

Sudden Unexpected Death In Epilepsy (SUDEP) – an update

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SUMMARY

Introduction. SUDEP is not so rare event, unexplained, underused and underestimated. Its awareness has recently contributed to a number of initiatives for global action and clinical and experimental research.

Aim. To undertake a literature review so as to update various aspects of SUDEP: pathophysiological mechanisms, potential markers for autonomic dysfunctions and risk factors, AEDs effects, non-AED management options, forensic/autopsy, patient-physician communications in patients with SUDEP risk.

Method. A literature review, up to Nov. 2012, was conducted using PubMed-Medline for SUDEP, no indexed citation and relevant papers.

Review. Interactions between the central and peripheral origin of cardiac and respiratory dysfunctions, triggered by epileptiform discharges in the cortical representation of the autonomic functions, may lead to SUDEP during simple partial autonomic seizures - even without other components of a seizure. A number of potential biomarkers of autonomic dysfunctions and risk of SUDEP are identified and proposed to use in its prevention: heart rate variability, long and short QT, arrhythmias, asystole, oxygen desaturation, apneas, hypoxia, postictal EEG suppression, circadian seizure pattern.

Conclusions. Risk factors for SUDEP, AEDs effects, non-AED management of preventive options and forensic autopsy in diagnosis of SUDEP are discussed. Periictal long term video EEG, ECG and oxygen saturation monitoring may contribute to better understanding of SUDEP mechanisms and eventually to its prevention. SUDEP occurs as fatal coexistence of several predisposing risk factors. Diagnosis of SUDEP is underestimated and underused. In patient with high risk factors for SUDEP, in particular, with AED noncompliance, prognosis of epilepsy should be discussed with patient.

Key words: SUDEP • animal seizure models and autonomic dysfunctions • potential biomarkers of SUDEP risk • risk factors of SUDEP • AEDs • autopsy

INTRODUCTION

During the last decade, the number of publication related to mortality in epilepsy and, in particular, to sudden unexpected death in epilepsy (SUDEP) has increased. Thus, contributing to awareness that SUDEP is not so rare tragic event, which for the majority of cases remains yet unpredictable, unexplained, underused and underestimated (Lathers and Schraeder, 2009; Hirsch et al., 2011; Zhuo et al., 2012; Bergmann et al., 2012). However, term “unexpected” may be less frequently used since in some patients with a combination of

known and suspected risk factors SUDEP could be expected. In recent studies, SUDEP is the main cause of all deaths, in at least, 20–30% in epilepsy patients (Lhatoo et al., 2010; Sillanpää and Shinnar, 2010; Terra et al., 2011). It raises important issue to be addressed from pathophysiological, therapeutic, legal and moral points of view. As a result, recently, a number of initiatives were undertaken to assess the state of knowledge about SUDEP and to work out recommendations, e.g. multidisciplinary workshop to refine current lines of

investigation (So et al., 2009). Appeal for global action and recommendations were proposed (Lathers, 2009; Lathers and Schraeder, 2009) e.g. the worldwide database on persons with SUDEP, that may provide information concerning the prevalence of SUDEP, and will contribute to the quest identification of preventive interventions. Some recommendations like ambulatory periictal simultaneous video EEG (VEEG), ECG and oxygen desaturation monitoring of patients at high risk of SUDEP have been implemented as valuable methods contributing to autonomic pathophysiology of SUDEP (Lhatoo et al., 2010; Toth et al., 2010; Seyal et al., 2011; Semmelroch et al., 2012; Moseley et al., 2012b).

In the older and recent literature, discussion regarding antiepileptic drug (AED) effects and SUDEP continues (Lathers and Schraeder, 2002; Ryvlin et al., 2011; Hesdorffer and Tomson, 2012; Hesdorffer et al., 2011, 2012; Aurlen et al., 2012; Pack, 2012). In SUDEP autopsy findings, no or subtherapeutic serum blood concentrations of AEDs is most frequently observed (Leestma et al., 1984, 1985, 1989; Vickery, 1997; George and Davies; 1998; Zhuo et al., 2012).

Recently, revisiting two previous classifications (Annegers, 1997; Nashef, 1997), an effort unifying definition and new classification of SUDEP was undertaken and proposed (Nashef et al., 2012). Precise definition and classification of SUDEP will contribute to scientific and medical communication, and is important from a legal point of view. The new classification consists of 6 classes and definitions: Definite SUDEP, Definite SUDEP Plus (this category is added, meaning that there is evidence which indicates that preexisting condition could have contributed to the death which otherwise is SUDEP), Probable SUDEP, Possible SUDEP, Near-SUDEP (this category is added for cardiorespiratory arrest that is successfully resuscitated), and includes Not SUDEP when a clear cause of death is known.

The following autonomic pathophysiological events may play an essential role in SUDEP: cardiac arrhythmias, respiratory dysfunction and dysregulation of systemic or cerebral circulation. Long-standing and intractable epilepsy can cause physiological and anatomical autonomic cardiovascular instability as a result of life-threatening tachy-, brady-arrhythmias and asystole which are commonly seen during ictal, interictal and postictal phases in epilepsy patients (Mukherjee et al., 2009). Some of these disturbances need attention and some of them may be benign (Velagapudi et al., 2012).

AIM

This review is aimed to update some aspects of SUDEP: pathophysiological mechanisms, potential biomarkers of autonomic dysfunctions in epilepsy patients, effects of circadian seizure pattern, risk factors, AEDs, non-AED management options, forensic/autopsy study, prevention of SUDEP, patient-physician communication in epilepsy patients with SUDEP risk.

METHOD

A literature review was conducted up to November 2012. The following search terms were used: SUDEP, cardiac and respiratory death, animal models and death, autonomic dysfunctions and AEDs, incidence and prevalence for SUDEP. The following databases were used: PubMed Medline, and non indexed citations. Relevant papers were included.

REVIEW

Incidence of SUDEP

The annual incidence of SUDEP was estimated to be, at least, 1 in every 370–500 to 1000–1100 persons in epilepsy (Leestma et al., 1989, Leesma, 1990); in patients with high risk for SUDEP it may account for 1 in 100–200 (Lathers et al., 1997). In young adult with high risk for SUDEP, such death is perhaps 40-fold greater than among those without epilepsy (Annegers and Coan, 1999). Recently, Bergmann et al. (2012) reported an annual incidence 0.2/1000 patient-years (PY) whilst an annual incidence 0.3–10/1000 PY is reported in the literature. It is estimated that standardized mortality rate (SMR) is 2–3-fold higher than in a non-epilepsy population. However, in remote symptomatic epilepsy in persons with developmental delay, Day et al. (2005) found that SMR is greatest due to seizures (SMR 53.1). The authors compared causes of mortality in persons with epilepsy (N = 10,300) and without (96,163) who died between 1980–2002 in California.

