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Sudden Unexpected Death in Epilepsy: An Overview

Vera C. Terra[1], Américo C. Sakamoto[1,]
Hélio R Machado[1] and Fulvio A. Scorza[2]
[1]*Centro de Cirurgia de Epilepsia (CIREP). Departamento de Neurociências e Ciências do Comportamento. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. Ribeirão Preto, São Paulo,*
[2]*Disciplina de Neurologia Experimental. Universidade Federal de São Paulo, Escola Paulista de Medicina (UNIFESP/EPM), São Paulo, Brasil*

1. Introduction

Epilepsy is one of the most frequent neurological disorders, both in children and adult persons. About 0.5-1% of general population suffer from epilepsy, which means that 50 million people in the world are affected. First years of life and very late adulthood are periods in human's life particularly predisposing to developing epilepsy. Patients with repetitive seizures may have a significantly lower quality of life, with frequent absences from work or school caused by seizures, difficulties in social life, frequent injuries, necessity of polytherapy and the risk of life-threatening situations, such as status epilepticus (Józwiak, 2007). People with epilepsy have also a two to three fold increased risk of death as compared to the age-matched general population and may die unexpectedly without a clear structural or pathologic identifiable cause. Increased risk of death primarily affects young adults mostly with drug resistant epilepsy and accounts for a large proportion of deaths among people with epilepsy. This condition is called sudden unexpected death in epilepsy (SUDEP).

SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without the evidence of a seizure, excluding *status epilepticus*, and without a toxicological or anatomical cause of death in *post-mortem* examination (Tomson et al, 2008). Diagnosis of SUDEP is sometimes difficult since *post-mortem* examination is not always available. Annegers (1997) suggested six criteria to consider the etiology of death as being SUDEP: 1. The diagnosis of epilepsy; 2. Death in a victim in a reasonable state of health; 3. Death should occur suddenly; 4. During normal activities and in benign circumstances; 5. Without a medical cause; 6. Not directly caused by a seizure or *status epilepticus* (Annegers, 1997). In this way, definite SUDEP cases need to have a *post-mortem* examination to ensure patient did not have a concomitant disease that can justify death and probable cases are considered that with clinical findings suggestive of SUDEP but where necropsy is not available. These strict criteria may hamper the diagnosis of SUDEP in many cases and, in these lines, other authors suggest that a formal *post-mortem* examination may be replaced by a verbal autopsy, contributing to a more realistic assessment of SUDEP incidence (Lathers & Schraeder, 2009).

SUDEP incidence rates are variable depending on the cohort studied, being directly affected by seizure frequency. In this way, it range from 0.35 per 1,000 person-years of follow-up in population-based studies to 9.3 per 1,000 person-years in patients with refractory epilepsy (Asadi-Pooya & Sperling, 2009; Ryvlin et al, 2009), with an intermediate incidence of 1-2/1,000 person-years in patients with chronic epilepsy. The highest rates occur in patients with 20 to 40 years old (Tomson et al, 2005).

Interest in sudden unexpected and unexplained death in individuals with epilepsy was rekindled during the early 1980s and more recently by antiepileptic drug (AED) trials, medico legal issues and epidemiologic studies (Annegers, 1997). Although, if we search in PUBMED database the word SUDEP, approximately 250 articles are found and most of them reports small series of patients or describe single patient cases, with few articles reporting large controlled series (case-control or cohort studies). Moreover, most articles that tried to identify SUDEP risk factors report few cases, being observational studies. In this way, definition of potentially risk factors is essential. No single risk factor is common to all SUDEP cases, suggesting multiple mechanisms or trigger factors are involved (Tomson et al, 2005). Most deaths of SUDEP are unwitnessed and occur at home, usually in bed and presumably overnight, in association with a seizure (Opeskin & Berkovic, 2003; Kloster & Engelskjøn, 1999). Many victims have pulmonary oedema on *postmortem* examination, and some show ischemic damage of the heart despite normal coronary arteries. Nevertheless, the precise reason for a particular seizure being fatal in an otherwise healthy individual is as yet undetermined (McGugan, 2000).

Studies suggested that patients suffering of SUDEP had a significant longer mean duration of epilepsy compared with controls and that more people succumbing of SUDEP had had a seizure within the previous year (Hiritis et al, 2007). Interestingly, considering all deaths in epilepsy, patients that died of SUDEP are reported to die at younger ages than non-SUDEP deaths. Other possible related risk factors described in the literature are male sex, generalized tonic-clonic seizures, high seizure frequency, specific AEDs, polytherapy with several AEDs, mental retardation, psychiatric illness, psychotropic co-medication and an earlier epilepsy onset (Vlooswijk et al, 2007; Lear-Kaul et al, 2005). Summarizing all citations, main risk factors seems to be young age, high seizure frequency, frequent generalized tonic-clonic seizures, nocturnal seizures, poor drug compliance, medical refractory epilepsies, high number of antiepileptic drugs and long duration of epilepsy, but this still need confirmation with controlled studies (Téllez-Zenteno et al, 2005; Ryvlin et al, 2009).

