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SUDDEN UNEXPECTED, UNEXPLAINED DEATH IN EPILEPSY AUTOPSIED PATIENTS

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ABSTRACT – Sudden unexpected, unexplained death in epilepsy (SUDEP) has been reported to be responsible for 2 to 17% of all deaths in patients with epilepsy. This study was conducted to determine the circumstances of SUDEP and the autopsy findings in these patients. Fifty-three individuals whose cause of death was related to epilepsy were identified and in 30 cases relatives or friends were interviewed about the circumstances of death and other information which allowed to classify the patients as SUDEP or not. The death certificates were also reviewed. We found 20 cases of SUDEP. Most of them were found dead lying on the bed with no evidence of seizure event, and most of them had pulmonary and/or cerebral edema as the cause of death. The incidence and the risk of SUDEP can only be fully ascertained if all sudden deaths had postmortem examination. Consensus in certifying SUDEP cases would allow better accuracy in national mortality rate.

KEY WORDS: sudden death, epilepsy, circumstances of death, pulmonary edema.

Morte súbita, inexplicada e inesperada em epilepsia: pacientes autopsiados

RESUMO – Morte súbita inexplicada e inesperada em epilepsia (SUDEP) é responsável por 2 a 17% das mortes em pacientes epilépticos. Este estudo visa determinar as circunstâncias de SUDEP e os achados de autópsia destes pacientes. Foram identificados 53 pacientes cuja causa de morte foi associada a crise epiléptica; em 30 destes, parentes ou amigos foram entrevistados quanto às circunstâncias das mortes e outros aspectos. Também foram revisados os certificados de óbito destes pacientes. Foram encontrados 20 casos de SUDEP. A maioria foi encontrada morta na sua cama por parentes, sem evidência de crise convulsiva, e a causa de morte foi edema cerebral e\ou pulmonar. A incidência e o risco relativo de SUDEP só podem ser adequadamente definidos se houver autópsia em todas as pessoas que morrem subitamente. Um consenso sobre SUDEP permitiria maior acurácia aos dados de mortalidade nacional.

PALAVRAS-CHAVE: morte súbita, epilepsia, circunstâncias de morte, edema pulmonar.

It has generally been assumed that patients with epilepsy have an increased mortality risk of approximately 2 to 3 times that of the general population[1,2]. In addition to the problems of their disease, patients with epilepsy carry the risk of sudden and unexpected death [3].

Spratling, in 1902, found that 4% of the deaths in a large epileptic colony were the direct result of a seizure without any other explanation, even after autopsy [4]. Sudden, unexpected, unexplained death in epilepsy (SUDEP) is now widely recognized, yet there is no agreement on classification of a terminal event, which is casually unwitnessed and incompletely documented [5]. SUDEP was defined as sudden occurrence of death in a person with epilepsy in the absence of a reasonable anatomic or toxicological explanation for death. Other causes of sudden death, such as cardiac ischemia, pulmonary embolus, cerebral hemorrhage, need to be excluded before a case is determined to be SUDEP, which usually requires a postmortem examination [6]. SUDEP has been reported to be responsible for 2 to 17 % of all deaths in patients with epilepsy [6]. Because of a poor understanding and therefore reporting of SUDEP, it is possible that in the absence of any clear cause, death may have been (falsely) ascribed to either status epilepticus, asphyxia or cardiorespiratory arrest [2].

The present study was conducted to determine the circumstances of sudden death in epilepsy and

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the autopsy findings in patients who underwent autopsy and were included in SUDEP cases.

METHODS

The study included all death certificates registered from January 1, 1990 to July 31, 1999. Postmortem examinations on all cases were done at the Medicolegal Institute of Curitiba – Brazil, where forensic pathologist examined the body, and usually performed a complete autopsy. Patients whose cause of death was epilepsy were identified and their bereaved relatives or friends were interviewed to document circumstances of death and other information. The interviews were about 30-minute long and included information about age, gender, race, occupation, school level, type of seizure disorder, family history of epilepsy, alcohol or drug addiction and circumstances of death. Information allowed to classify the individuals in definite SUDEP, probable SUDEP, possible SUDEP or others. Classification of epilepsy was based on the recommendations of the International League Against Epilepsy Commission (1989) [7].

Definite SUDEP is defined when all of the following criteria are met : 1) history of epilepsy; 2) death or cardiorespiratory compromise was sudden, and not due to status epilepticus; 3) death was unexpected (no life-threatening condition); and 4) death remains unexplained, after review of all evidence, including autopsy. Probable SUDEP is defined by 1, 2 and 3 as above, but data are insufficient because of lack of autopsy, but no alternative explanation for death exists. Possible SUDEP is defined by 1, 2 and 3 as above, but an alternative explanation of death is present. Usually only definite and probable cases are used to study SUDEP cases[6]. The other categories include fatal status epilepticus, neurocysticercosis, patients who were drunk in the occasion of the death or who were under life-threatening conditions.

