Somatic Comorbidities and Mortality in Epilepsy

Jan Novy
Service de neurologie, Département des neurosciences cliniques, Lausanne University Hospital (CHUV), Lausanne

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.

Epileptologie 2017; 34: 145 – 152

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].

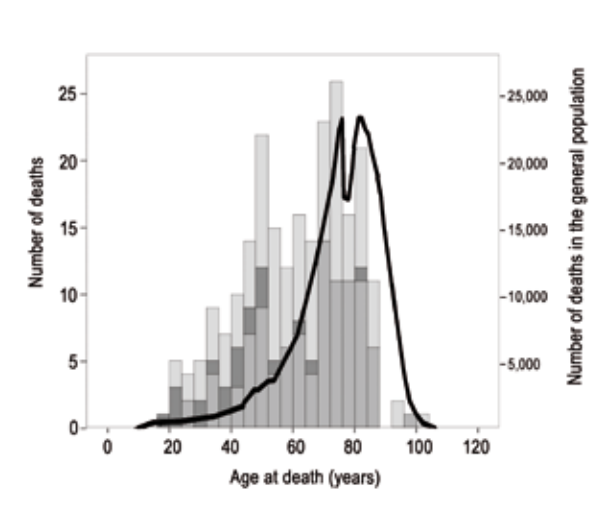

Figure 2: Distribution of age at death, in 4 year epochs, of all those who died whilst residents at the Chalfont Centre between 1988 and 2009. The frequency is displayed in number of cases. Light grey columns represent the number of people who did not have a post-mortem examination, all others had post-mortem 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

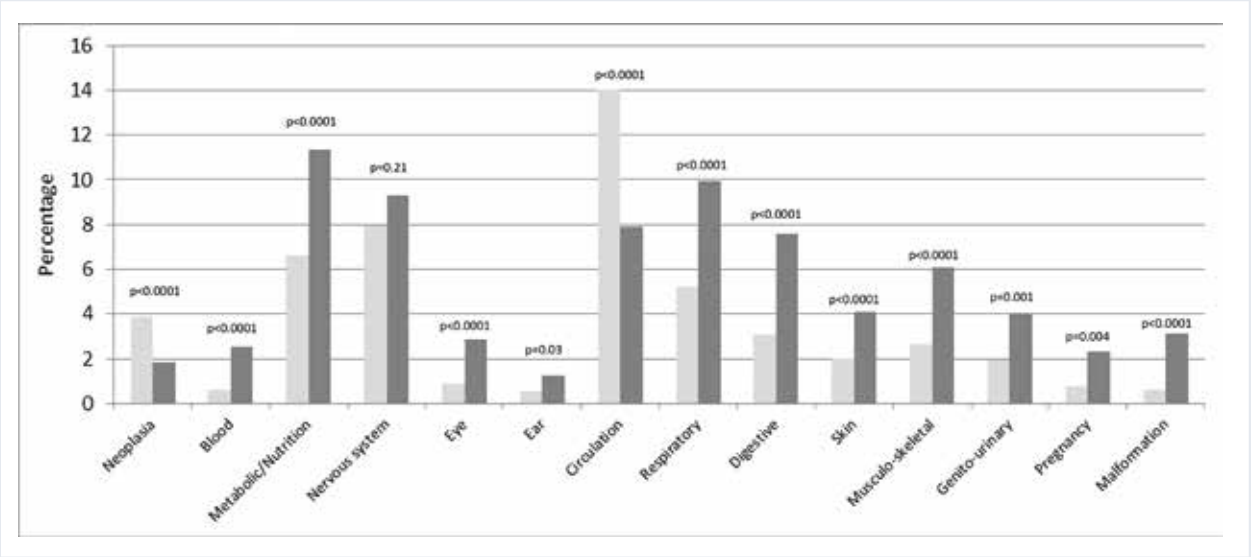

Figure 3: Distribution of somatic comorbidities in two different cohorts of people with epilepsy. Dark grey columns represent the referral centre cohort (total = 2016), light grey column the community cohort (total = 1278). Most comorbidities' types were significantly more frequent at referral centre.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