A cohort study accompanied 3,688 subjects aged 15 to 49 years with more than four prescriptions for AED. Patients were followed since first AED prescription to one of the options: age 50 years, death, or last registration on system. In this group were observed 163 deaths and 153 death certificates were examined to identify potential SUDEP cases. There were 18 definite/probable SUDEPs and 21 possible SUDEPs, yielding a minimum incidence of 0.54 SUDEP per 1,000 person-years and a maximum of 1.35 SUDEP per 1,000 person-years. Main risk factors observed were male sex, number of AEDs ever prescribed, prescription of psychotropic drugs and in males with a history of treatment with three or more AEDs. Authors suggested that a 1.7 fold increased risk of SUDEP might be associated for each increment in maximum number of AED administered (Tennis et al, 1995). Although, this increase may simple reflect severity of epilepsy and not the directly effect of AED in increasing SUDEP risk. A causal relationship of SUDEP with antiepileptic drugs administration has not been proved, but the sudden decrease of antiepileptic drugs serum

levels may cause cardiac arrhythmias potentially fatal (Garaizar, 2000). Although SUDEP has not been clearly associated with the use of any particular AED, some case-control studies have pointed to an association between SUDEP and polytherapy with AED and frequent dose changes independent of seizure frequency (Tomson et al, 2005). All currently available AED have been associated with SUDEP, but two specific drugs, carbamazepine and lamotrigine were considered by some authors as potentially increasing SUDEP risks. A review of Cardiff Epilepsy Unit data shows that carbamazepine was disproportionately represented in patients suffering SUDEP, achieving almost 85% of the cases described in some SUDEP series (Timmings, 1998).

Carbamazepine has a potential effect inducing lengthening of the ECG Q-T interval combined with a mild pro-arrhythmic action. This may cause transient cardiac instability leading to arrhythmic death (Timmings, 1998). Abrupt withdrawal of CBZ may lead to enhanced sympathetic activity in sleep as evidenced by heart frequency analysis and this increased activity in the setting of seizure-induced hypoxia could predispose to SUDEP (Hennessy et al, 2001). Isolated reports have described patients suffering of SUDEP or syncope associated with hyponatraemia generated by syndrome of inappropriate secretion of antidiuretic hormone (Kloster & Børresen, 1999; Ruiz et al, 2007). Interesting in all cases, patients were chronically using association of carbamazepine/oxcarbazepine and lamotrigine. Others authors have already suggested that current available studies do not support the hypothesis that CBZ is associated with a higher risk of SUDEP (Opeskin et al, 1999). In this way, it is unclear whether polytherapy, frequent dose changes, and high carbamazepine levels per se represent a risk factor or just reflect an unidentified aspect of an unstable, more severe form of epilepsy (Nilsson et al 2001). Anyway, a search for syndrome of inappropriate secretion of antidiuretic hormone in patients on carbamazepine and oxcarbazepine, and in cases of sudden death in epilepsy, is recommended.

With respect to lamotrigine, it has recently been shown that this DAE inhibit the cardiac rapid delayed rectifier potassium ion current and consequently increase the risk of cardiac arrhythmia and sudden unexpected death. Although Leestma et al (1997) suggested that the rate of SUDEP in patients using lamotrigine was unrelated to the drug, Aurlien et al (2007) registered in ten years, four consecutive cases of SUDEP in non-hospitalized patients that were all being treated with lamotrigine in monotherapy. However, as with other potential risk factors, there are no systematic studies that may confirm these suspicions.

In this way, to estimate the risk of SUDEP, Walczak et al (2001) determined SUDEP incidence and risk factors in a prevalence cohort of people with epilepsy enrolled prospectively. Most of the patients had been intensively evaluated and detailed information regarding possible risk factors for SUDEP was defined. In this study four thousand, five hundred seventy-eight patients were enrolled. One hundred eleven patients died during follow up, 28 of them of SUDEP. Three apparently independent risk factors for SUDEP were proposed: presence of tonic-clonic seizures, mental retardation and the number of anticonvulsant drugs used. Authors considered presence of tonic-clonic seizures as a major risk factor, since the great majority of patients that is in suspicion of SUDEP had history of experienced tonic-clonic seizure just before death, or circumstances of death when was carefully examined showed an evidence of tonic-clonic seizure preceding death. Also, death has been directly related to generalized convulsive seizures in an animal model of SUDEP (Faingold et al, 2010).

Based in this study, DeGiorgo et al (2010) validated a SUDEP-7 inventory. Inventory is composed by seven items which scores were based on the log of the odds ratio of the main

risk factors reported previously (Walczak et al, 2001) (Table 1). Authors suggested that a high index will be correlated with a major risk of patient to have SUDEP and that this data could be correlated with others suspected risk factors. Although this inventory was the first attempt to stagger patients in a numeric way, it was not fully accepted and it is not being used in SUDEP literature. A validation with a larger cohort of patients is required to demonstrate if it can contribute to identify patients at major risk.

SUDEP RISK FACTOR	SCORES
1. More than three tonic clonic seizures in last year	0 or 2
2. One or more tonic-clonic seizures in last year	0 or 1
3. One or more seizures of any type over the last 12 months	0 or 1
3. More than 50 seizures of any type per month over the last 12 5. months	0 or 2
4. Duration of epilepsy of ≥ 30 years	0 or 3
5. Current use of three or more antiepileptic drugs	0 or 1
6. Mental retardation, intelligent coefficient < 70 or too impaired test	0 or 2

Table 1. SUDEP-7 inventory, from DeGiorgio et al, 2010.

2. Mechanisms of SUDEP

SUDEP is probable related to a set of risk factors that may involve structural, functional and genetic causes (Figure 1). As well as risk factors, the pathophysiology of SUDEP remains unclear, but a post-ictal central or obstructive apnea or a cardiac arrhythmia seems to represent the most likely mechanisms (Ryvlin et al, 2009). Experimental studies have suggested that damage to the central nucleus may be of functional significance in patients with SUDEP in particular with regard to their susceptibility to cardiac arrhythmias. In this way, neuronal loss was observed in the medial division of the lateral amygdaloid nucleus in SUDEP cases, but it seems not to be a specific finding since this pattern was present in patients that did not suffered SUDEP (Thom-M et al, 1999). Corroborating the hypotheses of neuronal loss, there are evidences of heat shock protein positive neurons in the hippocampus in SUDEP, suggesting an ante-mortem neuronal injury (Thom et al, 2003).

