypothermia. Obviously it has to be included in a comprehensive multimodal evaluation including somatosensory evoked potentials, clinical examination, biological parameters (neuron-specific enolase), and neuro-imaging. The absence of EEG background reactivity and the so-called "malignant EEG patterns" seems robust

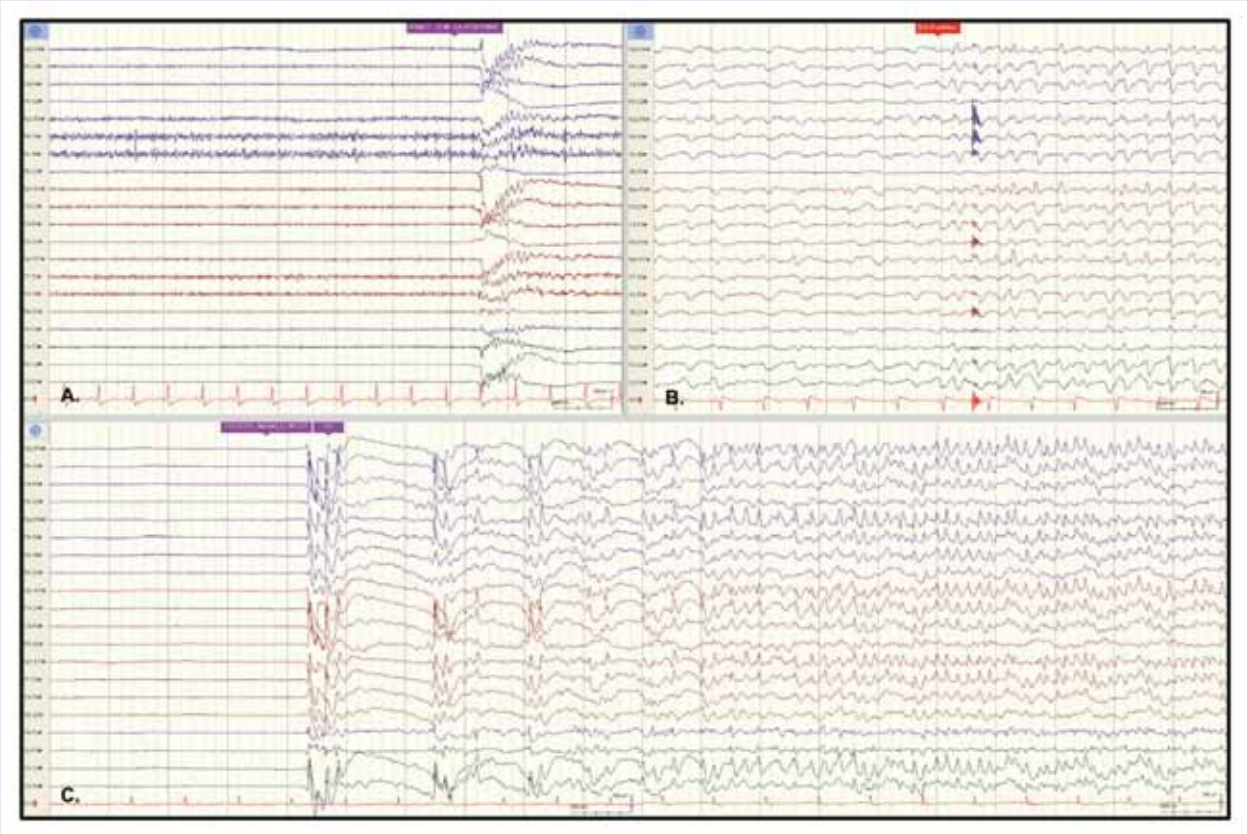

Figure 3: SIRPIDs in comatose patients after cardiac arrest on bipolar montage: Colored marks on the top represent the time of painful stimuli. Bipolar montage. Filter: highpass: 0.5 Hz / lowpass: 70 Hz / notch: 50 Hz. A) Rhythmic pattern. B) Periodic pattern. C) Ictal pattern; this evolving periodic pattern lasted for one minute, then decreased in amplitude and frequency over 30 seconds, and the suppressed background reappeared.

indicators of bad outcome, but decisions upon interruption of supporting care should never be taken based on a single parameter [23]. EEG recordings should be obtained in the best possible conditions, with all confounding factors under control, and assessed in view of the clinical context. It is to hope that more data will add to the current understanding of prognostication after cardiac arrest, and the implementation of integrated assessments using cognitive evoked potentials [24] may improve the reliability of this prognosis.

