

Incidence of SUDEP in a cohort of patients with refractory epilepsy

The role of surgery and lesion localization

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ABSTRACT

Objective: The aim of this study was to verify incidence and characteristics of sudden unexpected death in patients (SUDEP) with refractory epilepsy and its relation to previous surgery and lesion localization. **Method:** A cross sectional study was carried out in a cohort of 550 patients with refractory epilepsy followed up by the Epilepsy Surgery Program of the University Hospital of PUCRS, Porto Alegre, Brazil, between January, 1992 and July, 2002. Patients were allocated in two groups (operated and non operated). Seizure type, distribution of interictal spikes and MRI findings were correlated with the SUDEP outcome.

Results: The estimated incidence of probable SUDEP amounted to 29:1000 individuals. Probable SUDEP occurred in 1.2% of the 166 patients of the non operated group and in 3.7% of the 384 patients who were operated (OR=3.02, 95% CI 0.69-13.16) ($p=0.11$). Comparing patients who died to patients alive in the operated group a significant difference was observed concerning the following variables: SUDEP patients had a predominance of generalized seizures ($p=0.002$), extratemporal lesion on MRI ($p<0.001$) and epileptiform activity over extratemporal regions ($p=0.001$). **Conclusion:** In surgically treated patients with refractory epilepsy, an extratemporal location of the lesion and of the epileptiform discharges significantly correlated to SUDEP. Thus it is possible that in those patients; the underlying disease may play a role in the pathogenesis of SUDEP.

Key words: SUDEP, refractory epilepsy, epilepsy surgery, extratemporal epilepsy.

Incidência de SUDEP numa coorte de pacientes com epilepsia refratária: papel da cirurgia e da localização da lesão

RESUMO

Objetivo: O objetivo deste estudo é avaliar a incidência e características de morte súbita em pacientes com epilepsia refratária (SUDEP) e sua relação com cirurgia prévia e localização da lesão. **Método:** Estudo de Coorte realizado com 550 pacientes com epilepsia refratária seguidos no Programa de Epilepsia do Hospital Universitário da PUCRS, Porto Alegre, Brasil, entre Janeiro, 1992 e Julho, 2002. Os pacientes foram distribuídos em dois grupos (operados e não operados). Tipo de epilepsia, distribuição das descargas interictais e achados em RNM foram correlacionados com SUDEP. **Resultados:** A incidência estimada de SUDEP foi 29:1000 indivíduos. A incidência de provável SUDEP nos 166 pacientes do grupo de não operados foi 1,2% e nos 384 pacientes no grupo operado 3,7% (OR=3,02, 95% IC 0,69-13,16) ($p=0,11$). Comparando os pacientes que morreram com os sobreviventes do grupo operado houve diferença significativa nas seguintes variáveis: pacientes com SUDEP apresentam uma predominância de crises epiléticas generalizadas ($p=0,002$), lesões extratemporais na RNM ($p<0,001$) e atividade epileptiforme na região extratemporal ($p=0,001$). **Conclusão:** A localização da lesão e as descargas extratemporais em pacientes tratados cirurgicamente com epilepsia refratária correlacionaram-se significativamente com SUDEP. Então, é possível que nestes pacientes uma doença subjacente possa estar envolvida na patogênese da SUDEP. **Palavras-chave:** SUDEP, epilepsia refratária, cirurgia da epilepsia, epilepsia extratemporal.

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Sudden unexpected death in refractory epilepsy was defined as sudden death, with or without signs of a seizure, excluding evidence of status epilepticus, in which postmortem examination did not disclose the cause of death (SUDEP)¹. It is more common in patients with epilepsy when confronted with the general population²; accounting for an incidence of 1/1.000 cases³⁻⁵. The highest SUDEP rates, 9/1.000 person-years, have been reported in candidates for epilepsy surgery and in patients in whom surgery failed to control seizures (15 per 1.000 cases)^{6,7}.

Among the well known risk factors for SUDEP such as male sex, age between 20 and 40 years, generalized seizures, poor seizure control and poor compliance with medication, most of previous studies have not focused on lesion localization⁸⁻¹⁰. A particular risk for SUDEP was suggested in studies with groups from autopsy series that presented focal central nervous system lesions¹¹⁻¹⁴, however these findings were not supported in case-control studies^{15,16}. By now, available data do not yet allow firm conclusions to be made about the effect of epilepsy surgery on the risk of SUDEP¹⁷. SUDEP was also not associated with any particular type of epilepsy, such as localization-related symptomatic or cryptogenic epilepsy¹⁸.