Some differences between SUDEP in children and adults are discussed in the relevant literature. According to some authors, otherwise normal children with epilepsy do not have an increased risk of death compared with the general population, and SUDEP in children is very rare (1–2/ 10,000 PY (Camfield et al., 2002). Children with epilepsy have an increased risk of death related to severe underlying conditions and not directly related to seizure occurrence (Berg et al., 2004; Cam-

field and Camfield, 2005; Nickels et al., 2012). Camfield and Camfield (2005) found that mortality 20 yrs after epilepsy onset was 6.1% compared to 0.88% in the matched reference population. Out of 692 children with epilepsy 26 (3.8%) died, and in one of them probable SUDEP occurred. Percentage of death depended on the type of epilepsy: with absence the lowest (1%) and secondary generalized (15%) the highest. Similar data were shown in a 30 yrs population-based cohort of 467 children followed on a median of 7.87 yrs after diagnosis of epilepsy: 16 (3.4%) died (3.51 deaths/1000 PY (Nickels et al., 2012). Of these 1 (6.25%) died of probable SUDEP.

However, this opinion, in more recent studies with long-term follow-up after diagnosis of epilepsy, seems to be, at least partly, revised: SUDEP in children is not a rare event (Terra et al., 2009; Sillanpää and Shinnar, 2010; Terra et al., 2011; Meyer et al., 2011). Suspected underlying mechanisms include cardiac dysrhythmias, seizure-related apnoea and postictal respiratory arrest. In prospectively evaluated cohort of 1012 children, during about 10 years of observation, 53 (5.2%) patients died due to epilepsy or its clinical complications. SUDEP was diagnosed in 11 children (1.08%) and it was 20.7% of all who died (Terra et al., 2011). A 40 year follow-up of children with diagnosed epilepsy suggests that SUDEP may account for about 30% of all deaths in persons with epilepsy (Sillanpää and Shinnar, 2010).

It is not clear why SUDEP is rare in childhood, despite childhood onset of epilepsy is a risk factor for later death. The main reason seems to be that SUDEP is a result of a combination of several risk factors, and early onset of epilepsy is one of the risk factors, only. Combination with other risk factors which may develop later, and contribute to death.

It is also not clear why SUDEP occurs very rarely in the elderly in comparison with young adults. Several reasons may account for this. During years, a number of risk factors may develop leading to combination of dynamic interactions between them, reaching highest age-related level of risk for death.

In many children with SUDEP, low serum AED levels at time of death, and AED polytherapy do not seem to be significant, in contrast to these risk factors in adults (Ernest et al., 1992; Donner et al., 2001). This may, in part, explain the SUDEP difference between children and adults. Moreover, the age-dependent autonomic effects of seizures may be different in these groups of patients (Panayiotopoulos, 2004; Ferrie et al., 2007; Gonzales-Duarte et al., 2011).

Risk factors for SUDEP

The reported risk factors for SUDEP include high frequency of GTCS, nocturnal seizures, altered autonomic control, ictal or postictal apnoea and cardiac arrhythmias, alterations in cardiac repolarizations, noncompliance to AEDs, polytherapy, prolonged postictal EEG suppression, EEG records with considerable variability from record to record, menstruation period with activation of epileptiform discharges in EEG (an increase estrogen to progesterone ratio), young age at epilepsy onset, longer duration of epilepsy, structural brain lesions, dementia, asthma, white and particular black males, symptomatic etiology of epilepsy, alcohol abuse, street drugs, genetically determined subtle (latent) risk for cardiac disorders, long or short QT-related mutations, impaired serotonergic brain stem control of respiration and hypoxia; there are rather controversial effects of particular AEDs resulting in or modifying cardiac functions (Jay and Leestma, 1981; Leestma et al., 1989; Ernest et al., 1992; Lathers et al., 1997; Annegers and Coan, 1999; Day et al., 2005; Langan et al., 2005; Tomson et al., 2005; Nashef et al., 2007; Faught et al., 2008; Lathers et al., 2008; Schimpf et al., 2008; Hughes, 2009; Aurlen et al., 2009; Johnson et al., 2009; Ryvlin et al., 2009; Surges et al., 2009a; Glasscock et al., 2010; Ridsdale et al., 2011; Hesdorffer and Tomson, 2012; Majkowski and Olczak, 2012; Zhuo et al., 2012).

Hughes (2009) attempted to provide quantitative value for each of 17 risk factors. The sensitivity of these SUDEP values was 71.3%, the specificity – 81.8% and the positive predictive value – 84.6%. The most important risk factor was noncompliance with AEDs. Some of the risk factors seem to be independent ones e.g. nocturnal seizures, high frequency focal onset of generalized tonic-clonic seizures, altered latent autonomic cardiac or respiratory dysfunctions. The other risk factors like long term developing interictal EEG patterns or effect of particular AED in individual patients are still debatable. It has been, rightly, suggested that SUDEP is caused by the fatal coexistence of several predisposing and triggering factors resulting in heterogenous mechanisms leading to death.

Pathophysiological mechanisms of SUDEP

Autonomic structural and functional consideration. There is good evidence and cornucopia of literature showing that the nervous system is involved in cardiac arrhythmias which may occur in a normal myocardium. Extensive reviews of anatomy and function of cen-

tral and peripheral autonomic nervous system related to cardiac and respiratory death have been published (Natelson, 1985; Lutherer et al., 1989; Oppenheimer, 1990; Lathers et al., 1997). Ictal autonomic respiratory and cardiac dysfunctions are most probably due to direct or indirect excitation of limbic structure. The limbic forebrain consists of the hippocampal formation, the amygdaloid complex, the septal region, gyrus fornicatus, the piriform lobe and the caudal orbital frontal cortex. Connections of the limbic system with insula, basal ganglia, thalamus and cerebellum have been shown (Augustine, 1996; Surges et al., 2009a; Burghaus et al., 2011; Scorza et al., 2011). The intracerebral elements of the autonomic nervous system largely consist of connections between the limbic cortex and hypothalamus, pons and medulla oblongata.

It has been shown that the anterior agranular part of insula plays important role in periictal cardiac arrhythmia, ictal brady- and tachycardia leading to SUDEP (Surges et al., 2009a; Burghaus et al., 2011). Peri-ictal atrioventricular (AV) conduction block was reported in a patient with a lesion in the left insula (Surges et al., 2009b).

