

Mortality in children with severe epilepsy

10 years of follow-up

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ABSTRACT

Epilepsy is the main neurological condition in children and adolescents. Unfortunately patients with medical refractory epilepsy are more susceptible for clinical complications and death. We report a prospectively evaluated cohort of children followed for approximately 10 years. Fifty-three of 1012 patients died. Forty-two patients died due to epilepsy or its clinical complications and the main causes of death were pneumonia (in 16 cases), sepsis (in 9 patients), status epilepticus (in 8 patients). In 11 patients cause of death was sudden unexpected death in epilepsy (SUDEP). Mental retardation was significantly more frequent in patients who did not die from SUDEP. SUDEP may be a significant condition associated with mortality in children and adolescents with epilepsy. **Key words:** epilepsy, mortality, sudden death, children.

Mortalidade em crianças com epilepsia severa: 10 anos de seguimento

RESUMO

Epilepsia é uma das condições neurológicas mais comuns em crianças e adolescentes. Infelizmente, pacientes com epilepsias refratárias ao tratamento medicamentoso estão mais susceptíveis a complicações clínicas e óbito. Neste trabalho reportamos, em uma análise prospectiva, um *cohort* de crianças acompanhadas por aproximadamente dez anos. Cinquenta e três de 1012 pacientes foram a óbito. Quarenta e dois pacientes morreram em decorrência da epilepsia ou de suas complicações clínicas; as principais causas foram pneumonia (16 casos), sepse (9 casos) e estado de mal epilético (8 casos). Em 11 pacientes a causa da morte foi SUDEP. A presença de retardo mental foi significativamente associada a mortalidade em crianças e adolescentes com epilepsia. **Palavras-Chave:** epilepsia, mortalidade, morte súbita, crianças.

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Epilepsy in children is a major health problem with an incidence ranging from 20 to 190 cases/100,000 inhabitants¹. Epilepsy is associated with a high probability of injury and with clinical comorbidities, and the reported mortality incidence in epileptic individuals is two to three times higher than that in the general population^{1,2}. The mortality incidence is not clearly determined in the development

countries, but it appears to be more frequent in patients with mental retardation or with symptomatic epilepsy³. The lack of studies with a large number of pediatric patients, during a long-term period and involving standardized case selection, makes the comparison between the studies difficult⁴.

Sudden unexpected death in epilepsy (SUDEP) is probably the commonest di-

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rect epilepsy-related cause of death. Its incidence has been reported to be 1 per 100 person-years in patients with intractable epilepsy and 0.35 per 1,000 person-years in the general population⁵. There are few reports on death risks in the pediatric population solely, and only a small number of patients are usually analyzed^{6,7}. We report here the mortality incidence in a cohort of children and adolescents with epilepsy, in a Brazilian hospital.

METHOD

This refers to a prospective study that evaluated the incidence of epilepsy-related death in a cohort of children aged from zero to 18 years, from January 2000 to November 2010, in the Clinical Hospital of Ribeirão Preto. During the follow-up, patients were evaluated regarding the demographic and clinical data - age at epilepsy onset, epilepsy syndrome, seizure frequency, antiepileptic drug therapy (AED) and neurological development. All cases with dubious diagnosis of epilepsy were excluded from the study. Families were contacted in order to elucidate the death causes. Epilepsy etiology was classified as symptomatic (with known cause), probably symptomatic (with unknown etiology) and idiopathic (when clinical and electrographic findings were clearly related to an idiopathic syndrome⁸). Patients with exclusive febrile seizures or with a single seizure were not considered in this study. All families that were contacted were asked to sign informed consent according to ethical guidelines.

The SUDEP criteria were: [1] Child with epilepsy and with recurrent unprovoked seizures; [2] Child who died unexpectedly while in a reasonable state of health; [3] Death that occurred suddenly; [4] Death that occurred during normal activities, under benign circumstances; [5] Unknown obvious medical cause of death; [6] Death that was not directly caused by *status epilepticus*. We considered probable SUDEP when all the above-mentioned criteria were present, but post-mortem data were not available. Possible SUDEP was considered when conclusive and post-mortem data were lacking^{8,9}.

