MORTEMUS

MORTality in Epilepsy Monitoring Unit Study

USING IN-HOSPITAL PRE-SURGICAL MONITORING DATA TO ASSESS RISKS, MECHANISMS AND RISK FACTORS OF

SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

An ILAE and LFCE sponsored European study

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Main objectives of the study

- 1) To quantify the risk of death, SUDEP, and "near SUDEP"*, in patients with drug resistant partial epilepsy who have undergone long-term video-EEG monitoring;

- 2) To determine whether the risk of death and SUDEP was significantly increased during in-hospital periods when the patient was not under surveillance (night or week-end) as compared to periods of supervised monitoring;

- 3) To gather up to 20 cases of SUDEP / "near SUDEP"* for whom concomittant video, EEG and EKG data will be available, and will allow to determine whether the event primarily resulted from a cardiac or respiratory dysfunction;

- 4) To provide robust evidences, derived from the above data, regarding the respective role of cardiac versus respiratory dysfunctions in the pathophysiology of SUDEP, and the risk factors for developing such dysfunctions.

- 5) To study risk factors of SUDEP/near-SUDEP in patients with refractory epilepsy undergoing video-EEG monitoring

- 6) To evaluate the feasibility and rationale for launching a large scale European prospective study that aims to confirm the above retrospective data, and specifically to determine whether heart rate variability parameters can predict the risk of SUDEP.

*** "Near SUDEP":** If occurring while under nurse surveillance, a cardio-respiratory arrest is likely to benefit from an effective rescucitation procedure. At the present time, we would define near-SUDEP as a cardio-respiratory arrest, documented by proper clinical data, that recovered after external intervention, and would most likely resulted in a SUDEP without such intervention. Additional criteria might be considered and agreed upon in the future.

1) Rationale

SUDEP is the major cause of death in chronic refractory epilepsy (Tomson et al, 2005) and epilepsy surgery candidates have been identified to be at particularly high risk (Ryvlin et al., 2005). Although case-control studies have been useful in identifying risk factors, e.g. poor seizure control (Nilsson et al., 1999, Walczak et al., 2001, Langan et al., 2005) and lack of supervision (Langan et al., 2005), there is still a considerable debate regarding the pathophysiology of SUDEP (Ryvlin et al. 2003, 2005). More specifically the respective roles of primary seizure related apneoa (obstructive or not) and ictal asystolia are being discussed (Ryvlin et al. 2006). The recent observation that up to 15% of patients with drug resistant partial epilepsy might develop ictal asystolia over a mean follow-up of 18 months, as demonstrated by an implantable Reveal system (Rugg-Gunn et al. 2004), raises considerable concern regarding the need to search for such an abnormality and to propose a pacemaker whenever such an abnormality is observed. Conversely, despite the description of many cases of ictal asystolia, it remains unclear whether or not this might eventually result in SUDEP. Assuming a final cardiac fatal event, the potential role of dysfunction in autonomic cardiac control has also been discussed (Persson et al., 2005). Assessment of heart rate variability (HRV) has thus been suggested as a method with potential to predict the risk of SUDEP (Persson et al., 2005, 2006) based on preliminary data. Investigation of autonomic changes in relation to SUDEP has recently been identified by the European Brain Council as one of the priority topics in clinical research (Olesen et al. 2006).

It is clear that collaborative efforts are required to advance our understanding of mechanisms behind SUDEP and to develop methods to predict risks with prevention as the ultimate goal. We therefore propose a European collaboration with focus on patients undergoing evaluation for epilepsy surgery because (1) this is the population with the highest risk of SUDEP, and (2) these are patients for which a considerable amount of relevant data are being collected routinely. We suggest this as a project in two steps where the first, discussed in some more detail below, is based on a retrospective survey of epilepsy surgery centres in Europe. The objective of the first step is to identify cases of SUDEP or near SUDEP during pre-surgical monitoring in order to (i) assess the risks and (ii) analyse mechanisms, more specifically the role of ictal arrhythmia. This first phase will also serve to explore the possibilities to establish a collaboration between European centres for a prospective study with follow-up of risk of SUDEP among patients that have undergone pre-surgical evaluation and assessment of the predictive value of HRV in this respect.

