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Inhalt

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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).
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- 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.
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PD Dr. med. Jan Novy

Liebe Leserinnen und Leser, liebe Kolleginnen und Kollegen

Obwohl es seit langem bekannt ist, dass für Menschen mit Epilepsie traurigerweise ein Risiko vorzeitiger Sterblichkeit besteht, konnte erst in den letzten Jahrzehnten Licht in die Ursachen dieser Sterblichkeit gebracht werden. Studien mit historischen Krankenregistern, die an den Anfang des 20 Jahrhunderts zurückdatieren, konnten nachweisen, dass bereits damals ein Zusammenhang von vorzeitiger Sterblichkeit und Epilepsie bestand. Die Studien der letzten zwei Jahrzehnte zeigen, dass die Ursachen vorzeitiger Sterblichkeit und Epilepsie vielfältig sind. Plötzlich auftretender, ungeklärter Tod bei Epilepsie – SUDEP – die dramatischste Form vorzeitiger Sterblichkeit im Rahmen der Erkrankung, verdient hierbei besondere Beachtung, da sie vor allem junge Patienten betrifft. Auch andere Ursachen vorzeitiger Sterblichkeit müssen bedacht werden, so die Sterblichkeit assoziiert mit den zugrundeliegenden Ursachen von Epilepsie (zum Beispiel Hirntumore, bei denen der Tod häufig frühzeitig im Krankheitsverlauf der Epilepsie auftritt), Unfalltod, Status epilepticus, aber auch vorzeitige Sterblichkeit im Rahmen von somatischen Begleiterkrankungen. Darüber hinaus wird zunehmend klarer, dass Patienten mit Epilepsie ein Risiko frühzeitiger Sterblichkeit aufgrund von Krankheiten tragen, die in keinem offensichtlichen Zusammenhang mit der Epilepsie stehen.

Diese Ausgabe der Epileptologie ist den multiplen Facetten dieser frühzeitigen Sterblichkeit gewidmet. Wir freuen uns sehr, Beiträge von internationalen Experten auf diesem Gebiet gewonnen zu haben. Sara Zagaglia, Vera Braatz, und Josemir Sander werden die Gesamtsterblichkeit bei Epilepsie darstellen, indem sie die verschiedenen Ursachen erläutern. Carolina Ciumas und Philippe Ryvlin werden eine Übersicht über die neuesten Entwicklungen betreffend SUDEP, dessen Pathophysiologie und potenzielle Präventionsmöglichkeiten geben. Ich werde mit Aikaterini Serkedaki den Aspekt der somatischen Komorbiditäten, deren gehäufte Prävalenz bei Patienten mit Epilepsie und die Zusammenhänge mit der Krankheitsaktivität und frühzeitiger Sterblichkeit beleuchten. Abschliessend wird Aidan Neligan eine Zusammenfassung über die Sterblichkeit in Verbindung mit dem Status epilepticus und die Mut machenden Entwicklungen der vergangen Jahre geben. Ich möchte mich herzlich bei allen Autoren für ihre wertvollen Beiträge zu dieser Ausgabe bedanken. Ebenfalls bedanke ich mich bei Alexander Maurer für die deutschen Übersetzungen.

Obwohl die Möglichkeiten einer Prävention der frühzeitigen Sterblichkeit bei Epilepsie noch beschränkt sind, stellt die Information von Patienten, Angehörigen und medizinischem Personal eine wichtige Massnahme dar, insbesondere bei Persistieren von generalisierten Anfällen im Rahmen einer unzureichend kontrollierten Epilepsie. Die aktuellen Leitlinien der Amerikanischen Gesellschaft für Epilepsie (dargestellt im Beitrag von Carolina Ciumas und Philippe Ryvlin) unterstreichen umso mehr die Notwendigkeit, Risikopatienten durch Angaben der geschätzten Inzidenz des plötzlichen Todes in verschiedenen Patientengruppen zu informieren. Es gibt nur eingeschränkte Möglichkeiten, die Sterblichkeit aufgrund von Komorbiditäten zu beeinflussen, das sich stetig verbessernde Verständnis der zugrundeliegenden Mechanismen lässt jedoch hoffen, in der zukünftigen Patientenbetreuung diesbezüglich eine aktive Rolle einnehmen zu können.

Ich hoffe, dass Sie Interesse an der vorliegenden Ausgabe finden, und wünsche Ihnen eine angenehme Lektüre.

Jan Novy

PD Dr. med. Jan Novy

Dear Readers, dear Colleagues,

Although it is known for long that sadly people with epilepsy are at risk of premature mortality, the mechanisms of this mortality became increasingly clearer only over the last decades. Historical register studies going back to the beginning of the twentieth century revealed indeed that there was already premature mortality associated with the condition at that time. Research in the last two decades showed that causes of premature mortality in epilepsy are multiple. Sudden Unexpected Death in Epilepsy (SUDEP) being the most catastrophic form of premature mortality in the disease, deserves a special attention, it affects moreover mostly young patients. Other causes of premature mortality need to be considered as well; such as mortality associated with the underlying cause of the epilepsy (brain tumour for instance, mortality occurring in most cases early in the course of the disease), accidental death, status epilepticus, but also long term premature mortality in link with somatic comorbidities. It is indeed increasingly clear that people with epilepsy suffer from premature mortality on the long term from conditions that do not show any obvious relationship with the disease.

This issue of Epileptology will focus on the multiple aspects of premature mortality in epilepsy. We are particularly privileged to have contributions of international experts in this field for this issue. Sara Zagaglia, Vera Braatz and Josemir Sander will discuss the overall mortality in the disease reviewing the different causes. Carolina Ciumas and Philippe Ryvlin will review the most recent development regarding SUDEP, its pathophysiology and potential prevention. I will review with Aikaterini Serkedaki the aspect of somatic comorbidities, their increased prevalence in people with epilepsy and their relationship with the disease activity and premature mortality. Finally, Aidan Neligan will review mortality in status epilepticus and its temporal evolution which seems encouraging. I would like to thank all authors for their much appreciated contributions to this issue. I would also like to thank Alexander Maurer for the German translations.

Although prevention of premature mortality in epilepsy is still limited, informing patients, relatives and caregivers is important for SUDEP particularly in situations when epilepsy is not controlled when generalized convulsive seizures continue to occur. Recent practice guidelines of the American Epilepsy Society (discussed in this issue by Carolina Ciumas and Philippe Ryvlin) further highlighted the need to inform patients at risk. These guidelines provide incidence estimates in different populations for this purpose. There are currently limited ways to act on the mortality risk due to comorbidities, but the continuously improving understanding of its mechanisms brings the hope that the management of patients will be more proactive for that aspect in the future.

I hope that you will find this issue interesting and I wish you a pleasant reading.

Jan Novy

PD Dr méd. Jan Novy

Cher(ère)s lecteur(rice)s, cher(ère)s collègues,

Bien qu'il soit reconnu de longue date que les gens souffrant d'épilepsie ont tristement un risque de mortalité précoce, les mécanismes de cette mortalité ne se sont clarifiés que plus récemment durant ces dernières décennies. Des registres historiques du début du vingtième siècle ont en effet révélé que les patients souffrant d'épilepsie avait déjà à l'époque une mortalité précoce par rapport à la population générale. Les recherches de ces vingt dernières années ont montré que les causes de cette mortalité précoce sont multiples. La mort subite dans l'épilepsie (SUDEP) étant bien entendu la forme la plus dramatique, mérite une attention particulière également car elle touche le plus souvent des patients jeunes. D'autres causes de mortalité doivent également être prises en compte, comme les décès lié à la cause de l'épilepsie (comme les tumeurs cérébrales p.ex., ces décès survenant le plus souvent tôt dans le cours de l'épilepsie), les décès accidentelles, les états de mal épileptiques, mais également les décès précoces liés à des comorbidités somatiques. Il est devenu en effet de plus en plus évident que des patients souffrent d'une mortalité précoce lié à ces pathologies qui semblent sans lien avec l'épilepsie.

Ce numéro d'Epileptologie est consacré à ces multiples facettes de cette mortalité précoce. Nous sommes particulièrement privilégiés d'avoir pour aborder ce sujet des contributions de plusieurs experts internationaux de ce domaine. Sara Zagaglia, Vera Braatz, et Josemir Sander discuterons de la mortalité en générale dans l'épilepsie et résumeront ces différentes causes. Carolina Ciumas et Philippe Ryvlin passeront en revue les développements récents dans le domaine du SUDEP, sa physiopathologie et ses potentiels mesures de prévention. Je passerai en revue avec Aikaterini Serkedaki l'aspect des comorbidités somatiques, leur prévalence augmentée chez les patients souffrant d'épilepsie et leurs relations avec l'activité de la maladie et la mortalité en découlant. Finalement, Aidan Neligan fera le point sur la mortalité liée à l'état de mal épileptique et l'évolution encourageante de cette dernière ces dernières années. J'aimerai remercier tous ces auteurs pour leurs contributions très appréciées à ce numéro. J'aimerai également remercier Alexander Maurer pour les traductions allemandes.

Bien que la prévention de la mortalité précoce dans l'épilepsie soit encore limitée, l'information des patients, des proches et des soignants est importante particulièrement pour le SUDEP quand un contrôle de l'épilepsie n'est pas atteint et que les crises convulsives persistent. Les récentes recommandations cliniques de la société américaine d'épilepsie (AES), discuté ici par Carolina Ciumas et Philippe Rylvin, soulignent davantage cette nécessité d'informer les patients à risque en fournissant des estimations de l'incidence de la mort subite dans différentes populations des patients. Il n'y a que des moyens limités d'influer sur la mortalité liée aux comorbidités, mais la compréhension de ces mécanismes s'améliorant progressivement, nous pouvons espérer que la prise en charge des patients dans ce domaine sera plus proactive dans le futur.

En espérant que vous trouverez ce numéro intéressant, je vous souhaite une bonne lecture.

Jan Novy

Premature Mortality in People with Epilepsy

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Summary

Epilepsy is one of the most common neurological conditions, with an overall good prognosis for seizure control. Despite this, people with epilepsy have an increased risk of premature death compared to the general population. A practical classification of causes of death in epilepsy distinguishes causes directly related to epilepsy and seizure activity (status epilepticus, accidents and sudden unexpected death in epilepsy), structural underlying causes of epilepsy and causes indirectly related to epilepsy. This aetiological heterogeneity contributes to a polyphasic trend of increased risk of death throughout a person's life, even when seizures are in remission. In the first years after diagnosis of epilepsy, causes directly related to the pathogenesis of seizures are the most important determinants of premature death, while indirect causes and comorbidities have a stronger role in the long term. Psychiatric disorders, cardiovascular diseases and cancer are the main comorbidities that have been found to raise the risk of mortality on long-term follow-up studies. Premature mortality in epilepsy is an underestimated, complex and multifactorial problem with major public health impact. As such, it would be important to increase awareness among clinicians and researchers about the magnitude of the problem and the potentially preventable causes.

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Key words: Causes of death, SUDEP, seizure, comorbidities

Mort prématurée chez les personnes atteintes d'épilepsie

L'épilepsie est une des maladies neurologiques la plus commune avec globalement un bon pronostic pour le control des crises. Malgré cela, les personnes souffrant d'épilepsie ont un risque augmenté de mortalité prématurée en comparaison avec la population générale. La classification pragmatique des causes de décès distingue des causes directement en relation avec l'épilepsie et son activité en termes de crises (état de mal épileptique, mort accidentelle et mort subite inattendue dans l'épilepsie), les conséquences des causes structurelles sous-jacentes de l'épilepsie et les causes avec un lien indirect avec l'épilepsie. Cette hétérogénéité étiologique contribue à une distribution polyphasique du risque de décès tout au long de la vie du patient, même si les crises sont en rémission. Dans les premières années suivant le diagnostic d'épilepsie, les causes directement lié à la pathogénèse des crises sont le déterminant le plus important de la mortalité précoce, alors les causes indirectes et les comorbidités ont plus de poids dans le long terme. Les maladies psychiatriques, cardiovasculaires et néoplasiques sont les comorbidités principales qui ont été démontrées comme étant la cause du risque de mortalité dans les études de suivi à long terme. La mortalité prématurée dans l'épilepsie est un problème sous-estimé, complexe multifactoriel avec un impact major en termes de santé publique. En tant que tel, il est important de sensibiliser les cliniciens et chercheurs sur la magnitude du problème et sur ses causes potentiellement évitables.

Mots clés : Causes de mort, mort subite et inexpliquée du patient épileptique, saise, comorbités

Vorzeitige Sterblichkeit bei Menschen mit Epilepsie

Epilepsie ist eine der häufigsten neurologischen Erkrankungen, mit einer insgesamt guten Prognose bezüglich der Anfallskontrolle. Dennoch haben Patienten, die an einer Epilepsie leiden, ein erhöhtes Risiko vorzeitiger Sterblichkeit, verglichen mit der Allgemeinbevölkerung. Die pragmatisch orientierte Klassifikation der epilepsieassoziierten Todesursachen unterscheidet zwischen direkt in Zusammenhang mit der Epilepsie und der Anfallsaktivität stehenden Ursachen (Status epilepticus, Unfälle und plötzlicher unerwarteter Tod bei Epilepsie (SUDEP)), der Epilepsie zugrundeliegenden strukturellen Ursachen und Ursachen, die in indirekter Verbindung zur Epilepsie stehen. Diese Heterogenität bezüglich der Ursachen trägt, selbst bei anfallsfreiem Verlauf, zu einer polyphasischen Verteilung des Sterblichkeitsrisikos im Laufe des Lebens der Patienten bei. In den ersten Jahren nach der Diagnose der Epilepsie sind die Ursachen, die in direkter Verbindung zur Pathogenese der Anfälle stehen, die wichtigsten Determinanten von vorzeitiger Sterblichkeit, während die indirekten Ursachen und die Begleiterkrankungen die wichtigere Rolle im Langzeitverlauf darstellen. Psychiatrische, kardiovaskuläre und Krebserkrankungen konnten in Langzeit-Verlaufsstudien als wichtigste Begleiterkrankungen bezüglich des erhöhten Sterblichkeitsrisikos aufgezeigt werden. Frühzeitige Sterblichkeit bei Epilepsie ist ein unterschätztes, komplexes und multifaktorielles Problem, mit wichtigen Auswirkungen auf das Gesundheitswesen. Daher erscheint es als wichtig, sowohl klinisch als auch wissenschaftlich tätige Kollegen für die Tragweite des Problems und die potenziell vermeidbaren Ursachen zu sensibilisieren.

Schlüsselwörter: Todesursachen, plötzlicher unerwarteter Tod bei Epilepsie, Anfall, Begleiterkrankungen

Introduction

Epilepsy is one of the most common neurological conditions [1], with prevalence between 5 and 10 per 1000 people, and overall incidence of 50 per 100 000 people [2]. Most people developing epilepsy have a good prognosis for seizure control [3] and will achieve terminal remission on monotherapy [4].

Despite the overall good prognosis for seizure control, having epilepsy is potentially life-threatening as it is associated with an increased risk of premature death [2]. Epilepsy-related mortality remains underestimated and, although sometimes it is potentially preventable, public health interventions are lacking [2].

Premature mortality in epilepsy is a complex, multifactorial phenomenon. The death of a person with epilepsy may be totally unrelated to epilepsy or to the causes of epilepsy. A pragmatic classification of the causes of death in people with epilepsy distinguishes causes directly related to the epilepsy and seizure activity (status epilepticus, accidents and sudden unexpected death in epilepsy), deaths related to the underlying causes of epilepsy and deaths indirectly related to epilepsy [5]. It has been shown that the underlying organic causes such as brain tumours, cerebrovascular diseases and metabolic conditions are the main determinants of increased mortality in the early years after onset [6]. It is also true, however, that people with epilepsy have an increased risk of premature death throughout their life and this is the case even when seizures are in remission [7]. The pathophysiological mechanisms underlying this long-term risk have not yet been elucidated, although comorbidities as well as genetic factors have been postulated to play a role [8].

