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Sudden death in epilepsy (SUDEP) recorded in ambulatory EEG

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Abstract:

A woman with epilepsy died during a seizure and the event was recorded on ambulatory EEG. The circumstances were typical of SUDEP. The EEG revealed that the patient had had a generalised seizure that abruptly ended with cessation of all cerebral electrical activity. Two other cases recorded on videotelemetry demonstrating similar EEG features were reported in the literature. We postulate that abrupt irreversible Cerebral Electrical Shutdown (CES) during a seizure may be the primary mechanism of SUDEP.

Introduction:

Sudden death in epilepsy (SUDEP) is defined as a 'sudden unexpected witnessed or unwitnessed, non-traumatic and non-drowning death in a patient with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus where necropsy examination does not reveal a toxicological or an anatomical cause for death'.¹

On the basis of this definition and available epidemiological data, approximately 400 people are expected to die each year in Britain from SUDEP², yet the exact cause of death remains an issue for speculation. Interictal EEGs and cardiac monitoring during seizures are frequently reported but only rarely has the death occurred whilst EEG monitoring is taking place.^{3,4} We report a case of SUDEP whose death occurred whilst undergoing ambulatory EEG recording.

CASE REPORT

A right-handed woman in her fifties presented with poorly-controlled epilepsy. She had no perinatal neurological problems. At the age of 4 she developed her first spontaneous seizures. Details of her previous treatment were sketchy as she had only recently moved to the locality. One sibling and maternal twin had epilepsy. We have not been able to obtain a more detailed history, as we were unsuccessful in contacting her family.

The patient described simple partial and extra temporal seizures with occasional generalisation with tongue biting. The seizures were refractory to treatment for a range of anti-epileptic medications.

On examination, her right upper and lower limbs were slightly smaller compared to the left. Despite the limb asymmetry no neurological abnormality was found.

MRI scan of the brain was reported as showing left hippocampal atrophy on the basis of minor asymmetry. An interictal EEG revealed left anterior temporal theta activity without any paroxysmal epileptiform discharges. She had been on 350mg of Phenytoin daily since her youth. For the preceding 3 years she had also been taking Sodium valproate 1200mg per day. Phenytoin was withdrawn and Lamotrigine was introduced but her seizure control remained poor. She developed a tremor and her Epilim dose was reduced and maintained at the level of 1000mg per day. She lived alone at home.

Because of the uncertainty over the frequency of seizures an ambulatory EEG recording was arranged. She was due to be seen in the EEG department the next morning for review of the tape but did not attend. She had been found dead by a friend who called to drive her to the hospital. She had been found lying prone on the floor in her nightclothes with her arm outstretched towards the telephone.

The post mortem showed no signs of external injury. She had mild pulmonary congestion, lungs weighed 348g and 298g, respectively. There was no evidence of aspiration, pulmonary embolism or myocardial damage. She had minimal coronary atheroma but there was no evidence of an infarction. Stomach contents showed no evidence of medication. Her brain was not swollen and was macroscopically normal. Toxicological studies showed Lamotrigine level of 7.6µg/ml (normal range 12-15 µg/ml), Sodium Valproate was undetectable.

Results of the ambulatory EEG

The ambulatory EEG was set up at 1pm and it continued to record the cerebral activity until the next morning when the patient was found dead. The recording was undertaken using a digital Micromed MS 40 brain spy 12-channel recorder. A good quality recording was obtained throughout and the EEG was not contaminated with artefacts.

The record showed bursts of irregular slow and sharp waves occurring intermittently during the day but with increasing frequency during the night. Prolonged bursts of high amplitude spikes began to appear towards midnight.

The patient fell asleep around midnight and normal sleep stages 1-4 were recognised in the recording but no REM sleep noted. Paroxysmal activity became more frequent and prolonged around 8am, eventually becoming continuous with spike wave discharges developing to a seizure at 8.27.18am. Seizure activity then became polyspike (up to 6 spikes) and continued for 52 seconds. The seizure activity abruptly terminated at 8.28.10am and the EEG became a 'flat line'. (Fig)

Rhythmic movement artefact (possible head jerking) was detected involving the electrode T3, associated with muscle (EMG) activity that became less frequent and disappeared completely at 8.31am leaving a continuous flat EEG.