References

1. *Neligan A, Bell GS, Johnson AL et al. The long-term risk of premature mortality in people with epilepsy. Brain 2011; 134: 388-395*
2. *Trinka E, Bauer G, Oberaigner W et al. Cause-specific mortality among patients with epilepsy: Results from a 30-year cohort study. Epilepsia 2013; 54: 495-501*
3. *Olesen JB, Abildstrøm SZ, Erdal J et al. Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: a nationwide cohort study. Pharmacoepidemiol Drug Saf 2011; 20: 964-971*
4. *Neligan A, Bell GS, Shorvon SD, Sander JW. Temporal trends in the mortality of people with epilepsy: A review. Epilepsia 2010; 51: 2241-2246*
5. *Forsgren L, Hauser WA, Olafsson E et al. Mortality of epilepsy in developed countries: A review. Epilepsia 2005; 46: 18-27*
6. *Bell GS, Gaitatzis A, Johnson AL, Sander JW. Predictive value of death certification in the case ascertainment of epilepsy. J Neurol Neurosurg Psychiatry 2004; 75: 1756-1758*
7. *Novy J, Belluzzo M, Caboclo LO et al. The lifelong course of chronic epilepsy: the Chalfont experience. Brain 2013; 136: 3187-3199*
8. *Nashef L, Fish DR, Garner S et al. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. Epilepsia 1995; 36: 1187-1194*
9. *Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012; 53: 227-233*
10. *Bardai A, Lamberts RJ, Blom MT et al. Epilepsy Is a risk factor for sudden cardiac arrest in the general population. PloS One 2012; 7: e42749*
11. *Hauser WA, Annegers JF, Elveback LR. Mortality in patients with epilepsy. Epilepsia 1980; 21: 399-412*
12. *Rejdak K, Rubaj A, Glowniak A et al. Analysis of ventricular late potentials in signal-averaged ECG of people with epilepsy. Epilepsia 2011; 52: 2118-2124*
13. *Janousek J, Barber A, Goldman L, Klein P. Obesity in adults with epilepsy. Epilepsy Behav 2013; 28: 391-394*
14. *Foldvary-Schaefer N, Andrews ND, Pornsriniyom D et al. Sleep apnea and epilepsy: Who's at risk? Epilepsy Behav 2012; 25: 363-367*
15. *Zanzmera P, Shukla G, Gupta A et al. Effect of successful epilepsy surgery on subjective and objective sleep parameters – a prospective study. Sleep Med 2013; 14: 333-338*
16. *Singh G, Driever PH, Sander JW. Cancer risk in people with epilepsy: the role of antiepileptic drugs. Brain 2005; 128: 7-17*
17. *Brodie MJ, Mintzer S, Pack AM et al. Enzyme induction with antiepileptic drugs: Cause for concern? Epilepsia 2013; 54: 11-27*
18. *Mintzer S, Skidmore CT, Abidin CJ et al. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. Ann Neurol 2009; 65: 448-456*
19. *Clayton LM, Stern WM, Newman WD et al. Evolution of visual field loss over ten years in individuals taking vigabatrin. Epilepsy Res 2013; 105: 262-271*
20. *Novy J, Bell GS, Peacock JL et al. Epilepsy as a systemic condition: link with somatic comorbidities. Acta Neurol Scand 2017; Jun 1 Epub ahead of print*
21. *Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420: 860-867*
22. *Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105: 1135-1143*
23. *Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685-1695*