Accidental death

Accidents and injuries are more frequent among people with epilepsy than in the general population; although they are usually minor in severity, involving soft tissue contusions and lacerations, particularly in the context of a generalized tonic-clonic seizure some may be fatal [9]. The risk of fracture, either resulting from a seizure or predisposed by drug-induced bone mineral density loss, is elevated twofold; burns due to seizures may also be related to increased morbi-mortality [10]. Drowning is increased twenty-fold in people with epilepsy, usually happening in the context of swimming or bathing [11].

Sudden Unexpected Death in Epilepsy (SUDEP)

SUDEP is defined as a sudden unexpected death in an individual with epilepsy with or without evidence of a seizure, and excluding documented status epilepticus, where post-mortem examination does not reveal an anatomical or toxicological cause of death [12]. The incidence is higher in adults than in children. The risk in children from 0 to 17 years with epilepsy is 0.22/1,000 patient-years (95% confidence interval [CI] 0.16-0.31); in adults this risk increases to 1.2/1,000 patient-years (95% CI 0.64-2.32) [13]. The frequency of generalized tonic-clonic seizures (GTCS) appears to be the major risk factor, in direct relationship with the frequency of GTCS (the higher the frequency, the greater the risk). Nocturnal convulsions are potentially dangerous, especially when unwitnessed, as they may culminate in prolonged postictal respiratory depression. The presence of a witness who could detect seizures and promote proper stimulation could avoid the respiratory

arrest and is correlated with a decreased risk [2, 14]. Studies of long-term outcome of chronic epilepsy suggest that SUDEP is an important cause of death, but does not fully explain early mortality, to which comorbidities contribute [15]. The pathophysiology of SUDEP is still unexplained. Prolonged postictal generalized electroencephalographic suppression is related to sympathetic and parasympathetic dysregulation, and may lead to seizure-related respiratory depression [14]. Results from neuroimaging studies led to speculations that right-sided increased amygdala-hippocampal grey matter volume reflects an asymmetric central influence on autonomic outflow, which may contribute to cardiac arrhythmia; on the other hand, pulvinar damage may influence hypoxia regulation [16]. The genetic susceptibility to SUDEP is complex, polygenic and possibly a result of interaction with an increased burden of deleterious variants [17].

Status Epilepticus

Another cause of death directly associated with seizure activity is status epilepticus, a severe condition that can have long-term consequences and even fatal outcome [18]. In people with refractory status epilepticus, mortality is mainly related to prolonged mechanical ventilation, older age and aetiology [19, 20]. Seizure control without suppression-burst or isoelectric electroencephalogram is associated with better functional outcome [19]. It should be noted that most cases of refractory status epilepticus are not in people with established epilepsy but occur "de novo".

Comorbidities

While in the first years after epilepsy diagnosis causes directly related to the pathogenesis of seizures prevail [21], follow-up studies have suggested that indirect causes and causes associated with comorbidities have a stronger role in determining increased mortality in the long term [22]. A large-cohort study prospectively assessed the long-term risk of premature mortality associated with epilepsy in a large cohort of people with epilepsy in the UK, with a median follow-up of 22.8 years [22]. It showed that the Standardised Mortality Ratio (SMR) may follow a triphasic time course, with the highest risk in the first five years, then a plateau in the next ten years of follow-up and a suggestion of a further peak in premature mortality twenty years after the initial diagnosis. All-cause mortality was found to be elevated, and this trend was confirmed in all the periods of disease history. Cancers (including lung cancer), cerebrovascular diseases, pneumonia and ischaemic heart disease were the most common causes of death. Unlike findings from previous studies from the same cohort [23], even those with cryptogenic/idiopathic epilepsy were found to have a slight increase in the risk of all-cause mortality in the last ten years of follow-up. Notably, as over 70% of people in the cohort were seizure free at last follow up, the long-term increase in the risk of mortality seems independent of seizure control.

Ischaemic heart disease has been recognized as an important cause of death in epilepsy since 1984, when an increased SMR for heart disease mortality among young (< 65 years) people with idiopathic epilepsy who survived 10 years after diagnosis was found [24]. More recent studies [22, 25] confirmed this trend. A higher prevalence of cardiovascular risk factors in people with epilepsy compared to the general population has been reported [26].

The relationship between epilepsy and cancer is also of interest. All types of cancer were found to contribute to increased mortality in epilepsy [22, 25], even after exclusion of primary brain tumours [27]. The association between epilepsy and late-onset cancer is not clear from a pathogenic point of view [28]. Controversy exists about any association between prolonged use of antiepileptic drugs and increased risk of cancer. Some have found such associations [29, 30] whilst this was disputed by others [31].

Psychiatric comorbidity is common in epilepsy. Depression, anxiety disorders, psychosis and substance abuse have been recognized as the most prevalent psychiatric disorders in epilepsy [32]. A recent large Swedish cohort study [25] reported an increase in the risk of successful suicide amongst people with epilepsy, particularly if associated with a psychiatric diagnosis. In particular, the adjusted Odds Ratio for suicide was 23 in people with both epilepsy and depression. The study also highlighted that substance misuse contributed to the increased risk of suicide, highlighting the importance for clinicians to identify and address this problem early.

Conclusions

A large group of causes, either directly or indirectly related to seizures, contributes to premature mortality in people with epilepsy. For clinicians it is fundamental to be aware of the magnitude of the phenomenon and identify preventable conditions, in particular cardiovascular risk factors and psychiatric comorbidity.

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Sudden Unexpected Death in Epilepsy

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Summary

Sudden Unexpected Death in Epilepsy (SUDEP) is one of the most frequent causes of death among patients with drug resistant epilepsy, primarily affecting young adults between 16 and 45, with frequent generalized tonic-clonic seizures. This review summarizes current knowledge about SUDEP, its true risk and potential prevention, as well as recent practice guidelines for better informing patients and caregivers.

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Key words: Epilepsy, SUDEP, mortality in epilepsy

La mort subite et inexpliquée/inattendue dans l'épilepsie (SUDEP)

La mort subite et inexpliquée/inattendue dans l'épilepsie (SUDEP) est une des causes les plus fréquentes de décès parmi les patients souffrant d'épilepsie résistante au traitement, affectant principalement de jeunes adultes entre 16 et 45 ans qui présentent des crises généralisées convulsives fréquentes. Cette revue résume les connaissances actuelles sur le SUDEP, son risque réel, sa prévention potentielle, ainsi que les recommandations pratiques sur comment améliorer l'information des patients et des soignants à ce sujet.

Mots clés : Epilepsie, SUDEP, mortalité

Plötzlicher unerwarteter Tod bei Epilepsie (SUDEP)

Plötzlicher unerwarteter Tod bei Epilepsie (SUDEP) ist eine der häufigsten Todesursachen bei Patienten mit pharmakoresistenter Epilepsie. Die Betroffenen sind hauptsächlich junge Erwachsene zwischen 16 und 45 Jahren mit häufigen, generalisierten tonisch-klonischen Anfällen. Dieser Review fasst den aktuellen Kenntnisstand betreffend das SUDEP-Syndrom, seine tatsächlichen Risiken, die potenziellen präventiven Massnahmen sowie aktuelle Empfehlungen zur besseren Information von Patienten und medizinischem Personal zusammen.

Schlüsselwörter: Epilepsie, SUDEP, Sterblichkeit

Introduction

SUDEP is a non-accidental, non-suicidal and non-drowning death in people with epilepsy, unrelated to a documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death [1]. SUDEP represents one of the main concerns of the epilepsy community, in as much as this outcome typically affects young adults between the age of 16 to 45 [2]. The incidence of SUDEP in epilepsy is 27 times higher than sudden unexpected death in other populations [3], part of it explained by comorbidities, but even when adjusted for it, the risk is three fold higher for patients with epilepsy. Most of these young adults do not suffer from other serious conditions than seizures and neither their family nor theyselves are usually aware of the risk of SUDEP, making this event as devastating as the sudden cardiac deaths observed in the same age group. The age range of SUDEP occurrence also accounts for such death to represent the second leading neurological cause of total years of potential life lost, after stroke [4]. Patients with epilepsy are at high risk of premature mortality [5, 6]. Focal and generalized tonic-clonic seizures are the most common cause of death among children and adults with epilepsy [6, 7]. However, other seizure types, anti-seizure therapies, and comorbid disorders can also increase mortality. For many epilepsy populations, SUDEP is the principal cause of death [4]. Patients with epilepsy also have increased mortality compared with control populations, due to status epilepticus, motor vehicle accidents, falls, drowning, suicide, drug poisoning, assault, and pneumonia [5, 6]. SUDEP and other causes of epilepsy-related mortality are an enormous public health problem.

Overall, one SUDEP occurs every 10 minutes worldwide. The incidence for SUDEP risk is estimated to 0.22/1000 patient/years in children and 1.2/1000 patient/years in adults with epilepsy [8]. In patients with drug-resistant epilepsy, SUDEP incidence is about 0.5% [2], culminating to 0.93% in patients undergoing presurgical evaluation or having failed epilepsy surgery [9]. The main SUDEP risk factor currently known is the

presence of generalized tonic-clonic seizures (GTCS), with an odd-ratio of 19.1 (11.8 - 31.0) for patients with ≥ 3 GTCS/year as compared to those with no GTCS [10]. However, these data derive from retrospective case-controlled studies performed in population with lower SUDEP incidence than surgical cohorts, i.e. 0.1% and 0.2% [11]. Considering that 12% of patients had ≥ 3 GTCS/year [12], crude extrapolations suggest that the risk of SUDEP in such patients shall be around 1%/year (i.e. comparable to the highest figure described in epilepsy surgery cohorts) [9].

The incidence of SUDEP is very low in children with epilepsy [3]. However, certain types of childhood epilepsy, such as Dravet syndrome, put patients in the high risk category for developing SUDEP [13]. Surprisingly, a few SUDEP were recently reported in benign childhood epilepsy with centro-temporal spikes (BCECTS), maybe due to the fact that patients are often not treated with antiepileptic drugs [14]. After 40 years of follow-up, up to 20% of patients with childhood-onset epilepsy and no terminal 5-year remission will have died of SUDEP [15, 16]. Thus, while SUDEP remains a rare event for doctors, it represents a very significant risk for patients suffering from refractory seizures since childhood.

There is an increase interest in this topic over the last few years – just in 1995 there were less than 10 papers published using the term "SUDEP", since 2013 there are more than 60 papers indexed in pubmed for the search term "SUDEP" per year [17]. Although the interest for SUDEP is increasing, data shows that a significant proportion of general practitioners, especially pediatricians, are unaware of the true risk of SUDEP [18].

Classification of SUDEP

SUDEP can be categorized as following [1, 19, 20]:

(1) Definite SUDEP – cases in which death occurs in a relatively healthy person (apart from epilepsy).
(2) Definite SUDEP Plus – cases that would otherwise fulfill the definition of SUDEP, when evidence indicates that a preexisting condition, known before or detected after autopsy, might have contributed to the death, which otherwise would be classified as SUDEP.
(3) Probable SUDEP – cases that are similar to definite SUDEP, but the postmortem data is not available.
(4) Near-SUDEP – cases in which cardiorespiratory arrest was reversed by resuscitation efforts with subsequent survival for more than 1 hour.
(5) Possible SUDEP – when there is a competing cause of death, with insufficient data available to allow their attribution to this category. Death occurring in water, without circumstantial or autopsy evidence of submersion are also categorized here. If any evidence of submersion is present, the death should not be classified as SUDEP.

Mechanisms of SUDEP: Role of post-GTCS dysfunction of brainstem respiratory centers

Most SUDEP are unwitnessed, limiting our understanding of their underlying mechanisms. In the minority of witnessed seizures, SUDEP seems to be usually triggered by a generalized tonic-clonic seizure (GTCS) [2, 11, 21 - 24]. Exceptions to this rule have been scarcely reported [25], and might include rare gene mutations which might affect heart, lung, and brain (SCN1A, SCN2A, SCN5A, SCN8A, DEPDC5, CSTB, TSC1, TSC2, HCN2, HCN4, KCNQ1, KCNH2, NOS1AP, RYR2) [24]. Though controversial, there might be a relation between the presence of postictal EEG suppression and the risk of later SUDEP [26 - 30].

Our current understanding on how GTCS leads to SUDEP primarily derives from the rare monitored cases of patients who died of a SUDEP while undergoing in-hospital video-EEG recording of their seizures within the context of pre-surgical evaluation of their drug-resistant epilepsy. The MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) tackled this issue by organizing a worldwide survey of SUDEP and near-SUDEP captured in EMUs [23]. This research included 16 SUDEP cases and nine near SUDEP cases. The study showed that all monitored SUDEP occurred after a GTCS with a sequence characterized by: 1) a seizure usually occurring at night in an unsupervised patient sleeping in the prone position, 2) the presence of polypnea and tachycardia at the end of the GTCS, together with severe post-ictal EEG flattening, 3) the abrupt development of concurrent apnea and bradycardia or asystole between 30 seconds and three minutes post-ictal, 4) immediate death following this early cardiorespiratory arrest, or transient restoration of abnormal respiration and EKG during several minutes, leading to terminal apnea followed by terminal asystole. Importantly, patients dying of SUDEP do not seem to develop physiological reactions to counteract their prone position and trigger autoresuscitation. Even though the patients are found in the prone position, the face is usually tilted and the airways are not completely obstructed, and the witnessed cases of SUDEP indicate that patients experience breathing difficulty [31].

Interpretation of this sequence of events remains partly speculative. Apnea is already present during GTCS, and might be responsible for significant hypoxemia in some cases, contributed to by the prone position and ventilation-perfusion inequality [32, 33]. When GTCS ends, hypoxemia might account for both the polypnea and EEG suppression. However, an additional mechanism occurs within the next three minutes to account for the abrupt cardiorespiratory dysfunction. Seizures are known to trigger the release of endogeneous opioids and adenosine within the brain and brainstem, a mechanism thought to participate to seizure termination. This release of endogenous depressors may exacerbate the impact of GTCS-induced hypox-

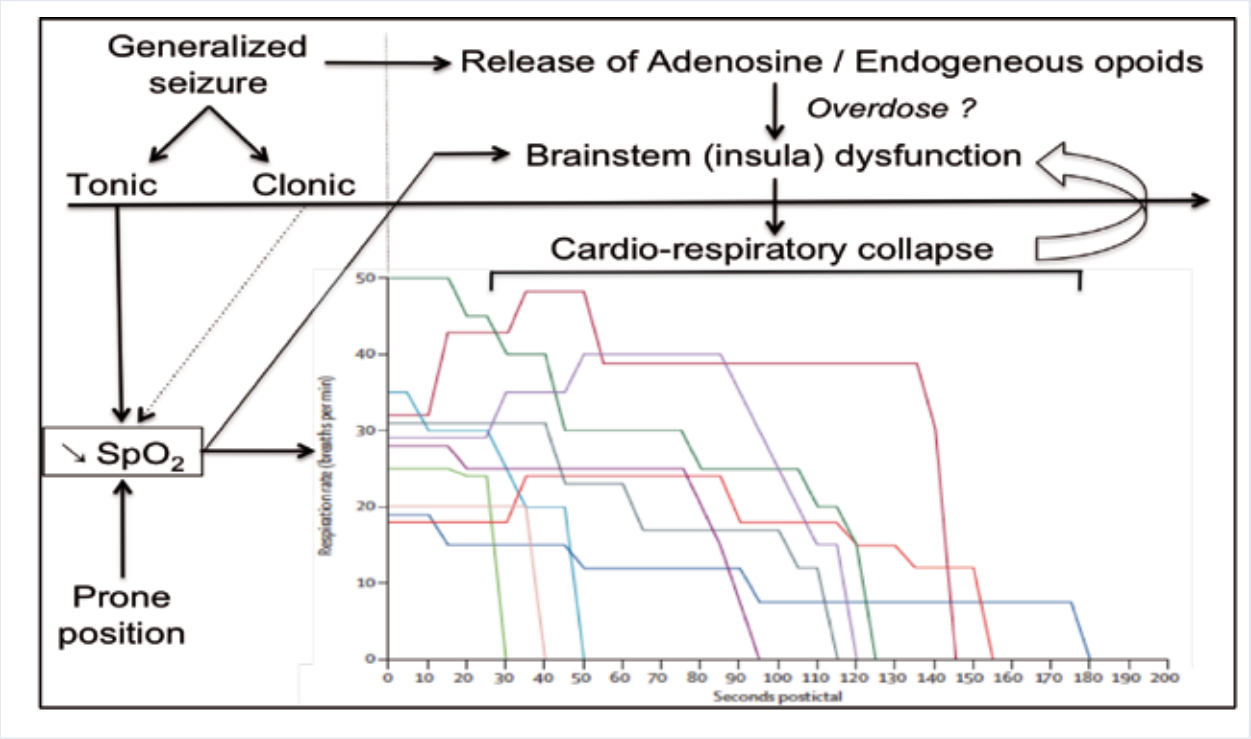

Figure modified from Ryvlin et al. 2013 [23]: The graph shows the apnea developing within the three minutes post-ictal in patients dying of a SUDEP while being monitored (each colored line represents the post-ictal respiratory rate of an individual patient), and the interpretation of the underlying mechanisms leading to death.

emia upon brainstem activities, eventually resulting in the sudden breakdown of cardiorespiratory functions observed in MORTEMUS. This would lead to immediate death or to further alterations of brain and brainstem oxygenation reflected by ineffective respiration until terminal apnea. While supported by a large bulk of evidence, MORTEMUS study did not provide direct variation of the respiratory functions, such as changes in pH, pCO2 and pO2. Near-SUDEP cases indicate the prevalent role of post-ictal apnea [34]. The later, the possible link between SUDEP and postictal generalized suppression of EEG could serve as a marker of SUDEP [26].