Animal models and SUDEP. Electrophysiological studies, using animal seizure models have been providing evidence for better understanding of autonomic nervous system in pathogenesis of seizure-related death. In anesthetized animal models, changes in peripheral cardiac sympathetic or parasympathetic neuronal discharges were associated with interictal subconvulsive behaviour (Lathers and Schraeder, 1982; Schraeder and Lathers, 1983). Lathers et al. (1983, 1987) proposed so called lockstep phenomenon, which was defined as cardiac sympathetic and vagal cardiac neuronal discharges intermittently synchronised with cerebral interictal epileptiform discharges. The lockstep phenomenon could contribute to SUDEP in patients who exhibited no overt seizure activity at the time of death; mechanisms have been postulated by which lockstep phenomenon may play this role (Stauffer et al., 1989). It implies that epileptiform discharges, involving central representation of cardiac and/or respiratory functions, may be associated with SUDEP without clinical seizure.

In more recent animal studies, role of the sympatho-parasympathetic imbalance was confirmed as possible cause of death in SUDEP. Cardiac sympathetic nerve activity was increased during limbic cortical seizures induced by kainic acid in anesthetized rats (Hotta et al., 2009). In this seizure model, modest changes in car-

diac sympathetic nerve activity contribute to predominantly parasympathetic effect on the heart and periods of asphyxia; ventilation rate changes might be associated with large sudden increases or decreases in cardiac sympathetic outflow during seizure. The normal relation of cardiac sympathetic nerve activity to ventilation is lost. In the same rat seizure model, the mechanism of death was due to profound cardiac dilatation and bradyarrhythmia leading to hypoperfusion of the brain and ultimately to hypoperfusion of the heart (Sakamoto et al., 2008).

Convulsive seizure, triggered by electroshock in Wistar rats, induce profound abnormalities in cardiac rhythm with serious ECG changes. Postictal bradycardia resulted in heart rate variability (HRV) with an increase in the high-frequency range of the power, what suggests an imbalance in the autonomic control of the heart with a postictal enhancement of parasympathetic tone (Damasceno et al., 2012).

The cardiac nerve studies in animal models suggest pathophysiological explanation for SUDEP and autonomic dysfunction in patients who had not observed clinical seizures, and/or only seizures of minimal severity preceding their demise (Hirsch and Martin, 1971; Terrence et al., 1975; Jay and Leestma, 1981). SUDEP in children has been reported without seizures immediately prior to death (Donner et al., 2001). It is possible that SUDEP may occur during epileptiform discharges due to imbalance in the parasympathetic/sympathetic systems without any other clinical symptomatology of epilepsy. Blumhart et al. (1986) suggested that onset of epileptic discharges in discrete areas of brain in deep limbic circuits and the connections of these structures with autonomic nervous system may produce arrhythmias without observed ictal discharges on the EEG.

Ictal cardiac autonomic symptoms such as palpitation and chest discomfort may occur as a sole manifestation of a partial seizures. Usually, a 24-h ECG Holter records do not show any interictal abnormalities. However, interictal EEG records may show focal slow wave trains in the left prefronto-antero-temporal region. AED therapy show positive effect on the ictal cardiac events (personal observation).

Definition of autonomic seizures. Historical terms of paroxysmal autonomic symptomatology have been, recently, reviewed by Moseley et al., (2012a). An international consortium proposed the following definition for autonomic seizures (Ferrie et al., 2007): "epileptic seizure characterized by altered autonomic function of

any type of seizure onset or in which manifestations consistent with altered autonomic function are prominent (qualitatively dominant or clinically important) even if not present at seizure onset". Autonomic seizure may occur in a form of status epilepticus (ASE). Both are specific electro-clinical syndrome for childhood (Panayiotopoulos, 2004; Ferrie et al., 2007). They occur in about 13% of children aged 3–6 yrs and in 6% – at age 1–15 yrs, lasting for more than 30 min up to several hours (Moseley et al., 2012a). However, autonomic seizure may occur in adults, as well. In Panayiotopoulos syndrome, autonomic seizure and ASE occur in 44% of seizures and often last for hours (Koutroumanidis et al., 2011). The epileptogenic zone in the syndrome is bilateral and multifocal, surrounding major fissures such as central, sylvian and mainly calcarine. The ictal autonomic symptomatology may be related to any epileptogenic cortical onset zone, parieto-occipital, fronto-temporal or frontal (Kanazawa et al., 2005; Saitoh et al., 2007; Specchio et al., 2010). It is possible that the central autonomic networks have a lower threshold to epileptogenic activation than those producing focal cortical semiology (occipital, frontal, central, parietal, and less often, temporal) (Mosley et al., 2012a). Seizure remains purely autonomic if ictal neuronal activation of non-autonomic cortical areas fail to reach symptomatic seizure threshold. It is quite possible that with spread of interictal activity in the hippocampus to the hypothalamus, the subclinical epileptogenic activity alters the function of other areas of the brain, resulting in changes in the autonomic control of heart rate and/or respiration. The study of cardiorespiratory dysfunction during autonomic seizure or ASE may provide a better understanding of SUDEP.

Potential markers of autonomic dysfunctions in epilepsy patients

Heart rate variability. The study based on 31 perictal VEEG and ECG recordings of 31 patients with epilepsy, undergoing pre-surgical evaluation revealed that postictal decreased HRV, lasting for 5–6 h, indicates a long-term postictal disturbances of the autonomic nervous system (Toth et al., 2010). In patients with generalized tonic-clonic seizures (GTCS), HRV was more decreased compared to other seizures (Strzelczyk et al., 2011). Analysis of spectral measures of frequency domain, in 24-h ECG Holter of HRV in epilepsy patients and controls, confirmed that an increased sympathetic tone in association with decreased parasympathetic

tone may contribute to mechanisms of SUDEP in young persons with epilepsy (Yildiz et al., 2011). Sympathovagal imbalance in epilepsy was shown by lower high-frequency power spectrum, when compared to controls, moreover, there was a trend for higher low frequency power spectrum values in patients on pharmacotherapy (Lotufo et al., 2012). As lower vagal and higher sympathetic tones are predictors of morbidity and mortality in cardiovascular samples, the findings emphasize the importance of investigating autonomic function in epilepsy in clinical practice; in particular, assessing HRV when planning treatment, since some AEDs may lead to cardiac arrhythmia. HRV alternations in epilepsy patients, related to parasympathetic dysfunction, were observed during interictal epileptiform discharges, as well (Zaatreh et al., 2003; Pradhan et al., 2011; Brotherstone and McLellan, 2012). In patients with frontal lobe epilepsy the mechanism of decreased HRV is probably different from that in patients with TLE. Patients with frontal lobe epilepsy have interictally faster heart rate what is attributed to lower parasympathetic drive (Harnold et al., 2009).

More refined HRV analysis and its correlation with defined SUDEP risk factors (The SUDEP-7 Inventory, Walczak et al., 2001) was performed by DeGiorgio et al. (2010). The authors found that specifically root-mean square differences of successive R-R intervals (RMSSD) of HVR were most useful as predictors for SUDEP. RMSSD, a measure of high frequency HVR, was inversely correlated with the SUDEP-7 Inventory score ($r = -64$, $p = 0.004$). RMSSD reflects the integrity of vagus nerve-mediated autonomic control of the heart and is associated with short term, rapid changes in heart rate.