24. Trinchieri G. Cancer and inflammation: An old intuition with rapidly evolving new concepts. Annu Rev Immunol 2012; 30: 677-706
25. Maradit-Kremers H, Nicola PJ, Crowson CS et al. Cardiovascular death in rheumatoid arthritis: A population-based study. Arthritis Rheum 2005; 52: 722-732
26. Spina L, Saibeni S, Battaglioli T et al. Thrombosis in inflammatory bowel diseases: Role of inherited thrombophilia. Am J Gastroenterol 2005; 100: 2036-2041
27. Onufrak S, Abramson J, Vaccarino V. Adult-onset asthma is associated with increased carotid atherosclerosis among women in the Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis 2007; 195: 129-137
28. Dali-Youcef N, Mecili M, Ricci R, Andrès E. Metabolic inflammation: Connecting obesity and insulin resistance. Ann Med 2013; 45: 242-253
29. Mehta S, Farmer JA. Obesity and inflammation: A new look at an old problem. Curr Atheroscler Rep 2007; 9: 134-138
30. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature 2006; 444: 875-880
31. Alam I, Lewis K, Stephens JW, Baxter JN. Obesity, metabolic syndrome and sleep apnoea: all pro-inflammatory states. Obes Rev 2007; 8: 119-127
32. Scarpellini E, Tack J. Obesity and metabolic syndrome: an inflammatory condition. Dig Dis 2012; 30: 148-153
33. Yehuda-Shnaidman E, Schwartz B. Mechanisms linking obesity, inflammation and altered metabolism to colon carcinogenesis. Obes Rev 2012; 13: 1083-1095
34. Uludag IF, Bilgin S, Zorlu Y et al. Interleukin-6, interleukin-1 beta and interleukin-1 receptor antagonist levels in epileptic seizures. Seizure 2013; 22: 457-461
35. Alapirtti T, Rinta S, Hulkkonen J et al. Interleukin-6, interleukin-1 receptor antagonist and interleukin-1beta production in patients with focal epilepsy: A video–EEG study. J Neurol Sci 2009; 280: 94-97
36. Lehtimäki KA, Keränen T, Palmio J et al. Increased plasma levels of cytokines after seizures in localization-related epilepsy. Acta Neurol Scand 2007; 116: 226-230
37. Bauer S, Cepok S, Todorova-Rudolph A et al. Etiology and site of temporal lobe epilepsy influence postictal cytokine release. Epilepsy Res 2009; 86: 82-88
38. Liimatainen S, Fallah M, Kharazmi E et al. Interleukin-6 levels are increased in temporal lobe epilepsy but not in extra-temporal lobe epilepsy. J Neurol 2009; 256: 796-802
39. Lehtimäki KA, Keränen T, Huhtala H et al. Regulation of IL-6 system in cerebrospinal fluid and serum compartments by seizures: the effect of seizure type and duration. J Neuroimmunol 2004; 152: 121-125
40. Yu N, Di Q, Hu Y et al. A meta-analysis of pro-inflammatory cytokines in the plasma of epileptic patients with recent seizure. Neurosci Lett 2012; 514: 110-115
41. Hulkkonen J, Koskikallio E, Rainesalo S et al. The balance of inhibitory and excitatory cytokines is differently regulated in vivo and in vitro among therapy resistant epilepsy patients. Epilepsy Res 2004; 59: 199-205
42. Mao LY, Ding J, Peng WF et al. Interictal interleukin-17A levels are elevated and correlate with seizure severity of epilepsy patients. Epilepsia 2013; 54: e142-145