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1 BAG, SL, 1.10.2012
2 diabetische periphere Neuropathie, postherpetische Neuralgie

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1 BAG, SL, 1.10.2012
2 Crepeau AZ et al. Levetiracetam: a comprehensive review, Expert Rev Neurother, 2010 Feb. 10(2), 159–171

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Epilepsie-Liga

forscht – hilft – informiert

PD Dr. med. Fabienne Picard, Epilepsie-Liga-Mitglied, hatte zum Ziel, mit einer DVD über Kunst und Epilepsie Menschen anzusprechen, welche sich vor dieser Krankheit fürchten, sie unheimlich finden und am liebsten nichts darüber wissen möchten. Sie verpackt Informationen mit Kunstgenuss, die Epilepsie-Liga freut sich über das Angebot, diese DVD in ihre Reihe aufnehmen zu dürfen.

Die DVD „Art + Epilepsie“ beleuchtet eine ungewöhnliche Seite der Epilepsie: Das Thema Kunst und Epilepsie wird aus drei unterschiedlichen Perspektiven verdeutlicht. Einerseits zeugen die Werke von Dostojewski, Flaubert und Van Gogh von der Innensicht epilepsiebetroffener Künstler. Andererseits stellt sich für die Betrachter der DVD die Frage, was die Bilder von Van Gogh und die Texte der beiden weltberühmten Dichter bei ihnen auslösen. Bleibt die Interpretation des Schauspielers und des Pianisten: Was machen Alain Carré und François-René Duchâble mit den Kunstwerken, wie interpretieren sie diese? Die DVD wurde in französischer Sprache produziert mit deutschen Untertiteln, begleitet von einem Booklet auf Deutsch und auf Französisch.

Bestellgutschein

Senden Sie mir bitte:

	D	F	I
Flyer „Epilepsie im Alter“	■	■	
Flyer „Mann und Epilepsie“	■	■	■
Flyer „Was ist Epilepsie“	■	■	■
Flyer „Ursachen von Epilepsien“	■	■	■
Flyer „Merkmale von Anfällen“	■	■	■
Flyer „Häufige Anfallsformen bei Kindern“	■	■	■
Flyer „Medikamentöse Behandlung“	■	■	■
Flyer „Erste Hilfe bei Epilepsie“	■	■	■
Flyer „Frau und Epilepsie“	■	■	■
Flyer „Kinderwunsch und Epilepsie“	■	■	■
Flyer „Reisen und Epilepsie“	■	■	■
Programmheft Veranstaltungen der Epilepsie-Liga	■	■	
Flyer „Autofahren und Epilepsie“	■	■	■
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Flyer „Arbeit und Epilepsie”	■	■	
Fachzeitschrift „Epileptologie“	■	■	
Flyer „Ketogene Diäten“	■	■	
Einzahlungsschein(e) zur Unterstützung der Epilepsie-Liga	■	■	■
Ratgeber für Legate	■	■	■
Ratgeber „Epilepsie und Versicherungen”	■	■	■
Flyer „Vagusnervstimulation“	■	■	
Flyer „Compliance“	■	■	

DVDs und übrige Publikationen siehe www.epi.ch

Ich (wir) möchte(n):

■ Einzelmitglied der Epilepsie-Liga werden und bezahle mindestens 50 Franken jährlich.

■ Kollektivmitglied der Epilepsie-Liga werden und bezahlen mindestens 100 Franken jährlich.

Epilepsie-Preise

Gerne machen wir Sie auf die Broschüre „Epilepsie. Auszeichnungen, Preise, Stipendien und Stiftungen 2012/2013“ von Günter Krämer und Claudia Mühlebach aufmerksam. Darin finden Sie alle Informationen (Termine, Bedingungen), die Sie für eine Bewerbung benötigen. Bitte weisen Sie mögliche Anwärter in Ihrem Umfeld auf die Broschüre hin. Diese können Sie auf www.epi.ch unter Publikationen herunterladen oder bei info@epi.ch bzw. der Geschäftsstelle der Epilepsie-Liga, Seefeldstrasse 84, Postfach 1084, 8034 Zürich, bestellen.