T-wave alteration (TWA) is suggested to be novel independent marker of SUDEP risk and cardiovascular mortality in addition to HVR (Strzelczyk et al., 2011). ECG and EEG studies of 16 adult patients of focal onset chronic uncontrolled GTCS revealed a postictal increase in TWA for 15 min, as well as higher postictal HR and decreased postictal HRV for the whole observation time to 30 min. The authors suggest to investigate the value of TWA for risk stratification in SUDEP.

Similar suggestions are based on ECG of patients with Dravet syndrome (DS) (Ergul et al., 2012). SUDEP rate in this syndrome is higher than in most forms of severe epilepsy. In 15 patients, with genetically diagnosed DS, 24-h ECG has shown that P wave, QT and QTc dispersions were significantly higher, and all HRV parameters

ters were significantly lower in DS patients as compared to the control healthy matched group ($p < 0.001$ for all values). The findings display an imbalance for cardiac autonomic dysfunction with increased adrenergic tone compared to other than DS epilepsy syndromes. The findings may correlate with SUDEP, and are independent of AED therapy (Delogu et al., 2011). In DS most cases are associated with mutations in the SCN1A gene that encodes a voltage gated sodium channel. Verapamil showed promise as an AED (Ianetti et al., 2009).

Cardiac channelopathies. ECG repolarisation changes, including QT prolongation, arrhythmias and cardiac death, were recognized as early as in 1940 in patients and without evidence for heart disease (Oppenheimer, 1990). It was considered that cerebral arrhythmogenesis may underlie sudden death in normal and in epilepsy populations.

Long and short QT syndrome (LQTS, SQTs) typically presents with syncope, atrial fibrillation, seizures or sudden death. Patients with QTS have been misdiagnosed with epilepsy and treated with AEDs. The gene, KCNH2, responsible for type 2 LQTS (LQT2) was cloned originally from the hippocampus and encodes a potassium channel active in hippocampal astrocytes (Johnson et al., 2009). The authors studied 343 consecutive young adult patients with LQTS. Epilepsy and AED treatment was more common in patients with LQT2. This association raises the possibility that LQT2 – causing perturbances in the KCNH2 – encoded potassium channel, may confer susceptibility for recurrent seizure activity. Cardiac channel molecular autopsy of the LQTS and catecholaminergic polymorphic ventricular tachycardia-susceptibility genes was discovered in a child with SUDEP. A novel missense mutation in exon 104 of RYR2-enclosed ryanodine receptor/calcium release channel was found (Johnson et al., 2010).

In 31 patients with genetic mutations consistent with LQTS, false positive epilepsy diagnosis was corrected after 9.75 yrs (median difference measured from first sudden loss of consciousness to a diagnosis of LQTS); median age at time of diagnosis was 21 yrs (MacCormick et al., 2009). During the delay period, 4 sudden unexpected deaths were reported. Interpretation errors of ECG were common.

Mice lacking Kv1.1 Shaker-like potassium channels encoded by the Kcna1 gene exhibit severe seizures and die prematurely (Glasscock et al., 2010). Deficiency of kv1.1 could underlie primary neurogenic cardiac dysfunction. The authors performed simultaneous video

EEG-ECG recording and found that Kcna1- null mice, display potentially malignant interictal cardiac abnormalities, including 5-fold increase in AV conduction blocks, as well as bradycardia and premature ventricular contractions. During seizures the occurrence of AV block increased and sudden death was recorded in kv1.1 deficient mice. Atropine ameliorated the AV block indicating that excessive parasympathetic tone contributes to the neurocardiac defect. These data suggest that the kv1.1 deficiency leads to an impaired neuronal control of cardiac rhythmicity due in part to aberrant parasympathetic neurotransmission, making kcnal a strong candidate gene for human SUDEP. Schimpf et al., (2008) reported that a short QTS is a genetic condition with gain-of-function mutations in KCNH2, KCNQ1, KCNJ2, encoding potassium channels and loss-of-function mutations in CACNA1C and CACNB2b encoding L-type calcium channel subunits. These studies suggest possible link between cardiac and cerebral channelopathies in QTS associated with seizures, and SUDEP (Tu et al., 2011).

Ictal asystole may be another potent marker for epilepsy patients at high risk for SUDEP in focal onset seizure (Irsel and Saygi, 2011). Katz et al. (1983) reported two SUDEP patients with partial complex seizures starting in both cases from the right antero-mesial temporal recruitment. Cardiac sinoatrial arrest lasting 8 and 10s, started shortly after seizure onset and prior to clinical and EEG generalisation. A similar observation was reported: a 20 s period of asystole began just prior to the secondary generalization in a patient with focal onset TLE during VEEG and continuous ECG (Agostini et al., 2012). Seizure onset started in the left temporal lobe with subsequent spread to the right temporal lobe. It is worthwhile to note that in routine 12 lead ECG was normal upon admission. A similar case of prolonged ictal asystole with newly diagnosed partial epilepsy originating in the temporal lobe has been reported (Marynissen et al., 2012). Since severe bradycardia and asystole occurs in 0.27–0.5% of patients who have seizure on VEEG monitoring units, cardiac telemetry is suggested for patients admitted into epilepsy monitoring units (EMU).

Postictal EEG suppression (PI EEG-Sup). SUDEP on rare occasions occurs during EEG. In retrospective analysis, 48 patients with GTCS were identified from 470 consecutive VEEG telemetry reports (Semmelroch et al., 2012). In 13 patients (27%) PI EEG-Sup pattern were identified (mean duration 38.1 s, range 6–69 s, me-

dian 38 s), and compared to 12 randomly selected controls. Those with this EEG pattern were significantly more likely to be motionless after seizure and needed nursing (suction, oxygen administration, placed in recovery position, vital sign checked). Prolonged PI EEG SUP (> 50s) appears to identify refractory epilepsy patients who are at risk of SUDEP (Lhatoo et al., 2010). The authors studied 10 adult patients who had 30 documented seizures during VEEG recording and who later died of SUDEP. PI EEG Sup beyond 80 s, the odds of SUDEP were quadrupled ($p < 0.005$). After adjustment for variables, for each 1s increase in duration of PI EEG Sup, the odds of SUDEP increased by a factor of 1.7% ($p < 0.005$). The studies show that the pattern is relatively common and may be a potential marker for mortality in epilepsy.

Correlation of PI EEG-Sup, after GTCS, with dysregulation of autonomic functions in patients has been reported (Poh et al., 2012). Duration of PI EEG-Sup correlated with increase of sympathetically mediated electrodermal wrist-worn sensors activity ($p = 0.003$) and decreased with parasympathetically modulated high frequency power of HRV ($p = 0.002$).

