THE MISTERY OF GUSTAVE FLAUBERT’S DEATH

Could sudden unexpected death in epilepsy be part of the context?

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Abstract – Epilepsy is the most common serious neurological condition and sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death. Information concerning risk factors for SUDEP is conflicting, but high seizure frequency is a potential risk factor. Additionally, potential pathomechanisms for SUDEP are unknown, but it is very probable that cardiac arrhythmias during and between seizures or transmission of epileptic activity to the heart via the autonomic nervous system potentially play a role. More than two decades ago, temporal lobe epilepsy was suggested as having been the “nervous disease” of Gustave Flaubert, one of the most important French novelists. In these lines, as the circumstances of his death were the subject of fabulous and mysterious speculations, we postulated in this paper that Falubert’s death could be due SUDEP phenomenon.

KEY WORDS: epilepsy, Gustave Flaubert, SUDEP, seizure.

O mistério da morte de Gustave Flaubert: pode a morte súbita em epilepsia fazer parte o contexto?

Resumo – A epilepsia é a condição neurológica crônica grave mais comum e a morte súbita em epilepsia (SUDEP) é a mais importante causa de morte diretamente relacionada à epilepsia. Informações sobre fatores de risco para SUDEP são conflitantes, porém, a alta frequência de crises epilépticas é um fator de risco em potencial. Além disso, os mecanismos causais para SUDEP ainda não estão conhecidos, mas é muito provável que arritmias cardíacas durante e entre as crises epilépticas ou a transmissão da atividade epiléptica para o coração via sistema nervoso autônomo desempenhem um importante papel. Mais de duas décadas atrás, foi proposto que a “doença nervosa” de Gustave Flaubert, um dos mais importantes novelistas franceses, era epilepsia do lobo temporal. Nesse sentido, como a morte de Gustave Flaubert ainda seja motivo de misteriosa especulação, nosso artigo propõe que a mesma poderia estar relacionada ao fenômeno de SUDEP.

PALAVRAS-CHAVE: epilepsia, Gustave Flaubert, SUDEP, crise epiléptica.

EPILEPSY: GENERAL ASPECTS

Epilepsy is the most common serious neurological condition and approximately 50 million people worldwide have it. In the US, about 100,000 new cases of epilepsy are diagnosed. In the UK, between 1 in 140 and 1 in 200 people (at least 300,000 people) are currently being treated for epilepsy. Epidemiological studies suggest that between 70 and 80% of people developing epilepsy will go into remission, while the remaining patients continue to have seizures and are refractory to treatment with the currently available therapies. The most common risk factors for epilepsy are cerebrovascular disease, brain tumours, alcohol, traumatic head injuries, malformations of cortical development, genetic inheritance, and infections of the central nervous system. In resource-poor countries, endemic infections, such as malaria and neurocysticercosis, seem to be major risk factors.

Epilepsies are characterized by spontaneous recurrent seizures, caused by focal or generalized paroxysmal changes in neurological functions triggered by abnormal electrical activity in the cortex. Because it involves hyperexcitable neurons, a basic assumption links the pathogenesis of epilepsy and the generation of synchronized neuronal activity with an imbalance between inhibitory [g-aminobu...
tyric acid (GABA)-mediated] and excitatory (glutamatergicmediated) neurotransmission, in favour of the latter. Seizures and epilepsy are usually divided into two groups: partial and generalized. Partial or focal seizures have clinical or EEG evidence of local onset and may spread to other parts of the brain during a seizure, while generalized seizures begin simultaneously in both cerebral hemispheres. Temporal lobe epilepsy (TLE) is the most common form of partial epilepsy, probably affecting at least 20% of all patients with epilepsy. It is the most common form of drug-refractory epilepsy. Atrophy of mesial temporal structures is well-known to be associated with TLE and hippocampal sclerosis, which is the most frequent histological abnormality in this form of epilepsy.