Absender/in

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Bitte frankieren

Schweizerische Liga gegen Epilepsie

Seefeldstrasse 84
Postfach 1084
CH 8034 Zürich

Epilepsie-Liga-Mitteilungen

Ausschreibung – Forschungsförderung

Förderung der wissenschaftlichen Forschung im Bereich der Epilepsie (vorwiegend Starthilfen) durch die Schweizerische Liga gegen Epilepsie (Epilepsie-Liga)

Die Epilepsie-Liga unterstützt wissenschaftliche Projekte im Bereich der Epileptologie im Gesamtbetrag von

CHF 20'000.—

pro Jahr. Insbesondere soll die Erforschung von Ursachen und Behandlungen der Epilepsie gefördert werden.

Stipendien für Aus- oder Weiterbildung oder Auslandaufenthalte werden nicht ausgerichtet. Hingegen können Reise- und Aufenthaltskosten (ohne Salär) für Kurzaufenthalte (maximal einige Wochen) finanziert werden, sofern sie dem Erlernen von Methoden dienen, welche im Rahmen eines unterstützten Projektes in der Schweiz eingesetzt werden.

Falls der Antragsteller/die Antragstellerin bereits anderswo Anträge für Unterstützung gestellt hat, ist offen zu legen, bei wem und mit welchem Ergebnis.

Termin für die Einreichung von Gesuchen: 31. Dezember 2012

Formulare und Wegleitung für Gesuchstellende können angefordert werden bei:

Schweizerische Liga gegen Epilepsie
Seefeldstrasse 84 | Postfach 1084
8034 Zürich
Tel. 043 488 67 77 | Fax 043 488 67 78
info@epi.ch

Bitte vormerken

Die nächste Mitgliederversammlung findet statt am 10. Mai 2013 von 11.30 bis 12.00 Uhr im Congress Centre Kursaal in Interlaken.

Vorschau Epileptologie 1 | 2013

Seltene Krankheiten (Orphan Diseases)

Als seltene Krankheiten („orphan diseases") werden meist genetisch bedingte Krankheitsbilder bezeichnet, die in Europa weniger als 5 pro 100 000 Einwohner betreffen. Seltene Krankheiten sind oft lebensbedrohliche oder chronisch einschränkende Erkrankungen, die häufig erhebliche negative Auswirkungen auf die Lebensqualität der Betroffenen und ihre Familien haben. Einige dieser „orphan diseases" sind mit oft therapieschwierigen Epilepsien verbunden. Vor allem diagnostische und therapeutische Aspekte einzelner seltener Erkrankungen, die gelegentlich auch Behandlungswege erfordern, die über die konventionelle medikamentöse antikonvulsive Therapie hinausgehen, aber auch ethische Überlegungen zu diesem Themenkomplex sind Thema der nächsten Ausgabe "Epileptologie".

Ausschreibung – Promotionspreis

Die Schweizerische Liga gegen Epilepsie (Epilepsie-Liga) vergibt alle 3 Jahre einen Preis in Höhe von

CHF 10'000.—

für die beste Dissertation auf dem Gebiet der Epileptologie.

Bewerbungen sind aus allen Fachbereichen und Berufsgruppen möglich und erwünscht, sowohl aus Grundlagen- als auch klinischen Fächern. Eine Altersbeschränkung erfolgt nicht.

Das Preisrichterkollegium setzt sich aus drei Vorstandsmitgliedern der Epilepsie-Liga zusammen, das bei Bedarf zusätzlich externe Gutachter hinzuziehen kann. Es trifft seine Entscheidung in geheimer Wahl.

Falls der Antragsteller/die Antragstellerin bereits anderswo Anträge für Unterstützung gestellt hat, ist offen zu legen, bei wem und mit welchem Ergebnis.

Die Preisverleihung erfolgt jeweils im darauf folgenden Jahr anlässlich der Jahrestagung oder Mitgliederversammlung der Epilepsie-Liga.

Bewerbungen sind **bis zum 31.12.2012** an die **Geschäftsstelle der Epilepsie-Liga** (Seefeldstrasse 84, Postfach 1084, 8034 Zürich) einzureichen und müssen beinhalten: vier Exemplare der abgeschlossenen und beim Dekanat eingereichten Dissertation, vier Exemplare einer Stellungnahme des Doktorvaters (dabei kann es sich auch um das entsprechende Gutachten für die Dissertation handeln).

Herzliche Gratulation!

