SUDDEN DEATH IN EPILEPSY: CASE REPORT AND LITERATURE REVIEW

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Abstract

Sudden Death in Epilepsy (SUDEP) was first described in literature in the nineteenth century as an entity whose pathophysiological mechanisms are still unclear. It is the most important cause of death in epileptic patients with recurrent tonic-clonic seizures, the sudden death risk being 24 times higher than in the general population. In this paper we approach aspects of incidence, risk factors, pathophysiological mechanisms and autopsy records in SUDEP cases. We present the case of a 28 year-old female, diagnosed with 8 years of Epilepsy Grand Mal, with increase in tonic-clonic seizures recurrences in the last month. Death occurred suddenly, autopsy, histopathological examination and toxicological examination revealing no obvious cause of death.

Keywords: sudden death, epilepsy, risk factors, pathophysiology, canalopathy, autopsy.

1. INTRODUCTION

Epilepsy is a neurological condition characterized by the recurrence and spontaneity of epileptic seizures. An epileptic crisis means abrupt, abnormal, uncontrolled, redundant and hypersynchronous activation of a neuronal area - called epileptogenic outbreak, an activation that translates semantically through episodes of motor, sensory, sensory, behavioral or non-altered states of consciousness [1,2]. For a diagnosis of epilepsy, at least two such crises, alterations of a preexisting determinant background, should occur [2]. The World Health Organization (WHO) reports more than 50 million patients with epilepsy, 80% of them living in developing countries [3]. In 1902, Spratling is among the first neurologists to emphasize the epithelial potential of tanatogenicity, saying: „Epilepsy can slow down life quickly without preventing it during a brief crash” [4]. According to Lhatoo and Sander (2002), the mortality rate among epileptics is 2 to 5 times higher compared to the general population, 40% of being related to epilepsy [5]. The increased mortality rate results in the first years after the diagnosis of the underlying disease (strokes, tumors) so that, in the coming years, death is ratified at the risk of epileptic seizures - accidents, trauma, status epilepticus, sudden unexpected death in epilepsy (SUDEP), all being associated with suicide in the context of depression [6]. Sheline et al. have tried to explain for the first time the link between epilepsy and depression, the common denominator being changes in the vegetative system. Thus, in patients with depression, a decrease in hippocampal size relatively to the control group was identified. The decrease in size was explained by Carney based on the neurotoxicity of glucocorticoids released during the epileptic seizure [7]. This process seems to induce an increase in RF corticotropin secretion that will activate the hypothalamic-pituitary-cortical adrenal axis. At the same time, RF corticotropin activates the sympathetic nervous system, both of which being observed in patients with major depression and in those with epileptic signs [7, 8]. Based on neuroimaging studies, Shamim et al. revealed in 2009 the existing hippocampal atrophy in both large depressive and epileptic
temporal lobe epilepsies [9]. In Nashef Linda’s view, SUDEP means sudden unexpected death in a non-traumatic, epileptic patient, without asphyxiation with or without evidence of a seizure, but with documented absence of epileptic status, where post-mortem examination does not reveal toxic causes or injuries with structural fatalities [10]. It should be noted that this operational definition is not universally accepted. In epidemiological studies, depending or not on the complexity of historical and autopsy data, the following classification system has been proposed:

- confirmed SUDEP - all conditions are met; the circumstances of death are known and there is an autopsy report;
- probably SUDEP - all conditions are met, but there is no autopsy report;
- SUDEP may not be excluded, but the data is insufficient, and the autopsy ratio is missing. [11]

It must therefore be understood that SUDEP is a category in which the autopsy records of death are missing [10,12]. From the incidence point of view, literature records various data depending on the studied population. The incidence varies between 0.5-1.5/1000 inhabitants/year among cohorts with unselected population (SUDEP-risk epileptic patients) and 9/1000/inhabitants/year in cohorts of patients with refractory epilepsy [13]. The incidence of SUDEP is higher in younger age, low compliance or multi treatment patients with refractory epilepsy, alcohol consumption, African Americans, males (7: 4) and decades II-IV [14]. In children, the incidence is low at 0.2/1000/inhabitants/year in cases with major neurological deficits. The cohort of patients with epilepsy followed 40 years of childhood. SUDEP occurred in 9% of cases, representing 38% of all causes of death, most of them being those with major neurological deficits, autism, juvenile myoclonic epilepsy, Dravet’s syndrome, tuberous sclerosis, duplication of chromosome 15q11-13 [15]. A study comparing the sudden deaths in the general population to those in epileptic patients shows a sudden death rate 24 times higher in epileptic patients than in the general population [13].