SUDDEN UNEXPECTED DEATH IN EPILEPSY

Epilepsy is associated with a two- to three-fold increase in mortality compared to the general population, and sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death. SUDEP is defined as non-traumatic and non-drowning death in patients with epilepsy that is sudden, unexpected, witnessed or unwitnessed, and with or without evidence of a seizure. Also in SUDEP, post mortem examination does not reveal a toxicological or anatomical cause of death (excluding documented status epilepticus). Comparisons of incidence estimates for SUDEP are difficult, since different definitions of SUDEP have been used, not all patients have a postmortem examination, and case ascertainment methods and source populations have varied. The incidence of SUDEP has been estimated to be 3.5/1000 person-years in a lamotrigine clinical trial, 0.5–1.4/1000 person-years in people with treated epilepsy, 5.9/1000 person-years in outpatients with epilepsy at a tertiary referral centre and 0.35/1000 person-years in a population-based study. The National General Practice Study of Epilepsy (NGPSE), a community-based study in the United Kingdom, saw the first case of SUDEP after 11,000 person-years of follow-up; the results of the Medical Research Council Antiepileptic Drug Withdrawal Study showed that SUDEP is a rare event among patients with epilepsy in remission. Information concerning risk factors for SUDEP is conflicting, but potential risk factors include: early adulthood, early onset of epilepsy, long duration of epilepsy, uncontrolled seizures (mainly in those with TLE), high seizure frequency, certain seizure types, higher numbers of antiepileptic drug (AED) and winter temperatures. Additionally, potential pathomechanisms for SUDEP are unknown, but it is very probable that cardiac arrhythmias during and between seizures, electrolyte disturbances, arrhythmogenic drugs or transmission of epileptic activity to the heart via the autonomic nervous system potentially play a role.

Following this reasoning, postmortem examinations in people dying of SUDEP have found hearts that are dilated and heavier than expected, and pulmonary edema in approximately 50–86% of cases. Furthermore, others have described pathological changes in the hearts of those dying with SUDEP, including fibrosis of the walls of small coronary arteries, atrophy of cardiomyocytes, myofibrillar degeneration, edema of the conductive tissue and morphological abnormalities of the cardiac conduction system. These abnormalities may be the consequence of repeated hypoxemia and/or may be associated with the increase of catecholamines during an ictal sympathetic storm.

Several studies have assessed the frequency and character of ictal cardiac rhythm during seizures and the most compelling evidence derives from the presence of ictal arrhythmias. When ictal cardiorespiratory variables were recorded in people with epilepsy, an increase in heart rate in 91% of 41 seizures and a transient bradycardia in five seizures (four patients) were found. Another study evaluated the electrocardiographic (ECG) changes during 51 seizures in 43 patients with refractory epilepsy. This showed that 70% of patients had either ECG abnormalities (16%), tachycardias (30%), or both (23%) during the ictal and/or post-ictal period. These changes may all be relevant to the pathophysiology of SUDEP.

Results of interictal cardiac investigations have also been described. In one study, resting ECGs in 75 patients with epilepsy were compared with normal ECGs recorded in age-matched patients without cardiac or neurological disorders; ventricular rate, PR interval, QRS duration, and QT interval (corrected for heart rate) were compared. Those with epilepsy had higher heart rates and longer QT durations than the age-matched controls. Heart rate and QT duration were, however, not outside the normal range. Others investigated whether patients with drug refractory epilepsy have cardiovascular abnormalities that might be related to sudden death. Twenty-three subjects underwent comprehensive cardiovascular evaluations (ECG, Holter-monitoring, echocardiography, ergometric exercise test and myocardial scintigraphy; if abnormalities were found, coronary angiography was also performed) before and during video-EEG monitoring. ST-segment depression was found in 40%, and this was associated with a higher maximum heart rate during seizures, suggesting that cardiac ischemia may occur in these patients. Although interictal changes in heart rate variability have been described in patients with epilepsy, their contribution to SUDEP remains to be determined.