Die Epilepsie-Liga gratuliert ihrem Ehrenpräsidenten Professor Dr. med. Franco Vassella zu seinem 80. Geburtstag. Sie überbringt ihm nicht nur Glückwünsche für Gesundheit und Wohlergehen, sondern auch Dank für seine besonderen Dienste in der schweizerischen Epileptologie, für die er 2011 an der Dreiländertagung in Graz mit der Tissot-Medaille ausgezeichnet wurde.

Der gebürtige Bündner studierte an den Universitäten Fribourg und Zürich. Nach dem Staatsexamen begann er seine klinische und wissenschaftliche Ausbildung im Bereich der neurologischen Wissenschaften an der Neurochirurgischen Universitätsklinik Zürich bei Professor Krayenbühl und in der Neurophysiologie am Physiologischen Institut der Universität Zürich bei Professor Wyss. Es folgte eine neuropädiatrische Ausbildung in der Kinderneurologie an der Karolinska-Universität in Stockholm. Franco Vassella bildete sich auch weiter am Hôpital St. Vincent-de-Paul in Paris und am Department of Neurology des Hospital for Sick Children in London.

1966 schloss der Jubilar an der Universitätskinderklinik Bern bei Professor Rossi ab, wo er in der Folge in enger Kooperation mit der Neurologischen Universitätsklinik und deren Abteilung für Epileptologie eine Abteilung für Kinderneurologie aufbaute. 1972 wurde er dort Chefarzt, 1975 vollamtlicher Extraordinarius und 1992 Ordinarius für Pädiatrie an der Medizinischen Fakultät der Universität Bern. Seine zahlreichen Aktivitäten in wissenschaftlichen Gesellschaften, seine vielen Publikationen und seine Lehrtätigkeit haben Früchte getragen. Franco Vassella ist uns bis heute Ansporn und Vorbild geblieben.

Dr. med. Günter Krämer für den Vorstand und die Geschäftsstelle der Schweiz. Liga gegen Epilepsie

Sincères félicitations!

La Ligue contre l'Epilepsie félicite son président d'honneur, le Professeur Dr Franco Vassella, pour ses 80 ans. Elle associe à ses meilleurs vœux de santé et de bonheur une profonde gratitude pour une vie consacrée à l'épileptologie suisse et réitère ainsi une admiration qui avait déjà trouvé son expression dans la remise de la médaille Tissot en 2011, à l'occasion du congrès trinational de Graz.

Né aux Grisons, le Professeur Vassella a fait ses études aux Universités de Fribourg et Zurich. Après son examen final, il a commencé une formation clinique et scientifique dans le domaine des sciences neurologiques à la Clinique universitaire de neurochirurgie à Zurich chez le professeur Krayenbühl et des études de neurophysiologie à l'Institut universitaire de physiologie chez le professeur Wyss. Il a enchaîné avec une formation neuropédiatrique au Département de neurologie pédiatrique de l'Université Karolinska à Stockholm. Franco Vassella a également suivi des formations complémentaires à l'Hôpital St. Vincent-de-Paul à Paris et au Departement of Neurology, Hospital for Sick Childen à Londres.

En 1966, le professeur Vassella obtenait son doctorat à la Clinique universitaire de Berne, auprès du professeur Rossi, où il mit ensuite sur pied un Service de neurologie pédiatrique en étroite collaboration avec la Clinique universitaire de neurologie et son Département d'épileptologie. En 1972, il y était nommé médecin-chef, en 1975, il devenait professeur extraordinaire à temps plein et en 1992, professeur ordinaire de pédiatrie à la Faculté de médecine de l'Université de Berne. Ses innombrables contributions dans des sociétés scientifiques, son activité fournie de publication et son engagement pour l'enseignement et le transfert de connaissances ont porté des fruits : Franco Vassella reste pour les jeunes générations un exemple motivant à suivre.

Dr méd. Günter Krämer pour le comité et le secrétariat général de la Ligue Suisse contre l'Epilepsie

Mise au concours – Soutien de la recherche

Promotion de la recherche scientifique dans le domaine de l'épilepsie (surtout sous forme d'aide initiale) par la Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie)

La Ligue contre l'Epilepsie soutient les projets scientifiques dans le domaine de l'épileptologie par un montant total de

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 décembre 2012

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

Ligue Suisse contre l'Epilepsie
Seefeldstrasse 84
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Mise au concours – Prix de promotion

La Ligue Suisse contre l'Epilepsie (Ligue contre l'Epilepsie) décerne tous les 3 ans un prix d'un montant de

CHF 10'000.—

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

31.12.2012

et comporter les pièces suivantes :

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

A noter

La prochaine assemblée générale aura lieu à Interlaken (Congress Centre Kursaal) le 10 mai 2013 de 11h30 à 12h00.