The present study was conducted to examine the incidence and characteristics of SUDEP in patients with refractory epilepsy and its possible relation to surgical treatment and lesion localization.

METHOD

A cross sectional study was carried out in a cohort of 550 patients with refractory epilepsy followed up by the Epilepsy Surgery Program of the Neurology and Neurosurgery Services of São Lucas Hospital, which is the University Hospital of Pontificia Universidade Católica do Rio Grande do Sul (PUCRS), between January, 1992 and July, 2002. Patients were allocated to one of two groups: Group 1 included 166 patients with refractory partial epilepsy, candidates for epilepsy surgery, waiting for hospital admission and presurgical evaluation, whereas group 2 included 384 surgically treated patients. The incidence of sudden death, as well as the mortality rate, was assessed in these patients.

The diagnosis of epilepsy and its type were based on history, physical examination, surface EEG and neuroimaging particularly magnetic resonance imaging (MRI).

Seizures were classified as generalized or focal. Following presurgical evaluation, epilepsy was classified as symptomatic, when one or more etiologies were identified by MRI, or cryptogenic, which were presumed to be symptomatic, but with normal MRI and unknown etiology^{19,20}.

Definite SUDEP was defined as sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in patients with epilepsy, with or without evi-

dence of a seizure and excluding documented status epilepticus. By definition, necropsy examination did not reveal any toxicological or anatomical cause of death. In the lack of autopsy, but still with no alternative explanation for death, SUDEP was considered probable¹.

The current health status of the patients was assessed by one of the researchers by telephone conversation using a questionnaire. Patients or relatives (in case of death or when patients were unable to be interviewed) were questioned about seizure status and, in those who died, about the circumstances of death (in bed, alone, during a seizure, type of associated seizure, and whether the event was witnessed or not). Seizure outcome was classified according to the modified seizure classification of Engel²¹.

Variables were assessed using the SPSS version 10.0. The test exact Fischer was used to evaluate statistical differences between the groups. The Mann-Whitney test was used to evaluate numeric variables (age, age at onset of the seizures, duration of epilepsy). The odds ratio for death was determined in both groups. A p value less than 0.05 was established as statistically significant. The study protocol was approved by the Institutional Ethics Committee.

RESULTS

After contacting all patients or relatives, 16 patients were reported to be dead. Definitive cases of SUDEP were not confirmed because no patient underwent autopsy. Previous epilepsy surgery did not correlate with the occurrence of SUDEP. Fourteen (3.7%) of the 384 patients who had surgery died, compared to 2 (1.2%) of the 166 who were not operated (OR=3.02, 95% CI 0.69-13.16) (p=0.11) (Table 1). The estimated incidence of SUDEP among the patients followed up by the Epilepsy Surgery Program (surgical candidates and surgically treated patients) amounted to 29 cases per 1.000 individuals. Its incidence among surgical candidates and surgically treated patients was, respectively, 12 cases per 1.000 and 36 cases per 1.000 inhabitants

Clinical characteristics of the operated group were described in Table 2. Among 384 operated patients, 221 (57.6%) were operated for temporal epilepsy and 163 (42.4%) for extratemporal epilepsy. Comparing patients

Table 1. Sudden unexpected death in refractory epilepsy (SUDEP) in patients submitted to epilepsy surgery and patients that were on the waiting list for epilepsy surgery.

Group	SUDEP		Total
	Yes	No	
Operated	14	370	384
Non operated	2	164	166
Total	16	534	550

Odds ratio (OR): 3.02, IC 95% OR=(0.69;13.16)(p=0.11).

Table 2. Clinical characteristics and outcome of the 384 operated patients.