MORTEMUS has described monitored SUDEP cases, however, about 80% of all SUDEP are unwitnessed [35], suggesting that witnessed GTCS are less likely to end up as sudden deaths. That might also be the case for GTCS in children, where parental supervision is prevailing, thus reducing the probability to end up as SUDEP.

The large majority of data obtained in animal models of SUDEP are in line with some of the above hypothesis and human observations. Indeed, DBA/1 and DBA/2 audiogenic seizure mice, as well as knockout mice for 5-HT2c, Kcna1, Scn1a and RyR2 genes, or with genetic deletion of serotoninergic neurons, all display a pattern whereby seizures will lead to postictal apnea and death [7, 24, 36, 37]. A similar mechanism was observed after bicuculline-induced seizures in sheep [38]. In some of these models, a seizure-triggered spreading depression in the brainstem appears to drive the respiratory and cardiac dysfunction leading to death [36, 37]. In another model, apnea and death were promoted by seizure-triggered adenosine release, and partly reversed with caffeine [39]. SUDEP was also prevented in DBA/2 mice by injection of selective serotonin-recapture inhibitor [40].

Risk factors for SUDEP

The most frequently described risk factor for SUDEP is the presence of GTCS. This is aggravated by an early onset of epilepsy and long history of epilepsy [41]. Presence of frequent GTCS (≥ 3 GTCS per year) increases the risk of SUDEP 15 times [42]. There are also risk factors that are potentially modifiable: poor adherence to antiepileptic medication, sub-therapeutic medication levels, alcohol consumption, lack of night surveillance, sleeping in the prone position and increase in seizure frequency [43].

Prevention of SUDEP

There is no treatment specific for SUDEP. Currently, the only treatments that might provide some protection against SUDEP are those aiming at reducing the frequency of GTCS [19]. There is thus an urgent need to make progress in SUDEP prevention.

There are a number of measures that are being proposed to reduce the occurrence of SUDEP, such as

compliance to the treatment plan, adequate treatment – especially in patients with GTCS, optimal dosage of antiepileptic drugs, use of lattice pillow and nocturnal supervision in patients with poorly controlled seizures. However, none were firmly proven to be effective. Regarding pharmacological treatments, there is a rationale for testing the impact of selective serotonin reuptake inhibitors (SSRI), as well as opiate- or adenosine inhibitors [44].

Recommendations

Neurologists are facing the challenge of whether to disclose the information about the risk of SUDEP. Only 4 to 6.8% of clinicians discuss this topic with their patients [45, 46]. Studies show that patients and parents of a child with epilepsy are more inclined to hear about the risk of SUDEP from their treating physician [47, 48]. Practice guidelines were recently published by the American Academy of Neurology [8], suggesting that clinicians should inform adult patients and parents of a child with epilepsy that: 1) SUDEP is a rare, yet possible outcome (1 in 1000 in adults and 1 in 4500 in children per year); 2) the presence of frequent GTCS is an important risk factor that should prompt optimal medical management, keeping the balance between benefits and risks of new therapeutic approaches; 3) seizure freedom is associated with a lower risk of SUDEP, and 4) when possible, nocturnal supervision is recommended, especially for patients with GTCS [8].

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Somatic Comorbidities in Epilepsy

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Summary

Although psychiatric disturbances and neuropsychological impairment are widely recognized as associated with epilepsy, somatic comorbidities are less commonly accepted features. They are, however, an important determinant in the outcome of people with epilepsy. This review article explores the epidemiological link between epilepsy and somatic comorbidities such as cerebrovascular and heart disease, dyslipidemia, dementia, etc. The vast majority of epidemiological studies show consistently that there is an increased burden of somatic comorbidities among people with epilepsy compared to the general population. Limitations of the epidemiological studies are reviewed, causal bias and resultant bias are discussed in detail. Even after taking into account these limitations, there are evidences that the global health of people with epilepsy should be a cause of concerns.

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Key words: Epilepsy, somatic, comorbidities, health

Comorbidités Somatiques dans l'Epilepsie

Bien que les troubles psychiatriques et neuropsychologiques sont largement connus pour être associés avec l'épilepsie, les comorbidités somatiques sont des caractéristiques moins fréquemment acceptées. Elles sont néanmoins, un facteur important du pronostic des personnes atteintes d'épilepsie. Cet article de revue explore le lien épidémiologique entre l'épilepsie et les comorbidités somatiques comme les maladies cardio- et cérébro-vasculaires, la dyslipidémie, la démence, etc. La grande majorité des études épidémiologiques montrent qu'il y a un fardeau des comorbidités somatiques systématiquement plus important parmi les personnes souffrant d'épilepsie en comparaison à la population générale. Les limitations des études épidémiologiques sont revues, les différents biais (biais résultant et de causalité) sont discutés en détail. Même après avoir pris en compte ces limitations, il y a des preuves que la santé globale de personnes avec de l'épilepsie doit être une cause de préoccupation.

Mots clés : Epilepsie, comorbidités, somatiques, santé

Somatische Komorbiditäten bei Epilepsie

Während psychiatrische Störungen und neuropsychologische Einschränkungen bekanntermassen mit Epilepsie vergesellschaftet sind, ist dies bei somatischen Komorbiditäten weniger bekannt. Sie sind jedoch eine wichtige Determinante im Krankheitsverlauf von Patienten mit Epilepsie. Dieser Übersichtsartikel befasst sich mit dem epidemiologischen Zusammenhang zwischen Epilepsie und somatischen Komorbiditäten wie zerebrovaskuläre und Herzkrankheiten, Dyslipidämie, Demenz etc. Die grosse Mehrheit dieser epidemiologischen Studien zeigt durchwegs, dass es ein häufigeres Auftreten von somatischen Komorbiditäten bei Patienten mit Epilepsie im Vergleich zur allgemeinen Bevölkerung gibt. Grenzen der epidemiologischen Studien werden analysiert, kausale Voreingenommenheiten und resultierende Vorurteile (Bias) werden im Detail besprochen. Auch unter Berücksichtigung dieser Limitationen gibt es Hinweise darauf, dass die globale Gesundheit von Patienten mit Epilepsie Ursache zur Besorgnis sein sollte.

Schlüsselwörter: Epilepsie, somatische, Komorbiditäten, Gesundheit

Introduction

Though seizures are the most obvious and striking feature of epilepsy, it is widely recognized that epilepsy can be associated with psychiatric disturbances [1] and neuropsychological impairment [2, 3]. Despite a large number of studies suggesting that people with epilepsy have an increased burden of somatic comorbidities compared with people without epilepsy [4 - 18], somatic comorbidities are less widely accepted features of epilepsy. They are, however, an important determi-

nant in the outcome of those patients as, even if their seizures are in remission and they are off medication, people with epilepsy still have an increased risk of premature mortality [19].

We review here the studies assessing the prevalence of somatic comorbidities in people with epilepsy. We also discuss the limitations of such studies and the relationship between somatic conditions and epilepsy.

Definition

"In a patient with a particular index disease, the term comorbidity refers to any additional co-existing ailment" according to Feinstein in 1970. When studying comorbid conditions, scores are often to simplify the heterogeneity of the conditions considered. Two scores are commonly used to take into account the background somatic health burden of an individual in order to correct the influence of comorbidities on the outcome of given situations or conditions: Charlson's score [20] and Elixhauser's score [21]. Both scores list a set of somatic (and some psychiatric) conditions, allocating them a rank which correlates with the mortality risk of the given comorbidity.

With studies showing that some comorbid conditions are preferentially associated with some other conditions, the term comorbidities has been increasingly used to refer to the greater than coincidental association of two conditions in the same individual [6, 22], implying a causal link, although the original definition did not infer about the nature of the association.

Comparing prevalence, incidence and proportion of somatic comorbidities in people with epilepsy

Studies with different methodologies have shown that people with epilepsy have more somatic conditions than the general population of the same age, gender and geographical location. We will focus here on the most recent and best designed studies.

In 1997, a US community based study [9] which prospectively followed over 3 years people aged over 55 years, compared 65 people with epilepsy with 4,944 controls for cardiovascular risk factors, performing ECGs, arterial blood pressure measurements, and blood tests. Cardiovascular risk factors (hypercholesterolemia, left ventricular hypertrophy, history of myocardial infarction and peripheral arterial disease) were significantly higher in people with epilepsy after adjusting for demographic data. After excluding people with a previous stroke (more frequent in people with epilepsy and expectedly associated with cardiovascular risk factors), people with epilepsy still had a significantly greater prevalence of any cardiovascular risk factors with odds ratios of 1.8 in the early onset group (onset before 40 years old) and 2.1 in the late onset group (onset after 40 years old).

A UK study using the General Practice Research Database studied the prevalence of a wide range of somatic conditions in people with epilepsy compared to the general population [5]. These conditions included cerebrovascular accident, neoplasia, cerebral degenerative conditions, migraine, ischemic heart disease, congenital cardiac abnormalities, diabetes mellitus, respiratory conditions, gastro-intestinal bleeding, osteo-articular conditions and eczema. When analysing age groups, all comorbidity categories were significantly more frequent in people with epilepsy (odds ratios ranging from 1.2 to 2.8) among people aged between 16 and 64. All comorbidities except congenital and musculoskeletal were significantly more frequent in people with epilepsy (odds ratios ranging from 1.2 to 1.6) among people aged over 64.

A Canadian study used the data of two health surveys of the Canadian population (the National Population Health Survey (NPHS) and the Community Health Survey (CHS)) to assess prevalence of somatic comorbidities in people with epilepsy compared to the general population [6]. Both surveys used a supervised questionnaire and thus recorded self-reported conditions. The study included 49,026 people from NPHS and 130,822 from CHS. Prevalence of a wide range of somatic conditions (glaucoma, fibromyalgia, cancer, bronchitis/emphysema, chronic fatigue, stroke, bowel disorders, cataracts, diabetes, stomach ulcers, urinary incontinence, thyroid conditions, heart disease, asthma, high blood pressure, migraine, arthritis, back problems, and allergies) was assessed. Significantly increased prevalence ratios were found in both surveys for 13 out of 18, and 14 out of 17, assessed comorbid conditions in people with epilepsy in comparison with the general population with odds ratios ranging from 1.2 to 4.7, the latter being for stroke. Only neoplasias and glaucoma were not significantly increased in both surveys.

A study [14] using the data from the Dutch National Survey of General Practice in 2001, assessed the prevalence of somatic comorbidities of 276,921 people of whom 1,259 had epilepsy. The authors found a significantly increased prevalence of nine conditions (congenital conditions, anaemia, non-ischemic heart disease, stroke, obesity/lipid profile abnormalities, all neoplasia types, and neurological conditions other than multiple sclerosis, Parkinson's disease, and migraine) in people with epilepsy compared to the general population, out of 31 conditions assessed. Odds ratios ranged between 1.4 and 5.8, the latter being for stroke.

A Californian survey including 41,494 people of whom 550 reported having epilepsy [10] assessed the prevalence of self-reported comorbidities. The survey was conducted over two years (2005 and 2006). Somatic conditions assessed were diabetes, asthma, other chronic lung diseases, high blood pressure, high cholesterol, heart disease, stroke, arthritis, and cancer. People with epilepsy reported significantly more frequently all conditions assessed compared with people without

a history of epilepsy for each year of the survey. Odds ratios ranged between 1.4 and 4.4, the last being for stroke.

In 2005, a study [13] assessed the prevalence of comorbid conditions of 4,323 people with epilepsy compared to 4,323 age-, gender-, region- and employment-matched people without epilepsy in the Ingenix Employer Database (private in the US). The authors found significantly higher prevalence of congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, migraine, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy including leukaemia and lymphoma, metastatic solid tumour as well as HIV infection in people with epilepsy compared to controls. Odds ratios ranged between 1.8 and 10.5, the last being for cerebrovascular disease.

There is only one Swiss study assessing comorbidity in people with epilepsy [23] using data from the CoLaus study, assessed cardiovascular and psychiatric comorbidities in a sample of people with epilepsy. In this study using random samples of Lausanne residents, participants were interviewed, examined, blood pressure was measured, and glucose level and lipid profile were analysed. Forty-three people with epilepsy were compared with 3,676 matched controls showing no significant differences among cardiovascular risk factors. The study was, however, clearly limited by the small sample size.

The latest study [24] used South Carolina statewide hospital discharges and outpatients clinic visit datasets and assessed the prevalence of comorbidities in 64,188 people with epilepsy compared to 89,808 people with lower extremity fracture as controls. Somatic comorbidities and symptoms were found to be present in 85.6% of people with epilepsy compared to 65.1% in people with lower extremity fracture. Among the 18 comorbid conditions assessed (cardiovascular disease, intestinal problems, asthma, gastric reflux, anaemia, stroke, diabetes, peptic ulcer, traumatic brain injury, nutritional deficiency, gastro-intestinal bleed, osteoporosis, vision loss, hearing loss, Parkinson's disease, HIV/AIDS, multiple sclerosis, migraine), only osteoporosis was not significantly increased in people with epilepsy with odds ratios ranging between 1.3 and 4.2, the highest being for stroke.

Only a few studies assessed the incidence of new medical conditions in people with prevalent epilepsy. A European prospective 24 month follow-up study [25] assessed the occurrence of medical events reported by 951 people with epilepsy compared to 909 of their friends and relatives. People with epilepsy were found to have a significantly higher incidence of medical problems requiring medical intervention with a hazard ratio of 1.1 when excluding seizure-related conditions. Analysing the diagnoses reported showed that only nervous system-related and ear-nose-throat conditions were significantly more often reported by people with epilepsy. Among nervous system related conditions, headaches and seizures (as manifestation of the epilepsy) represented 89% of the total. It was not clear, however, what proportion of headaches were postictal headaches. Among ear-nose-throat conditions, rhinitis and pharyngitis represented 70% of the total. The authors acknowledged having difficulties interpreting the higher incidence of ear-nose-throat events and wondered whether over-reporting secondary to more frequent medical contacts could be a possibility.