FIRST ANNOUNCEMENT

8. Dreiländertagung 2013

Gemeinsame Jahrestagung der Deutschen und Österreichischen Gesellschaften für Epileptologie und der Schweizerischen Liga gegen Epilepsie

Gast: Arbeitsgemeinschaft für prächirurgische Diagnostik und operative Epilepsietherapie

Deadline Abstract-Einreichung
15. Januar 2013

08.–11. Mai 2013

Congress Centre Kursaal Interlaken, Schweiz
www.imk.ch/epilepsie2013

Organized by IMK Institut für Medizin und Kommunikation AG

MICHAEL PREIS 2013

Für die beste, zum wissenschaftlichen Fortschritt beitragende Arbeit auf dem Gebiet der Epileptologie.

Im Jahr 1963 zur Anregung der Epilepsieforschung erstmals ausgeschrieben, ist der von der STIFTUNG MICHAEL, einer privaten deutschen Stiftung, ausgelobte MICHAEL PREIS zu einer der höchst angesehenen internationalen Auszeichnungen für Beiträge zur wissenschaftlichen und klinischen Forschung auf dem Gebiet der Epileptologie geworden.

Der jetzt mit **20'000 Euro** dotierte MICHAEL PREIS wird alle zwei Jahre verliehen, i.d.R. auf dem Internationalen Epilepsie Kongress ; er möchte vor allem für jüngere Wissenschaftler (normalerweise nicht älter als 45 Jahre) Anreiz und Ermunterung sein, wissenschaftliche und klinische Forschung auf dem Gebiet der Epileptologie zu betreiben. Für den MICHAEL PREIS 2013 können bis zu drei Publikationen oder bisher noch nicht veröffentlichte Manuskripte **in englischer Sprache** eingereicht werden; mindestens eine dieser Arbeiten muss aus den Jahren 2011 / 2012 stammen. Die Arbeiten müssen, zusammen mit einem Lebenslauf, per electronic mail **spätestens bis zum 31. Dezember 2012** bei der STIFTUNG MICHAEL eingegangen sein.

.

Mitglieder des Preisrichter-Kollegiums sind:
Uwe Heinemann, Berlin, Deutschland
Matthias Koepp, London, Grossbritannien
Solomon Moshé, New York, USA

Adresse für Einsendungen und / oder für weitere Information (bitte per electronic mail):

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Seit 2006 wird der MICHAEL PREIS von der Firma UCB International gesponsert.

Alfred-Hauptmann-Preis

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.

Arbeiten werden besonders aus den Fachgebieten Neurologie, Pädiatrie, Psychiatrie, klinische Pharmakologie, Neurophysiologie und Neurobiologie erwartet.

Die ausgezeichneten Personen erhalten eine Urkunde. Darüber hinaus ist der Preis mit

10’000 Euro

dotiert. Das Preisgeld wird ab 2009 von der Firma UCB GmbH (Deutschland), Monheim, zur Verfügung gestellt. Es können mehrere Einzelpersonen oder Arbeitsgruppen ausgezeichnet werden.

Die Arbeiten sollten in englischer Sprache verfasst sein. Zusätzlich zu den Arbeiten sind folgende weitere Unterlagen einzureichen:

- ein Lebenslauf,
- eine Stellungnahme des Klinik-/Institutsvorstandes zur Bewerbung,
- für den Fall von Mehrautorenarbeiten, bei denen nicht alle Autoren am Preis beteiligt werden sollen, eine Aussage über den Anteil der einzelnen Autoren an der publizierten Arbeit.

Die Arbeiten sind in vierfacher Ausführung bis zum

31.12.2012

an den Vorsitzenden des Kollegiums zu senden:

Herrn Dr. med. Günter Krämer
Medizinischer Direktor
Schweizerisches Epilepsie-Zentrum
Bleulerstrasse 60
CH 8008 Zürich

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, Günther Sperk, Univ.-Prof. Dr. Abteilung Pharmakologie, Medizinische Universität, Innsbruck.