Physiologic studies in humans during seizures identified in some cases a central apnea, occasionally followed by asystole; in others patients, cardiac arrhythmia, of reflex neural origin, have been detected (Garaizar, 2000; Hennessy et al, 2001). The cardiac mechanism of greatest interest is the precipitation of arrhythmias by seizure discharges via the autonomic nervous system (Jehi & Najm, 2008). Studies assessing autonomic tone with functional tests as deep breathing, Valsalva maneuver, isometric exercise, cold pressor and tilt-table observed a higher vasomotor tone, higher sympathetic tone, lower parasympathetic tone, lower parasympathetic reactivity and more severe dysautonomia in the refractory epilepsy subjects. In this way, refractoriness may lead to an alteration in cardiovascular autonomic regulation, which might be a predisposing factor for SUDEP (Mukherjee et al, 2009).

There are few studies reporting genetic mutations in patients with SUDEP and most of them evaluated genes responsible for long QT syndrome. Recent studies demonstrated mutations in the SCN5A and KCNH2 genes coding for the cardiac sodium channel alpha subunit and raises the possibility that the mutation may explain both the epilepsy and the sudden death (Aurlien ET AL, 2009; Tu et al, 2010) and since, channelopaties may be another risk factor for SUDEP to be considered in patients with epilepsy.

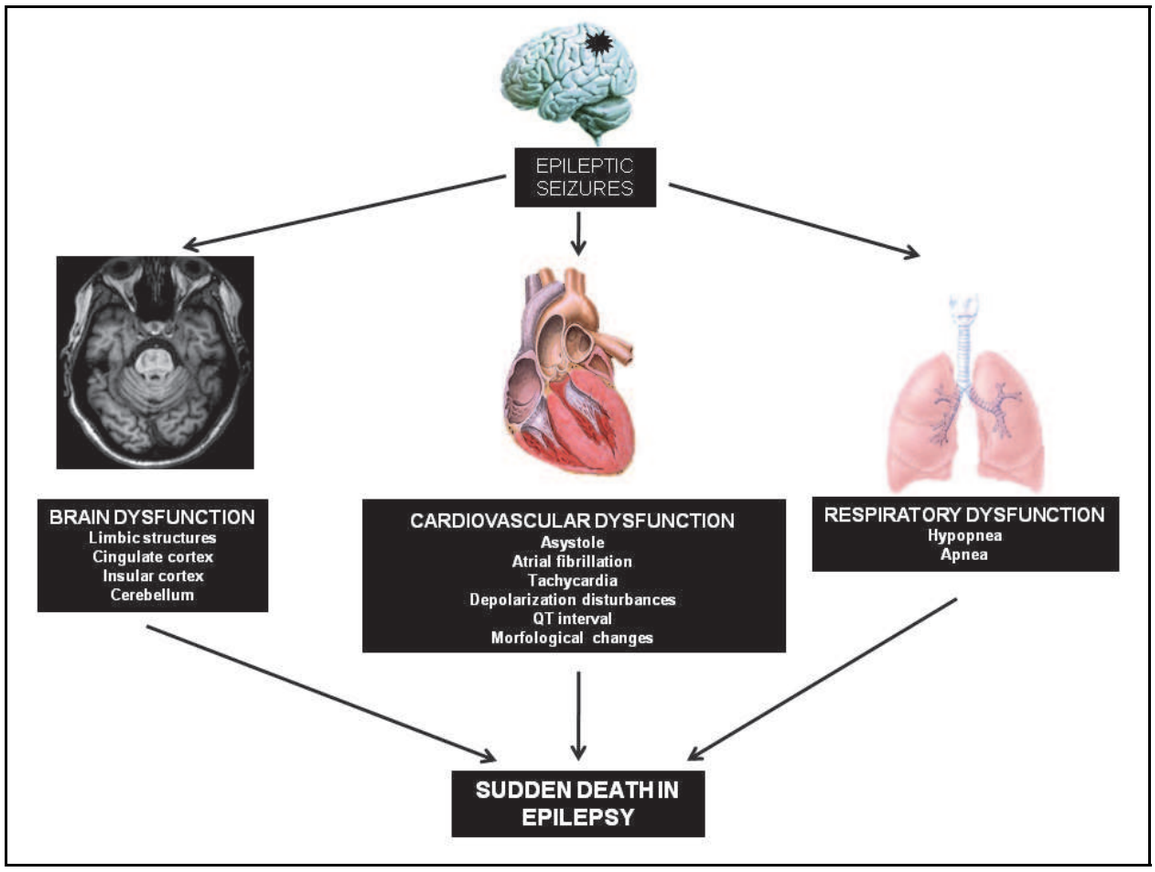

Fig. 1. Main possible mechanisms involved in SUDEP. Epileptic seizures act directly in lung, heart and brain, with multisystem dysfunction. In brain, repetitive epileptic seizures and antiepileptic drugs may act leading to brain volume loss and developing aberrant pathways. In heart, dysfunctions causing bradychardia or tachycardia *per se* could culminate in SUDEP, but this may be associated to morphological abnormalities. Considering respiration, mechanisms involved are related to decreased ventilation.

