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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