In the studies performed on adult populations, the following factors were identified: early age, male gender, low compliance, refractory epilepsy, alcohol consumption. In case-control studies in which the control group was represented by non-SUDEP patients who died from epileptic death, the most criticized risk factors were the tonic-clonic seizure that preceded death and the subtherapeutic values of antiepileptic medication [13]. This last factor was considered by Walczak in 2003, when he demonstrated that antiepileptic medication values decrease postmortem because they will be further metabolized, so the toxicological evidence is inconclusive in this case. In studies where the control group was formed of living epileptic patients, the risk factors were: early age, increased frequency of seizures, extended period since diagnosis, increased number of antiepileptics. A large number of crises (> 3/year) increases the risk 8 times [16-19].

Two case-control studies identified as a risk factor the association of two antiepileptics, despite a better control of the frequency and severity of seizures. It is assumed that the sedative effect of antiepileptics leads to an increase in the posterior period and increased susceptibility to central apnea. The risk factors identified in literature thus depend on the control group. A meta-analysis of 880 cases of SUDEP devoted to the no-thymus rhythm demonstrated the correlation of SUDEP with sleep. It was noted that 69.3% of the SUDEP cases occurred during sleep and 30.7% during the wake-up period. It is suggested that this association is due to the ventral decubitus following the sleeping crisis [20]. They are also joined by patients with mutations in the coding genes for potassium and sodium channels, the largest cohort subjected to molecular autopsy showing a correlation between canalopathies and SUDEP, including 61 SUDEP cases [21]. For example, the SCN1A mutation is associated with generalized epilepsy and febrile seizures. The explanation lies in the expression of the gene in the cardiac tissue, which would predispose to arrhythmias of the epileptic carriers [22]. Another risk factor is the variability of heart rate, due to autonomic system disfunctions [13]. Changes in the ECG of the R-R interval are associated with sudden death in the general population. Cardiac frequency variations have been shown to be more common among epileptics. However, it is not known whether this
is the consequence of epilepsy per se, of antiepileptic medication or of associated comorbidities. Observational studies on both animal and human models demonstrate the existence of cardiac, respiratory and cerebral mechanisms (cerebral shutdown) [23-25]. Alicia Golman et al. reported the discovery of a defective gene that controls potassium channel transduction (KvLQT) with both cardiac and cerebral expression, the mice with this gene evidencing EEG changes like epilepsy and arrhythmias. This gene is involved in the long QT syndrome, coding potassium channels with narrower transmembrane units, leading to an increase in the repolarization period, which explains electrocardiographic changes. The development of a genetic screening test for this gene is anticipated in patients with epilepsy, to identify the risk of SUDEP and to treat it with beta blockers or pacemakers [26].

For now, the various and multifactorial pathophysiological mechanisms are not fully elucidated. Although it is the most common neurological disease in the world, it is also the most „neglected”. Two theories of SUDEP pathogenesis are postulated. The first criminalizes postictal cerebral inhibition, leading to posterior apnea which, together with obstructive apnea, leads to the occurrence of cardiac arrhythmias on the background of acidosis with consecutive hyperpotassemia. The second pathogenic theory supports the role of adrenergic stimulation which, together with tonic-clonic seizures, by the tachycardia effect and shortening of the diastole, will lead to ischemia with subsequent fibrosis in the irrigated deficient areas (with subendocardial fibrosis), territories in which in the following tonic-clonic crises will generate arrhythmias [27]. These are associated with a susceptibility to the existing arrhythmias in epileptic patients through neuro-vegetative disautonomia. The electroencephalographic (EEG) video of SUDEP patients monitored in epilepsy monitoring units shows a consistent involvement of the respiratory and cardiac events that precede death. In literature, the reference point of the SUDEP etiology is the MORTEMUS study, a retrospective study conducted between January 1, 2008 and December 29, 2009, on patients admitted to epilepsy monitoring units in Europe, Israel, Australia and New Zealand. The aim was to recover data on all cardio-respiratory stops recorded in these units and to determine their incidence. Epileptic monitoring units from other regions were invited to report similar cases to further explore the mechanisms. Data analysis led to the following results: 147 (92%) of the 160 units responded to the survey. There were 29 cardio-respiratory stops, including 16 SUDEP (14 night), 9 cases of near SUDEP (SUDEP resuscitated) and 4 deaths from other causes. Existing cardiac and respiratory data available for 10 cases of SUDEP showed a consistent and previously unrecognized pattern in which tachypnoea (18-50 breaths per minute) followed generalized tonic-clonic seizures, resulting in transient or terminal apnea with exitus. When it was transient, this disfunction occurred later with terminal apnea, manifested 11 minutes after the end of the seizures, followed by cardiac arrest. The incidence of SUDEP in adult epilepsy monitoring units was 5.1 (95% CI 2 · 6-9.2) per 1,000 patient-years, at a risk of 1.2 (0.6-2.1) at 10,000 VEEG monitorings. [28, 29].