43. Quirico-Santos T, Meira ID, Gomes AC et al. Resection of the epileptogenic lesion abolishes seizures and reduces inflammatory cytokines of patients with temporal lobe epilepsy. J Neuroimmunol 2013; 254: 125-130
44. Bauer S, Köller M, Cepok S et al. NK and CD4+ T cell changes in blood after seizures in temporal lobe epilepsy. Exp Neurol 2008; 211: 370-377
45. Alapirtti T, Waris M, Fallah M et al. C-reactive protein and seizures in focal epilepsy: A video-electroencephalographic study. Epilepsia 2012; 53: 790-796
46. Espinola-Klein C, Gori T, Blankenberg S, Munzel T. Inflammatory markers and cardiovascular risk in the metabolic syndrome. Front Biosci 2011; 16: 1663-1674
47. Kanda T, Takahashi T. Interleukin-6 and cardiovascular diseases. Jpn Heart J 2004; 45: 183-193
48. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000; 101: 1767-1772
49. Pradhan AD, Manson JE, Rifai N et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286: 327-334
50. Danesh J, Kaptoge S, Mann AG et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: Two new prospective studies and a systematic review. PLoS Med 2008; 5: e78
51. Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: Effects of an early invasive or noninvasive strategy. JAMA 2001; 286: 2107-2113
52. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. N Engl J Med 2009; 361: 888-898
53. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. Annu Rev Immunol 2009; 27: 485-517
54. Griffiths CE, Strober BE, van de Kerkhof P et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010; 362: 118-128
55. Simon T, Taleb S, Danchin N et al. Circulating levels of interleukin-17 and cardiovascular outcomes in patients with acute myocardial infarction. Eur Heart J 2013; 34: 570-577
56. Xie JJ, Wang J, Tang TT et al. The Th17/Treg functional imbalance during atherogenesis in ApoE(-/-) mice. Cytokine 2010; 49: 185-193
57. Kumar DV, Prasad BV, Vishwanth HL, Kamath V. A study on interleukin -1beta and lipid profile as markers of cardiovascular risk in rheumatoid arthritis. J Clin Diagn Res 2013; 7: 1298-1302
58. McSorley MA, Alberg AJ, Allen DS et al. C-reactive protein concentrations and subsequent ovarian cancer risk. Obstet Gynecol 2007; 109: 933-941
59. Poole EM, Lee IM, Ridker PM et al. A prospective study of circulating C-reactive protein, interleukin-6, and tumor necrosis factor alpha receptor 2 levels and risk of ovarian cancer. Am J Epidemiol 2013; 178: 1256-1264
60. Tsilidis KK, Branchini C, Guallar E et al. C-reactive protein and colorectal cancer risk: A systematic review of prospective studies. Int J Cancer 2008; 123: 1133-1140
61. Zhou B, Liu J, Wang ZM, Xi T. C-reactive protein, interleukin 6 and lung cancer risk: a meta-analysis. PloS One 2012; 7: e43075
62. Clendenen TV, Lundin E, Zeleniuch-Jacquotte A et al. Circulating inflammation markers and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers 2011; 20: 799-810
63. Il'yasova D, Colbert LH, Harris TB et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers 2005; 14: 2413-2418
64. Reeves KW, Weissfeld JL, Modugno F, Diergaarde B. Circulating levels of inflammatory markers and mammographic density among postmenopausal women. Breast Cancer Res Treat 2011; 127: 555-563