The purpose of the first retrospective study would be to obtain a sufficient number of patients who have suffered a SUDEP, or near-SUDEP (see definition below), during video-EEG monitoring, where both EKG, EEG, and video data could help determining the primary cause of SUDEP. According to the rate of SUDEP in drug resistant partial epilepsy, that varies between 2 and 9/1000 patients year, it would require between 6000 and 26000 one week long monitorings to observe one SUDEP. Assuming an average incidence of 4/1000 patients year, 13.000 such monitorings would be required to observe a SUDEP. This grossly corresponds to the total number of long term monitoring that we could gather from the 16 main French epilepsy centres involved in pre-surgical evaluation, stressing the need for the very large European survey proposed in MORTEMUS. Furthermore, if occurring while under nurse surveillance, a cardio-respiratory arrest is likely to benefit from an effective rescucitation procedure, and to be then considered as a near-SUDEP. Criteria still need to be aggreed upon

to precisely define a near-SUDEP, that is a clinical event that would most likely have resulted in a SUDEP without external intervention.
To our knowledge, only three patients have yet been reported to suffer a SUDEP while being monitored, either in-hospital during video-EEG monitoring (Bird et al. 1997; Lee 1998), or while undergoing ambulatory EEG (McLean and Wimalaratna 2007). All three patients showed evidence of sudden cessation of EEG activity, without prior indication of cerebral ischemia as typically observed in cardiac arrest. In addition, pulse artefacts could still be recorded during two minutes in one of these patients. In some of these patients, as well as in another case with a recorded near SUDEP event (So et al. 2000), central apnoea was considered the most likely cause of SUDEP.

We believe that at least twenty additional cases (including near SUDEP) would be needed to provide a better view of the pathophysiology of SUDEP.

A secondary objective of this retrospective study will be to evaluate the risk of SUDEP during pre-surgical monitoring, especially at times when the patient might not be under surveillance (night or week-end). These data could help proposing guidelines regarding the optimal organisation of long term monitoring.

2) Feasibility and preliminary results

A retrospective survey has been recently conducted in France to collect all cases of SUDEP or near-SUDEP that has occurred in the 16 main epilepsy centres involved in pre-surgical long term monitoring, during the last 15 years. A total of 11.000 monitorings were collected, grossly corresponding to 200 patient-years of in-hospital duration, including 125 patients-years of monitoring under surveillance (in most French centres, patients were not recorded at night).

Preliminary results show that 3 patients died, including two SUDEP at night in patients not monitored and one fatal cardiac arrest while under monitoring, and 3 others were considered as near-SUDEP due to a long lasting cardio-respiratory arrest that required rescucitation (including two with concommitant EEG/EKG data).

These preliminary figures suggest that the rate of SUDEP/near-SUDEP might be higher than expected in patients undergoing pre-surgical long-term monitoring (2,5% per year as compared to the figure of 0,4% per year usually reported in drug resistant partial epilepsy), especially during periods of non monitoring. This might be partly due to AEDs tapering.

These figures also show that the extension of the study to European countries is likely to provide a sufficient number of cases (up to 20) to allow major advances in our understanding of SUDEP pathophysiology.

We anticipate that about 10 fold more long-term monitoring should be pooled to collect a total of 20 informative cases of SUDEP or near SUDEP, with available video-EEG/EKG data. This would represent a total of approximately 100.000 one week long monitoring, and 2000 patient/years. This requires the majority of western European countries and centres to actively participate in this study.

3) Methodology

MORTEMUS will primarily consist in gathering retrospective data from a number of pre-identified epilepsy centres involved in pre-surgical long term video-EEG monitoring. To obtain reliable epidemiological figures, it will be important to minimise the bias of having centres that recorded SUDEP or near SUDEP more likely to participate to this survey than those where such events did not occur. The following steps will be followed:

- a) Identification of all centres involved in pre-surgical long term video-EEG monitoring within each participating country, taking advise from the corresponding national chapter of the ILAE.

- d) Each centre will then be contacted and offered to participate in this survey. Maximal efforts will be developed at this stage to avoid the above suggested bias.

- e) Centres that agree to participate will be asked to provide the following information:

- 1) Number of deaths (**D**), probable or definite SUDEP (**S**), and near SUDEP (**NS**) that have occured in patients during a long-term video-EEG monitoring across a period of time that will be specified (in centres active for several decades, it might prove beneficial to restrict the retrospective study to the last 15 years, in as much as combined video-EEG and EKG data are unlikely to be available prior to this period);

- 2) Number of patients (**P**) with epilepsy who underwent a long-term video-EEG monitoring during the same period of time;

- 3) Average number of in-hospital days (**HD**) during long-term video-EEG monitoring;

- 4) Average duration of effective monitoring (**MD**) under nurse surveillance, including the number of days (with or without week-ends) and nights, as well as the number of day-time and night-time hours;

- f) Clinical research assistant(s) (CRA) will then collect additional data that will vary from one centre to another, depending on several factors:

- 1) Regarding the number of patients **P,** most centres should be able to provide an updated list of patients. In the event that such a list would not be readily available, CRA will be in charge in extracting this information.