Out of the respiratory factors, neurogenetic pulmonary edema has been identified in 84% of the patients with SUDEP, appearing to be due to massive adrenergic alpha stimulation, generalized vasoconstriction, pulmonary and systemic hypertension, alveolar capillary pressure reversal, with subsequent plasma extravasation in intra-alveolar space and alveolar flooding [13]. The literature also cites an important damage to the alveolar endothelium, with the release of pro-inflammatory marker and ARDS [23]. Central apnea syndrome characterized by stopping breathing in sleep seems to be due to the propagation of electrical discharge at respiratory centers [13]. In this regard, the MORTEMUS study revealed that, in patients in whom the electric front was propagated in the tonsil, the respiratory rate decreased from 17 r/ min to 1 r/ min, followed by hypoxia with hypercapnia. These two events will stimulate bulb respiratory centers with tahipnea at the end of the crisis, which will intensify acidosis, due to its inefficiency caused by the neurogenic pulmonary edema installed during the crisis [15, 27]. Thus, central apnea will lead to exitus, both directly and indirectly, with acidosis, followed
by hyperpotassemia, with fatal malignant arrhythmias (\textit{torsade de pointes}). Postcritical episodes of apnea with a duration of 10-63 seconds, accompanied by oxygen desaturation of arterial blood [15], were highlighted. Additionally, asystole may cause secondary apnea. Asphyxia secondary to upper airway obstruction, especially in patients found in anteflected position (favoring aspiration) at the time of death. Laryngeal spasms and postcritic strides that can co-participate in death may additionally be added [30]. Malignant arrhythmias (ventricular fibrillation and \textit{torsade de pointes}) were evidenced by simultaneous EEG and EKG monitoring, both intra- and postcritically.