2.1 Respiratory mechanisms

Monitoring of seizures and respiratory function with pulse oximetry has shown that ictal respiratory changes accompany tonic-clonic seizures and even partial seizures, especially those of temporal lobe origin in both, children and adults. This changes diminished central drive that may be associated or not with peripheral airway obstruction (Blum, 2009). The finding of pulmonary edema in 86% of patients that suffered SUDEP at *postmortem* examination may support this obstructive theory (Salmo & Connolly, 2002).

Investigators have documented a range of respiratory parameters (respiratory effort, airflow, oxygen saturation) in conjunction with time-locked audio-video electroencephalograms and electrocardiograms to provide a more complete picture of the physiologic changes that occur during seizures. Apnea, mainly central, was present in all patients with generalized seizures and approximately one third of patients with complex partial seizures (Walker & Fisch, 1997). In other group of patients with partial seizures without secondary generalized convulsions, 34.8% of seizures had desaturations below 90%,

31.8% had desaturations below 80% and 12.5% had desaturations below 70%, which was significantly correlated with seizure duration and with electrographic evidence of seizure spread to the contralateral hemisphere. In this study, central apneas or hypopneas occurred in 50% of 100 seizures and mixed or obstructive apneas occurred in 9% of these seizures. Considering these findings, authors concluded that ictal hypoxemia occurs often in patients with localization-related epilepsy and may be pronounced and prolonged even with seizures that do not progress to generalized convulsions (Bateman et al, 2008).

Interestingly other study observed a close temporal relationship between spread of seizures to the contralateral hemisphere and the onset of seizure-associated apnea. Apnea onsets are more tightly linked to time of contralateral spread than to time of seizure onset, suggesting that contralateral seizure spread in patients with temporal lobe epilepsy may be a risk factor for ictal-related respiratory dysfunction (Seyal & Bateman, 2009). This finding did not alter the ability of postictal respiratory function, respiratory rate and amplitude that is even increased after the end of the seizures (Seyal et al, 2010).

Ictal/postictal hypoventilation may contribute to SUDEP with the resulting hypoxemia and acidosis leading to inadequate cortical function recovery and eventual cardiac failure (Bateman et al, 2010; Lhatoo et al, 2010). Alternatively, excessive post-seizure brainstem inhibition might result in blunting or transient abolition of central hypoxic and hypercarbic respiratory drive, with consequent post-ictal respiratory arrest, hypoxia exacerbation and death due to hypoxia/insufficient re-establishment of respiration and terminal cardiac arrhythmia (Timmings, 1998).

Corroborating this hypoventilation theory, studies of audiogenic seizure susceptible mice with generalized convulsive seizures demonstrated that electrocardiographic activity was detectable for four to six minutes after respiratory arrest and death was reversible with ventilation. If not reversed these animals die from respiratory arrest after generalized seizure, that is, die of SUDEP (Faingold et al, 2010).

2.2 Cardiac mechanisms

Cardiac arrhythmogenesis and cryptogenic epilepsy can be due to ion channel dysfunction and may coexist in the same patient, leaving them more susceptible for recurrent arrhythmias. In this way, epileptic survivors of near-sudden cardiac death may be at significantly greater risk of suffering of SUDEP (Badheka et al, 2010). Cardiac mechanisms involved in SUDEP may be associated with heart rate dysfunction, morphology of cardiac waves, anatomic disorders or what some authors refer as brain collapse. Considering this last hypothesis, recently there is a description of a patient submitted to ambulatory EEG that suffered a generalized tonic-clonic seizure that abruptly ended with cessation of all cerebral electrical activity and after a few seconds patient evolved to asystole and death. The circumstance was typical of SUDEP and in this case seems to be related to abrupt irreversible cerebral electrical shutdown during a seizure (McLean & Wimalaratna, 2007).

Also, the circadian heart-rate variability might be of relevance to SUDEP risk. Studies evaluating heart rate observed that patients with epilepsy may have one or more abnormalities of rhythm and/or repolarization during or immediately after seizures. Abnormalities included asystole, atrial fibrillation, marked or moderate sinus arrhythmia, supraventricular tachycardia (Figure 2), atrial premature depolarization, ventricular premature depolarization and bundle-branch block (Nei et al, 2000). Electrocardiogram

(ECG) abnormalities is more frequently observed in patients with refractory focal epilepsies (Surges et al, 2010), generalized tonic-clonic seizures and prolonged complex partial seizures (Nei et al, 2000). In this way, ictal or postictal dysregularion of the autonomic nervous system, affecting heart rate variability may contribute to SUDEP incidence.