- 2) Regarding the average number of in-hospital days **HD**, and duration of effective monitoring **MD,** many centres perform stereotyped evaluations in the majority of their patients, with only a few having shorter or longer monitoring. For those centres, calculation of HD and MD should be easy and reliable. CRA will check those figures by looking at the detailed data of 20 patients randomly selected. In the few centres where the duration of long term monitoring greatly varies from one patient to another, CRA will extract those figures from 50 randomly selected patients.

- 3) Files and data (including video-EEG and EKG whenever possible) from patient who died or suffered a near-SUDEP will be collected by the CRA at each participating centres. Additional relevant information regarding these events, not necessarily available in

the patient's file, will also be gathered by interviewing staff members in charge of the patient or who witnessed the event.

- g) Analysis of data will include calculation of D, S and NS rate, as well as SMR for the entire in-hospital period, as well as for the sub-periods under nurse surveillance or not. The control population used for calculating SMR will be adjusted on age, gender, and country of origin. Detailed analysis of data from patients who died or underwent a near SUDEP will be examined by the scientific committee, in order to verify whether the event fulfilled or not the criteria for SUDEP of near-SUDEP, and to determine the most likely cause of the event (ie cardiac versus respiratory primary dysfunction).

- h) A case control study of risk factors associated with D, S and NS will then be undertaken in a second step. For each D, S and NS case previously identified, we will identify the five patients who underwent a long-term monitoring in the same centre at or just around the same time without suffering D, S or NS, and will use them as controls for a number of potentially relevant data. This additional study will first verify whether classical risk factors of SUDEP among patients with drug resistant partial epilepsy, also apply to our population, both for D, S and NS. Thanks to the fact that all the patients have undergone a long term video-EEG monitoring, we will also be able to look at specific electro-clinical parameters not yet studied as risk factor for SUDEP. We will also be able to investigate the pronostic role of HRV abnormalities, whenever good quality EKG data will be avalaible.

CRA(s) will be responsible for collecting data of control cases, while data analysis will be supervised by the scientific committee.

- i) Future prospective study. Should the retrospective part of this project be successful in engaging a large number of European centres, and provided that these centres agree, a specific protocol for a prospective study will then be developed and implemented. This would imply the establishment of a common database for patients that undergo pre-surgical monitoring, collection and centralised analysis of ECG data including HRV from the pre-surgical monitoring and an extended follow-up of mortality more specifically SUDEP.

4) Reports, publications, and authorship

Individual centres retain the proprietary rights of their own data and can publish them without prior approval by the Scientific Committee (SC) of this project. The SC is responsible for the analysis of data and for preparing publications and reports. Any publication on the results of the primary survey will be accompanied by a list including the name of one representative of each centre reporting to the survey. Should the centre contribute a case of SUDEP/near-SUDEP the name of the reporting physician will also be included among the authors of publications based on the analysis video-EEG recordings and of the case-control study.

5) Time line

- August 2007:	Grant approval by the European Commission of the ILAE
- October 2007:	Hiring of a CRA
- **November 2007:**	Finalising the protocol documents

- **December 2007:**	Identification of all potential participating centres
- **January 2008:**	Agreement from the centres to participate
- **February-April 2008:**	Collection of data from the centres
- **May-October 2008:**	On site checking and collection of data by the CRA
- **November-December 2008**:	Analysis of data
- **January-May 2009**:	Collection of control cases for the case control study
- **June-July 2009:**	Analysis of data
- **August 2009:**	End of study – Final report

6) Financial Plan

- 1 full time equivalent CRA for two years (mars 2007 – march 2009):	70.000€
- A total of 60 european travels (including airfare and accommodation):	24.000€
- Logistical expenses:	5.000€
- Statistical counseling:	3.000€
- **TOTAL**	**100.000€**

Financial resources

- French League Against Epilepsy *(2005 IEC benefits)**:***	60.000€
- European Branch of the ILAE:	40.000€
- **TOTAL**	**100.000€**

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