Oxygen desaturation occurred in one-third of patients with localization related seizures undergoing inpatient VEEG telemetry as a part of presurgical work up (Seyal et al., 2011). Ictal-related oxygen desaturation is accompanied by hypercapnia, this in turn with ictal-related abnormal lengthening and shortening of the QTc on ECG, and with increased risk of sudden cardiac death. The authors have report that the likelihood of abnormal QTcH (Hodges correlation method) prolongation is increased 4.3 fold with seizures that are associated with oxygen desaturation (below 90%) – in comparison to seizures without oxygen desaturation. The likelihood of abnormal shortened QTcH increases with seizures that are accompanied by oxygen desaturation with an odds ratio of 2.13 compared with seizures without desaturation. There is a significant association between the depth and duration of oxygen desaturation and mean range of QT values. The authors suggest that these findings may be related to the pathophysiology of SUDEP.

It was confirmed (Moseley et al., 2012b) that cerebral oxygen saturation findings are associated with SUDEP-7 Inventory risk factors (Walczak et al., 2001). In the prospective evaluation study, six patients with 10 GTCS were monitored with prolonged scalp EEG and two regional sensors of cerebral oxygen satura-

tion (rSO(2) in EMU. Minimum rSO(2) values were recorded in the 5 min preceding ictal onset, during seizure, and in the 5 min followed postictally. The seizures were associated with significantly lower minimum ictal ($p = 0.003$) and postictal ($p = 0.004$) % rSO(2) values than the minimum preictal value. Patients with a rSO(2) decrease of $\geq 20\%$ tended to have higher SUDEP inventory scores (mean SUDEP – 7 Inventory score was 7 ± 2.8).

Using the same method, ictal-related oxygen desaturation ($< 85\%$) in patients with partial seizures was reduced in 16 patients taking selective serotonin reuptake inhibitor (SSRI) in comparison to control patients who were not taking SSRI ($p = 0.01$) (Bateman et al., 2010a). The protective role of SSRI in reducing oxygen desaturation was strengthened by the robust evidence concerning the function and development of the medullary serotonergic system for the brainstem hypothesis in the sudden infant death (SIDS), which is related to the neurotransmitter serotonin abnormalities in the medulla oblongata (Kinney et al., 2009). The leading hypothesis about pathogenesis of SIDS results from defects in brainstem-mediated protective responses to homeostatic stressors occurring during sleep in infants under one year of age. The parallels are drawn between SUDEP and SIDS which may share pathophysiologic mechanisms linked to defects in the serotonin system (Tao et al., 2010; Richerson and Buchanan, 2011). The authors discussed the possibility, that underlying pathology in the serotonin system of patients with epilepsy lowers the threshold for seizures, increasing the risk of depression and sudden death.

The role of serotonin in respiratory arrest (RA) is shown in DBA mice models of SUDEP. In the models, audiogenic generalized convulsive seizures (GCS) result in death due to RA (Faingold et al., 2011). Serotonin (5-HT) normally enhances respiration in response to elevated CO₂ levels, which occurs during GTCS in patients. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), blocked GCS-induced death in both DBA/2 and DBA/1 mice. The authors examined the effects of a 5-HT against m-chlorophenylpiperazine (mCPP) to test the generality of serotonergic effects on DBA mice. In DBA/2 mice, mCPP pretreatment significantly reduced RA incidence without blocking seizure susceptibility. In contrast, in DBA/1 mice, even higher doses of mCPP were ineffective in blocking seizure-induced RA. Fluoxetine is the only agent tested that blocks RA selectively in these SUDEP models.

Apnea. The degree of desaturation was significantly correlated with seizure duration ($p = 0.001$), and with EEG evidence of seizure spread to contralateral hemisphere ($p = 0.003$) (Bateman et al., 2008). A close temporal relationship between spread of seizures to the contralateral hemisphere and the onset of seizure-associated apnea in patients with refractory TLE, undergoing VEEG telemetry with intracranial electrodes, was shown by Seyal and Bateman (2009); apnea onsets were more tightly linked to time of contralateral spread than to time of seizure onset. TLE patients with contralateral seizure spread may be at higher risk for ictal-related respiratory dysfunction. Oxygen desaturation was accompanied by increase of end-tidal carbon dioxide, what suggests that it is a consequence of hypoventilation. Central apnoeas and hypoapnoeas occurred with 50% of 100 seizures. Two cases of SUDEP in patients with intractable TLE and secondarily GTCS, undergoing VEEG, ECG, and respiratory changes were reported (Bateman et al., 2010b). Ictal/postictal hypoventilation with the resulting hypoxemia, cardiac arrhythmia and acidosis leading to failure of recovery of cortical function and eventual cardiac failure contributed to SUDEP. Central apnea, as the initial manifestation of partial complex onset seizure, was associated with oxygen desaturation in 37 year-old man, leading to SUDEP during sleep VEEG and respiratory monitoring (Nadkarni et al., 2012). However, periictal apnea and hypoxia occur commonly with GTCS and to a less degree with complex partial seizures (So, 2008).

Effects of circadian seizure pattern on SUDEP

Cardiovascular disease, the most common cause of death in the non-epilepsy population, has an intrinsic variation depending on cyclic and circadian events (Elliot, 2001). Between 6 AM and noon there was 40% higher risk of heart attacks, and 29% increased risk of cardiac death. This cardiac death pattern may be relevant for SUDEP.

The sleep/wake, day/night, and 24-h periodic evolutions of 223 GTCS in 71 children was investigated (Ramgopal et al., 2012). GTCS were more occurring during sleep ($p < 0.001$) and most frequently between 12–3 AM and 6–9 AM ($p < 0.05$). Patients, with generalized EEG onset, had more tonic-clonic evolutions between 9 AM and 12 PM ($p < 0.05$). In patients with extra-temporal focal seizures they were more likely to evolve during sleep ($p < 0.001$), than in patients with temporal or generalized seizure onset on EEG. Sleep

and older children age were the most important predictions of GTCS evolution. The authors conclude that the results may help to individualize treatment pattern and SUDEP prevention.

In other study, it was shown that nocturnal seizures seem to be an independent risk factor for SUDEP (Lamberts et al., 2012). The study was based on autopsy and conformed to the definition in 154 SUDEP cases, and 616 controls living with epilepsy and having “exclusively diurnal” or “nocturnal seizures”. SUDEP was primarily a sleep-related (58%) and unwitnessed (86%) event. Those with sleep related SUDEP were more likely to have history of nocturnal seizures than those who had non-sleep related SUDEP. The difference was significant after correction for previously defined SUDEP risk factors by Langan et al. (2005). The authors’ advice supervision of nocturnal seizure to protect against SUDEP.