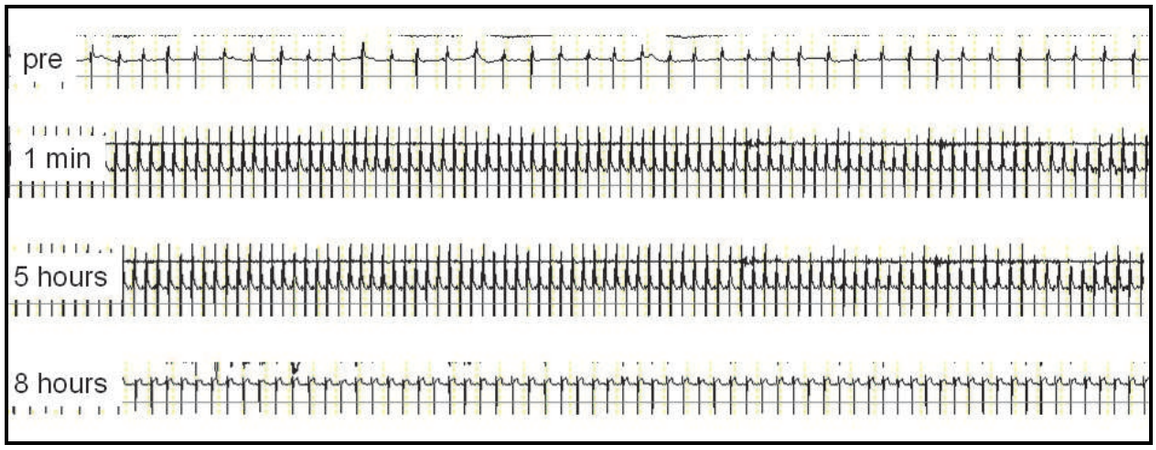

Fig. 2. Ictal tachycardia in a patient with temporal lobe epilepsy. Cardiac rate is illustrate one minute before seizure onset (pre), one minute after seizure onset (1 min), five hours after seizure end (5 hours) and 8 hours after seizure end (8 hours).

Heart rate abnormalities may be relative to tachycardia or asystole and heart rate variability reflects the integrity of vagus nerve-mediated autonomic control of the heart (DeGiorgio et al, 2010). Tachycardia is the main cardiac abnormality observed during seizures (Walker & Fisch, 1997) and fatal tachyarrhythmia as one plausible cause for SUDEP. This arrhythmia is more frequently observed during generalized tonic-clonic seizures, but tachycardia may be observed also in complex partial seizures (Surges et al, 2010). Evaluating the different studies, we observed interesting findings. Person et al (2007) observed that there was no major effect of epilepsy on heart rate variations in patients with untreated epilepsy, recently diagnosed. However, when patients were used as their own controls, heart rate variability was significantly lower after initiation of the treatment with AED and even more during the night, when the risk of SUDEP seems to be higher (Persson et al, 2007). Considering this hypothesis, Surges et al (2009) evaluated retrospectively the heart rate variability in 14 patients with chronic epilepsy (seven of them died from SUDEP). Authors could not determine a clear-cut ECG abnormality that may be considered as a predictor for SUDEP. However, in other studies, authors observed an elevation of heart rate immediately after seizures, which were maintained for 5-6 hours postically, indicating a long-term postictal disturbance of the autonomous nervous system, suggesting that seizures may cause prolonged heart dysfunction (Toth et al, 2010; Pinto et al, 2011).

Although seizure-induced asystole is a rare complication and tended to follow a period of apnea, epilepsy can be correlated to severe bradycardia or asystole (Walker & Fisch, 1997). The event appeared mainly in focal epilepsies and ictal bradycardia and asystole have been implicated in the etiology of SUDEP. Some authors suggested that this abnormality is most

related to left side lateralization and that abnormally long postictal periods with altered consciousness might be associated with reduced cerebral perfusion because of ictal asystole. This could be related or not to central ictal apnea (Rocamora et al, 2003). In this way, Zubair et al (2009) described a patient with a history of complex partial seizures and drop attacks that presented during the video-monitoring a complex partial seizure with brady-arrhythmia followed by asystole. This patient was treated with a cardiac pacemaker and on follow-up, despite patient continued to present simple and complex partial seizures, drop attacks disappeared, confirming its cardiogenic origin.

Considering morphology of QRS complex, co-registered EEG and ECG showed a significant increase in the mean corrected QT (QTc) during interictal discharges, when compared retrospectively patients that died of SUDEP and patients that were still alive (Tavernor et al, 1996). Comparing patients with chronic epilepsy and normal matched control, the mean interictal QTc among epilepsy patients was significantly shorter than the QTc in the control group. Duration of the epilepsy, type of seizures and number of antiepileptic drugs were not significantly correlated to QTc. Nevertheless, patients with cryptogenic temporal lobe epilepsy had a mean QTc significantly shorter than patients with symptomatic epilepsy (Teh et al, 2007). Shortening of QTc also occurred in patients during the early postictal phase and significantly more often in secondarily generalized tonic-clonic seizures (Surges et al, 2010). Other authors reported the opposite, i.e. a significant lengthening of corrected QT cardiac repolarization time during some epileptic seizures considering this QT abnormality a potential risk factor for SUDEP (Brotherstone et al, 2010).

Anatomic examination of the heart of patients that died from SUDEP demonstrated an increased weight in some cases, suggesting that cardiac pathology including cardiac conduction pathology and coronary artery atheroma may contribute to SUDEP. In some of the epileptic deaths subtle abnormalities of the conduction system were identified and these may contribute to death by causing cardiac arrhythmia, when associated with apnoea, bradycardia or other cardiac arrhythmia related to an epileptic seizure (Opeskin et al, 2000). In patients with SUDEP, histological evaluation reveled foci of fibrotic changes that predominated in the deep and subendocardial myocardium of the SUDEP cases. Patient in this group were mainly young women with a mean late epilepsy onset, and infrequent seizures (P-Codrea et al, 2005). Authors suggested that fibrosis may be the consequence of myocardial ischemia as a direct result of repetitive epileptic seizures and these changes, when coupled with the ictal sympathetic storm, may lead to lethal arrhythmias (P-Codrea et al, 2005).