The vast majority of epidemiological studies show consistently that there is an increased burden of somatic comorbidities among people with epilepsy [4 - 18, 24]. Three small studies did not reach the same conclusions [23, 26, 27]. The former studies suggested that this increase was global without a clear predominance for a specific condition or a group of conditions. The distribution of the comorbid conditions showed the same trend between people with and without epilepsy [5, 6]. This increase seems independent of basic demographic factors [4, 5, 9, 13]. Odds ratios showed comparable trends with ranges between 1.1-1.8 and 3.0-6.4. Stroke consistently had the highest odds ratios. In line with this increased prevalence of somatic comorbidities, people with epilepsy also appear to be at higher risk of developing new medical problems (even if there is less evidence). Only one study [9] explored the evolution of the prevalence over time and found that the prevalence of some comorbidities tends to normalise (though some conditions remain significantly increased over the long term) even if the reason was not clear (remission or mortality). An evolution over time of the prevalence of somatic comorbidities in people with epilepsy was suggested by prevalence disparity between incident and prevalent epilepsy [7]. All studies above considered prevalence and incidence of specific conditions, but it is not clear what proportion of people with epilepsy have comorbidities or not. Two studies using hospital cohorts [26, 28] suggested that between 47 and 89% of people with epilepsy have comorbidities. Those studies considered intellectual disabilities or neurological deficits as comorbidities and the cohort of one of these studies [26] appeared markedly selected.

Limitations of epidemiological studies on comorbidities in epilepsy

These studies used different data and designs; self-reported diagnoses, registers or clinical cohorts. Studies using self-reported diagnoses are potentially biased by the reliability of those diagnoses. Brooks et al. [29] assessed the validity of questions designed to identify lifetime and active (on medication or seizure in the last 3 months) epilepsy at a sample of 1,727 people with epilepsy and 1,100 without epilepsy followed at Boston Medical Center. They found a sensitivity of 81% and a

specificity of 99% for active epilepsy and a sensitivity of 84% and a specificity of 99% for lifetime epilepsy. This is higher than other somatic conditions, possibly because of the emotional burden and the stigma linked to epilepsy.

Okura et al. [30] assessed 2,047 residents of the Olmsted County, Minnesota in 1998 for self-reported common diagnoses compared with medical records. The authors found 66% sensitivity for diabetes, 68% for heart failure, 78% for stroke, 82% for hypertension, and 89% for myocardial infarction. All diagnoses had a specificity higher than 92%.

Studies using registers [5, 7, 9, 13, 14, 17, 24, 28] relied on diagnoses made by treating practitioners but captured only people who were stably registered in the databases used, possibly underestimating more mobile people who are usually healthy [5]. This might have underestimated the proportion of healthy people among people without epilepsy, possibly leading to underestimates when they compared the prevalence of comorbidities to people with epilepsy. Studies using register data may also be biased by different diagnostic criteria among the physicians reporting the conditions [31]. Only two studies used standardised diagnostic tests for comorbidities (laboratory or clinical) [4, 23], which understandably led to smaller cohorts.

Finally, studies using clinical cohorts [26] were limited by the sample size, the selected nature of the sample and the difficulties in finding adequate controls. In this last study, there was a significant proportion of people with intellectual disabilities (49%) among people with epilepsy whereas it was absent in controls. While the high prevalence of intellectual disabilities could be attributed to factors related to epilepsy, this also suggests very different settings between people with epilepsy and controls, potentially biasing the prevalence of other conditions. The authors also acknowledged that there was a significant difference of socio-economic level between people with epilepsy and controls.

The vast majority of the studies discussed above are cross-sectional, thus over representing people with long disease duration surviving long enough and not going into long-term remission [32], thus representing a length bias. Only one study, published as an abstract, assessed the longitudinal evolution of prevalent somatic comorbidities [9]. The study showed that the prevalence of some comorbidities (not specified in the abstract) normalised over time, possibly suggesting that some comorbidities increased early in the course of epilepsy may not be detected later in cross-sectional studies, possibly because of the premature mortality they induce.

Only rare community studies have data available on epilepsy status [8], and most studies assessed lifetime diagnosis of epilepsy. This inability to assess the epilepsy status probably aggregated different populations such as people in long term remission and people with active more severe epilepsy [33]. As expected, people in remission represented the vast majority of people assessed in epidemiological studies in the community [19, 34 - 38]. Studies using hospital cohorts reported varying proportions of people with active epilepsy, between 23% ("still had seizures") [26] and 57% ("seizure in the last year") [28], but this parameter was not included in the analysis. Therefore, little is known about epidemiology of comorbidity in the people with chronic epilepsy. Other populations not directly contactable by phone (such as people in institutions, nursing homes) may not have been contacted in studies using phone interview [8, 10, 27] or may not have been sampled in studies using phone books as a general population database [23].

Somatic comorbidities in epilepsy and socio-economic factors

Psychosocial and socioeconomic difficulties were found to be associated with an increased incidence of epilepsy in community-based studies [15, 39 - 43]. Socio-economic level is also a major determinant of general health and mortality [44, 45]. People with epilepsy have been shown to have lower academic achievement [46, 47], a higher rate of unemployment [48], greater difficulties when applying for employment [49], and are less frequently married than the general population [23, 47, 50 - 52]. It has been suggested that people with epilepsy also take less physical exercise, possibly because of depressive symptoms, fear of seizures, or feared potential interference with treatment [53 - 56]. This relative lack of physical exercise could also predate epilepsy as it was recently shown that people with lower cardiovascular fitness at military conscription are at higher risk (hazard ratio of 1.74) of developing epilepsy after adjusting for other factors (such as presence of cerebrovascular or neurological conditions) [57]. It was, however, not clear if the incidence of epilepsy in people with lower cardiovascular fitness was related to higher incidence of cerebrovascular conditions as the cause of epilepsy over the 40 years of the follow-up. These factors may represent an obvious confounder in the burden of somatic comorbidities, as the increased burden of somatic conditions may result from the unfavourable socioeconomic level of people with epilepsy.

Data from the US National Health Interview Survey, a personal interview survey, included 30,445 adults of whom 1.4% were reported to have epilepsy [11]. The study assessed the prevalence (self-reported) of cancers, arthritis, heart disease, stroke, asthma, diabetes, severe headache or migraine, neck pain and lower back pain in the previous three months. In this cohort, data on socio-economic aspects such as ethnic origin, education level, marital status, and employment status were available. Prevalence for all conditions assessed, except diabetes, was found to be significantly increased in people with epilepsy compared with the people with-

out epilepsy when adjusting for demographic socio-economic factors including ethnicity. Odds ratios were between 1.4 and 7.7, the highest being for stroke. There was evidence that socio-economic factors account for some part of the burden of somatic comorbidities, but marginally.

The Epilepsy Comorbidities and Health (EPIC) survey [12] used questionnaires mailed to random samples of U.S. households from two previous surveys. Several somatic comorbidities were assessed and the questionnaires also collected demographic data, data on household size and income, geographic region and ethnicity. Altogether 3,488 people with epilepsy were compared with a control sample of the same size matched for demographic and socio-economic factors. People with epilepsy were found to have significantly increased prevalence of sleep apnoea, tremor, migraine headache, chronic pain, fibromyalgia, neuropathic pain, and asthma with odds ratios between 1.3 and 2.0.

These studies strongly suggest that the increased burden of somatic comorbidities in people with epilepsy is independent of socio-economic factors and thus not related, or at least not fully, to life habits, social and environmental factors.

Healthcare utilisation, cost, and mortality of people with epilepsy as indirect markers of the somatic comorbidities burden

The increased burden of somatic comorbidities could potentially be biased by the comparison of people seeing a physician regularly with people without medical follow-up. Some authors [12] have compared this phenomenon to Berkson's bias. This bias [58] suggests that people with two conditions are over-represented in clinical care settings (in terms of hospitalisation or outpatient clinic time) than would be expected from the combination of both conditions considered individually. Similarly, people followed by physicians for a medical condition (epilepsy in our case), could be more likely to receive and report the diagnosis of other disorders because of their greater contact with medical care services. This form of bias was also referred to as "medical diagnosis bias" [12]. The authors concluded that this bias was unlikely to fully explain the increased burden of somatic comorbidities self-reported by people with epilepsy in their study. Some conditions commonly screened (diabetes and hypertension) were not found to be increased, whereas if the increased burden of comorbidities were due to this bias, all conditions assessed would be increased.

Hypothesising that the increased burden of somatic comorbidities is fully related to reporting bias, then healthcare utilisation and its costs, as well as the mortality due to comorbidities of people with epilepsy, would not be expected to be significantly different from people without epilepsy.

A study [59] used data from the fourth UK national morbidity survey in 60 general practices in 2002 to assess the diagnosis for each consultation over a period of 4 weeks. The authors assessed the diagnoses established for the consultation in 1,662 people with epilepsy compared to 502,482 people with other conditions but without epilepsy. All analyses were adjusted for age, gender, and social class. Except for infectious conditions, in all ICD chapters people with epilepsy had more frequent diagnoses than people without epilepsy, with odds ratios between 1.2 and 1.9. Assessing the proportion of people consulting for diabetes, ischaemic heart disease, heart failure, hypertension, dementia, stroke, degenerative brain disorders, peptic ulcers, gastro-intestinal bleeding and arthritis, people with epilepsy consulted significantly more frequently than people without epilepsy for all conditions assessed except hypertension and peptic ulcers, with odds ratios between 1.3 and 7.7; the highest odds ratio was for stroke.

Another study [60] used data from the Veteran Health Administration from 2001 to 2005 to assess inpatient admissions of 824,483 people, of whom 1,610 had epilepsy. People with epilepsy had a five-fold increased relative odds of inpatient medical admission. The authors found that heart attack, gallbladder disease, anaemia, angina pectoris, arrhythmia, cancer, thyroid disease, cerebrovascular disease, chronic obstructive pulmonary disease, peripheral vascular disease, dementia, prostate hypertrophy, hypertension, diabetes and heart failure were significantly more frequent diagnoses related to inpatient admission in people with epilepsy than in controls, with odds ratios ranging from 1.4 to 4.7.

A recent study [61] analysing data of a US health insurance database found that < 50% of the healthcare cost of people with epilepsy were epilepsy-related and the authors concluded that comorbid conditions accounted for most of the healthcare costs of epilepsy. Some comorbid conditions included (such as brain tumours and psychiatric conditions) may have been considered as the cause of epilepsy: these were not differentiated from somatic comorbidities.

One study [62] used the billing data obtained from general practices, neurologists and hospitals over a period of 4 months in the Marburg-Biedenkopf district in Germany in 2008 to ascertain epilepsy costs. Inpatient admission represented the majority of all direct (i.e. healthcare) costs (33%). Among inpatient admission costs, 62% were epilepsy-related (newly diagnosed epilepsy, status epilepticus, prolonged EEG recording, epilepsy surgery, fracture/injury after seizure); more than a third of all inpatient admission costs, however, were not related to epilepsy. The authors did not state which proportion of those costs was related to psychiatric comorbidities.

The relationship between comorbidities and mortality in people with epilepsy will be fully discussed in

more details in another article. One mortality study [19] can be used to assess indirectly the effect of comorbid conditions. The authors found an increased mortality rate in people with epilepsy compared with the general population after more than 20 years of follow-up, when a contribution of the underlying cause of epilepsy to mortality seems unlikely. The overall standardised mortality ratio (SMR) was 2.2. More than eighty percent of those people were, moreover, in terminal remission and only a negligible proportion of deaths were epilepsy-related.

These studies strongly support the hypothesis that the increased burden of somatic comorbidities reported in previously-discussed epidemiological studies is not due to a reporting bias. The studies above suggest a real increase in the healthcare needs for treatment of conditions not directly related to epilepsy as also shown by the significant costs incurred. Finally, premature mortality in patients in remission is another unequivocal sign of the presence of somatic comorbidities with epilepsy.

Causal bias

Some comorbidity may be linked with epilepsy through a causal association, i.e. they may in fact be the underlying cause of epilepsy. Stroke, brain tumours, and degenerative brain conditions are probably the most common confounders, and not surprisingly their prevalence was found to be increased in people with epilepsy, with the greatest odds ratios [5, 6, 11, 59].

In its last report, the ILAE Commission on classification and terminology [63] highlighted the need to consider epilepsy as a symptom ("all epilepsy is symptomatic of something"), suggesting categories such as genetic or structural/metabolic to describe the causes of epilepsy. Not surprisingly given the difficulties in ascertaining the aetiology of epilepsy, the majority of studies on comorbidities did not incorporate the cause of epilepsy and some conditions considered as comorbid conditions might have been the cause of epilepsy. The cross-sectional design of the vast majority of the studies could not provide data about the temporal relationship between comorbidities and epilepsy. Knowledge that some conditions post-dated epilepsy could have been used at least to ascertain that some conditions were comorbid and not causal [8].

The causal bias present in most studies on comorbidities does not, however, invalidate the finding that people with epilepsy have a greater burden of somatic comorbidities, as this bias affects only a small minority of the range of conditions assessed.

Stroke is the most common example. Several studies which excluded acute symptomatic seizures showed that people having had a stroke are at significantly higher risk of developing epilepsy than the general population (incidence ratio up to 17) [64, 65]. There is evidence, however, that even taking into account this bias, people with epilepsy have a higher incidence of comorbid stroke. A study using the UK General Practice Research Database assessed the incidence of stroke in 4,709 people with late-onset epilepsy (after age 60) who had no history of cerebrovascular disease, other acquired brain injury, brain tumour, drug or alcohol misuse or dementia compared to the same number of matched controls [66]. People with epilepsy (thus without a history of previous stroke) showed a significantly increased incidence of stroke with a hazard ratio of 2.9. However, it is not clear how extensively the presence of previous stroke was investigated at epilepsy onset; for instance, which type of imaging (CT or MRI scan) was used to identify cerebrovascular lesions.

Brain tumour is also a common cause of epilepsy; seizures are the initial manifestation in 30 - 50% of cases leading to the diagnosis, and further 10 - 30% of people with brain tumour will present with seizures later in the course of the disease [67]. Some cortical tumours [68] like dysembryoplastic neuroectodermal tumours (DNTs) are associated with epilepsy in virtually all cases [69]. Cortical localisation of the tumour appears to be a particularly high risk [70] as are low grade tumours [71], though this may be related to the longer survival associated with those tumours, making more likely the development of epilepsy in the course of the disease [72]. Despite the potential causal bias with brain tumours, people with epilepsy have been suggested as having an increased incidence of extra cranial cancers [73, 74] and extra cranial cancers were consistently shown to cause premature mortality in epilepsy [75 - 81].

Dementia is another comorbidity that can represent the cause of epilepsy [82]. People with dementia (Alzheimer's disease or vascular dementia) have a substantially increased epilepsy incidence ratio (7.1 to 9.3) compared to control populations [83]. Incidence characteristics seem specific to the underlying condition as epilepsy incidence is maximal early in the course of Alzheimer's disease whereas it is maximal late in the course of vascular dementia [83, 84]. It was also shown that people with epilepsy are at increased risk of developing dementia. A Dutch study [85] reviewed nine years of follow-up in three national Dutch registers, comparing 4,505 people with epilepsy with 82,077 controls. Between the ages of 50 and 64, people with epilepsy had a significantly higher incidence of dementia when compared with controls, with relative risks between 1.9 and 3.6. It is, however, impossible to ascertain what proportion of people with epilepsy had subclinical degenerative conditions at epilepsy onset that only became clinically apparent later. In a previous study [86], it was suggested that onset of epilepsy before dementia was frequent especially in the few years preceding the diagnosis of dementia. The situation might be even more complicated as it was suggested experimentally that epilepsy and Alzheimer's disease can interact, possibly aggravating each other [87].