Drei neue Informationsflyer

Die Reihe der Informationsflyer „Info Epilepsie" der Epilepsie-Liga wurde durch drei wichtige Themen ergänzt: Ketogene Diäten, Vagusnervstimulation und Zusammenarbeit mit dem Arzt, auch Compliance oder Adhärenz genannt.

Die Vagusnervstimulation ist eine Möglichkeit zur Behandlung von Epilepsien, die auf Medikamente alleine nicht ausreichend ansprechen. Dazu wird ein batteriebetriebenes Stimulationsgerät in Art eines Herzschrittmachers unterhalb des Schlüsselbeins unter die Haut implantiert und mit dem Nervus vagus am Hals verbunden.

Ketogene Diäten sind extrem fettreiche, kohlenhydratarme, Eiweiss- und Kalorien-bilanzierte Diäten, die den Stoffwechselzustand des Fastens nachahmen. Diese Diäten kommen prinzipiell für alle Menschen mit einer Epilepsie in Frage, bei denen eine übliche medikamentöse Behandlung allein nicht erfolgreich ist, unabhängig vom Lebensalter.

Eine erfolgreiche Zusammenarbeit von Patienten und Ärzten (Patientinnen und Ärztinnen sind selbstverständlich mit gemeint), setzt gegenseitiges Vertrauen und Respekt voraus. Zum Gelingen einer Therapie braucht es beide Partner. Das gilt in besonderem Masse für die Epilepsiebehandlung.

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

Trois nouveaux dépliants informatifs

Trois nouveaux thèmes importants sont venus enrichir la série des « Infos Epilepsie » de la Ligue contre l'Epilepsie : le régime cétogène, la stimulation du nerf vague et la collaboration avec le médecin, également appelée compliance ou adhérence.

La stimulation du nerf vague est une méthode de traitement des épilepsies qui restent réfractaires aux seuls traitements médicamenteux. Elle consiste à implanter sous la peau, un peu en dessous de la clavicule, et de relier au nerf vague situé dans le cou, un générateur à piles ressemblant à un stimulateur cardiaque.

Les régimes cétogènes sont extrêmement riches en matières grasses, pauvres en hydrates de carbone, avec chiffrage des apports de protéines et de calories, qui imitent l'état métabolique d'un jeûne. Ces régimes entrent en considération pour toutes personnes épileptiques chez lesquelles le traitement médicamenteux seul reste sans effet, indépendamment de leur âge.

Pour être couronnée de succès, la collaboration entre patients et médecins (les patientes et les femmes médecins sont évidemment incluses) doit être marquée par la confiance et le respect mutuels. Les deux parties doivent travailler ensemble à la réussite d'une thérapie. C'est particulièrement vrai dans le cas d'un traitement antiépileptique.

Les dépliants informatifs peuvent être demandés à la Ligue contre l'Epilepsie, tél. 043 488 67 77 ou info@epi.ch.

2013

22.-26.1.2013 | Brno, Tschechien
3rd Course on Epilepsy Surgery. Advanced course
Information: Dr. Çigdem Özkara,
e-mail: cigdemoz@istanbul.edu.tr

16.-23.3.2013 | San Diego, USA
65th 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

21.3.2013 | Zürich
SAPP-Workshop: Epilepsie und Schwangerschaft/ Stillzeit
Information: Schweizerische Arbeitsgemeinschaft für perinatale Pharmakologie (SAPP),
e-mail: sappinfo@bluewin.ch,
www.sappinfo.ch

21.-23.3.2013 |Leipzig, Deutschland
57. Wissenschaftliche Jahrestagung der Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung (DGKN)
Information: Conventus Congressmanagement & Marketing GmbH, Justus G. Appelt, Carl-Pulfrich-Strasse 1, D 07745 Jena, Deutschland,
Tel. 03641 / 3116311,
Fax 03641 / 3116240,
e-mail: dgkn@conventus.de,
www.conventus.de

6.4.2013 | Zürich, Schweiz. Epilepsie-Zentrum
Frühjahrssymposium
Information: Silvia Baader,
Tel. 0041 / 44 / 3876304,
Fax 0041 / 44 / 3876396,
e-mail: silvia.baader@swissepi.ch,
www.swissepi.ch