2.3 Brain mechanisms involved in SUDEP

The limbic system is often seen as a structure that ties together higher functions with autonomic and motor control to generate integrated behavior (Figure 3). This includes cortical control of the heart rate, particularly considering operculo-insulo-mesiotemporal-orbital pathway and the cingulate cortex (Devinsky *et al.* 1995). Simulation of the cingulate cortex may produce tachycardia or bradycardia (Pool *et al.* 1949). Asystole observed after cingulate cortex stimulation suggest a cortical control of heart rate on physiological basis. A parasympathetic-mediated pathway that involves the limbic system is possible the way bradyarrhythmia occur and may be implicated for the mechanism of SUDEP (Leung et al, 2007).

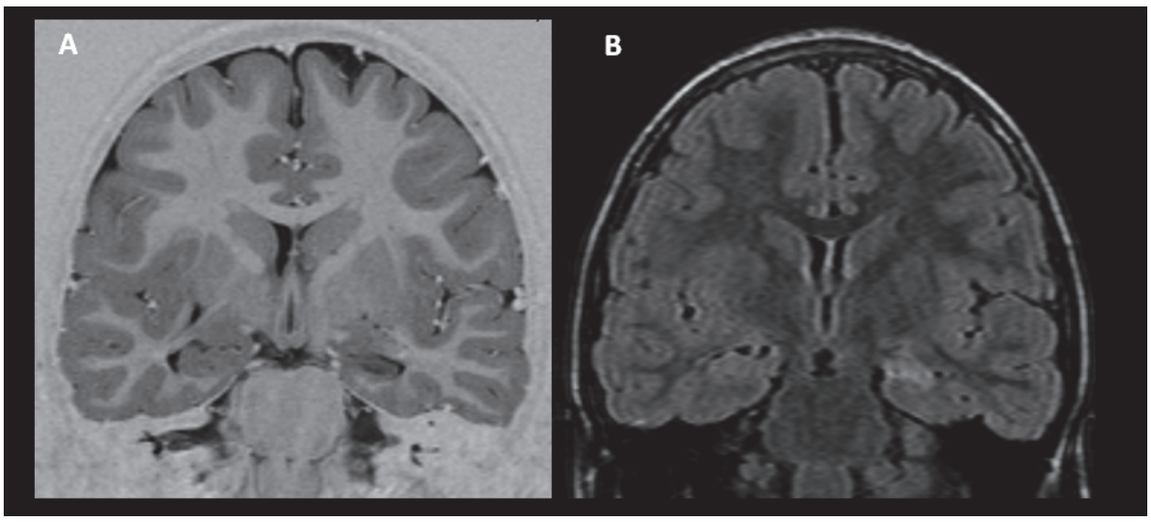

Fig. 3. Left mesial temporal sclerosis, a main cause of refractory epilepsy and observed in some patients that died from SUDEP.

Data from intracranial EEG records demonstrated that bradyarrhythmic episodes were mostly associated with temporal lobe seizures, nevertheless, seizure involvement of insular cortex or cingulated cortex could not be excluded (Altenmüller *et al.* 2004, Devinsky *et al.* 1997; Rossetti *et al.* 2005; Kahane *et al.* 1999). Also, some studies suggest amygdala central nucleus damage may contribute to SUDEP considering that his structure can play a role in respiratory timing (Nashef et al, 1996; Stollberger & Finsterer, 2004; Ryvlin et al, 2006; So, 2008; Surges et al, 2009.

Therefore, studies demonstrated a reduction of sympathetic cardiovascular modulation after temporal lobe epilepsy surgery that might result from decreased influences of interictal epileptogenic discharges on brain areas involved in cardiovascular autonomic control. Temporal lobe epilepsy surgery seems to stabilize the cardiovascular control in epilepsy patients by reducing the risk of sympathetically mediated tachyarrhythmias and excessive bradycardiac counter-regulation, and might contribute to reduce the risk of SUDEP (Hilz et al, 2002). Moreover, left temporal lobe epilepsy surgery is associated with a reduction (but not a normalization) of the overall mortality associated with chronic epilepsy. In patients with right-sided mesial temporal lobe sclerosis however, the postoperative mortality has remained similar to other groups with medically intractable seizures (Hennessy et al, 1999)

Interestingly, laterality of epileptic foci has been reported as related to ictal bradyarrhythmia, with left-side-onset being often observed, although the cerebral patient dominance may also need to be taken into account (Kahane *et al.* 1999; Tinuper et al. 2001). The laterality observed made researchers suspect parasympathetic system activation may be more influenced by the lef side or dominant hemisphere (Oppenheimer *et al,* 1992). The induction of bradyarrhythmia by direct stimulation of the left insular cortex but not the right insular cortex corroborates this hypothesis (Leung et al, 2007).

Others brain regions such as the cerebellum may be involved with breathing and cardiac control (Lutherer et al, 1983; Harper et al, 2000; Xu et al, 2001; Harper, 2002; Xu & Frazier, 2002; Harper et al, 2005.). Cerebellum has been correlated with regulation of blood pressure (limiting extreme changes in blood pressure with hypotension or hypertension) and breathing rhythm (Harper et al, 2005). Patients with epilepsy frequently have abnormalities