Variables/outcome	Alive (n=370)	SUDEP (n= 14)	p
Age (years)	25.6±13.2	14.0±18.6	0.34 ^a
Age at onset of the seizures	4.5±8.5	0±7.9	0.15 ^a
Duration of epilepsy (years)	17±11.8	8.5±18.4	0.76 ^a
Male sex	213 (57.5%)	8 (57.1%)	0.95
Type of seizure			
Generalized	31 (8.4%)	2 (14.3%)	0.002
Partial	339 (91.6%)	12 (85.7%)	
Type of epilepsy			
Cryptogenic	58 (15.7%)	3 (21.4%)	0.47
Symptomatic	312 (84.3%)	11 (78.6%)	
Video-electroencephalogram			
E A T R	218 (58.9%)	3 (21.4%)	0.01
E A E R	152 (51.1%)	11 (78.6%)	
Magnetic resonance imaging			
Normal	56 (15.1%)	3 (21.4%)	<0.001
Hippocampal sclerosis	198 (53.5%)	1 (7.1%)	
Extratemporal lesion	116 (31.4%)	10 (71.4%)	
Engel classification for surgery outcome			
Class I	339 (91.6%)	12 (85.7%)	0.34
Class II	0	0	
Class III	0	0	
Class IV	31 (8.3%)	2 (14.2%)	
Type of surgery			
Focal cortical resection	370	14	

SUDEP: sudden unexpected death in refractory epilepsy; ^aMedian±SD; EATR: epileptiform activity in the temporal region; EAER: epileptiform activity in the extratemporal region.

Table 3. Presence of risk factors for SUDEP in the 16 patients with probable SUDEP.

Risk factors/Groups	Operated n=14	Non operated n=2	p
Male sex	7 (50%)	1 (50%)	0.999
Age 20-40	11 (78%)	2 (100%)	0.999
Generalized seizure	11 (78%)	2 (100%)	0.999
Poor seizure control	14 (100%)	2 (100%)	0.999

SUDEP: sudden unexpected death in refractory epilepsy.

with probable SUDEP to patients alive in the operated group, a significant difference was observed concerning the occurrence of generalized seizures (p=0.002), of an extratemporal lesion on MRI (p<0.001) and of epileptiform activity over extratemporal regions (p=0.001).

The presence of risk factors for SUDEP was similar in patients with probable SUDEP coming from the operated and non operated groups (Table 3).

There were no deaths secondary to the surgical pro-

cedure. The frequency of epileptic seizures diminished in all patients in the postoperative period, except for one whose seizures recurred in the first postoperative week. This was the only patient who died during the first postoperative month; the other deaths occurred between 6 to 84 months after surgery. Mean time of death after surgery was 35±27months.

Among the non-operated patients, two died while waiting for surgery. One died at home and on her bed after a brief generalized seizure; she had no previous history of heart disease. The other patient was awaiting surgery for temporal lobe epilepsy and died sleeping in bed at night after a generalized seizure.

DISCUSSION

Within our large cohort of patients with medically-refractory partial epilepsies, the main findings were that the incidence of SUDEP was similar between operated and non operated patients, waiting to be admitted for presurgical evaluation. In addition, we found that in the operat-

ed group, the presence of secondary generalized seizures, an extratemporal irritative zone and a structural lesion in extratemporal regions correlated with SUDEP.

Large, non-selected cohorts of patients with medically refractory seizures such as the one studied here tend to present similar profiles in terms of age, seizure duration, seizure frequency and type. In our Center, once patients are identified as potential surgical candidates they enter a presurgical waiting list and are admitted sequentially for evaluation and surgery. There is no bias of referral for presurgical evaluation, particularly because MRI is performed only during inpatient evaluation. Thus, even though we do not report in detail the clinical profile of patients in the waiting list, they certainly share similar features as the ones who had had surgery at the time. These features, thus, are unlikely to have biased the results.

Although improvements in surgical outcome of patients with extratemporal epilepsy have been reported in recent years - mostly due to refinements in patient selection, seizure recurrence following this procedure is still high in comparison to patients operated for temporal epilepsy^{22,23}. Pragmatically speaking, thus, we did not find differences in the occurrence of SUDEP in connection with post-surgical seizure status, neither in patients with temporal lobe nor in those with extratemporal lobe epilepsy. Rather, we found that having an extratemporal focus or lesion was the main correlate of SUDEP. Our data do not allow a conclusion as to whether a greater occurrence of secondary generalized seizures in the epilepsy history might have mediated the correlation between SUDEP and extratemporal epilepsy. This may be so, particularly because the occurrence of generalized seizures, *per se*, correlated with SUDEP in the operated patients. Because SUDEP is less frequent with temporal lobe epilepsy²³, the message to be retained from our findings is that when following patients operated for extratemporal epilepsy, the risk of SUDEP should be closely considered in those who preoperatively had or post-operatively remain with secondary generalized seizures. An important corollary of this finding is that surgical procedures aiming at alleviating the seizure burden, that is, to control the secondary generalized seizures, may well be valid, even when partial seizures remain refractory to medication. This is not an uncommon scenario, the benefits of which, however, are largely neglected.