GUSTAVE FLAUBERT: LIFE WITH EPILEPSY

The French novelist Gustave Flaubert (1821-1880) (Figure) was one of the most important forces in creating the
modern novel as a conscious art form and in launching, much against his will, the realistic school in France\(^{42-47}\). Famous for his novel *Madame Bovary* (1857), Flaubert was a perfectionist, who did not make a distinction between a beautiful or ugly subject: all was in the style\(^{42-47}\). The idea, he argued, only exists by virtue of its form – its elements included the perfect word, cunningly contrived and verified rhythms, and a genuine architectural structure\(^{42-47}\).

Gustave Flaubert was born on December 12, 1821, in Rouen, France. His father, Achille-Cleophas Flaubert was a doctor and an important Rouen citizen, and his mother, Anne-Justine-Caroline Fleuriot, was a physician's daughter\(^{46,47}\). He had an older brother, Achille, and a younger sister, Caroline, with whom he had a close relationship\(^{43-45}\). Gustave began to develop his writing skills at an early age and wrote plays, which he put on for his family at the age of nine or ten\(^{46,47}\).

In the 1830s Flaubert attended the Collège Royal de Rouen, writing for its newspaper, reading Shakespeare, travelling extensively and at the age of fourteen began in earnest his own writings, inspired by his unconsummated love affair at this time with the much older and married Elisa Schlésinger\(^{46,47}\). In this period, he had easy access to prostitutes and this led to venereal disease (syphilis) from which he never recovered\(^{46,47}\). In 1844 Flaubert had his first epileptic seizure, however, some authors described that his epilepsy may have started earlier\(^{42,44,46}\). During his first seizure, Flaubert was driving a carriage with his brother, front the twinkling lanterns of an obliging carriage and a distant inn, when suddenly he fell to the floor as if he were dead. It was like “being swept away in a torrent of flames . . . sudden as lightning . . . an instantaneous interruption of memory . . . a letting go of its entire contents”\(^{42,46}\). About a month after his first seizure, Flaubert wrote to a friend: “You must know that I had a kind of cerebral congestion, in other words a miniature attack of apoplexy, accompanied by nervous disorders”\(^{42,45}\). It is interesting to note that this first seizure was followed by four others, and Flaubert’s condition gradually worsened\(^{46}\). Clearly, he was helplessly crippled by his seizures, which became hideous terror for him and recurred at intervals throughout his life\(^{46,47}\). Flaubert was treated with regular bleedings, mercury massages, and bromide, the antiepileptic drug of that time\(^{42}\).

**GUSTAVE FLAUBERT: DEATH DUE EPILEPSY?**

Based on the preceding considerations, Flaubert’s work contains extensive and interesting autobiographic notes. On the other hand, the etiology of his epilepsy cannot be clarified in biographic material or oral and written traditions\(^{42}\). However, febrile convulsions, trauma, infection, or congenital anomalies with secondary onset of epilepsy should be considered\(^{42}\). Moreover, neurosyphilis as a potential cause of epilepsy is rather unlikely because of the early onset in childhood or adolescence\(^{42}\). Concerning the kind of Flaubert’s epilepsy, we are totally in agreement with the very elegant considerations evaluated by Arnold and colleagues\(^{42}\): “Psychopathological considerations suggest primary involvement of mesial temporal lobe structures with typical findings of ictal and interictal mood behavior, as well as unstructured visual aura features such as déjà vu and macropsia, which is commonly seen in mesial temporal lobe epilepsy”.

Unfortunately, Flaubert suddenly died in 1880, at the age of 58\(^{42,46}\). The circumstances of his death were the subject of fabulous and mysterious speculations\(^{46}\), since various suppositions about his cause of death were made after Flaubert’s lifetime. In these lines, although some detailed bibliographic reports suggest a stroke as cause of his death, an epileptic seizure also be considered responsible by Falubert’s death\(^{42}\). Thus, considering here an epileptic seizure as cause of Flaubert’s death, we also can speculate a new perspective: Could be exist a possible relation between Flaubert’s death and SUDEP?