11.-14.4.2013 | Istanbul, Türkei
7th World Congress on Controversies in Neurology (CONy)
Information: ComtecMed, 53 Rothschild Boulevard, PO Box 68, Tel Aviv, 61000,Israel,
Tel. 00972 / 3 / 5666166,
Fax 00972 / 3 / 5666177,
e-mail: info@comtecmed.com,
www.comtecmed.com/CONy

8.-11.5.2013 | Interlaken
8. Gemeinsame Jahrestagung der Deutschen und Österreichischen Gesellschaft für Epileptologie und Schweizerischen Liga gegen Epilepsie
Information: IMK Institut für Medizin und Kommunikation AG, Münsterberg 1, CH 4001 Basel,
Tel. 0041 / 61 / 2713551,
Fax 0041 / 61 / 2713338,
e-mail: congress@imk.ch,
www.imk.ch

16.5.2013 | Chur
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Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch, www.epi.ch

16.5.2013 | Bern, Inselspital
134. Epilepsie- und EEG-Kolloquium
Information: Inselspital, EEG-Sekretariat, 3010 Bern,
Tel. 0041 / 31 / 6323054,
e-mail: regula.kunz@insel.ch

18.-24.5.2013 | Cleveland, Ohio, USA
6th International Epilepsy Colloquium
Information: e-mail: medcme@case.edu,
www.casemed.case.edu/cme

5.-7.6.2013 | Montreux
2nd Congress Swiss Federation of Clinical Neuro-Societies (SFCNS)
Information: Music & Convention Center Montreux,
www.imk.ch/sfcns2013

14.6.2013 | Bern, Inselspital
Epilepsie Laienveranstaltung
Information: Inselspital, EEG-Sekretariat, 3010 Bern,
Tel. 0041 / 31 / 6323054,
e-mail: regula.kunz@insel.ch

23.-27.6.2013 | Montreal, Canada
30th International Epilepsy Congress
Information: ILAE/IBE Congress Secretariat,
7 Priory Hall, Stillorgan, Dublin 18, Ireland,
e-mail: claire@epilepsycongress.org

15.8.2013 | Basel, Hotel Hilton, 9.30 – 18.00 Uhr
Basler Epilepsietag: Epilepsie – Therapeutische Optionen
Information : Tel. 0041 / 61 / 2654166
e-mail: jfleury@uhbs.ch

4.-6.9.2013 | Ljubljana, Slowenien
13th European Conference on Epilepsy & Society
Information: IBE Congress Secretariat,
7 Priory Hall, Stillorgan, Dublin 18,
Ireland,
Tel. 0353 / 1 / 2056720,
Fax 0353 / 1 / 2056156,
e-mail: Ljubljana@epilepsycongress.org

19.9.2013 | Bern
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e-mail: info@epi.ch,
www.epi.ch

21.-26.9.2013 | Wien, Österreich
21st World Congress of Neurology
Information: Univ.-Prof. Dr. Bruno Mamoli,
Garnisongasse 7/22, A 1090 Wien, Österreich,
Tel. 0043 / 1 / 512809019,
Fax 0043 / 1 / 512809180,
e-mail: oegn@admicos.com,
www.oegn.at

23.-27.9.2013 | Montreal, Kanada
30th International Epilepsy Congress
Information : ILAE/IBE Congress Secretariat,
7 Priory Hall, Stillorgan, Dublin 18, Irland,
Tel.00353 / 1 / 2056720,
Fax 00353 / 1 / 2056156,
e-mail: montreal@epilepsycongress.org,
www.epilepsymontreal2013.org

26.9.2013 | Zürich, Schweiz. Epilepsie-Zentrum
Herbstsymposium
Information: Silvia Baader,
Tel. 0041 / 44 / 3876304,
Fax 0041 / 44 / 3876396,
e-mail: silvia.baader@swissepi.ch,
www.swissepi.ch

30.9.-06.10.2013 | Jerusalem, Israel
5th 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

10.10.2013 | Genf
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Fax 0041 / 43 / 4886778,
e-mail: info@epi.ch, www.epi.ch

6.-10.12.2013 | Washington, DC, USA
67th Annual Meeting of the American Epilepsy Society
Information: American Epilepsy Society, 342 North
Main Street, West Hartford, CT 06117-2507 USA,
Tel. 001 / 860 / 5867505,
Fax 001 / 860 / 5867550,
e-mail: info@aesnet.org, www.aesnet.org

30.11.2013 | Zürich
Patiententag
Information: Epilepsie-Liga, Seefeldstrasse 84,
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