Causal bias also applies to conditions such as multiple sclerosis. There is epidemiological evidence that multiple sclerosis prevalence is significantly increased in epilepsy [13, 24]. This is in keeping with reports showing an increased prevalence of epilepsy in people with multiple sclerosis, as between 3 and 8% of people with multiple sclerosis have epilepsy [88, 89]. Most often epilepsy onset follows multiple sclerosis occurrence; in a study [90] of 70 people with comorbid epilepsy and multiple sclerosis, only 11 had epilepsy prior to multiple sclerosis onset. Despite the fact that multiple sclerosis is primarily a subcortical disease, cortical lesions are not uncommon and are less frequently detected with imaging than at pathology [91 - 93]. In detailed case studies, discharges on EEG recording and seizure semiology were in keeping with the location of cortico-subcortical lesions [94 - 96]. The association of epilepsy and multiple sclerosis is thus explained by a causal bias in the majority of cases.

Some comorbidities may be linked through an indirect causal association, such as cardiac abnormalities in people with epilepsy caused by a stroke. The association between cardiac abnormalities and epilepsy might conceivably be biased by the increased prevalence of stroke in epilepsy, with cardiac abnormalities representing an underlying cause of stroke as a cause of epilepsy. It is therefore not surprising that left ventricular hypertrophy (odds ratio 1.8) was found to be associated with unprovoked seizures [97], possibly being a sign of a cardiac condition underlying stroke. Adjusting for demographic factors, a history of previous stroke, cardiac abnormalities, and hypertension, left ventricular hypertrophy remained significantly associated with unprovoked seizures, suggesting that the association between left ventricular hypertrophy and epilepsy may be independent from the presence of stroke and other cardiac abnormalities. Another study [98] showed that people with epilepsy, of whom none had cerebrovascular disease as the cause ascertained by MRI scan, had significantly more frequent repolarisation abnormalities on ECG when comparing 22 people with epilepsy with 19 age matched controls. A Dutch study assessed sudden cardiac arrest confirmed with very early prehospital cardiac recordings (99). The proportion of people with epilepsy was significantly increased in the sample of people with cardiac arrest studied in comparison with a matched general population (odds ratio 3.3). A proportion of people with epilepsy (41%) had cardiovascular and (8%) cerebrovascular comorbidities; as expected both comorbidities were strong predictors of cardiac arrest, but epilepsy remained an independent predictor (odds ratio 2.9) after adjusting for cerebrovascular and cardiovascular conditions and cardiovascular risk factors.

Similarly, in epilepsy caused by a clear genetic syndrome, other somatic features of the underlying genetics could be confounded with somatic comorbidities of epilepsy. For instance, atrial septum defect in a person with epilepsy and Down syndrome [100], and renal angiomyolipoma in tuberous sclerosis [101], should be considered as part of the syndromic cause and not as proper comorbidities of epilepsy.

To summarize, the cause of epilepsy needs to be considered when studying comorbidities of epilepsy, though it might be challenging with clinical data alone to establish which particular condition is the cause of epilepsy. The knowledge of the cause of epilepsy also allows the identification of concurrent conditions or symptoms which can be considered as true comorbidities and which are not a feature of the cause of epilepsy. Causes of epilepsy have also been suggested as important determinants of response to medication [102, 103]. Despite this potential causal bias for several conditions (stroke, tumours, or cardiac abnormalities indirectly), there is evidence that these comorbidities are linked to epilepsy independently from its cause.

Resultant bias

Epilepsy and somatic comorbidities may also be linked through a resultant association, as comorbid conditions may also be the result of epilepsy and its treatment.

Unsurprisingly, the prevalence of fractures was found to be significantly increased in people with epilepsy [5] as traumatic injuries can be the result of seizures.

Long term somatic adverse event of antiepileptic treatment has been recently reviewed in a past issue (issue 32). Long term exposure to AEDs is known to be associated with a decrease in bone density [104 - 106]. Older age, female gender, lower weight, exposure to enzyme-inducing AEDs, and AED polytherapy have been shown to be independent risk factors [107, 108]. Enzyme induction has been shown to increase the clearance of dihydroxylated vitamin D [109] and decrease oestradiol in women [110], resulting in decreased bone density. Calcium and vitamin D supplementation was suggested to have little effect in the prevention of fractures in people taking AEDs [110]. It was also recently shown that switching from enzyme-inducing AEDs to non-enzyme-inducing AEDs increases the bone density after only two years of therapy [111].

Enzyme-inducing AEDs were also shown to influence cardiovascular risk factors. Several studies have shown that people on inducing AEDs have significantly higher total cholesterol, LDL cholesterol and triglyceride levels in the long term [112 - 114], which can be improved by switching to non-inducing AEDs [115]. Increased lipid synthesis is probably mediated by increased clearance of cholesterol metabolites thus decreasing the negative feedback on cholesterol synthesis [116]. Levels of other cardiovascular risk factors markers such as lipoprotein (a), CRP [115] and homocysteine [117] were also found to be increased in people taking

enzyme-inducing AEDs. Enzyme-inducing AEDs were also suggested to decrease thyroid hormone levels (T3 and T4); this was, however, judged to be subclinical [118 - 120]. Enzyme-inducing AEDs have also been shown to decrease testosterone in men [121] and oestradiol and dehydroepiandrosterone (DHEA) in women [122] and induce sexual dysfunction [123].

Liver enzyme induction is however not the unique mechanism potentially leading to somatic comorbidities. Valproate has also been shown to be associated with increased insulin levels independent of weight, compared with healthy controls [122] or people on lamotrigine [124]. A young age at valproate initiation was a risk factor [122]. It was suggested that valproate caused impaired liver insulin metabolism independent of weight [125]. Total cholesterol and triglyceride have also been suggested as being significantly higher in people on valproate than in people on other AEDs or healthy controls even after adjustment for obesity [126]. Valproate has also been suggested as a risk factor in the development of polycystic ovary syndrome probably by hyperinsulinism, inhibition of testosterone conversion to oestradiol and theca cell stimulation [127]. It has been shown that switching to lamotrigine improved the lipid profile, weight, fasting serum insulin, testosterone level and the number of cysts seen at ultrasonography [128].

Newer AEDs are either less potent liver enzyme-inducers (e.g. topiramate or oxcarbazepine) or devoid of inducing properties (e.g. levetiracetam, lamotrigine, pregabalin) [129]. A recent study [130] showed weakly inducing AEDs (topiramate and oxcarbazepine) and non-inducing AEDs (levetiracetam) significantly increased cardiovascular risk factors such LDL cholesterol, homocysteine, and apolipoprotein B after six months of monotherapy. The evidence are however weaker than for older generations AEDs.

Topiramate has also been suggested as potentially having long term effects on bones, as it was shown to decrease parathyroid hormone while increasing markers of bone turnover [131]. In one study, lamotrigine and levetiracetam seemed to not have significant effects on bone metabolism, whereas gabapentin was suggested to decrease bone density [132, 133]. Gabapentin was also associated with non-traumatic fractures [134] and a cross-sectional study suggested that levetiracetam may decrease bone density [135], but it was not clear in these studies whether previous exposure to inducing AEDs was taken into account.

Non-inducing AEDs also seem to have a more favourable profile regarding cardio-vascular effects [115]. Valproate, gabapentin, pregabalin and vigabatrin were, however, also described as favouring weight gain [136]. Despite many AEDs being associated with weight gain the prevalence of being overweight and obesity were found to be only probably and indirectly related to AED treatment [137].

This matter is further complicated by the fact that the choice of AEDs may depend on the socioeconomic level of the people being treated. A Swedish study recently showed in a paediatric population that newer AEDs, which seem less prone to long term metabolic side effects, are more often prescribed to children whose families have a higher socioeconomic level [135]. A higher rate of prescription of liver enzyme-inducers in people with lower socioeconomic levels may worsen further the already higher burden of somatic comorbidities in people with lower socio-economic level.

Enzyme-inducing AEDs were found to increase the risk of occurrence of cardiovascular comorbidities but there is evidence that treatment does not fully explain the increase in burden of cardiovascular conditions in people with epilepsy. A Danish study assessed the incidence of stroke, cardiovascular conditions and death in 4,614,807 people of whom 54,693 had epilepsy [138]. Excluding those with previous stroke, people with epilepsy, whether or not on AEDs, had significantly increased risk for vascular events compared with people without epilepsy.

As a result, direct effects of seizures, such as traumatic injuries, should not be considered as comorbidities as they represent a direct physical consequence of epilepsy. Traumatic consequences of seizures can be also delayed. Cognitive decline in people with refractory epilepsy was indeed found to be associated with degenerative lesions in keeping with post-traumatic encephalopathy [139]. This finding suggests that repeated head injuries can induce or at least participate in cognitive decline seen in patients with refractory epilepsy. Hypothesis would correlate with neuropsychological findings showing that intellectual quotient (IQ) decline over the years is correlated with the frequency of generalized tonic-clonic seizures [140].

Exposure to AEDs should be taken into consideration when assessing somatic comorbidities in epilepsy, as AEDs contribute to some somatic conditions even if they represent only one factor among several.

Conclusion

There are plenty of evidences that people with epilepsy have more somatic comorbidities when compared with the general population. The relationship is nevertheless complex as epilepsy cannot be considered as a condition of its own but rather the consequence of very heterogeneous cause and constellations. Some of the comorbid conditions can also origin in the treatment of the disease. Although the pathogenesis of somatic comorbidities in epilepsy is not straight forward, the treating physician should be aware of the increased prevalence of other health issues in patients with epilepsy. Somatic comorbidities should not be overlooked as they may represent, aside the morbidity they induce, a potentially preventable source of premature mortality.

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Somatic Comorbidities and Mortality in Epilepsy

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Summary

Premature mortality in people with epilepsy is not fully explained by Sudden Unexpected Death in Epilepsy (SUDEP) or accidental death. Evidences that they suffer from premature mortality due to somatic conditions seemingly unrelated to disease are reviewed here. Epidemiological studies in the community found indeed premature mortality due to pneumonia, cerebrovascular disease, malignant neoplasms, and ischemic heart disease. Occurrence of comorbidities seems to be associated with greater epilepsy severity in term of seizure frequency. There are also suggestions that life expectancy might be influenced by the seizure frequency (not considering SUDEPs). Seizures inducing repeated peak of systemic inflammation may favour the development of vascular as well as neoplastic diseases. Repeated seizures may also have an enduring harassment effect on the cardiovascular system. The long term effect of unabated seizures on patient's health should not be overlooked, it should be a source of motivation not to give up trying to improve seizure control in patients with drug resistant epilepsy.

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Key words: Health, seizures, inflammation

Comorbidités somatiques et mortalité

La mortalité précoce mise en évidence chez les patients souffrant d'épilepsie n'est pas complétement expliquée par la survenue de morts subites dans l'épilepsie (SUDEP) ou de mort accidentel. Il existe en effet des preuves que ces patients souffrent d'une mortalité due à des problèmes médicaux apparemment sans lien avec la maladie. Des études épidémiologiques dans la population générale ont en effet mis en évidence une mortalité précoce chez les patients souffrant d'épilepsie avec pour causes des pneumonies, maladie cérébro-vasculaire, cancer, et maladie coronarienne. La survenue de ces comorbidités semble associée à une sévérité plus importante de l'épilepsie (en termes de fréquence de crise). Certaines études ont également suggéré que l'espérance de vie des patients souffrant d'épilepsie était influencée par la fréquence des crises, ceci sans considérer les décès dus au SUDEP. Les crises épileptiques induisant des poussées d'inflammation systémique de manière répétée pourraient favoriser le développement de pathologie vasculaire et néoplasique. Des crises non-contrôlées pourraient également mettre à l'épreuve le système cardiovasculaire, avec un retentissement à long terme. Les effets à long terme sur la santé de crises épileptiques non contrôlées ne devraient pas être sous-estimées et devrait être une source de motivation de continuer à essayer sans cesse d'améliorer le contrôle des crises.

Mots clés : Santé, crises, inflammation

Somatische Komorbiditäten und Sterblichkeit

Die vorzeitige Sterblichkeit bei Patienten, die an einer Epilepsie leiden, wird durch das SUDEP-Syndrom (plötzlicher unerwarteter Tod bei Epilepsie) oder Unfalltod nicht vollständig erklärt. Nachweislich bestehen Zusammenhänge zwischen der vorzeitigen Sterblichkeit und somatischen Erkrankungen, die nicht in direktem Zusammenhang mit der Epilepsie stehen. Epidemiologische Studien in der Allgemeinbevölkerung konnten in der Tat eine vorzeitige Sterblichkeit für Patienten mit Epilepsie aufgrund von Pneumonien, zerebro-vaskulären Erkrankungen, Neoplasien und koronarer Herzkrankheit aufzeigen. Das Auftreten von Begleiterkrankungen scheint zudem mit der Schwere der Epilepsie, bezogen auf die Anfallshäufigkeit, zusammenzuhängen. Einige Studien legen auch nahe, dass es einen Zusammenhang zwischen der Lebenserwartung von Patienten mit Epilepsie und der Anfallshäufigkeit gibt, Fälle von SUDEP ausgeschlossen. Durch wiederholtes Auslösen von systemischen entzündlichen Vorgängen könnten Anfälle das Entstehen von vaskulären Erkrankungen und Neoplasien fördern. Ebenfalls könnten wiederholte Anfälle einen dauerhaften, schädlichen Einfluss auf das kardiovaskuläre System haben. Der Langzeiteffekt von nicht kontrollierten Anfällen

auf die Gesundheit sollte nicht unterschätzt werden, vielmehr sollte er eine Motivation darstellen, die Versuche einer optimalen Anfallskontrolle auch bei Patienten mit therapierefraktärer Epilepsie nicht aufzugeben.

Schlüsselwörter: Gesundheit, Anfälle, Entzündung

Introduction

We have discussed previously the increased prevalence of comorbid condition in people with epilepsy compared with general population. The relationship between comorbid conditions and epilepsy is however difficult to disentangle as there are a number of biases potentially interfering in this context such as the underlying cause of epilepsy, the consequences of the disease and its treatment, socio-economic difficulties of people with epilepsy as well as frequent medical contact that could all lead to an overestimation of the real prevalence of somatic comorbidities. Should this reported increased prevalence be fully explained by these different biases, no major difference in term of mortality would be expected aside from deaths directly related to epilepsy. In that case, we would indeed expect that the health of people with epilepsy in the community would not be markedly different from the general population. This is, however, clearly not the case, as there are several evidences that people with epilepsy suffer from premature mortality due to causes not directly related to the disease.

Mortality due to somatic comorbidities

Several studies can be used to assess indirectly the effect of comorbid conditions. One study was particularly valuable because of its very long duration [1]. The authors assessed the standardized mortality rate of people with epilepsy in a UK prospective community follow-up study (National General Practice Study of Epilepsy, NGPSE). They found an increased mortality rate in people with epilepsy compared with the general population after more than 20 years of follow-up, when a contribution of the underlying cause of epilepsy to mortality seems unlikely. Premature mortality was also found in epilepsy diagnosed as cryptogenic or idiopathic. The overall standardized mortality ratio (SMR) was 2.2. More than eighty percent of those people were, moreover, in terminal remission and only a negligible proportion of deaths were epilepsy-related. Those people had significantly increased SMRs for pneumonia (6.6), cerebrovascular disease (2.9), malignant neoplasms (2.6), and ischemic heart disease (1.5). Other studies [2, 3] found premature mortality cause by cardiovascular and respiratory causes, but those studies did not distinguish patients with pre-existing cerebrovascular cause of epilepsy from developing vascular comorbid conditions. Early mortality in the community is mostly related to the underlying presumed cause of epilepsy [2, 4]. There is an underrepresentation of life threatening causes of epilepsy in studies of longstanding epilepsy in comparison with studies of incident epilepsy; this correlates with the peak of premature mortality found in the first years after epilepsy onset [5]. These studies relied on death certificates which were shown not to be fully reliable, as they often did not take epilepsy into account [6].