As we know, the risk of sudden death is clearly increased in the epilepsy population, and SUDEP is the most common seizure-related category\(^{40,48,49}\). SUDEP is mainly, but not exclusively, a problem for patients with chronic uncontrolled epilepsy\(^{49}\). Accordingly, among the rarely witnessed cases of SUDEP, the majority of patients proved to suffer a partial or generalized seizure immediately prior to death, suggesting a seizure-related cardiac or respiratory dysfunction\(^{45,30}\).
In an elegant largest case-control study, Nilsson and colleagues demonstrated that seizure frequency is a strongest risk factor for SUDEP. In their study, fifty seven SUDEP cases were included, of whom 91% had undergone necropsy. The relative risk of SUDEP increased with number of seizures per year and the estimated relative risk was 10.16 (95% CI 2.94–35.18) in patients with more than 50 seizures per year, compared with those with up to two seizures per year. In the same way, Walczak and co-workers, in a prospective cohort study, determined the incidence of and risk factors for SUDEP. The incidence of SUDEP was 1.21/1,000 patient-years and a progressive risk for SUDEP was found with increasing seizure frequency. The authors support the idea that tonic-clonic seizures are an important proximate cause of SUDEP and concluded that the occurrence of as few as 1-3 such seizures per year was associated with an increased risk factor. From a pathophysiological point of view, SUDEP directly result from the occurrence of seizures, in particular generalized tonic-clonic seizure. Though the respective role of seizure-induced respiratory and cardiac fatal abnormalities remains uncertain, recent studies suggest that high-risk ictal arrhythmias occur in much greater proportion of patients with refractory epilepsy than previously believed, representing the leading cause of SUDEP. Quite interesting, as uncontrolled seizures (mainly in those with TLE) and high seizure frequency are the most important risk factors for SUDEP, it is plausible to believe that factors could influence negatively the cardiovascular system of the patient with epilepsy leading to cardiac abnormalities and hence SUDEP.

Following these reasoning, as Gustave Flaubert’s case points to the possible coexistence of a serious and poorly controlled form of temporal lobe epilepsy, it is plausible to believe that Flaubert’s death could be associated with SUDEP. Although early mortality series at the beginning of the 20th century reported deaths from status epilepticus to be more common, deaths associated with repeated seizures were also recognised. For example, in 1904, Spratling wrote of epilepsy as a disease that, “destroys life suddenly and without warning through a single, brief attack...and does so from in 3 to 4% of all who suffer from it” and in this view, Flaubert’s case is not so chronologically distant from the interesting paper described above.

Finally, apart from data related here, various diagnoses made by medical and nonmedical persons during and after Flaubert’s lifetime was reviewed by Gastaut group and cannot be ruled out. These authors admitted some interesting notes: (a) Flaubert suffered from organic and not psychogenic epilepsy, more precisely “complex partial epilepsy of occipital-temporal origin, secondary to lesion of the left posterior hemisphere with occasional secondary generalization of seizures.”; (b) Flaubert’s epilepsy modified his behaviour without affecting his genius; (c) Gustave Flaubert’s case, like Dostoevski’s, should serve as a defence witness for the unfortunate epileptics thought to be destined for intellectual deterioration only because of the repetition of their seizures.

While admitting the deficiencies in our knowledge about the circumstances of Flaubert’s disease and death, regardless of how it was really evaluated, it seems reasonable to assume that the risk of sudden death is clearly increased in the epilepsy population actually, and SUDEP is the most important direct epilepsy-related cause of death. In conclusion, as recently reported clarification of risk factors and establishment of the mechanisms of SUDEP are important for establishing preventative measures for SUDEP and for striving for the best control of seizures.

REFERENCES