65. Stark JR, Li H, Kraft P et al. Circulating prediagnostic interleukin-6 and C-reactive protein and prostate cancer incidence and mortality. Int J Cancer 2009; 124: 2683-2689
66. Grote VA, Kaaks R, Nieters A et al. Inflammation marker and risk of pancreatic cancer: a nested case-control study within the EPIC cohort. Br J Cancer 2012; 106: 1866-1874
67. Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. Nat Rev Neurol 2009; 5: 492-504
68. Meierkord H, Shorvon S, Lightman SL. Plasma concentrations of prolactin, noradrenaline, vasopressin and oxytocin during and after a prolonged epileptic seizure. Acta Neurol Scand 1994; 90: 73-77
69. Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. Epilepsy Res 1998; 30: 77-83
70. Ronkainen E, Ansakorpi H, Huikuri HV et al. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2005; 76: 1382-1386
71. Mukherjee S, Tripathi M, Chandra PS et al. Cardiovascular autonomic functions in well-controlled and intractable partial epilepsies. Epilepsy Res 2009; 85: 261-269
72. Ansakorpi H, Korpelainen JT, Huikuri HV et al. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2002; 72: 26-30
73. Druschky A, Hilz MJ, Hopp P et al. Interictal cardiac autonomic dysfunction in temporal lobe epilepsy demonstrated by [123I]metaiodobenzylguanidine-SPECT. Brain 2001; 124: 2372-2382
74. Devinsky O, Perrine K, Theodore WH. Interictal autonomic nervous system function in patients with epilepsy. Epilepsia 1994; 35: 199-204
75. Ansakorpi H, Korpelainen JT, Suominen K et al. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. Epilepsia 2000; 41: 42-47
76. Wannamaker BB. Autonomic nervous system and epilepsy. Epilepsia 1985; 26: S31-S39
77. Xhyheri B, Manfrini O, Mazzolini M et al. Heart rate variability today. Prog Cardiovasc Dis 2012; 55: 321-331
78. Stein PK, Kleiger RE. Insights from the study of heart rate variability. Ann Rev Med 1999; 50: 249-261
79. Stollberger C, Wegner C, Finsterer J. Seizure-associated Takotsubo cardiomyopathy. Epilepsia 2011; 52: e160-167
80. Rossi P, Bernard F, Aissi K et al. Takotsubo cardiomyopathy after seizure. BMJ Case Rep 2010; 2010
81. Cunnington C, Garg S, Balachandran KP. Seizure-associated takotsubo cardiomyopathy presenting with unheralded ventricular fibrillation. Int J Cardiol 2012; 162: e21-23
82. Ferlisi M, Tomei R, Carletti M et al. Seizure induced ventricular fibrillation: a case of near-SUDEP. Seizure 2013; 22: 249-251
83. Nef HM, Möllmann H, Kostin S et al. Tako-Tsubo cardiomyopathy: intraindividual structural analysis in the acute phase and after functional recovery. Eur Heart J 2007; 28: 2456-2464
84. Akashi YJ, Nakazawa K, Sakakibara M et al. 123I-MIBG myocardial scintigraphy in patients with "Takotsubo" cardiomyopathy. J Nucl Med 2004; 45: 1121-1127
85. Parodi G, Bellandi B, Del Pace S et al. Natural history of tako-tsubo cardiomyopathy. Chest 2011; 139: 887-892
86. Sharkey SW, Windenburg DC, Lesser JR et al. Natural history and expansive clinical profile of stress (Tako-Tsubo) cardiomyopathy. J Am Coll Cardiol 2010; 55: 333-341
87. Adams JE 3rd, Bodor GS, Dávila-Román VG et al. Cardiac troponin I. A marker with high specificity for cardiac injury. Circulation 1993; 88: 101-106
88. Woodruff BK, Britton JW, Tigaran S et al. Cardiac troponin levels following monitored epileptic seizures. Neurology 2003; 60: 1690-1692
89. Eskandarian R, Asghari N, Darban M, Ghorbani R. Cardiac troponin levels following complicated and uncomplicated epileptic seizures. Arch Med Res 2011; 42: 439-442
90. Sieweke N, Allendörfer J, Franzen W et al. Cardiac troponin I elevation after epileptic seizure. BMC Neurol 2012; 12: 58
91. Scorza FA, Abreu AM, Albuquerque MD et al. Quantification of respiratory parameters in patients with temporal lobe epilepsy. Arq Neuropsiquiatr 2007; 65: 450-453
92. Berilgen MS, Sari T, Bulut S, Mungen B et al. Effects of epilepsy on autonomic nervous system and respiratory function tests. Epilepsy Behav 2004; 5: 513-516
93. Dütsch M, Devinsky O, Doyle W et al. Cerebral autoregulation improves in epilepsy patients after temporal lobe surgery. J Neurol 2004; 251: 1190-1197

Address for correspondence:
PD Dr méd. Jan Novy
Unité d'épileptologie/EEG
Service de neurologie
Département des neurosciences cliniques
BH07
CHUV
CH 1011 Lausanne
Tél. 0041 21 314 2383
Fax 0041 21 314 1290
Jan.Novy@chuv.ch