To explore the occurrence of premature mortality caused by somatic comorbidities, we performed a follow-up study of people with long standing epilepsy [7] in which cause of death was ascertain by post-mortem examination. Patients in this cohort were in a long term care institution (Chalfont centre, UK); they were admitted because of employment discrimination and they were working as part of the policy of self-sustainability of the institution (**Figure 1**). Such patients would be followed up in an outpatient clinic nowadays. We found a peak of premature mortality around age 45 in this cohort (**Figure 2**). As expected in a cohort of long standing epilepsy, aetiology did not account for the mortality in this cohort, as the vast majority established epilepsy in childhood or early adolescence and most were admitted years later. People with sinister underlying conditions were not admitted as long-term residents for employment and pathologically verified causes of death were not found to be a predictor of age at death. SUDEP is a major contributor to the early mortality of chronic

Figure 1: Examples of patients with epilepsy admitted in an institution (Chalfont centre for epilepsy, UK) who had a lifelong follow-up, providing rare insights in the long term course of the disease. Those patients were not disabled otherwise and were admitted for employment as part of the institution aim of self-sustainability. Such patients would be encountered in an outpatient clinic nowadays. Reproduced with permission [7].

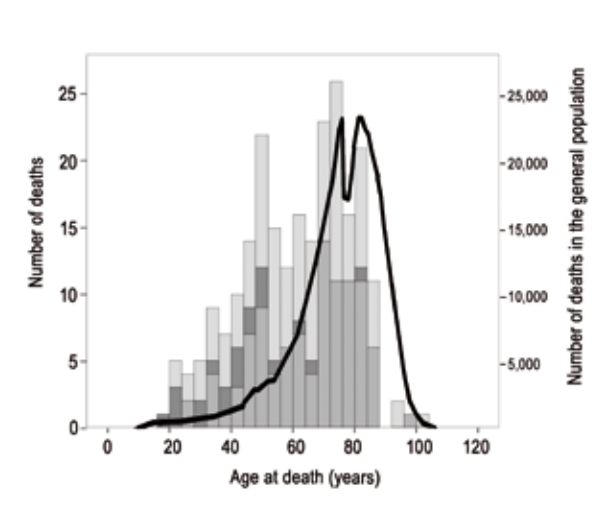

Figure 2: Distribution of age at death, in 4 year epochs, of all those who died whilst residents at the Chalfont Centre between 1988 and 2009. The frequency is displayed in number of cases. Light grey columns represent the number of people who did not have a post-mortem examination, all others had post-mortem examination; dark grey those who died of SUDEP and medium grey those who died of other causes determined at post-mortem examination. The superimposed black line (scale on right) shows the distribution of age of death in the general population in the UK in the median year of death (1997). This figure shows premature mortality with a mortality peak around age 50, in comparison with the general population. This premature mortality is not fully explained by SUDEPs (post-mortem proven). Reproduced with permission [7].

epilepsy [8], and it was the second most common cause of death. Post-mortem-confirmed (i.e. definite) SUDEP was only responsible for some of the early deaths, suggesting that epilepsy can also lead to premature death through other mechanisms such as somatic comorbidities. In this study, a meaningful proportion of sudden deaths without suspected contribution of other conditions (40%) that might have been diagnosed clinically as SUDEP were in fact shown to be deaths caused by comorbid conditions. Those cases were not classified in the new SUDEP plus category (where a comorbid condition is thought to contribute to death without being clearly the cause) [9], as the cause was clearly related to comorbid, mostly cardiac conditions. There is no study comparing the sensitivity of clinical diagnosis of probable SUDEP against post-mortem verified definitive SUDEP. Our results may imply that a proportion of clinically probable SUDEP cases [9] may in fact be the result of comorbid conditions. Our findings are in keeping with a study [10] suggesting people with epilepsy are at increased risk of cardiac arrest (confirmed by cardiac recordings). Without ECG confirmation, these cardiac arrests were likely to have been considered as probable SUDEPs.

In this series clearly differentiating between deaths due to the underlying cause of epilepsy, seizure-related deaths or unrelated causes (comorbidities), somatic comorbidities clearly played a role in the premature mortality. When excluding SUDEP and other seizure-related deaths (mostly head trauma) and in the absence of death due to underlying epilepsy causes, there was still a clear peak of premature mortality at around age 45 - 50 (**Figure 2**). Those who died of causes other than SUDEP or directly epilepsy-related deaths had similar ages of death for cardiovascular, respiratory or other comorbidities, suggesting that no single cause was responsible for premature deaths; this accords with reports showing that long-term excess mortality rates are seemingly not directly related to the disease [1, 11]. Treatment seems not to be an obvious bias; there was no disparity in terms of exposure to enzyme-inducing AEDs, as the whole cohort (with one exception) was exposed for years (if not decades) to enzyme-inducing AEDs. People with more severe epilepsy were exposed to a higher number of different treatments, and mostly to a greater number of newer AEDs which seem less inclined to induce long term cardiovascular complications, but prolonged experience with these agents is limited. The burden of somatic comorbidity in people with epilepsy could conceivably be worsened by more severe disease.

Relationship between mortality due to somatic comorbidities and epilepsy

Few studies have explored the relationship between somatic comorbidities and epilepsy characteristics. Epilepsy severity was found to be the major determinant in those studies, variably defined as greater seizure frequency and/or overall treatment exposure. A greater prevalence of ECG repolarisation abnormalities [12], of obesity [13], of obstructive sleep apnoea [14, 15] and higher mortality rate due to cancer [16] was indeed reported in people with drug resistant epilepsy. In some of those studies, greater exposure to antiepileptic medication was hypothesized to be the explanation, as AEDs are widely thought to be an important factor in many comorbid conditions [17, 18]. There also is evidence that cumulative exposure to AEDs can be associated with long term adverse events (such as visual field loss on vigabatrin), but there is considerable inter-individual variability [19]. In a study comparing two different cohorts of people with epilepsy (one in the community with relatively mild epilepsy and another at referral centre with intractable epilepsy) [20], we did also find a difference in term of prevalence of somatic comorbidities, people with more severe epilepsy having significantly more somatic comorbidities (OR:2.6), independently from other demographical factors (**Figure 3**). This increased prevalence of somatic comorbidities was independent from the treatment exposure (using the

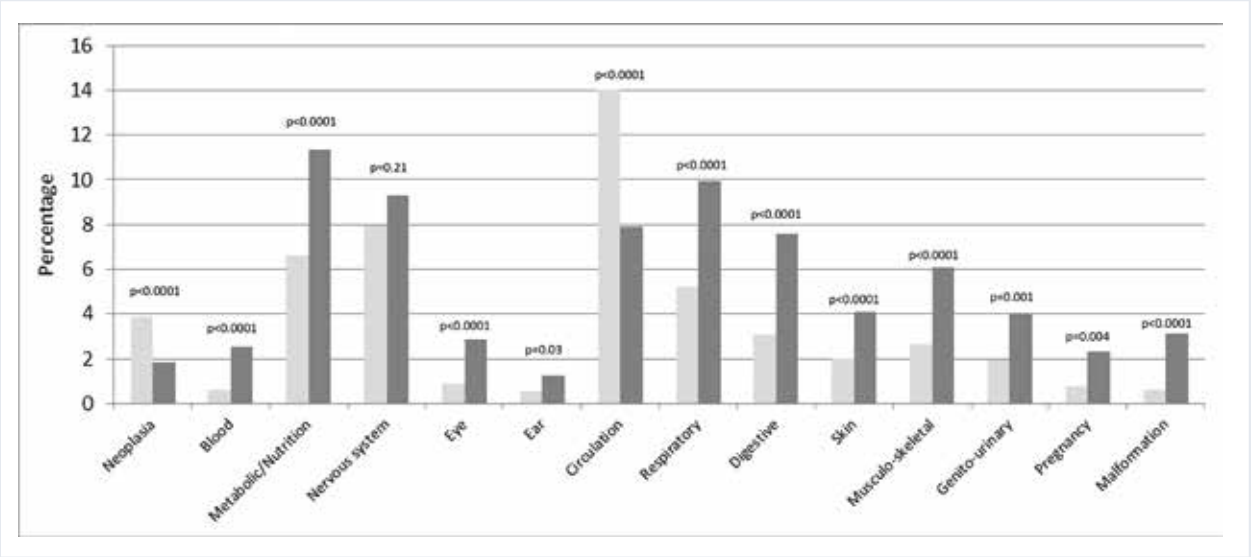

Figure 3: Distribution of somatic comorbidities in two different cohorts of people with epilepsy. Dark grey columns represent the referral centre cohort (total = 2016), light grey column the community cohort (total = 1278). Most comorbidities' types were significantly more frequent at referral centre. Reproduced with permission [20].

number of medication the patient was exposed to as a surrogate), suggesting that long term effect of medication is unlikely to explain the development of somatic comorbidities as a general factor. The study was, however, unable analysing the effect of the treatment on individual condition.

In the long term follow-up study of people with long standing epilepsy discussed above [7] in which cause of death was ascertain by post-mortem examination, disease severity (defined here by seizure frequency) was a major predictor of age of death in non-epilepsy-related deaths as diagnosed post-mortem, suggesting that comorbidities (or their consequences) may be linked with epilepsy severity. We could not analyse the occurrence of comorbidities between the person's admission and death, but the effect of disease severity seems not to be due to the presence of somatic comorbidities present early in the course of the disease, as higher prevalence of somatic comorbidities at admission was not a predictor of age at death.

Seizure frequency which was relatively stable in most residents studied showed a linear relationship with age at death when considering all deaths including seizure-related deaths but also when considering only deaths due to comorbidities, suggesting that seizures themselves can accelerate the occurrence of comorbidities. In this cohort, a seizure frequency of more than 4 seizures monthly decreased the life expectancy due to comorbidities by 12 years in comparison with a seizure frequency of less than 1 seizure monthly (considering only deaths that were not epilepsy related). In this study, it was impossible to analyse the seizure semiology, as during the decades over which the study stretched the classification changed several times (sometimes with only intensity appreciation). It is therefore unclear whether some seizure types are more deleterious than others (such generalized convulsive seizures) or if the overall activity of the disease is the major determinant. These data might suggest that unabated seizures might have an enduring long term effect on health, leading to the development of somatic comorbidities seemingly unrelated to the disease.

Physiological effects of seizures

Epilepsy is not the only condition associated with an increased prevalence of seemingly unrelated comorbid diseases. In studied cases, chronic low grade systemic inflammatory response is thought to be a major factor in the occurrence of cardiovascular and neoplastic comorbidities [21 - 24] in inflammatory conditions [25 - 27] but also in obesity, metabolic syndrome or sleep apnoea [28 - 33], conditions that are not primarily inflammatory.

Similarly it is increasingly recognized that seizures induce a systemic inflammatory response. Several clinical studies showed that there is a plasma peak of pro-inflammatory interleukin 6 after seizures [34 - 39] lasting up to 72 hours [40]. Those changes were also found interictally in people with chronic epilepsy [38, 41]. Other pro-inflammatory changes, such as increased interleukin 1β (IL-1β) or tumour necrosis factor α (TNF-α) or decreased interleukin 1 receptor antagonist (IL-1ra) have been shown less consistently [34 - 37]. A recent study [42] found significantly higher levels of interleukin 17 (IL-17), interferon γ (IFNγ), IL-1β, interleukin 6 (IL-6) in people with epilepsy than in healthy controls. Studying in more details IL-17, it was significantly higher in postictal periods than interictally and, when measured in the cerebrospinal fluid (CSF), the level was significantly higher than in subjects with demyelinating

conditions. Resection of hippocampal sclerosis in people with mesio-temporal lobe epilepsy was also found to decrease significantly (at 2 months) some inflammatory cytokines such as IL-1β,TNF-α after 6 months of seizure freedom without treatment changes while other cytokines (such as IL-6) did not show significant changes [43]. Seizures were also suggested as having an effect on natural killer cells (NK) and T-lymphocytes, increasing their blood count [44], but this increase occurred along with an increased blood count of most leukocyte cell types and may be due to de-marginalisation of those cells. Recently C-reactive protein (CRP) was also shown to be increased post-ictally in people with epilepsy in comparison with healthy controls with a median of 3.5 versus 0.7mg/ml [45]. All these studies on cytokine release were carried out in telemetry wards, a secure environment, making it unlikely that major traumatic lesions would explain the increase in inflammatory cytokines.

These cytokines were associated with the development of a wide range of somatic conditions. Increased serum IL-6 levels were shown to be an independent cardiovascular risk factor [46, 47]. In healthy people, increased IL-6 was shown independently to predict the occurrence of other cardiovascular risk factors of myocardial infarction [48] and diabetes type 2 [49]. In people with previous myocardial infarction, it independently predicts the occurrence of congestive heart failure [50] and cardiovascular deaths [51]. IL-17 is widely thought to contribute to the development and maintenance of chronic inflammatory conditions such as asthma, rheumatoid arthritis, inflammatory bowel disease [52, 53], and inhibitors of this pathway recently showed efficacy in inflammatory conditions in clinical trials [54]. The effects of interleukin 17 in atherosclerosis are debated with conflicting results [55, 56]. Levels of IL-1β were shown to correlate with dyslipidaemia in people with rheumatoid arthritis [57]; higher levels of IL-1β were associated with higher triglyceride, total cholesterol, LDL cholesterol, and decreased HDL cholesterol. Increased CRP level was found to predict the occurrence of several cancer types (ovarian [58, 59], colorectal [60], or lung cancer [61]), independently from other risk factors such as smoking. Other mediators, such as interleukin 6, seem not to predict cancer occurrence independently from weight gain, despite one study showing predictive value in the occurrence of ovarian cancer [62], but they have been shown to predict mortality in cancer, though this association may be explained by a correlation between cancer extension and level of inflammatory mediators [63 - 66]. This could suggest that unabated seizures may lead to repeated inflammatory peaks that would promote cardiovascular conditions and cancer. This hypothesis would accord well with our findings that a higher seizure frequency accelerates the occurrence of significant comorbid condition leading eventually to premature mortality. Some authors also wondered whether systemic inflammatory changes induced by seizures could also favour the occurrence of pneumonia which is a major cause of mortality in epilepsy [1].

Seizures may also induce repeated physiological stress that could contribute to mortality. Through the same mechanisms that are thought to contribute to SUDEP [67], unabated seizures could, in the long term, damage the cardiovascular system. Seizures, mostly generalized tonic clonic seizures, were shown to induce the release of stress hormones such as prolactin, noradrenaline and vasopressin [68]. People with epilepsy (mostly those with temporal lobe epilepsy) have been shown interictally to have decreased heart rate variability [69, 70] independently from antiepileptic medication; these changes could be related to seizures as they were suggested to be influenced by the seizure frequency [71, 72]. Decreased heart rate variability in people with epilepsy is in keeping with cardiac imaging studies. Single photon emission computerized tomography (SPECT) studies using iodine-131-meta-iodobenzylguanidine (MIBG) to assess cardiac sympathetic post-ganglionic innervation have shown a significant decrease in post-ganglionic denervation in people with temporal epilepsy when compared to controls [73]. These changes have long been thought to be the results of structural changes, probably in mesio-temporal (including amygdalar) regions [74 - 76]. Sympathetic heart denervation underlying decreased heart rate variability is thought to increase heart sensitivity to adrenaline [67]. In that context, decreased heart rate variability has long been known to be a predictor of cardiac mortality, independently from other risk factors [77, 78]. Seizures can also induce structural heart changes. Seizures were also reported as inducing transient dilatation of the cardiac wall (Takotsubo cardiomyopathy, sometimes referred to as left ventricular failure and apical ballooning) leading at times to cardiogenic shock [79, 80], or severe arrhythmias (ventricular fibrillation) [81, 82]. Nuclear medicine and pathological studies in non-seizure-related Takotsubo myopathies have suggested that sympathetic hypersensitivity [83] accompanying sympathetic denervation may be an important cause [84]. Severe structural abnormalities were found in the acute phase of Takotsubo cardiomyopathy, but longer term structural effects are less clear [83]. The long term outcome of non-seizure-related Takotsubo cardiomyopathy appears, however, to lead to premature mortality [85, 86]. This premature mortality was suggested in one study [85] as being explained at least partly by the comorbidities associated with the condition (using the Charlson score) possibly suggesting that Takotsubo cardiomyopathy is the indirect sign of damage sustained by the heart by systemic conditions rather than being an independent predictor of premature mortality. There is some evidence that seizures can induce an elevation of troponin I, a sensitive marker of cardiac injury [87]. A first small series of 11 people assessed for epilepsy surgery did not find any elevation after mostly complex partial seizures [88]. A study of 30

complicated (followed by significant systemic repercussions such as desaturation or hypotension) compared to 30 uncomplicated generalized tonic clonic seizures [89] found significantly higher troponin I values after complicated rather than uncomplicated generalized seizures; all values were, however, in the normal range. Finally a recent large study of 741 consecutive people admitted to hospital with consecutive generalized tonic clonic seizures [90] found an elevation of troponin I after 6.7% of the seizures. None of these people had known ischemic heart disease, and troponin I elevation was asymptomatic in all cases. There was no obvious explanation to these elevations; Takotsubo cardiomyopathy was excluded by echocardiography, and serial ECGs and monitoring were unremarkable. Predictors of elevation were the presence of cardiovascular risk factors such as diabetes, hypertension or hypercholesterolemia, suggesting that generalized tonic clonic seizures can induce reversible cardiac ischemia in people at risk.