RESULTS

There were 15001 death certificates registered at Medicolegal Institute of Curitiba from January 1, 1990 to July 31, 1999. Over this period, 53 (0.35%) individuals had epilepsy as their main disease, according to the death certificates, and had no other diseases that might have caused their death.

Contact with friends or relatives was tried, but was successful in only 30 cases. In the other 23 cases, direct contact with a friend or a relative was impossible because the address was changed or wrong. Thirty persons were personally interviewed from October 1999 to January 2000 and included: parents (9), spouse or partner (4), uncle or aunt (6), brother or sister (5), friend (4), son (1), and the patient's doctor (1). The interval between interview and death ranged from 8 months to 10 years.

Among the 30 cases, 20 were classified as definite SUDEP. Ten of them could not be categorized as SUDEP because they did not met the SUDEP criteria.

Deaths not categorized as SUDEP (10 cases)

Death due to alcohol intoxication appeared to be likely in 5 patients although the blood level of alcohol could not be measured at the Medicolegal Institute.

One patient was under life-threatening conditions.

One patient died because of aspiration of gastric contents. Cause of death was certified as asphyxia, (due to) food inhalation (due to) epilepsy.

In one case, the key person interviewed was not sure if the patient had a history of epilepsy and was not able to give any further information.

One patient died after status epilepticus (seizure lasted longer than 30 minutes).

There was one case of anatomic explanation for death (neurocysticercosis).

Cases of SUDEP (20)

Age, race, and gender - The patients ranged in age from 17 to 47 years, with the average age on death being 30 years. There were 14 males and 6 females. Three patients were black and 17 were white. The two peak decades of SUDEP were 21 to 30 years and 31 to 40 years old (Table 1).

Type of seizure disorder - The exact type of seizure disorder could be specified in all cases, and all the

Table 1. Unexpected, unexplained death in epileptic patients: age, race and gender.

Age (years)	0-10	11-20	21-30	31-40	41-50
White male	-	1	6	3	3
White female	-	-	1	2	1
Black male	-	-	-	-	1
Black female	-	-	1	1	-
Total	-	1	8	6	5

Table 2. Frequency of generalized seizure in 20 cases of SUDEP.

Frequency of generalized seizure	Number of cases
≥ 1 \ day	4
≥ 1 \ week	6
≥ 1 \ month	4
≥ 1 \ 3 months	3
≥ 1 \ year	1
Unknown	2

patients who had SUDEP (20) had generalized tonic-clonic (GTC) seizures. The type of seizure was classified based on information from the interview with friends or relatives, as well as the seizure frequency (Table 2).

Therapy - Four patients were not taking antipileptic drugs in the year before death. In 3 cases, information available at the time of the interview was inconclusive in regard to their recent anticonvulsant therapy. The other patients (13) were taking antiepileptic drugs. Nine of them were on monotherapy : phenobarbital (7), carbamazepine (1) or diphenylhydantoin. Four patients were on polytherapy: phenobarbital and carbamazepine (3) and phenobarbital and diphenylhydantoin (1).

Circumstances of death - Thirteen epileptic patients were found dead in bed, by family or friends. All of them had retired seemingly well and were found dead the following morning (11 cases), afternoon (1) or at the same night (1). The exact position of the body and of the bedclothes were noted in very few cases. The most frequent circumstance that

Table 3. Circumstances of death among patients whose relatives or friends were interviewed.

Patient	SUDEP	Witnessed death	Circumstances of death
1	Yes	Yes	Died after a seizure while sleeping at night in bed
2	Yes	No	Found dead in bed in morning, incontinent of urine
3	Yes	No	Found dead in bed in morning, incontinent of urine
4	Yes	Yes	Died after a seizure at night, in bed
5	Yes	No	Found dead in bed in morning, incontinent of urine
6	Yes	Yes	Died after seizure, in morning, in bed, while sleeping
7	Yes	Yes	Died after several seizures, in bed, at night, incontinent of urine
8	Yes	No	Found dead in bed in morning
9	Yes	No	Found dead in bed in morning
10	Yes	No	Found dead in bed in morning
11	Yes	No	Found dead in bed in morning
12	Yes	No	Found dead in bed in the afternoon, incontinent of urine
13	Yes	No	Found dead in bed, in morning, cyanotic, opened eyes
14	Yes	No	Found dead in bathroom floor in morning (kneeled)
15	Yes	Yes	Died after seizure at work, in morning
16	Yes	No	Found dead in bed in morning
17	Yes	No	Found dead in bed in morning
18	Yes	No	Found dead in couch at night, incontinent of urine
19	Yes	No	Found dead in bed at night, incontinent of urine
20	Yes	No	Found dead in street in morning
21	No	No	Found dead in bed in morning
22	No	No	Died after seizures (status epilepticus), sleeping in bed at night
23	No	No	Found dead in bed in morning, beside empty alcohol bottle
24	No	No	Died after alcohol abuse, in a hospital, at night
25	No	No	Found dead in the street after alcohol abuse at night
26	No	No	Found dead in kitchen, kneeled in chair, after meal, in morning
27	No	Yes	Died on couch, after alcohol abuse, in the afternoon
28	No	No	Found dead in bed in morning, incontinent of urine
28	No	Yes	Died in a hospital, in the afternoon, incontinent of urine
30	No	Yes	Died after seizure in the afternoon, cyanotic, incontinent of urine