Ictal changes: tachycardia, arrhythmia, Q-T interval prolongation were documented in temporal lobe epilepsy and bradycardia, followed by tachycardia in all cases of generalized convulsive seizures [29]. Simultaneous recordings of ECG and EEG revealed tachycardia in 74-92\% of the complex focal seizures. Based on these findings, it is assumed that arrhythmia precedes SUDEP as the cause of death. Lathers J. \textit{et al} (2009) evidenced a synchronicity of ictal and interictal discharge with increased sympathetic heart activity (31). During the crisis, patients experience a reduction, often prolonged, in heart rate, posteriorly causing a marked decrease in cerebral infusion and potential death [15]. It is assumed that the electric front propagates to the amygdala and hence, through its connections (through the central nuclei), to the bulb-medullary cardio regulatory centers. The sympathetic storm and strong intra-vagal intra-ictal inhibition may be an alternative mechanism of death by increasing ventricular ectopic activity, leading to the development of malignant arrhythmias [32]. Another mechanism involved in the pathophysiology of SUDEP is that of cerebral shutdown [24]. Both generalized tonic-clonic and partial focal crises are associated with the abolition of consciousness. Patients with these seizures do not respond to orders and questions during the post-ictal stage; however, patients with partial seizures are able to follow visual images. These data suggests that, although consciousness is reduced in partial seizures, these situations are closer to a state of diminished consciousness than a post-ictal coma, as it appears after generalized tonic-clonic seizures, which could increase the risk of SUDEP [32]. The works performed in the 1930’ies and 1950’ies by Wilder Penfield and Herbert Jasper forwarded the theory that subcortical structures, such as the diencephalic and cerebral trunk, are involved in controlling consciousness, forming the downstream cross-system facilitator [33,34]. This system is composed of discrete neurotransmitter-specific nuclei, including raphe nucleus, \textit{ locus coeruleus}, tegmental ventricular area, pedunculopontine and laterodorsally nucleus of the vagus, and the parabral complex [34]. If a crisis spreads to the bone marrow stem and affects these nuclei, it could alter patient’s level of consciousness. Blumenfeld proposed the hypothesis of network inhibition, which involves maintaining of consciousness through interactions between the cortex and subcortical structures. Once the electrical front from the epileptogenic cortical outbreak propagated to the subcortical structures, the GABAergic interneurons will be activated, inhibiting the downstream cross-linked facilitator system and thus affecting its specific and nonspecific functions. Once inhibited, the cortical activity is suppressed, resulting in loss of consciousness [35]. The existing data support this theory because SPECT imaging in patients with temporal lobe epilepsy showed an increase in the blood flow, beginning with the structures of the temporal lobe and descending into the midsection and spinal cord. In addition, records of cholinergic neurons in the pedunculopontine tegmental nucleus demonstrate that the acetyl cholinergic neurons from the facilitated downstream cross-linking system are inhibited during limbic convulsions. The loss of consciousness caused by the inhibition of this system undermines the patient with generalized tonic-clonic seizures at an increased risk of SUDEP, as protective reflexes are suppressed during post-ictal coma [36]. Apparent lack of causes of death does not exclude some abnormalities that could have

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contributed to death, as causes or consequences of epilepsy or co-morbidities related or not to epilepsy. Most often, they involve detection of a pulmonary, cardiac or cerebral pathology. A review of 145 SUDEP subjects identified macroscopic brain changes in 54% of cases, consisting of cortical thickness abnormalities, subcortical nodular heterotopias, abnormal gill patterns, lacunarisms, low-grade tumors, or hippocampal changes - such as asymmetry, diminution, and malrotations. Changes in brain weight were recorded in 136/145 (94%) of cases. There was no correlation between SUDEP, age, sex, and brain volume, comparatively with the control cases. Also, no connections between swelling, SUDEP and brain weight were identified, resulting in a \( P < 0.005 \). From a microscopic point of view, changes were identified in 89% of the cases under analysis. The most common evidence was cortical malformations, vascular malformations (15%), tumors (7%) and hippocampal sclerosis (21%). The most frequent microscopic modification was marked neuronal eosinophilia - 80/145 (55%) - limited in most cases to the hippocampus, destruction of the cortical hexamaline structure, lamination gliosis in the external and internal granular layers, in 16% of the cases being evident in the cortex, basal ganglia, thalamus and cerebellum. Other changes: focal axonal lesions, amygdala gliosis [15].

2. CASE REPORT

To illustrate SUDEP we present the case of a 28 year-old female A.R., urban. Named A.R. was found deceased in bed with a pillow in the morning; the closest statement was known for epilepsy under treatment with Fenitoin and Phenobarbital.

This appears in the 8-year medical records with the diagnosis of Epilepsy Grand Mal (GM) with numerous admissions. The last admission was 1 month before death, upon the increase in the frequency of GM-consciousness crises, with inter-critical psychiatric disorders of discomfort type. EEG: frequent paroxysms from which a polymorph (4-7 Hz, 100H, 20 U.V) with a duration of 1-1.5 s in the bilateral frontal-temporal derivations, predominantly remaining when opening the eyes. Alpha wide and sharp dominant alpha (9-11 Hz, 200-220 UV) rhythmic pathway previously migrated; hyperpnea maintains the same aspect of the route. Clinical-anamnestic data corroborated with paraclinical explorations support the above diagnosis. Evolution was favorable with antipsychotic therapy associated with psychotherapy. Recommendations: Treatment according to Rp (Phenytoin 3 pills/day, Carbamazepine 200 mg 2 pills/day, Phenobarbital 1 pill/evening), providing a socio-family psycho-protective climate, periodic medical check-up if necessary, maintenance of medico-social, psycho-protective measures previously set.