Despite the extensive evidence that seizures can lead to long lasting (interictal) damage to the cardiovascular system, there is currently no evidence that seizures can induce long lasting changes to the respiratory system. Three studies [91 - 93] assessed interictal respiratory function parameters (respiratory frequency, vital capacity (CV), forced vital capacity (FVC), forced expiratory volume (FEV), oxygen saturation, and end expiratory carbon dioxide partial pressure (pCO_2) in samples of people with epilepsy compared with controls and did not find any significant differences. Epilepsy surgery whether followed by seizure freedom or not, appears not to change respiratory parameters (respiratory frequency, oxygen saturation, and expiratory carbon dioxide partial pressure) [93]. This normality appears somewhat puzzling in the light of premature mortality in people with epilepsy due to pneumonia [1, 6]. As discussed above, there is also evidence in the community that premature mortality due to pneumonia is not seizure related as it is also found in people in remission [1].

Conclusions

People with epilepsy harbour a premature mortality due to somatic comorbidities. Although there is no direct evidence, it seems very likely that the disease activity (seizure frequency) has an influence on the overall health. The mechanisms by which this occurs is still hypothetical. Systemic inflammatory responses possibly induced in the long term by unabated seizures could induce cardiovascular comorbidities independently from other risk factors. Similar mechanisms to those thought to underlie Sudden Unexpected Death in Epilepsy (SUDEP) could also damage indolently the cardiovascular system in the long term in people with unabated seizures. The long term effect of unabated seizures on patient's health should not be overlooked, it should be a source of motivation not to give up trying to improve seizure control in patients with drug resistant epilepsy.

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The Mortality of Status Epilepticus

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Summary

Generalised Convulsive Status Epilepticus (SE), traditionally defined as a persistent generalised seizure lasting longer or intermittent generalised seizures with incomplete recovery of consciousness in between seizures of duration longer than 30 minutes, is associated with significant morbidity and mortality. In this review we examine the factors associated with high mortality and poor prognosis, in particular discuss prognosis associated with the major aetiologies of SE as well as the relative impact of other prognostic factors such as age and duration of SE. We also discuss whether the prognosis and associated mortality of SE has changed over time, particularly in the last 20 years in light of improved treatment options and the increasing advocacy of earlier and more aggressive treatment in the context of prolonged seizures.

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Key words: Status epilepticus, mortality, epidemiology

Mortalité chez l'état de mal

L'état de mal épileptique (SE) généralisé convulsif, traditionellement défini par la persistence de crises généralisées ou la reprise incomplète de conscience pendant plus de 30 minutes est associé avec une morbidité et mortalité significative. Dans cette revue, nous examinons les facteurs associés avec une mortalité élévée et un mauvais pronostic, avec une emphase particulière sur les causes principales d'état de mal épileptique et également l'impact relatif d'autres facteurs comme l'âge et la durée de l'épisode. Nous discuterons également si le pronostic et la mortalité associée à l'état de mal se sont modifiés avec le temps, plus particulièrement dans les derniers 20 ans, au vu du nombre croissant d'options de traitement et de l'identification plus précoce ainsi que du traitement plus aggressif de crises prolongées.

Mots clés : État de mal épileptique, mortalité, épidemiologie

Sterblichkeit bei Status epilepticus

Der Status epilepticus convulsivus (SE), traditionell definiert als ein Persistieren von generalisierten Anfällen oder unterbrochenen, generalisierten Anfällen mit inkomplettem Wiedererlangen des Bewusstseins für länger als 30 Minuten, ist assoziiert mit einer signifikant erhöhten Mortalität und Morbidität. In diesem Review untersuchen wir die Ursachen, die in Verbindung mit einer hohen Sterblichkeit und einer schlechten Prognose stehen, wobei der Schwerpunkt bei den Hauptursachen des SE und dem Einfluss anderer Faktoren wie Alter der Patienten und Dauer des SE liegt. Wir diskutieren ebenfalls, ob sich die Prognose und die dem Status epilepticus assoziierte Sterblichkeit im Laufe der Zeit verändert haben, insbesondere innerhalb der vergangenen 20 Jahre, auf dem Hintergrund der zunehmenden therapeutischen Möglichkeiten und dem rascheren Erkennen sowie der aggressiveren Behandlung von prolongierten Anfällen.

Schlüsselwörter: Status epilepticus convulsivus, Mortalität, Epidemiologie

Introduction

Generalised Convulsive Status Epilepticus (SE), traditionally defined as a persistent generalised seizure lasting longer or intermittent generalised seizures with incomplete recovery of consciousness in between seizures of duration longer than 30 minutes, is associated with significant morbidity and mortality [1, 2].

Despite the fact that SE has been recognised at least since 700-600CE [1], it took until the early 1990s before the first staged treatment protocol for the management of SE appeared [3]. This is perhaps for a long time, whilst the high associated mortality of SE was well known, that SE was a rare event, typically only seen in people with chronic epilepsy in long-term institutions

or asylums and often in the context of anti-epileptic drug (AED) withdrawal [1, 2]. Moreover, it was only in the mid- to late 1990s that the first population cross-sectional studies were published, permitting an accurate estimation for the incidence rate of SE for the first time (**Table 1**). In addition, such studies provided a more accurate estimation of the associated mortality of SE as given the prospective nature of the studies, they were less prone to selection bias.

Any discussion on SE needs to be centred on three fundamental questions which will form the basis of the reminder of this review: 1) What is the overall mortality rate associated with SE? This is typically defined in terms of the 30-day case fatality rate or the proportional mortality rate. 2) What factors determine the prognosis of SE and by extension the mortality rate? 3) Has the mortality rate associated with SE changed over time and if so why?

Mortality rates in status epilepticus

In discussing the mortality of SE we will primarily focus on the results of seven cross-sectional studies [4 - 10] published from Richmond, Virginia [4], Rochester, Minnesota [5], French-speaking Switzerland [6], Germany [7], Bologna, Italy [8], California [9], and North London [10]. The first of the population-based studies was from Richmond, Virginia in 1995, with the second highest reported mortality rate of 22% [4]. This high mortality may in part be explainable by the high proportion of African-Americans (20%) in this study, in whom the incidence of SE was three-fold that of white Americans [4]. This may have been in part due to socioeconomic factors and unequal access and quality of medical care for the different populations in this study. This finding of a higher incidence and higher associated mortality in African-Americans was replicated in the Californian study [9]. Of these studies, all but one was prospective in nature.

Overall the incidence of SE typically ranged from 10 - 20 cases per 100,000 person years although the re-

Table 1: Seven population-based studies of status epilepticus*

	Richmond Virginia USA[4]	Rochester, Minn, USA[5]	French speaking Switzerland[6]	Hessen, Germany[7]	Bologna, Italy[8]	California	London[10]
Year	1989-1991	1965-1984	1997-1998	1997-1999	1999-2000	1991-1998	2002-4
Population (denominator)	202,774	1,090,055	1,735,420	743,285	336,876	N/A	605230
Number of cases	166	199	172	150	44	19,491	226 total
Incidence of SE (per 100,000 per year)	41 (raw) 61 (adjusted)	18.3 (adjusted)	9.9 (raw) 10.3 (adjusted)	15.0	13.1	6.2 (4.9-8.5)	176 first-ever episode of SE
Female:male ratio of cases	1:1.21	1:1.92	1:1.72	1:1.93	1:0.742	1:1.1	17-23 (adjusted) 12.5-14 (adjusted; first-ever episode of SE)
History of prior epilepsy	42%	46%	42.4%	33%	39%	N/A	1:1.12
Case fatality	22.3%	19%	7.6%	9.3%	39%	10.7%	7%4
Inclusions/Exclusions	Patients one month of age or less were excluded	-	Patients with post anoxic encephalopathy were excluded	Only patients of 18 years of age or over were included	Only patients of 20 years of age or over were included	Only generalised convulsive SE cases were included	3%
Case ascertainment	Prospective hospital record review	Retrospective review using record linkage system	Prospective hospital record review	Prospective hospital record review	Prospective Active surveillance of hospital admissions	Prospective hospital discharge record review	Only convulsive SE was included;

1 = Raw data, 2 = Adjusted ratio, 3 = Adjusted figures, from the regions with the best case ascertainment (and least likely to selection bias), 4 = Excluding febrile seizures

*From reference [11].

ported incidence was significantly higher (41 - 61 per 100,000 person years) in the Richmond study [4]. The overall mortality rate (30-day case fatalities) ranged from 3% in the paediatric study from North London [10] to 39% in the small study from Bologna, Italy [8] which seems to represent a significant outlier. The earlier American studies reported higher mortality rates (22% [4] and 19% [5]) compared to the later Swiss (7.6%) [6] and German (9.3%) [7] studies, which probably provide a more accurate and representative estimate of the mortality of SE. Of note the EPISTAR study excluded people with SE and post-anoxic encephalopathy which has the highest associated mortality, thereby explaining the slightly lower mortality rate (7.6%) in this study [7]. Mortality in SE demonstrates a J-shape relationship with age, with very low mortality rates in children, with increasing mortality rates with increasing age, particularly after the age of 60. In the Richmond study, the mortality rate was only 3% in children, comparable to that seen in the North London SE in Childhood Surveillance Study (NLSTEPSS) [10], yet the mortality rate was 41% in those aged > 60 years [4]. This is in part mitigated by the fact that the aetiology of SE varies with age, with febrile SE (prolonged form of a febrile convulsion) making up about a third of cases of SE in children, which is associated with a very low mortality rate. In contrast post-anoxic SE, which is almost invariably fatal, is a significant cause of SE in the elderly [11].

The impact of aetiology on the prognosis

The number of causes that predominate in epidemiological studies of SE is surprisingly small, with 7 - 8 major aetiologies typically identified [11]. In contrast, in a recent review of uncommon cause of SE, which were pragmatically defined as a single cause accounting for < 1% of all cases documented in the major pop-

Table 2: Major aetiologies of SE[1]

	Richmond[4]	Rochester[5]	Switzerland[6]	Hessen[7]	Bologna[8]	California[9]	London[10]
Low AEDs	21%(P)/34% (A)	1%	8.1%[3]	8.7%	-	3.9%	0.5%
CNS Infections	52%(P)/5% (A)	8.5%	-	0%	-	0.6%	10.2%
Febrile	-	8%	14.9%[4]	0%	-	2.5%	32%
CVA	10%(P)/22%(A)	19.1%	30.5%[5]	66.7%[1]	41%	12.4%[2]	0.5%
Alcohol	13% (A)	-	-	8.7%	7%	8.1%	0%
Trauma	3% (A)	4.5%	-	7.3%	10%	0.4%	1.5%
CNS Tumours	7% (A)	-	-	12%	5%	1.8%	-
Metabolic disturbance	5% (P)/15%(A)	3.5%	-	8.7%	24%[6]	8.7%	3%
Degenerative brain disease/CNS anomalies	38%(P)/25%(A)	5.5%	-	26.7%[2]	10%	13.3%[3]	32%
Medication induced/ overdose	2% (P)/3% (A)	2%	-	10.7%	-	-	1%
Anoxia/Hypoxia	5% (A) (anoxia) 5%(P)/13% (A) (hypoxia)	10%	Excluded	-	9.1%	8%	0.5%
Cryptogenic	5%(P)/3%(A)	13.5%	8.7%	8.7%	-	-	7%

A = adults; P = paediatric (from reference [11]), [1] Some studies only give percentages for some aetiologies, [2] In the Richmond study, aetiologies were separately given for the paediatric and adult populations [4], [3] Percentage of total cohort. (Low AEDs was the cause of SE in 18.9% of patients with epilepsy), [4] Patients with epilepsy only

[5] Non-epileptic patients, [6] Combination of systematic metabolic disorders and postanoxic encephalopathy

Table 3: Approximate frequency and mortality of SE in different aetiologies

Aetiology	Proportion of cases of SE	Associated acute mortality in patients with SE
Drug reduction/withdrawal, poor compliance or low AED levels	10-20%	0-10%
Cerebrovascular Disease	10-40%	20-60%
Metabolic Disorders	5-15%	10-40%
Acute CNS Infections	1-12%	0-33%
Anoxia-Hypoxia	5-12%	60-80%
Alcohol	5-15%	0-10%
Head Trauma	0-10%	0-25%
Brain Tumours	0-10%	0-20%
Cryptogenic/Idiopathic	5-15%	5-20%

Amalgamated figure [11]

ulation studies (**Table 1**), identified 181 different uncommon causes of SE [12]. Inevitably rare causes, once identified will become increasingly recognised. This is particularly true of the autoimmune encephalopathies such as anti-NMDA receptor encephalitis, which nevertheless overall remain a rare cause of SE, although is a more prevalent cause of refractory and supra-refractory SE. The major aetiologies and their relative frequency in the population studies are shown in **Table 2**.

Specific Aetiologies of Status Epilepticus and Mortality

Stroke and status epilepticus

Stroke is a significant cause of SE in people aged > 60 years particularly in those with no prior history of seizures (**Table 2**).

In a comprehensive study of the frequency of SE post-stroke, 3,205 people with a first time stroke(s) were identifed over an 8 year period. Of these, 159 had first time post-stroke seizures and SE was recognised in 31 cases, and was the first presentation of epilepsy in 17, occurring within 14 days of the stroke. In four cases the stroke occurred simultaneously with SE, and in the remaining 10 cases, SE developed after one or more seizures. After follow-up of 47 months, 48.3% (15) had died, of which five deaths were directly attributable to SE. Additional seizures occurred in over half (8) of the initial SE cases and all 14 patients with SE occurring after one or more seizures. The study concluded that SE in stroke has a poor prognosis but that inital SE as a first epileptic symptom was not predictive of developing subsequent seizures [13].

In the US Nationwide Inpatient Sample study covering an eight year period, 718,531 hospitalisations with acute ischaemic stroke (AIS) were identified of whom generalised convulsive SE (GCSE) developed in

1,415 (0.2%). 102,763 were admitted with intra-cranial haemorrhage (ICH) of whom GCSE developed in 266 (0.3%). In-hospital mortality was significantly higher in those with GCSE and AIS or ICH, particularily if analysis was restricted to patients with length of stay greater then one day (AIS: 28.4% vs 9.2%, p<.01; ICH: 30.1% vs 24.3%, p=0.03). Other markers of morbidity like pneumonia, need for mechanical ventilation, tracheotomy and length of stay > seven days were all statistically associated with concomittant SE [14].