Autopsy studies

Autopsy findings, which are minimal or non-existent in autopsies of subjects with epilepsy diagnosis, may be frustrating for the forensic pathologist and the family of the deceased, as well. Even early researches at the beginning of the 20th century revealed that 4% of deaths in patients with epilepsy may be the direct result of seizures without any explanations (Terrence et al., 1975). The survey study of US coroners and medical examiners assessed their postmortem examinations of 510 patients with epilepsy who had died suddenly without obvious reason (Schraeder et al., 2009). The authors conclude that pathologists are significantly more likely than non-pathologists to inquire routinely about the history of cardiac disease, remove the brain for examination or collect blood samples for AED and psychotropic drug levels. There is a need for a thorough autopsy of persons with epilepsy when the cause of death is not obvious.

Autopsy findings may reveal potential signs of generalized seizures such as bite marks on the tongue’s surface or bruising of the muscles. The diagnosis of SUDEP in the absence of a reasonable anatomic or toxicological explanation for death should be supported by negative autopsy findings to exclude other causes of sudden death, such as positional air obstruction (Tao et al., 2010), cardiac ischemia, pulmonary embolus or cerebral hemorrhage. Otherwise unrecognized causes of death may be falsely ascribed as SUDEP.

Autopsy findings and the cause of death in cases of SUDEP are usually minimal and attributed to cerebral

edema, pulmonary edema, or pulmonary hemorrhage, and inadequately explained death in these patients (Antoniuk et al., 2001; So, 2008). Considering the whole population of patients with epilepsy, 60–70% of cases reveal brain lesion (most commonly signs of an old trauma) which may explain the epilepsy. Neuropathological findings in SUDEP include cerebral edema as well as other structural brain lesions (up to 58% of cases), such as old infarcts, hippocampal sclerosis, cortical dysgenesis, vascular malformation, oligodendroglioma, neurodegenerative brain disease, and microcephaly, cerebral hemiatrophy, diffuse cerebellar degeneration (Leestma et al., 1989; Shields et al., 2002; Zhuo et al., 2012). Histopathologic examination usually reveals acute neocortical and brainstem hypoxic neuronal changes, which may also be observed in hippocampal and basal ganglia neurons (Thorn, 1997).

No findings at autopsy suggest an underlying arrhythmogenic predisposition as features of arrhythmia (Tu et al., 2011). The features cannot be observed in the post mortem examination and studies failed to identify pre-existing ECG or structural abnormalities that distinguish SUDEP persons (So, 2008). In some cases, interstitial cardiac fibrosis has been reported (Nattel et al., 1998) or features of slight myocardiocytes hypertrophy, without evidence of cardiac fibrosis. In addition to respiratory abnormalities such as pulmonary edema, central and obstructive apnea and hypoxia are well documented findings in patients with epilepsy (Stöllberger and Finsterer, 2004).

In the toxicological examination most frequently there are no AED levels measurable at the time of death (Leestma et al., 1985), or sub-therapeutic serum levels of AED have been found (Leestma et al., 1984, 1989; Vickery, 1997; George and Davis, 1998). In more recent autopsies in 12 patients with a medical history of seizure disorders (11 with SUDEP, 1 with non-SUDEP) AED levels at autopsy were either not detectable (5) or sub-therapeutic (4); 2 had therapeutic and 1- above the therapeutic range (Lathers et al., 2011).

In retrospective large study of forensic autopsy cases from 2007 to 2009, a total 104 sudden unexpected deaths related directly or indirectly to epilepsy/seizure in the State of Maryland were diagnosed (Zhuo et al., 2012). Of these, 74 (71%) patients met a general accepted definition of SUDEP. The age of SUDEP individuals ranged from 14 to 63 years; the majority were aged 21–50 years (78.4%). Males were more likely than females to die of SUDEP (1.5:1). SUDEP occurred in 95.9% in-

side their residence, with 50 subjects (70.4%) found either in bed or on the bedroom floor near the bed.

According to their medical history, 50 subjects were reported as being prescribed AEDs (Zhuo et al., 2012) and yet at postmortem toxicological analysis, AEDs were detectable only in 26 subjects. In other words, 48% of the SUDEP cases had no traces of AED ingestion.

In the study, in 74 SUDEP cases, seizure disorder or epilepsy was listed as primarily causes of death in 66 cases, and the term SUDEP as an official cause of death in 8 (10.8%) cases, only. These findings confirm earlier opinion that the diagnosis of SUDEP is underused in the USA (Lathers and Schaefer, 2009). This may explain why the incidence of SUDEP was remarkably low and similar during the years 1976–1986 in the same county (Leestma et al., 1989). The same observation was confirmed by Bergmann et al. (2012) in Austria.

Besides of the fact that SUDEP has not been commonly known, its identification by death certificates was often unreliable, for the cause of death in epilepsy was often inaccurately recorded (Coyle et al., 1994; Medical Service Study Group of Royal College of Physicians, 2009). In childhood deaths, only 55% of deaths attributable to epilepsy was the diagnosis of epilepsy actually noted on death certificates (Harvey et al., 1993).

Forensic autopsy studies show two important facts: 1) SUDEP term, as a cause of death in epilepsy, is underused and underestimated, despite that SUDEP is the most common seizure-related category of death in epilepsy; 2) AED non-compliance is one of the most important risk factor for SUDEP. Non-adherence to AEDs in 26% of adults was associated with a three-fold increased risk of mortality compared to adherence (Faught et al., 2008). Periodic measurement of AEDs blood serum concentration and to maintain concentration at therapeutic levels, seems to be most critical factor eliminating one of the high risks for SUDEP. In the patients who do not adhere to prescribed doses, physician should raise and discuss with them potential SUDEP problems.

Antiepileptic drugs and SUDEP

Clinical awareness of SUDEP increased in 1993 when the FDA drew the attention of practitioners and pharmaceutical companies to the question of whether the use of new AEDs contributes to SUDEP or prevents it. The available data were reviewed and estimated that SUDEP rates in patients receiving gabapentin, lamotrigine, tiagabine, topiramate, and zonisamide were