of cerebellum, especially diffuse atrophy and this finding is probable related to chronic use of AEDs, age, presence of generalized tonic-clonic seizures, duration of epilepsy, or the seizure activity itself, causes also related to SUDEP occurrence (Engel, 1993; Specht et al, 1997; Sandok et al, 2000; Lawson et al, 2000; Hagemann et al, 2002). In respect to AED, it seems that prolonged use of phenytoin or phenytoin intoxication may induce severe irreversible cerebellum volume loss that chronically may predispose individuals to SUDEP (Masur et al, 1990; Ney et al, 1994). Cerebellum lesions or dysfunction is reported in patients with sudden infant death syndrome, a sleep-related syndrome suspected of resulting from a failure of enhanced respiratory efforts that compensate transient hypotension. This syndrome may also be related to an inability to recover from an excessive CO_2 challenge (Martin et al, 1996; Harper, 1998; Harper et al, 2000a; Harper et al, 2000b). Moreover, cerebellum injury was reported in patients with congenital central hypoventilation syndrome, a condition with deficient response to hypercapnia and hypoxia, with possible dysfunction of cerebellum, thalamic nuclei, basal ganglia and limbic structures (Harper et al, 2000b; 2005). In adults, a high incidence of obstructive apnea is observed in patients with olivopontocerebellar geneneration (Chokroverty et al, 1984). Considering all together, these evidences may suggest cerebellum lesion may directly affect the ability of central nervous system to react to acute respiratory and cardiac changes, such as apnea and hypopnea, or extreme hypotension or arrhythmia. These dysfunctions may be quite common in patients with epilepsy, especially during generalized tonic-clonic seizures, with a repetitive exposure to this risk in patients with refractory epilepsies. These dysfunctions seem also to be more evident during sleep, time when SUDEP is more common and, in this way, cerebellum lesion with consequent functional impairment may be a main risk factor for SUDEP occurrence and methods to prevent it, such as use of lower doses of AED should be considered.

Considering that parasympathetic activity is possible involved in SUDEP mechanisms, it is interesting to evaluate the effect of vagus nerve stimulation (VNS) on SUDEP incidence. VNS is a non-pharmacological therapy approved by the FDA for treatment of patients with epilepsy who are unsuitable candidates for epilepsy surgery. The precise mechanism of action of VNS remains unknown, but available evidence suggests that central autonomic nervous system pathways are involved, since vagus nerve influences many regions of central nervous system, through its extensive connectivity with nucleus of solitary tract which projects to reticular formation, hypothalamus, hippocampus, amygdale, dorsal raphe nucleus, locus ceruleus, thalamus and cerebral cortex. The most frequently VNS adverse effects typically occur during stimulation, but there are no apparent effects of VNS on vagally mediated visceral function (Schachter, 2006). In many series of patients chronically implanted with VNS, SUDEP cases are reported (Annegers et al, 1998; 2000; Ardesch et al, 2007; El Tahry et al, 2010). However, a cohort study of 791 implanted with VNS system (Annegers et al, 1998) and extended for 1,819 individuals (Anneger et al, 2000) showed a similar mortality and SUDEP rates to those reported from cohorts of severe epilepsy. Experimental models of epilepsy had demonstrated VNS-induced changes in hippocampal neurotransmitter levels, increasing hippocampal noradrenaline concentration. VNS also increased the latency between pilocarpine infusion and the onset of epileptiform discharges, and reduced the duration and severity of pilocarpine-induced limbic seizures (Klein & Ferrari, 2009). Other authors demonstrated an increase in the number of cells in the dentate gyrus, dentritic complexity and BDNF expression after acute or chronic VNS stimulation

(Raedt et al, 2011). However, although these morphological and functional changes have been described, there was not a significant impact on the incidence of SUDEP, suggesting that another factor, such as better seizure control might be involved.

2.4 Experimental models

Experimental models of epilepsy are fully studied in different research centers, but there are few models that can mimic SUDEP. Maybe the most related model in the literature is the one described by Szabó et al (2005) of genetic idiophatic epilepsy in baboons. Authors studied the occurrence of natural death in these animals and the pathological findings in necropsy (Szabó et al, 2009). Overall, animals with epilepsy died early than no epileptic animals and, considering group with epilepsy, animals that had a definite cause of death died significantly younger age than those epileptic animals whose cause of death could not be determined. Predominant causes of death in these animals with epilepsy were infection and trauma. Interestingly animals with unknown cause of death had a history of more frequent seizures and a longer duration of epilepsy. Autopsy of animals with unknown cause of death revealed pulmonary edema and chronic fibrotic changes in the myocardium and since animals were in a good health and died suddenly and unexpectedly the cause of death was considered SUDEP. This interesting model may be the best one available to study mechanisms and risk factors of SUDEP in human since clinical and pathological findings are very close in both species. In this way, authors suggested that phylogenetic similarities between species may permit transpose research information and contribute to elucidation of this devastating complication.

Other experimental models were described in the literature that confirms the suspicions of respiratory and cardiac mechanism involved in SUDEP genesis (Tupal et al, 2006; Scorza et al, 2009). In these models it was raised the possibility that an imbalance in neurotransmitter level, especially serotonin, may contribute to autonomic changes. Serotonin down regulation was observed in a model of epileptic mice that have respiratory changes and death following epileptic seizures. Pharmacological enhancement of serotonin in this model reduced significantly seizures related respiratory arrest. One other model of experimental epilepsy (epilepsy-prone rats – GEPR) with decreased hippocampus serotonin receptor shows an increase in seizure susceptibility, but it is not possible yet to exclude the role of other neurotransmitters in this model. Studies with positron emission tomography in patients with epilepsy have shown conflicting results about serotonin receptor expression, with reports of decreased, increased or unchanged binding (Theodore, 2003). In this way, although more studies are needed to elucidate this issue, it seems plausible to consider, at least with respect to serotonin levels in experimental epilepsy, that there is a cause effect relation between serotonin deficiency and respiratory abnormalities and seizure susceptibility and this may be considered as a possible factor influencing SUDEP risk.