occurred before death (5 cases) was one or more generalized seizures witnessed by members of family or friends. Two patients were found dead in various rooms of the house. One of them was found in bathroom floor and the other one was lying on the couch. Table 3 describes the circumstances of each death, and whether it was witnessed or not, including the non-SUDEP cases.

Autopsy findings - In all cases of SUDEP in this study there were no significant findings in the general autopsy. The cause of death was attributed to cerebral edema (7 cases), pulmonary edema (8), pulmonary hemorrhage (1) or cerebral and pulmonary edema (4). Although most certainly related to the convulsive disorder, these lesions do not adequately explain death in these patients.

History of epilepsy in the family - History of epilepsy in the family was found in 12 cases. Seven patients had not epilepsy in their families, and one person interviewed was not able to give this information.

Psycho-motor development - Two of the 20 patients were mentally retarded, but were not receiving any specific treatment for their mental disorder. The other 18 patients were considered of normal intelligence.

Alcohol abuse - Nine of the 20 SUDEP cases had a history of alcohol abuse for at least 2 years, although none of them were reported as drinking excessively before death.

DISCUSSION

We realize that SUDEP patients in our retrospective study would not have been identified unless epilepsy was entered on their death certificate. As a consequence, our data can not be used for assessment of the true incidence of SUDEP in our population, but represent a minimum rate.

Mortality statistics related to epilepsy indicate that affected persons have a higher death rate than unaffected age-matched controls in the general population and that when the causes of death in an epileptic population have been analyzed, there always exists a group in which no anatomic cause of death can be established after an autopsy [8]. These are usually SUDEP cases. The diagnosis of SUDEP is generally a diagnosis of exclusion, the explanation given when there is no clear cause of death [9].

During the period in which most of our cases were collected, 15001 autopsies were performed at Medicolegal Institute of Curitiba; of these, 0.13% (20 cases) were SUDEP. Leestma et al. report the incidence of SUDEP in such a population to be 1.2 to 1.8% [8].

The average age at the time of death in our SUDEP series was 30 years. Terrence et al, in a comparable study, reported a figure of 32 years [4]. Leestma et al. reported a mean age of death of 28 years [10]. The two peak decades of SUDEP in our study were the third and fourth decades, while in Terrence's study the second and fifth decades were the highest [4].

In our study, blacks comprise almost 15% of the deaths, and white patients were 75% which corresponde to the race distribution of the studied population. In Nashef's study all 14 cases classified as SUDEP were white [11]. In Terrence's study, blacks make up approximately 25% of the deaths [4].

In our study, gender distribution on SUDEP cases was: 14 males (70%) and 6 females (30%). Nilsson et al. also reported a male predominance of 59.6% (34 males) [12]. Harvey et al. noted that among children with epilepsy there were 6 boys (54%) in 11 SUDEP cases[13].

When the characteristics of a seizure were described, all appeared to be GTC. Ficker et al. reported that among 9 SUDEP patients, 8 had GTC seizures[14].

The most common frequency of seizure in this 20 SUDEP cases was one or more than one seizure a week - 6 patients (30%), while in Nashef's study, 9 patients (35%) of 26 had one or more 1 seizure a month[5].

With regard to the drugs prescribed, 9 (45%) of our SUDEP cases were on monotherapy (7 were taking phenobarbital, 1 carbamazepine and 1 diphenylhydantoin). Four of them had been taking a combination of two anticonvulsant drugs (phenobarbital and carbamazepine or diphenylhydantoin). Seven patients were not being treated or this information was not available. In Terrence's study, 3 of 8 SUDEP cases were prescribed phenytoin and phenobarbital, and the other 5 patients were taking a combination of 3 or 4 drugs. None of them was on monotherapy [15].

SUDEP has been associated with subtherapeutic anticonvulsant levels, which may be due to inadequate dosage, non-compliance, or abnormal pharmacocinetics[16]. The prevalence of low levels among asymptomatic epileptics in the community is unk-

nown[16]. Unfortunately, the blood levels of anticonvulsant drugs were not avaible at Medicolegal Institut of Curitiba.