The data were evaluated by the SPSS statistical program and both descriptive and categorical variables (Chi-square and Student t test) were considered. A p value <.05 was considered statistically significant.

RESULTS

A group of 1012 patients aged from zero to 18 years were monitored from January 2000 to November 2010. Epilepsy in that group was classified as: focal symptomatic (63.7%), probably symptomatic (20.8%) and idiopathic (15.5%). Twenty-five patients (3%) were lost during the follow-up. Fifty-three patients or 5.6 persons-year died during the study period; 31 of which were boys.

The epilepsy onset occurred between birth and 11 years of age (mean 1.5 years±2.2). The mean age of death was 9.2 years±5.7 (range: 2 to 23 years). All patients showed symptomatic epilepsy. Almost all patients presented daily seizures (71.7%). Weekly seizures occurred in 17% of the cases and rare seizures (one to two seizures/year) in 11.3% of the patients. Mental retardation was present in 92.5% of the patients (being mild in 17%, moderate in 20.8%, and severe in 54.7%). All patients were under AED treatment: 9.4% of the subjects were being given one drug, 28.3% two drugs, 54.7% three drugs, and 7.5% four drugs. Serum AED concentrations at the time of death were not available.

Image findings revealed diffuse atrophy (32.1%), destructive lesions (15.1%), cortical developmental malformations (9.4%) and gliosis (7.5%). Other lesions included mesial temporal sclerosis (in three patients), leucodystrophy (in one patient), tuberous sclerosis (in one patient), hydrocephaly (in one patient), and Dandy-Walker Syndrome (in one patient). Normal brain image was observed in 15.1% of the cases.

The main causes of death were pneumonia (in 16 cases), sepsis (in nine patients) and *status epilepticus* (in eight patients). In each case there was one patient who died from head injury, one from cardiac failure, one from acute complications due to epilepsy surgery, one from drowning, one from pulmonary embolism, one from metabolic acidosis, one from falciform anemia, one from chemotherapy (a patient with leukemia) and one from hemorrhagic cerebrovascular accident (a patient with mitochondrial epilepsy).

Neither a clinical nor a neurological cause of death could be identified in 11 patients and dying of SUDEP was considered. Seven patients were found dead in bed in the morning or after a daytime sleep and four patients died of subtle cardiorespiratory arrest, directly related to a seizure.

Comparison between patients with and without SUDEP did not show any significant statistical differences related to gender, to epilepsy syndrome, to MRI findings, to number of AED, to seizure frequency and to seizure type (Table). Patients with moderate or severe mental development retardation were at a significant greater risk of dying from causes other than SUDEP (p=0.02).

DISCUSSION

The mortality rate in patients with epilepsy is 2-5 times higher than that found in the general population¹⁰. Our series consist of a group of children and adolescents with epilepsy that had been prospectively evaluated over ten years. There were 53 death cases - 11 of SUDEP - in the group of 1012 patients. Some authors have reported an increase in both children and elderly adults' mortality,

which is usually associated with neurological deficit and clinically associated diseases⁴. Mortality is rare in patients with idiopathic epilepsies, and that was not observed in our group, although idiopathic epilepsies had been observed in 15.5% of our patients. Those observations suggested that patients with symptomatic epilepsies were at greater risk of dying¹¹.

Systemic infections were the main cause of death in our group, followed by SUDEP and *status epilepticus*. In the general population, SUDEP incidence is between 1:500 and 1:1,000 person-years, whereas it is close to 1:200 for patients with severe forms of epilepsies¹². SUDEP mechanisms are not well understood and the possible factors that involve them may be cardiovascular system abnormalities, central apnea or primary brain failure, during or just after a seizure^{13,14}. Genetic factors related to channel genes in the cardiac musculature may interfere in its normal depolarization/repolarization process, predisposing the subjects to cardiac failure, prolonged QT interval, and increased susceptibility to cardiac arrhythmias¹².