3. Patient information and prevention

There is no consensus regarding the information if risk of SUDEP should be delivered to all patients with epilepsy, but it seems reasonable to individualize this information according to patient particularities (Ryvlin et al, 2009). Some authors recommend universal discussion of SUDEP considering that patients and their families have the right to know about the risks of epilepsy and the reasons for treatment, while others consider that SUDEP should be discussed

only with patients at high risk (Brodie & Holmes, 2008). This controversial issue has greater weight due the reports of patients with idiopathic epilepsies, with rare seizures that suffered SUDEP and considering these patients are more susceptible to poor drug compliance and then tonic-clonic seizures, it should be advisable to discuss this matter with them.

A study conducted in Ingland found that people with epilepsy wanted to know more information about the causes of epilepsy and other matters, such as SUDEP (Prinjha et al, 2005). However, a study conducted in Australia demonstrated that risk factors for SUDEP are not amenable to modification and in this way, discussion of SUDEP with patients could not alter outcome. Authors consider that information of SUDEP may adversely affect patients and families quality of life and suggested that an open and frank discussion of SUDEP risk should be reserved to those patients that seek the information (Beran et al, 2004).

The mechanisms underlying SUDEP are unclear, and there are no effective preventative therapies (Brodie & Holmes, 2008). However, even without precise knowledge of the underlying pathogenic mechanism(s), SUDEP prevention could start with the identification of the most prominent risk factors. SUDEP seems to occur more commonly during sleep and it preferentially affects young adults with medically intractable epilepsy (especially tonic-clonic seizures), individuals who also have neurologic comorbidity, and patients receiving antiepileptic drug polytherapy (Asadi-Pooya & Sperling, 2009). Considering SUDEP is probable a multifactorial event and not all risk factors are determined, now prevention should be centered on that most potential suspected risk factors, with effective seizure control, an optimal antiepileptic drug compliance, night supervision (since almost all deaths occur at night), control of tonic-clonic seizures, prevention of airway obstruction and postictally respiratory stimulation (Tao et al, 2010; Ryvlin et al, 2009; Langan et al, 2005; Langan et al, 2000). Also patients should routinely be investigated for the presence of ictal arrhythmias and whenever necessary the insertion of a pacemaker may be indicated, preventing life-threatening cardiac arrest, syncope and trauma (Strzelczyk et al, 2008). Ideally, caregivers should be able to deliver appropriate first aid after epileptic seizures with the guarantee of properly airway flow, stimulation to decreases the duration of postictal apnea and encourage epilepsy patients to sleep in the supine position. It is not clear whether these practices will prevent SUDEP, but they may be reasonable measures to suggest when discussing this issue with patients (Walczak et al, 2001). This prophylaxis orientation should be a routine during epilepsy patient attendance (Jehi & Najm, 2008).

Early identification of patients at risk of SUDEP would offer a unique opportunity for intervention to prevent this devastating condition (Jehi & Najm, 2008). Compliance with treatment clearly influences the frequency of tonic-clonic seizures, being of paramount importance in SUDEP prevention. Also compliance should be encouraged since it may prevent SUDEP in an epilepsy population with rare seizures, which is less closely followed. Physicians should make an effort to control tonic-clonic seizures with the fewest antiepileptic drugs as possible since politherapy has been also implicated as a risk factor for SUDEP (Walczak et al, 2001).

There are few studies that examined thoroughly brain of patients that suffered SUDEP especially that areas considered to have a main function on respiratory and cardiovascular regulation and these issues represent a specific line of research in the SUDEP field that should be investigated. Early and successful epilepsy surgery for drug-resistant epilepsy may significantly reduce the risk of SUDEP, thus patients with definite pharmacologic refractory epilepsies should be referred to an epilepsy surgery center (Shuele et al, 2007).

Confirming this statement studies involving epilepsy surgery programs clearly suggested that successful epilepsy surgery reduces the impending risks of SUDEP. In cohorts in whom the estimated risk of SUDEP is almost 1% per year without surgery, SUDEP incidence was significantly lower following epilepsy surgery (Schuele et al, 2007; Jehi & Najm, 2008).
Although, not all refractory epilepsy patient is eligible for surgery and in this way, clarification of risk factors and establishment of the mechanisms of SUDEP are important so that as many people as possible can be saved from SUDEP (Bells & Sander, 2006). Further large-scale, multicenter, case-control or cohort prospective studies are needed to assess the role of AEDs and other potential risk factors in order to form a basis for treatment strategies aiming seizure control and prevention of SUDEP (Tomson et al, 2005). Postmortem examinations of all potential SUDEP patients are also essential, with a dedicated forensic protocol that will permit the correct differential diagnosis (So, 2006).

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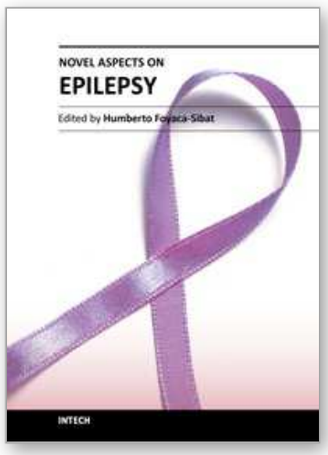

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This book covers novel aspects of epilepsy without ignoring its foundation and therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis as a leading cause of epilepsy in developing countries. We are looking forward with confidence and pride in the vital role that this book has to play for a new vision and mission. Therefore, we introduce novel aspects of epilepsy related to its impact on reproductive functions, oral health and epilepsy secondary to tuberous sclerosis, mithocondrial disorders and lisosomal storage disorders.

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