Current Literature
In Clinical Science

Sudden Unexpected Death in the Epilepsy Monitoring Unit

Incidence and Mechanisms of Cardiorespiratory Arrests in Epilepsy Monitoring Units (MORTEMUS): A Retrospective Study.

Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, Boon P, Crespel A, Dworetzky BA, Høgenhaven H, Lerche H, Maillard L, Malter MP, Marchal C, Murthy JMK, Nitsche M, Pataraia E, Rabben T, Rheims S, Sadzot B, Schulze-Bonhage A, Seyal M, So EL, Spitz M, Szucs A, Tan M, Tao JX, Tomson T. *Lancet Neurol* 2013;12(10):966–977.

BACKGROUND: Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in people with chronic refractory epilepsy. Very rarely, SUDEP occurs in epilepsy monitoring units, providing highly informative data for its still elusive pathophysiology. The MORTEMUS study expanded these data through comprehensive evaluation of cardiorespiratory arrests encountered in epilepsy monitoring units worldwide. METHODS: Between Jan 1, 2008, and Dec 29, 2009, we did a systematic retrospective survey of epilepsy monitoring units located in Europe, Israel, Australia, and New Zealand, to retrieve data for all cardiorespiratory arrests recorded in these units and estimate their incidence. Epilepsy monitoring units from other regions were invited to report similar cases to further explore the mechanisms. An expert panel reviewed data, including video electroencephalogram (VEEG) and electrocardiogram material at the time of cardiorespiratory arrests whenever available. FINDINGS: 147 (92%) of 160 units responded to the survey. 29 cardiorespiratory arrests, including 16 SUDEP (14 at night), nine near SUDEP, and four deaths from other causes, were reported. Cardiorespiratory data, available for ten cases of SUDEP, showed a consistent and previously unrecognised pattern whereby rapid breathing (18–50 breaths per min) developed after secondary generalised tonic-clonic seizure, followed within 3 min by transient or terminal cardiorespiratory dysfunction. Where transient, this dysfunction later recurred with terminal apnoea occurring within 11 min of the end of the seizure, followed by cardiac arrest. SUDEP incidence in adult epilepsy monitoring units was 5·1 (95% CI 2·6–9·2) per 1000 patient-years, with a risk of 1·2 (0·6–2·1) per 10 000 VEEG monitorings, probably aggravated by suboptimum supervision and possibly by antiepileptic drug withdrawal. INTERPRETATION: SUDEP in epilepsy monitoring units primarily follows an early postictal, centrally mediated, severe alteration of respiratory and cardiac function induced by generalised tonic-clonic seizure, leading to immediate death or a short period of partly restored cardiorespiratory function followed by terminal apnoea then cardiac arrest. Improved supervision is warranted in epilepsy monitoring units, in particular during night time.

Commentary

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death among persons with chronic refractory epilepsy (1). The current accepted definition is a sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death, occurring in benign circumstances in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus (2). SUDEP typically affects patients with drug-resistant epilepsy. The average incidence is 4 deaths per 1,000 patient-years; for patients with uncontrolled childhood-onset epilepsy, there is a 12% cumulative risk over 40 years. Epidemiologic risk factors include generalized tonic-clonic seizures, particularly nocturnal; male sex; age of onset of epilepsy <16 years; duration of epilepsy >15 years; and polytherapy (3,4).

Epilepsy Currents, Vol. 14, No. 2 (March/April) 2014 pp. 78–80

Other than identifying risk factors, there has been limited progress in our understanding of SUDEP. Most cases are thought to be peri-ictal (1). Putative mechanisms fall into 1 of 3 camps: cardiac, pulmonary, or cerebral ("cerebral shutdown") causes. Further study is difficult as SUDEP is relatively rare and inherent within the name itself, cases are unpredictable. Prior information comes from either witnessed reports, typically family members, or published reports (9 in the literature) of cases occurring within epilepsy monitoring units (EMUs). These cases are important as through careful analysis of video-EEG monitoring, a better understanding of pathophysiological mechanisms may be elucidated. Ryvlin and colleagues through the MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) gathered an international cohort of such cases. They performed a systematic retrospective survey of EMUs located in Europe, Israel, Australia, and New Zealand; collected data of all cardiorespiratory arrests; estimated incidence of cardiorespiratory arrests in surveyed EMUs; analyzed patterns; and explored mechanisms to explain SUDEP. Previously published cases were included.

One hundred and sixty EMUs that routinely perform video-EEG studies for >24 hours were invited to participate. One hundred and forty-seven (92%) completed the survey. Units were questioned about the number of video-EEG studies done during the studied period (January 1, 1968, to December 31, 2007), average length of hospital stay, average duration of monitoring, and average duration of monitoring during presurgical video-EEG. Over 130,000 video-EEGs were done, predominantly in adults (70%), and almost half (49%) were for presurgical video-EEG evaluation. Presurgical evaluation had a mean duration of 9 days leading to 1,771 patient-years. In 27 units from 11 countries, there were 29 cardiorespiratory arrests.

Cardiorespiratory arrests were classified into the following categories:

1. SUDEP (definite or probable)—Definite SUDEP is defined by lack of cause of death by postmortem examination, whereas no postmortem examination is available for probable SUDEP.