Two of our 20 SUDEP patients were mentally retarded, and 18 were considered of normal intelligence. Nashif et al. related that at least 22 of 26 SUDEP patients were considered of normal intelligence, and one had a history of self-harm[5]. Hirsh and Martin noted that among 19 young epileptics who had unexpected death, 6 had mild to moderate mental retardation, but none was sufficiently impaired to require institutionalization [17].

Nine (45%) of the 20 patients had a history of excessive use of alcohol. Ficker et al. reported alcohol abuse in 3 patients (42.8%) out of 7 SUDEP cases [14]. Both alcohol excess and medication withdrawal can precipitate seizures, but may also predispose to autonomic instability thus increasing the risk of ictal death[5].

We found that 15 (75%) SUDEP occurred at home during normal activities, and 13 (65%) of the cases were found dead in bed. This finding is consistent with previous observations that only a small proportions (25%) of the deaths were witnessed [12]. In Ficker's study, 8 (88.8%) of the 9 SUDEP patients were found death at home and only 2 (22.2%) had a seizure witnessed before being found dead [14]. Nashef et al. reported that among 14 young SUDEP patients, 11 (78.5%) were found dead at home [11]. In another Nashef's study, 6 (54.5%) of 11 cases of SUDEP were unwitnessed[18]. Klenerman et al. noted that the most common scenario of SUDEP was also a patient found dead in bed with no evidence of a seizure having occurred[19].

Although several suggestions have been made, pathophysiological mechanisms underlying SUDEP remain unclear[20]. In this study, at autopsy, pathological findings were limited to lungs and brain, with no abnormalities elsewhere to explain death. Seven (35%) cases had cerebral edema as the cause of death. In 4 (20%) cases, the cause of death was both cerebral and pulmonary edema. In 9 (45%) cases, the cause of death was pulmonary edema in 8 and hemorrhage in 1. Terrence et al. related that among 8 SUDEP patients, 2 had cerebral edema as a postmortem finding and all of them had lung weights that uniformly exceeded the expected value, with gross evidence of pulmonary hemorrhage and edema[15].

One may reasonably argue that the pulmonary edema found in our cases might not have been sufficient to constitute the cause of death. However, the pulmonary edema indicates that the lethal event in the unexpected death of epileptics is not instantaneous but rather takes time to develop [15].

Robin has proposed the following sequential events in the pathophysiology of neurogenic pulmonary edema: 1) hypothalamic injury, 2) massive centrally mediated alpha-adrenergic discharge, 3) generalized vasoconstriction, 4) high systemic and pulmonary vascular pressure, 5) redistribution of blood volume, 6) injury to pulmonary capillary endothelium, and 7) pulmonary edema [21].

Increased awareness of the circumstances preceding SUDEP may help to prevent them by increasing their expectedness in the minds and action of potential victims, families, clinicians, and others who interact with these individuals[16]. However, the extent and nature of the risk of premature death in epileptics has been insufficiently reported[22]. Previous studies have suggested that low age, being male, remote symptomatic epilepsy, intractability (poor response to treatment), alcoholism, treatment noncompliance, and recent head trauma are associated with increased risk of SUDEP[12]. However, the value of these observations is limited because, in general, the studies lack relevant control groups, comprise few cases and are often based on selected populations of patients[12].

Most SUDEP cases, as in this study, are unwitnessed, and many are believed to be seizure related. This may simply reflect time spent alone, but an alternative explanation, at present only speculative, is that a witnessed seizure is less likely to be fatal [11]. Jivanainem and Lehtinen proposed that epileptic patient should not sleep alone; this would increase the likelihood that assistance would be summoned when a patient has a convulsive seizure[23].

Patients with intractable epilepsy contemplating treatment options, whether medical or surgical, should be allowed to consider the small but definite risk of SUDEP in making their decision [18]. In Nashef's study, many relatives who had been told or led to believe that epilepsy could not be fatal, stated in retrospect that they would have preferred to know of the possibility of premature death, however remote [5]. Furthermore, patients and their relatives may welcome the opportunity to express intuitive anxieties regarding possible consequences of generalized seizures, and in so doing, keep the risks involved in perspective[18]. On the other side, epileptic patients should be encouraged to live their lives as

normally as possible, and try not to be overprotected[24].

Theoretically, the incidence and the relative risk of SUDEP can only be fully ascertained if all sudden deaths in epilepsy patients, especially children had postmortem examinations. This expectation is unlikely ever to be met, even in a prospective cohort study of epileptic patients [25]. In addition, consensus in certifying SUDEP cases would allow better accuracy in national mortality data based on death certification [11]. It may be important to emphasize to doctors that SUDEP should become a recognized and therefore accepted, cause of death[26].

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