The incidence of SUDEP in children and adolescents is highly variable, but it is thought to be extremely rare¹⁵⁻¹⁷. Nevertheless, SUDEP had been identified as being the cause of mortality in 12% of the children followed over a five-year period, suggesting that that incidence may not be so rare¹⁸.

Factors related to SUDEP in children may be different from those observed in adults. The role of mental retardation, of medically refractory epilepsy, of AED polytherapy, of subtherapeutic AED levels, of young age and of high seizure frequency, and the description of a seizure just before SUDEP still need to be clarified¹⁶.

In this study, almost all patients died at home (63% died during their sleep) and post-mortem examinations were not performed. Therefore, definitive SUDEP could not be established. SUDEP is found to be more prevalent worldwide than assumed and some authors suggested that verbal autopsy may be the only means of establishing a possible or probable cause of death¹⁹. No correlation between the demographic data and the death risk was observed, except when developmental delay was considered. Patients that died from SUDEP and were not sleeping died during a seizure witnessed by parents or caregiver. Deaths that were not associated with SUDEP were more frequent in patients with moderate or severe cognitive and neurological impairment. Camfield and Camfield²⁰ realized a long term follow up in a cohort of children with symptomatic generalized epilepsy and found that outcome was nearly always death or a life of dependency, although approximately 30% of the cases had seizure remission. Others authors also found an increased risk of unexpected death in patients with ep-

Table. Demographic data comparing patients with SUDEP and other death causes. Statistical analysis: Student t test (numerical data) and χ^2 (categorical data).

	SUDEP (n=11)	Not SUDEP (n=42)	p value
Epilepsy onset (years)			
Mean (SD)	1.75 (2.2)	1.5 (2.2)	0.81
Age at death (years)			
Mean (SD)	7.3 (4.1)	9.7 (5.9)	0.23
Number of AED			
One or two (%)	5 (45.5)	15 (35.7)	0.73
Three or four (%)	6 (55.5)	27 (64.3)	
Gender			
Male (%)	5 (45.5)	26 (61.9)	0.49
Female (%)	6 (55.5)	16 (38.1)	
EEG			
Focal (%)	6 (55.5)	29 (69.0)	1.0
Generalized (%)	2 (18.2)	10 (23.8)	
Seizure I			
Focal (%)	4 (36.4)	13 (30.9)	0.73
Generalized (%)	7 (63.6)	29 (69.1)	
Seizure frequency			
Rare (%)	2 (18.2)	4 (9.5)	0.59
More than once/month (%)	9 (81.8)	38 (90.5)	
Mental retardation			
Normal + mild (%)	6 (55.5)	7 (16.7)	0.02
Moderate + severe (%)	5 (45.5)	35 (83.3)	

SUDEP: sudden unexpected death in epilepsy.

ilepsy, most of the patients with intractable epilepsy²¹. This seems to contribute to our findings that patients with symptomatic epilepsy are more susceptible for clinical comorbidities, and hence death. Confirming this finding our group demonstrated that patients with refractory epilepsy that became seizure free after epilepsy surgery had a lower SUDEP rate²². Other authors demonstrated a higher risk of SUDEP in patients with extra-temporal epilepsy²³.

Although a higher mortality in boys had been reported^{4,6}, we could not confirm that finding. We also did not find a relation between the number of AED and the risk of SUDEP. Some authors have suggested that polytherapy may have been associated with a more severe form of epilepsy, not representing a potential risk alone²⁴.

In conclusion, our study has demonstrated that SUDEP may be a significant condition associated with mortality in children and adolescents with epilepsy and, therefore, this risk should be informed to parents. Measures to minimize SUDEP risks should include seizure control, reduction of stress, participation on physical ex-

ercises and night supervision²⁵. In this way, correct medication intake to the achievement of an optimal seizure control should be encouraged, and other causes of mortality should be prevented, especially in severely mentally retarded patients. A long-term follow-up of patients with chronic epilepsy and prospective studies in large populations should be the best way to finally identify the major risk factors involved in children and adolescents' SUDEP.

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