In the Hessen study [7], long-term mortality rate in patients with a first episode of cerebrovascular-related SE was 57% compared to 48% in people with acute stroke without SE, suggesting a synergistic effect between SE and stroke resulting in greater morbidity and mortality. Multivariate analysis indicated that patients with status epilepticus had, after 6 months, twice the risk of death compared with patients with stroke without SE (hazard ratio of 2.12, CI 1.04-4.32, p=0.0392) [7].

This potential synergistic effect between cerbrovascular disease and SE was investigated in a prospective cohort study of 83 patients with SE and stroke (44 with acute and 39 with remote stroke) and compared them to 159 controls (acute stroke only). Acute stroke and SE had a mortality of 39%, representing an almost threefold increase compared to those with acute stroke only (14%) or those with SE and remote stroke (5%), ($p < 0.001$). In addition there was almost an eight-fold difference in mortality between the acute stroke and SE group and the remote stroke and SE group. This difference was not accounted for by age, sex or radiographic lesion size. Logistic regression analysis demonstrated a statistically significant synergistic effect of combined injuries of cerebral vascular ischaemia and SE [15].

In a large US study on mortality rates in SE using hospital admission and discharge coding data, cerebrovascular disease was a predictor of in-hospital mortality with an odds ratio of 2.08 (CI 1.13-3.82) and a mortality rate of 22% ($p < 0.0001$) and also for the need for mechanical ventilation ($p < 0.0001$) [16].

The relative frequencies of the major aetiologies and their associated mortality rates are shown in **Table 3**.

SE and antiepileptic drug reduction or withdrawal or low antiepileptic drug levels

In patients with a prior diagnosis of epilepsy, noncompliance with anti-epileptic medication (AEDs) is often postulated as being the most common cause of SE. Whilst this may be true in adults, it is not the case in children. In the NLSTEPSS [10], only one case of SE was attributable to low antiepileptic drug concentrations, although low serum levels of AEDs were the cause in 21% of cases in children in the Richmond study [4].

In a retrospective review of all admissions with status epilepticus to a single institution in San Franscico in the 1980s, 25% of cases of status epileptius identified were related to withdrawal of AEDs, with 90% of patients having a good outcome (defined as unchanged from baseline, or mild neurologic deficits that allowed independent living) such that the authors conclude "... that patients with a history of epilepsy who develop SE because of anti-convulsant drug withdrawal or break-through seizures can be expected to respond well to acute anticonvulsants." [17].

In a study of 83 episodes of SE from Berlin, low levels of AEDs were the primary cause of the SE in 27.7% of the non-refractory cases but no refractory cases ($p < 0.001$) allowing the authors to conclude that "SE caused by insufficient levels of AEDs is usually not refractory" [18].

Alcohol, substance abuse and drug-induced SE

Alcohol abuse (intoxication or withdrawal) has been found to be a common cause of SE in many population-based and hospital-based studies,with a reported range of 8.1-25%, although alcohol was not reported to be a major cause in some studies such as the Minnesota [5] and EPISTAR [6] studies. Cases of alcohol-related SE are generally associated with a favorable outcome with most studies reporting a mortality rate of 0 - 10% (9.6% in the California study) [9].

In a study of all 249 cases of GCSE in adults admitted to a single centre over a 12 year period, 27 cases (10.8%) were identified in whom alcohol abuse was the only identifiable precipitating cause. In 12 (44%), SE was the initial presentation of alcohol-related seizures. 22 (81.5%) had returned to baseline at the time of discharge although time to gross recovery of mental status was ≥ 12 hours in 24 of the 27 patients. Four (14.8%) had new neurological deficits at the time of discharge. The only death (3.7%) occurred in a 60 year old in whom status epilepticus continued despite four hours of treatment [19].

Drug toxicity or abuse is generally a more common cause of SE in hospital-based studies compared to population-based studies, and the relative frequency and mortality rate varies markedly between different studies, with reported rates of 2 - 14% of cases. Cocaine (43%) and theophylline (21%) were the most commonly implicated drugs in the San Francisco study [17].

Severe acute cerebral anoxia/hypoxia and SE

Anoxia, usually after cardiac arrest in adults, can result in deep coma with myoclonic jerking, and this is assumed by some authorities, but not all, to be a form of "SE" [1]. This dichothomy of opinion is evident by the fact that post-anoxic SE cases were excluded from the EPISTAR study [6]. In the population based studies,

hypoxia is the cause of SE in 8 - 13% of cases with an associated mortality typically in the range of 60 - 80% but others have reported mortality rates of up to 100% albeit in small sample studies.

In a study of 166 postanoxic survivors of cardiac arrest treated with hypothermia, postanoxic SE was present in 24% with a mortality rate of 80% compared to the overall mortality rate of 71% ($p < 0.001$). Post-anoxic SE was associated with a higher mortality regardless of the type of acute cardiac rhythm or hypothermia treatment [20].

In the large US study of mortality in convulsive SE hypoxia-ischaemic brain injury-associated SE was the strongest predictor of mortality with an odds ratio of 9.85 (CI 6.63-14.6) and a mortality rate of 69% and was a significant risk factor for the need for mechanical ventilation ($p < 0.0001$) [16].

CNS infections, encephalitis and status epilepticus

Acute CNS infections and encephalitis are an important cause of SE particularly in chidren, typically accounting for about 1 - 12% of all cases in various series from the developed world. In the California study, acute CNS infection was the cause of SE in 0.6% of cases with a median age of 42 years and a mortality rate of 32.6% [9]. In the NLSTEPSS [10] 6% (11) of children had acute bacterial meningitis and 4% (7) a viral CNS infection. Moreover 3 of the 7 children who died had acute bacterial meningitis.

In a retrospective study of all admissions to a paediatric ICU in Montréal over a 10-year period, there were 147 admissions with SE of which 20 (13.6%) were due to bacterial meningitis and 20 (13.6%) due to encephalitis, both of which were associated with high morbidity and mortality [16].

Population-based studies tend to show a rather more favorable outcome, with a lower frequency of refractory cases. In the California Encephalitis Project (CEP), a project aimed at determining the cause of encephalitis, all patients identified with encephalitis were subdivided into 3 categories: refractory SE (defined as SE requiring anesthetic coma for management (Group I); Non-refractory SE (Group II); and patients without seizures (Group III). 4% had refractory SE, 40% non-refractory SE and 56% no seizures. Cases of refractory SE associated with encephalitis tended to be younger (median age = 10) and had a poor outcome with 28% dying within 2 years and 56% neurologically impaired or undergoing rehabilitation [22].

Other causes of status epilepticus

Brain tumours are an uncommon cause of SE, representing 2 - 5% of cases in most studies although 12% of cases of SE in the Hessen study. The associated mortality rates are 0 - 36%.

Trauma is also an uncommon cause of SE, typically accounting for between 0 - 10% of cases in the major studies with an associated mortality of up to 20% (**Table 3**).

Metabolic disorders are the cause of status epilepticus in 2 -15% of cases in reported series with an associated mortality rate of up to 31%. In the San Fransisco Study [17], 4% of cases were due to metabolic causes, 50% of whom failed to respond to 1st-line treatments and were associated with poor outcome (severe neurologic deficit requiring full supportive care or death) in 65%. Acute metabolic disturbance (electrolyteimbalance, hypoglycaemia, hypocalcaemia) was the aetiology of SE in approximately 3% of children in NLSTEPSS [10].

Moreover patients with metabolic disorders in the US hospital mortality study, presenting with GCSE were significantly more likely to require mechanical ventilation ($p < 0.0001$) with a 3-fold increase in mortality for those requiring mechanical ventilation compared to those who did not (7.43% vs 2.22%, odds ratio 2.79) [16].

Cryptogenic SE/Non-onset refractory SE

Despite investigations, the aetiology of SE remains undetermined in many cases. In the Richmond study [4], approximately 5% of cases were classified as idiopathic with a mortality rate of 22%. In the Minnesota study [5] 17.5% of cases of SE were classified as idiopathic/cryptogenic while the aetiology of SE was unknown in 13 (8.7%), one (7.7%) of whom died in the Hessen study [7].

In a retrospective review of all cases of unprovoked seizure and status epilepticus in Richmond over a 30 year period, 291 people with a first brief unprovoked seizure and 16 with SE, there were 5 deaths (all aged > 65) in those with SE. Compared with people with seizure, the adjusted relative risk for death in those with SE was 2.4 over 10 years. This risk was more marked among those aged > 65 years (RR=5.1, CI 1.6-15.7) and for those with SE who later developed epilepsy (5/16, 31.3%) (RR=6.3, CI 1.5-26.0). The standardised mortality ratio (SMR) for SE was 2.6 (CI 0.8-5.3) [23].

There has been an attempt in recent years to define a new syndrome, NORSE (new-onset refractor which is nevertheless of questionable clinical utility. All cases described occured in young adults in previous good health with an antecedent febrile illness. In a recent retrospective review of 130 cases of new onset refractory status epilepticus from 13 academic US centres, 52% (67) remained cryptogenic with the common iden-

tified aetiologies being autoimmune (19%) and paraneoplastic (18%) encephalitis. Overall 77 (62% of 125) had a poor outcome of whom 28 (22%) died [24].

Other prognostic factors

In addition to aetiology, other prognostic factors include age, duration of SE at presentation, level of consciousness, EEG findings, type of SE, prior history of epilepsy and comorbidities. Apart from aetiology, increasing age and longer duration of SE are associated with a higher mortality rate [25] although the negative predictive effect of the duration of SE appears to lessen the longer it persists (> 10 hours) [26]. This in turn reflects the poorer prognosis with the later stages of SE, in particular refractory status epilepticus (requiring anaesthetic intervention) and super refractory status epilepticus (SE of > 24 hours duration despite anaesthetic drugs). A combination of the above factors is used in the two most widely utilised SE prognostic scales: the SE severity score (STESS) (level of consciousness, type of SE, age and past history of epilepsy) [27] and the Epidemiology-Based Mortality Score in SE (EMSE) (aetiology, age, comorbidities and EEG findings) [28].

Has status epilepticus mortality changed over time?

With the advent of increasing treatment options, establishment of treatment protocols for the acute management of SE and the advocacy of earlier and more aggressive intervention in the management of prolonged seizures (which is the rationale for the recently proposed definition of SE [29], raises the important question whether the mortality rate of SE has changed over time. There are however a very limited number of studies that allow for such an analysis.

In the Californian study [9] the incidence and mortality of SE was examined from 1991 through to 1998 using a state-wide database of all people with a hospital diagnosis of SE [7]. The overall case fatality was 10.7%, but with a much lower rate of 3.5% for those admitted with a primary diagnosis of generalised convulsive SE. Whilst the overall mortality for SE remained stable over the period of observation, the mortality of those admitted with a primary diagnosis of SE decreased from 4.7 to 3,2%. At the same time the annual incidence of SE decreased by 42% between 1991 and 1998 from 8.5 to 4.9/100,000 ($p < 0.001$) possibly suggesting more efficient and aggressive treatment of out of hospital prolonged seizures and SE [9].

Two more recent studies have looked at trends in SE-related hospital admissions and mortality in the United States, using representative samples of hospitals from national databases [30, 31]. In one study data from the US National Hospital Discharge Survey was used to identify hospital discharges with SE between 1979 and 2010 [30]. In total 760,117 discharges with SE were identified over the 32 years. In that time the incidence of SE increased from 3.5/100,000/year in 1979 to 12.5/100,000/year in 2010, representing an overall increase of 12.5% per year, with the most significant increase occurring between 1979 and 1991 (17.7% annual increase). There was a subsequent decrease in the incidence of SE in the 1990s before a further increase in the 2000s. The corresponding cumulative in-hospital mortality was 9.2% (95% CI 9.1,9.2) with no significant observed variation over the 32 years.

The second study utilised the Healthcare Cost and Utilisation Project Nationwide Inpatient Sample data to identify SE hospital admissions and SE associated mortality between 1999 and 2010 [31]. When considered as the primary cause of death, the age-adjusted mortality rate for SE increased by 5.6% between 1999 and 2010 from 0.179 per 100,000 to 0.189 per 100,000, with a corresponding increase of 56.4% in age-standardised SE hospital admissions from 8.86 per 100000 in 1999 to 13.86 per 100,000 in 2010 [31].

A more recent study looked at SE (and epilepsy) mortality rates in England and Wales between 2001 and 2013, which suggested a fall in SE mortality rates by 44% over the period of observation although such a finding needs to be cautiously interpreted as the mortality rates were presented without the corresponding SE incidence rates [32].

Conclusions

Whilst SE accounts for only about 10% of epilepsy rated deaths, it is nevertheless associated with significant morbidity and mortality. The overall mortality rate is about 10% with the SE aetiology being the primary prognostic factor, whilst age, SE duration, SE type and EEG findings are also of importance. There is conflicting evidence as to whether SE mortality rates have changed over time and this merits further study.

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Schweizerische Epilepsie-Liga
Ligue Suisse contre l'Epilepsie
Lega Svizzera contro l'Epilessia
Swiss League Against Epilepsy

Basel: Neuigkeiten zur Epilepsiebehandlung

Heute gibt es mehr und bessere Möglichkeiten als vor ein paar Jahrzehnten, epileptische Anfälle zu verhindern und die Lebensqualität der Betroffenen zu verbessern – auch wenn sensationelle Durchbrüche auf sich warten lassen.

Welche Medikamente sind neu oder kommen demnächst auf den Markt? In welchen Fällen ist eine Stimulation sinnvoll, und gibt es hier spannende Entwicklungen? Warum können wir heute mehr und früher operieren, und was gibt es Neues zur Ernährungstherapie?

In unserer Veranstaltung in Basel bringen kompetente Neurologinnen und Neurologen interessierte Fachpersonen auf den neuesten Stand und stellen sich deren Fragen und Diskussion. Unser Präsident, Prof. Dr. Stephan Rüegg, führt durch die Veranstaltung.

Fachveranstaltung der Schweizerischen Epilepsie-Liga, gratis

Donnerstag, 23. November 2017, 14.15 Uhr bis 16.40, anschl. Apéro
Kantonsspital, Zentrum für Lehre und Forschung, kleiner Hörsaal des ZLF
Hebelstrasse 20, 4031 Basel

2 Credits SNG, 1,5 Credits SGAIM, 16,5 FPH-Points
Vollständiges Programm und Anmeldung: www.epi.ch/fach

Eine Publikumsveranstaltung zu den gleichen Themen findet ab 19 Uhr statt.

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Ich (wir) möchte(n):

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Webcastings

Pour la première fois, vous pouvez voir et entendre nos manifestations a posteriori, et même faire une recherche par mots-clés.

Notre premier webcasting est celui du colloque francophone « Crises épileptiques et non épileptiques », qui a eu lieu à Neuchâtel cette année. Regardez-le pour mieux distinguer les crises épileptiques des malaises avec perte de connaissance brève et des crises non-épileptiques psychogènes, et pour savoir plus sur l'épilepsie et les comorbidités psychiatriques.

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

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

CHF 25'000.—

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.

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für die beste Dissertation an einer Schweizer Hochschule 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.

Preisrichterkollegium ist die Forschungskommission der Epilepsie-Liga, die bei Bedarf zusätzlich externe Gutachter hinzuziehen kann. Es trifft seine Entscheidung in geheimer Wahl.

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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

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

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

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31 décembre 2017

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Voir instructions : www.epi.ch/soutien_recherche

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

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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 la Commission de la recherche de la Ligue contre l'Epilepsie. Il peut être complété au besoin par des experts externes. La décision est prise par vote secret.

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Les dossiers de candidature doivent parvenir au Secrétariat général de la Ligue contre l'Epilepsie (Seefeldstrasse 84, 8008 Zurich, info@epi.ch), sous forme électronique ou en cinq exemplaires, jusqu'au

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Tag der Epilepsie
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14.-17.3.2018 I Berlin, Deutschland
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13.-16.6.2018 | Fürth, Deutschland
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