An interesting issue raised by our findings concerns the potential reasons why there was no correlation between the occurrence of SUDEP and seizure free status after surgery. One potential explanation relates to the possibility that the secondary generalized seizures, and not all types of seizures, may be relevant for the post-operative risk of SUDEP. Should this be the case, then, whether a patient is or is not seizure free after operation is only

relevant if the remaining refractory seizures include secondary generalized seizures. Our data does not allow a firm conclusion about this, but certainly suggest that this may be the case, reinforcing that the control of secondary generalization is a valid surgical goal, irrespective of the anticipated degree of control of partial attacks.

The exact mechanism of SUDEP remains unknown, but it is very probable that cardiac arrhythmia during and between seizures plays a potential role^{8,18,24,25}. Cardiorespiratory abnormalities are more often reported in patients with temporal lobe epilepsy, where there is evidence of ictal and interictal autonomic dysregulation, predominantly with sympathetic overactivity²⁶. Alterations in heart rate variability have been reported not only in adults but also in children with epilepsy. Patients with epilepsy appear to have a reduction in some heart rate variability measures, suggesting a decreased sympathetic tone, which may be related to the drug therapy or to epilepsy itself²⁷⁻²⁹.

In our patients no history of heart disease was found among those deceased and no association was established with heart disease in any of the surgical candidates. As previously reported, even asymptomatic patients with epilepsy may have mild alterations in the electrocardiogram at rest such as faster ventricular rates³⁰ or increases in the mean QTc interval during ictal period³¹.

People with epilepsy may die suddenly and unexpectedly without a structural pathological cause. Most SUDEP cases are likely to be related to seizures²⁹. The fatal event generally occurred in association with generalized tonic-clonic seizure^{8,18}. Nashef et al. suggested that most cases of SUDEP represented ictal or postictal seizure deaths, occurring in individuals with a history of generalized tonic clonic seizures, and in both primary generalized and localization-related epilepsy³². No significant association between the type of epilepsy and the fatal outcome was observed in the patients assessed. Most of these patients were classified as having symptomatic epilepsy (84.1% of surgically treated patients).

Hennessy et al., in a study of mortality after temporal lobe epilepsy surgery, verified that SUDEP rates were lower than those reported for similar patient populations with chronic epilepsy²³. Sperling et al. suggested that elimination of seizures after surgery reduces mortality rates in individuals with epilepsy to a level indistinguishable from that of the general population, whereas patients with recurrent seizures continue to have high mortality rates³³.

A major weakness of this study is that no definitive case of SUDEP could be confirmed, because no patient underwent necropsy examination. However, the age range of the patients who died and their otherwise healthy conditions makes it unlikely that causes other than potential intoxication with antiepileptic drugs or other substance might have been an external, non-SUDEP, cause of death.

By all accounts, we obtained no evidence that this concurred to the fatal outcome of the patients who died.

Finally, we believe that a major finding here was that secondary generalized seizures in patients operated for refractory extratemporal epilepsies correlated with SUDEP. Thus, all efforts should be undertaken to eliminate this seizure type and the perspective of such control should be viewed as a clearly valid goal of extratemporal epilepsy surgery. Not infrequently, the results of presurgical evaluation in patients with extratemporal epilepsies point to epileptogenic zones which may not be thoroughly localizable or completely resectable. This is the case when, for instance, relevant irritative or ictal onset zones associated with dysplastic, gliotic or other lesion types involve eloquent cortex. Because the prevalent view is that resective surgery should be reserved only for those patients in whom complete seizure freedom is anticipated (or, at least, a major possibility), the possibility that subtotal resections (complemented or not by subpial transections, as an example) might completely control the generalized attacks while incompletely controlling partial attacks has not been explicitly explored. Our findings suggest that this may be a relevant issue which should be formally evaluated in future studies.

In conclusion, our data suggest a similar SUDEP incidence among operated and non operated patients. In the group of surgically treated patients, extratemporal refractory epilepsy and the presence of secondary generalized seizures significantly correlated to SUDEP and perhaps, in those patients, an interaction between the underlying disease and the generalized attacks may play a key role in the pathogenesis of SUDEP.

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