Autopsy Findings

The forensic autopsy records: 170 cm waist, normal constitution.

External examination evidenced: red-violet cadaver lividities, arranged on the anterior, lateral and dorsal sides of the trunk and limbs, which complies with the compression zones with the subjacent plane, at the imbibition stage, cadaveric resolution rigidity; at necropsy, blood is bubbled in the oral cavity in a significant amount.

Internal examination revealed: at the level of the cephalic extremity, the temporal muscle as a red hemorrhagic infiltrate with irregular edges and irregularities with dimensions of 5/3 cm; cerebral hemispheres, discrete flattened circumscriptions, and deep grooves; the leptomeningeal vessels desiccated, filled with blood. The section of the brain, 1.5-3 mm thick, appears glossy, with the limit between the gray matter and the blurred oval center; free, symmetrical, discontinuous lateral ventricles with purple choroid plexuses.

The trachea and the main bronchi have pinkish mucus, with the lumen occupied by aerosol serotype, in a significant amount; both purple, marooned, with dimpled crepitation, fill the pleural cavities, touching the free edge and partially covering the fibrous pericardium; on cross-section, dark violet color, liquid blood flows in increased amounts, mixed with a foamy serositis; through the transparency of the visceral pleura, minimal, circumscribed, especially interscizural translucent petitions of the viola.
The cord is of ordinary size, with the epicardium showing numerous and minimal stern costal faces of viola, circumscribed. Cavity cavities contain liquid blood. On cross-sections, especially in the lower left ventricular wall, subendocardia, white-pearly streaks with reduced elasticity are lost among the myocardial fibers;

Macroscopic diagnoses: infiltrated epicranian hemorrhage; cortical atrophy; pulmonary edema; miocardo-sclerossis;

A toxicological and histopathological examination was performed, evidencing the presence of barbiturates - phenobarbital 135.4 μg/ml (therapeutic dose), beclamide - anticonvulsant (barrel, bile, liver, stomach and gastric contents, kidneys) indicating a toxic dose; no pesticides, carbamate, organophosphorus, organochlorine, toxic, benzodiazepine, TCA, ethyl alcohol, methyl alcohol, drugs have been identified.

Histopathological examination (Ematossilin & Eosin) confirmed the macroscopic changes, concluding: cord - subendocardial interstitial fibrosis, fibrous valvular endocardium; brain - on the addressed fragment (Charcot-temporal lobe) cortical atrophy, nodular gliosis, astrocytic-like pyramidal neurons; temporal muscle fragment - with hemorrhagic infiltration among the striated muscle fibers;

Here presented is a series of data that advocates SUDEP: a case diagnosed with Epilepsy Grand Mal 8 years before death, with recurrent seizures found during the morning in ventral decubitus, in bed, where death occurred suddenly and unexpectedly, being related to sleep and in which the necrotic, toxicological and histopathological examinations identifying no cause of death. Myocardosclerosis detected in necropsy is difficult to explain in a 28 year-old person without coronary pathology. Perivascular gliosis (Fig.1) and the amylase body described at cerebral level on the temporal fragment addressed show a neuronal suffering, nodular gliosis areas (Fig. 2). These may represent possible epileptogenic outbreaks, as frequent paroxysms were obtained in the temporal derivations in EEG, where polymorphs (4-7 Hz, 100H, 20 UV) lasting 1-1.5 s in the frontal - temporary bilateral - branches were noticed.

Fig.1. Perivascular gliosis, HM stain, microscopy 10X

Fig. 2. Nodular gliosis, HE stain, microscopy 20X

Pulmonary edema is not pathognomonic, however, in this context, it can point to SUDEP. A meta-analysis of 880 cases of SUDEPs with documented circadian rhythm showed that, in 69.3% of the cases, death occurred during sleep and the remaining 30.7% - during wakefulness [18].

3. CONCLUSIONS

Sudden death in a patient with epilepsy remains a controversial topic in literature and in neurophysiology research.

The factors invoked in the manifestation of SUDEP are: early age, generalized seizures, long time after diagnosis, poor control of seizures, sleep-related death, the ventral position in which the subject was found, autopsy
and histopathological confirmed pulmonary edema, to which postmortem investigations identified no toxic causes or fatal structural damage.

References