similar to those receiving standard AEDs. Thus, new AEDs were not associated with an increased risk, and SUDEP reflected, rather, population rates and not specific AEDs (Lathers and Schraeder, 2002). However, although the estimated SUDEP rates are similar in patients receiving old and new AEDs, this does not mean that some AEDs cannot affect latent disorders e.g. central and /or peripheral autonomic nervous system. Increased autonomic instability and SUDEP was related to subtherapeutic serum concentration of AEDs (Lathers and Schraeder, 1995). SUDEP due to CBZ (Ernest et al., 1992; Lathers et al., 1997; Timmings, 1998) and lamotrigine (Aurlen et al., 2012; Hesdorffer et al. 2011) has been reported. CBZ may prolong AV conduction time, inhibit ventricular ectopic activity and induce bradycardia, what usually occurs with associated cardiac disturbances (Benassi et al., 1987; Boesen et al., 1983; Kennebäck et al., 1991). On the other hand, phenytoin and chlorthalidopoxide depress cardiac sympathetic neural discharges and exhibit antiarrhythmic properties (see Lathers et al., 1997). However, despite these mainly casuistic reports, no conclusive evidence of greater risk associated with the use of individual specific AEDs was found in recent population study reports (Ryvlin et al., 2011; Hesdorffer and Tomson, 2012; Hesdorffer et al., 2012). It was shown that the relationship of AEDs with SUDEP may be susceptible to confounding by tonic-clonic seizure frequency and polytherapy. In crude analysis based on the three case-control studies (for LTG on two), Hesdorffer et al., (2011) found that GTCS frequency, AED polytherapy, and number of AEDs were associated with an increased risk for SUDEP. However, analysis of individual AEDs and number of AEDs adjusting for GTCS frequency, revealed no increased risk associated with AEDs as monotherapy, polytherapy or total number of AEDs (Hesdorffer et al., 2012). Thus, GTCS frequency remained strongly associated with the increased risk for SUDEP.

In another population based study, the risk of SUDEP with LTG versus active comparators and placebo in randomized clinical trials conducted between 1984–2009 was reported (Tomson et al., 2012). Among 7774 subjects, in 42 randomised clinical trials, there were 39 all-cause deaths. The risk of definite or probable SUDEP was compared between arms for each trial type: placebo-controlled, active comparator, crossover. Of 29 on-treatment deaths, 8 were definite/probable SUDEP, 4 – possible, and 17 were non-SUDEP. There was no statistically significant difference in rate of SUDEP be-

tween LTG and comparator groups. However, the authors noted that the confidence intervals were wide and a clinically important effect cannot be excluded. Indeed, in a nested case-control study in Norway, significantly higher proportion of female SUDEP cases were on LTG than among those with epilepsy who were not taking LTG (Aurlen et al., 2012). The study was based on 26 cases of SUDEP: definite (16), probable (3) and possible (7); 15 patients were female and 11-male. Of these, 10 patients (38.5%) were treated with LTG: 9 of these were females. The incidence of SUDEP was estimated as 1.0/1000 PY when all cases were included, and 0.7/1000 PY for definite and probable. The incidence of definite and probable SUDEP in woman on LTG was estimated as 2.5/1000 PY and 0.5/1000 PY in female who were not taking LTG ($p=0.007$). However, as highlighted by Pack (2012), the Norwegian study did not control for GTCS frequency.

No evidence-based AED intervention to prevent SUDEP exists. However, it was shown that adjunctive AEDs at efficacious doses may have reduced the incidence of definite or probable SUDEP by more than seven-fold compared with placebo in patients with previously uncontrolled seizures (Ryvlin et al., 2011). The study was based on a meta-analysis of placebo-controlled randomized trials. The rate of SUDEP in patients who received efficacious AED doses was 0.9/1000 PY and was 6.9/1000 PY in those allocated to placebo. The data provide evidence in favor of active treatment for patients with refractory epilepsy. However, Hesdorffer et al., (2012) rightly noted that studies assessing the impact of AEDs on the risk for SUDEP are limited because SUDEP is a rare event and it is impossible to conduct randomized clinical studies. SUDEP is rare but this diagnosis is underused. Moreover, there is unpredictable short lasting coincidental combination of heterogenous minor and latent risk factors which may be fatal (Majkowski and Olczak, 2012). Further observations to define risk mechanisms in the use of particular AEDs in individual subjects with epilepsy and possible latent autonomic disorders are needed. Results of population based studies may not be applicable to individual patients. Assessing HRV may be useful since some AEDs can show hazardous effects in cardiac excitability, potentially leading to cardiac arrhythmia (Lotufo et al., 2012).

SUDEP and non-AED management options

Evidence regarding the benefit of pets at home, nursing

intervention, pacemaker implantation, surgical treatment for SUDEP and vagal nerve stimulation prevention is limited. However, awareness regarding pathophysiology and management options of SUDEP seems to be useful in guiding more individualized treatment in the situation when there are no effective preventive therapies. Since cardiac arrhythmia plays a potential role in SUDEP, preventive administration of omega 3-fatty acids to reduce the risk of cardiovascular mortality, is recommended (Cysneiros et al., 2009).

Pets. The relationship between the presence of pets in homes of epilepsy patients and occurrence of SUDEP was studied in 1092 patients during 2000–2009 (Terra et al., 2012). Of these, 11 patients (1%) had a diagnosis of SUDEP. None of the SUDEP cases had pets in their homes at the time of death, while in the control group (n = 1081) the frequency of pet-ownership was 61%. In the author's opinion, domestic animals can buffer reactivity against acute stress, diminish stress perception and may have a positive effects on well-being, thus improving epilepsy outcome.

Periictal nursing. It was shown that in retrospective analysis of VEEG telemetry data periictal nursing intervention was associated with a reduced duration of seizure-related respiratory dysfunction and with reduced duration of postictal generalized PI EEG-SUP (Seyal et al., 2012). Interventions included administration of supplemental oxygen, oropharyngeal suction and patient repositioning. Interventions were based on nursing clinical judgement at the bedside (the patients were not randomized). There were 21 GTCS with no interventions and 84 GTCS with interventions. In the later group, the duration of hypoxemia was shorter ($p = 0.0014$) when intervention occurred before hypoxemia onset (mean duration 53.1 s) than when it was delayed (mean duration 132.2s). Also there was a shorter duration of PI EEG-Sup. The authors conclude that validation of these preliminary data with prospective study is needed before definite conclusions can be reached regarding the efficacy of periictal interventions in reducing the risk of SUDEP in an out-patient setting. In another study, PI EEG-Sup (duration 38.1s) was observed in 13 out of 48 patients (27%) (Semmelroch et al., 2012). These patients were significantly more likely to be motionless after seizure and had nursing interventions.

Pacemaker. Severe tachycardia and asystole occur most frequently in focal onset seizures involving insular, orbital frontal and anterior temporal lobe areas. To implant a permanent pacemaker in these patients

to prevent syncope and/or death is in use and it is suggested that this approach be used in clinical practice (Agostini et al., 2012; Marynissen et al., 2012). However, in some patients medical treatment of epilepsy may be effective to prevent cardiac asystole. In case of new onset left frontal lobe epilepsy with frequent events of ictal bradycardia and asystole with near-syncopal episodes, oxcarbazepine was effective in seizure control (Enkiri et al., 2011).