The exact time of death could not be determined, as respiration and heart rate were not recorded simultaneously. No pulse artefact could be identified, nor retrieved by further offline analysis.

EEG did not show any evidence of slow wave activity that could be attributed to hypotension or cerebral hypoxia.

In summary, the EEG changes consisted of a seizure with continuous spike-wave discharges followed by an abrupt change to a 'flat EEG' that failed to recover.

DISCUSSION

Our patient died in the early hours when alone and was typical of SUDEP in all aspects of definition although a little older than most cases.

It is likely that SUDEP occurs due to more than one mechanism.

Tachycardia^{5,6} is a frequent observation during seizures due to sympathetic over-activity. Bradycardia and Asystole are also reported in association with seizures.⁷⁻⁹

Prolonged QT syndrome can present as seizures¹⁰ and sudden death may occur.¹¹ Prolongation of QT may occur during seizures but this association is not seen in patients who subsequently succumbed to SUDEP.¹²

Centrally mediated respiratory failure has also been proposed as a mechanism for SUDEP.¹³ Pulmonary oedema was found in the majority of SUDEP patients in a population study of 44 cases in Denver.¹⁴ In a sheep model of SUDEP, apnoea was demonstrated associated with pulmonary oedema in animals that died of SUDEP but not those that survived.¹⁵ In a series of 335 SUDEP cases 15 deaths were witnessed. They, too, suggested that the mechanism of death is likely to be central apnoea. However, there was no EEG data available in these cases.

Bird et al described a case report that demonstrated flattening of the EEG, first on the right hemisphere and then bilaterally. Pulse artefacts continued for a further 120 seconds suggesting that the primary cause of death was not cardiac.³ Mary-Ann Lee reported a similar case in 1998.⁴ This case, too, showed sudden electrical silence following a seizure. A case of near SUDEP showed postictal central apnoea followed by cardiac arrest (successfully resuscitated)¹⁷. They suggested centrally mediated apnoea as a cause of SUDEP. However, the exact timing of apnoea to EEG changes that followed the flattening was not stated in the paper.

The patient described in this paper died during a seizure and the ambulatory EEG showed sudden change of electrical activity to a flat line. Sudden cessation of all electrical activity of the brain during a seizure is a unique phenomenon. Abrupt flattening of the EEG does not occur in cerebral ischaemia or hypotension. Electrophysiological sequelae of ischaemia and hypotension is well described in textbooks of electroencephalography: "A sequence of electrical events can clearly be demonstrated in complete cerebral ischaemia due to cardiac arrest, excessive hypotension or mechanical interruption of cerebral blood flow. During the first 3 – 6 seconds after the arrest of circulation no clinical or electrical EEG changes can be observed. When the arrest lasts about 3 – 13 seconds slow waves of increasing amplitude and decreasing frequency appear. If the arrest of circulation is prolonged the attenuation of activity and flattening of the EEG occurs."¹⁸

It is of interest that all cases of SUDEP captured on EEG (Bird et al³ and M A Lee⁴) were associated with sudden flattening of the EEG prior to death. We propose that one of the causes of SUDEP is due to sudden irreversible 'CEREBRAL ELECTRICAL SHUTDOWN' (CES) associated with a seizure. In other words the death occurs secondary to primary brain failure. Cardiorespiratory failure that leads to death, therefore, is mediated centrally by CES.

It is possible that primary brain failure is due to seizure-related neuronal injury. A recent comprehensive study using HSP-70 and c-JUN immunohistochemistry had shown markers of neuronal injury in patients with SUDEP but not in controls.¹⁹

Timely intervention (attempts at resuscitation) at early stages may reverse the consequence of CES as in the case of the So et al report.¹⁷

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Legends

Figure: Sudden termination of polyspike and slow wave discharges with flattening of the EEG. (Ambulatory recordings using digital Micromed MS 40 BrainSpy 12 channel recorder. 10 second sample, 10 uV/mm amplitude, filter 70Hz/TC 0.3)

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