2. Near SUDEP (fatal or nonfatal)—Patients whosurvived resuscitation for more than 1 hour after cardiorespiratory arrest. If fatal, cardiorespiratory arrest is responsible for irreversible brain damage leading to brain death.

3. Non-SUDEP—Sudden death in a person with epilepsy with a clear cause of death.

Among the 29 cardiorespiratory arrests, 16 were SUDEP (8 definite and 8 probable), 9 were near SUDEP (2 fatal), and 4 died from other causes (2 subarachnoid hemorrhage, 1 myocardial infarction, 1 brain edema complicating subdural grids). Incidence of SUDEP in the EMUs was calculated on the basis of an estimation of total patient-years spent in the studied units. The calculated incidence was 5.1 (95% confidence interval [CI]: 2.6–9.2) per 1,000 patient-years, and a SUDEP risk of 1.2 (95% CI: 0.6–2.1) per 10,000 video-EEG monitoring procedures.

Available video-EEG or EKG recordings were analyzed by three predetermined investigators. Characteristics of the preceding seizure, postictal EEG flattening, and respiratory and heart rate abnormalities were assessed. Postictal generalized EEG suppression was defined as the generalized absence of EEG activity greater than 10 μV in amplitude, allowing for muscle, movement, breathing, and electrode artifacts. Although controversial (5-9), postictal generalized EEG suppression has been identified in other studies as being associated with SUDEP (5,6) . Apnea was defined as a recording segment longer than 10 seconds without respiratory movemnt.

In all evaluated cases, a seizure occurred immediately before events leading up to cardiorespiratory arrest,supporting the hypothesis that SUDEP is a peri-ictal event. Seizure occurrence is however, more likely to occur in an EMU, particularly in patients admitted for a presurgical evaluation who have antiepileptic medication reduction and withdrawal. The recorded seizure was a generalized tonic-clonic seizure in all SUDEP cases, and in 7 of 9 near SUDEP cases. This finding is consistent with the prevailing view that the occurrence of generalized tonic-clonic seizures, particularly nocturnal, increases SUDEP risk. In the study, the vast majority of SUDEP and fatal near SUDEP occurred at night. Among the 16 SUDEP and fatal near SUDEP cases in which body position could be assessed, 14 were prone at the time of cardiorespiratory arrest. The observation of prone position in SUDEP patients has previously been reported (10).

Data were available to assess respiratory and cardiac events prior to cardiorespiratory arrest in ten patients with monitored SUDEP. Four consistent features were seen: 1) immediate postictal phase was characterized by rapid breathing between 18 and 50 breaths per minutes while heart rate varied from 55 to 145 beats per minute; 2) postictal generalized EEG suppression was observed in all SUDEP cases once EEG was no longer obscured by artifacts; 3) an early cardiorespiratory dysfunction developed in all patients during the first 3 minutes postictally (bradycardia culminating in asystole in nine patients, periods of apnea with variable onset between 25 and 180 seconds postictally, and a parallel worsening of cardiac and respiratory dysfunction that peaked between first and third minutes); and 4) terminal apnea always preceded terminal asystole. Overall these findings reveal that the recorded generalized tonic-clonic seizure was followed by a short period of normal or increased heart and respiratory rates, after which a combination of central apnea, severe bradycardia and, most often, transient asystole occurred together with postictal generalized EEG suppression, peaking between 1 and 3 minutes postictally. These findings were terminal in one-third of patients. Among the others, there was a transient restoration of cardiac function associated with abnormal respiration, which then rapidly deteriorated to terminal apnea and finally terminal asystole.

The ability to scrutinize cardiac, respiratory, and EEG data among SUDEP patients renders the results of this study unique and important. These data suggest that the pathophysiology of SUDEP cannot be solely defined into 1 of 3 camps; there exists a complex interaction of cerebral, pulmonary, and cardiovascular sequelae precipitated by generalized tonic clonic seizures leading to a postictal cascade of centrally mediated events. The findings are however, limited and our understanding of the pathophysiology of SUDEP has not significantly improved. Few cases had fully available EEG, respiratory, and cardiac data . The cardiac data when available was limited to a single ECG rhythm channel which does not provide clear information about cardiac dysrhythmias or the morphology of QRS complexes. Defining respiratory movements by visual analysis alone is not precise and tells us nothing about the timing of apneas or degree of hypoxia. Oximetry and partial CO_2 pressure measurements were not available. Future studies should include more extensive monitoring of blood pressure, cerebral perfusion, and oximetry.

The reported occurrence of cardiorespiratory arrests in multiple EMUs highlights the importance of close observation. Rapid withdrawal of antiepileptic medications and inadequate monitoring put patients at risk. Deaths in the study occurred in patients that received inadequate monitoring and delayed resuscitation. The evening hours are a vulnerable time and, unfortunately, it is during these hours when many hospitals have a reduced number of staff.

Further study of SUDEP is important and necessary to better understand who is at risk, to more fully explain pathophysiological mechanisms, and to develop strategies aimed at prevention. An international effort to prospectively identify cases will aid in this effort. EMUs throughout the world should come together to share information as these cases do occur. Unfortunately, particularly in the United States, there is hesitation given legal concerns. Standardized means of assessing neurological, cardiac, and respiratory parameters will enable us to better study deaths that occur in EMUs and importantly, as evidenced by the results of this study, will likely prevent some unnecessary deaths.

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