Epilepsy surgery. Successful epilepsy surgery was associated with reduced risk of premature mortality. However, more recent studies with long-term follow-up have raised doubts as to whether better survival is attributable to surgery, only. The results may be due to differences between the operated and non-operated groups, as treatment decisions were not randomised (Bell et al., 2010). It is suggested that seizure outcomes following epilepsy surgery and risk for SUDEP may both be governed by a common underlying biologic process linked to cardiac changes and autonomic regulations (Jehi, 2010). Seizure worsening and its predictors after unilobar epilepsy surgery between 1990 and 2007 were retrospectively analysed (Sarkis et al., 2012). A total of 276 patients with postoperative seizure recurrence were identified. Monthly averaged seizure frequency worsening was found in 9.8% patients, GTCS – in 8%, new-onset GTCS – in 1.4%, new onset of status epilepticus – in 2.2% and SUDEP – in 1.4%. The higher risk of worsening was seen in extratemporal resection as compared to temporal lobe resection ($p = 0.018$), in patients with low preoperative seizure frequency ($<30/\text{month}$) ($p = 0.0003$), incomplete resection ($p = 0.010$) and multiple ictal patterns ($p = 0.030$).

In another study, follow-up of 306 patients with drug-resistant epilepsy, who underwent temporal lobe resection between 1975–1995, mortality was analysed until 2009 (Seymour et al., 2012). In 3569 PY, death occurred in 19 patients (SMR 2.00): (14 men and 5 women). SMR was significantly elevated in patients with mesial temporal sclerosis (SMR 2.50), higher in men (SMR 3.12) and right-sided resections (SMR 3.33). SUDEP was identified in 1.96%. The risk of premature death, undergoing TLE surgery, decreasing over time, remained above the risk seen in the standard population.

Vagal nerve stimulation (VNS). Based on a cohort of 1819 patients with epilepsy (followed 3176.3 PY) receiving VNS, the mortality (SMR = 3.6) and SUDEP (4.1/1000 PY) rates were similar to those reported for severe epilepsy (Annegers et al., 2000).

Prevention of SUDEP

The possibility to prevent SUDEP is rather limited and preventive actions depend on etiology and pathophysiology of the death causes. Dupuis et al. (2012) reported a case of Takotsubo syndrome (TKS, “stress myocardiopathy, broken-heart syndrome”) after epilepsy and a review of 59 identified TKS after focal or generalized epilepsy. The syndrome occurs mostly in females (84%, mean age 63 yrs) and may induce cardiac arrhythmia. Near-SUDEP was reported in one patient. Animal models of SUDEP have shown similar cardiac lesions to those seen in TKS. According to the authors, these observations strengthen the hypothesis of a link between these conditions. Since TKS after epilepsy is relatively common, the authors suggest serum troponin levels are measured and that cardiac follow-up occurs.

In the case of short QT syndrome, quinidine prolongs the QT interval and normalizes the effective refractory periods of the atrium and ventricle in patients (Schimpf et al., 2008). Recent interictal, ictal and postictal ECG, respiratory and EEG studies are able to identify some biomarkers for SUDEP risk. In such persons preventive measures may be considered, e.g. cardio-protective drugs, low fat diet, respiratory therapy, heart rate monitors, pulse oximetry, bed motion monitors, implantation of defibrillator, nocturnal respiration monitoring devices. However, false positive alarms limit their value. To detect seizure is still problematic. At present, EEG algorithms are not capable of defining seizure precursors (Lehnertz et al., 2007). Even in some cases professional postictal resuscitation it is not successful (Swinghamer et al., 2012). However, what seems to be underestimated, and should be mandatory, is careful medical history including habits of the patient and his /her family health history, including genetic aspects, analytical laboratory tests related to suspected dysfunctions or impairments.

Patient-physician communication: when to discuss SUDEP. With increasing awareness of possibility of SUDEP occurrence, the question arises as to whether to discuss SUDEP with patients. The NIH/NINDS sponsored a 3-day multidisciplinary workshop to advance research into SUDEP and its prevention (Hirsch et al., 2011). In addition to research on SUDEP and practical medical preventive devices, education of all people with epilepsy about SUDEP – as a part of their general education on the potential harm of seizures, except in extenuating circumstances, was recommended. Debates about “truth-telling” are in practice controversial.

Relatively well identified risk factors and their significance have, at most, statistical value. Clinical practice in epilepsy centres varies widely. The Scottish Intercollegiate Guidelines Network (supporting the review of M.J. Brodie) suggests that information on SUDEP is “essential”, and UK National Institute of Clinical Excellence (NICE) recommended that “tailored information on the person’s relative risk of SUDEP should be part of the counselling process”. The Joint Epilepsy Council of UK charities suggests that patients and their families have the right to know about risks of epilepsy and the reasons for treatment. However, the risk of SUDEP is not the same across all epilepsy patient populations (Brodie and Holmes, 2008). The co-author to the paper (GLH), contends rightly that it is not necessary, or advisable, to discuss SUDEP with all patients, but only with those who are at high risk. Survey of current practice among UK neurologists in response to NICE guidelines, revealed that 5% of responders discussed SUDEP with all patients, 25% – with majority, 61% – with a few and 7.5% with none (Morton et al., 2006). The variation the authors found probably reflects patients’ variable needs for knowledge about their condition.

Waddell et al., (2012) analyzed a retrospective case note review in established diagnosis of epilepsy attending clinic during the first half of 2009. Documented SUDEP discussion was noted in 14 out of 345 (4%) patients with GTCS and non-compliant with AED medication. Patients were informed more likely if potentially modifiable risk factor were identified.

In the Albanian authors’ opinion (Kruja and Vyshka, 2012), step-by-step approach and gradual informing are helpful and psychologically acceptable to disclose the risk of SUDEP to the family on a child with epilepsy is a necessary act. Talk or not to talk and its way depends also on the patient’s cultural and psychological profile, and developed empathic channel of patient-physician communication (Majkowski, 2007; Fröscher, 2012). To disclose the risk of SUDEP to patient with epilepsy or to his/her family may cause serious stress, which in turn will result in a decrease of quality of life. Since non-compliance is one of the most significant risk factors, in particular, in combination with nocturnal and focal onset frequent seizures with generalisation, would justify starting discussions with the patient about these worse prognostic consequences.

CONCLUSIONS

SUDEP occurs as a result of a fatal coexistence of sev-

eral predisposing risk factors which are known and frequently unknown. Diagnosis of SUDEP is underestimated and underused as judged by autopsy findings. Careful medical and family history, related to cardiac or sleep respiratory autonomic dysfunction, is mandatory. Periictal long-term VEEG, ECG and oxygen saturation monitoring may be potential biomarkers of autonomic dysfunction. It may contribute to better understanding of SUDEP complex and heterogenous mechanisms, and eventually its prevention. In patients with high risk factors for SUDEP, in particular, AED non-compliance, and frequent seizures during sleep, prognosis of epilepsy should be discussed.

CONFLICT OF INTEREST DISCLOSURE

The author has no conflict of interest to declare.

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