

Sudden Unexpected Death in Epilepsy (SUDEP): Is there a link between the brain and heart?

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Epilepsy is a common neurological condition characterised by a tendency towards disruption of the normal electrochemical activity of the brain, resulting in recurrent seizures¹. Epilepsy affects approximately 50 million people globally². Every year approximately 1 in a 1000 patients who suffer from chronic epilepsy die suddenly, unexpectedly, and without pathological findings at post-mortem³. This phenomenon is termed sudden unexpected death in epilepsy (SUDEP).

What is SUDEP?

Sudden unexpected death in epilepsy (SUDEP) is defined as ‘a sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in a patient with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause of death’⁴. Sudden death is much higher in patients with epilepsy than in normal populations, with mortality ratios up to 40:1^{5,6}. Sudden death accounts for 8-17% of all deaths in epilepsy^{3,7} and post-mortem examination of SUDEP cases often fails to find a pathological cause of death⁴. As cardiac electrical disorders also have a negative post-mortem, this leads to the hypothesis that there may be a connection between epilepsy and cardiac arrhythmogenic disorders. In support of this hypothesis, the incidence of SUDEP increases with increasing severity and intractability of epilepsy⁵.

What are the risk factors for SUDEP?

There is a well-documented correlation between severe, intractable epilepsy and a heightened risk of SUDEP^{4,5,7}. The risk factors most frequently associated with SUDEP are:

- poor seizure control
- a lack of compliance to prescribed anti-epileptic drugs (AEDs)
- polytherapy
- abrupt medication changes
- early-onset epilepsy.

The occurrence of frequent seizures, particularly generalised tonic-clonic seizures have been found to predispose patients to SUDEP⁴. However this association between SUDEP and epileptic seizures accounts for some of the evidence only, and there may be other environmental and genetic factors that contribute to SUDEP. SUDEP is significantly more common in males. Environmental factors such as alcohol abuse, vitamin D deficiency and prone sleeping position have also been shown to increase the risk of SUDEP^{3,7}. A seemingly protective effect is the presence of another person in the same room, especially during sleep⁴.

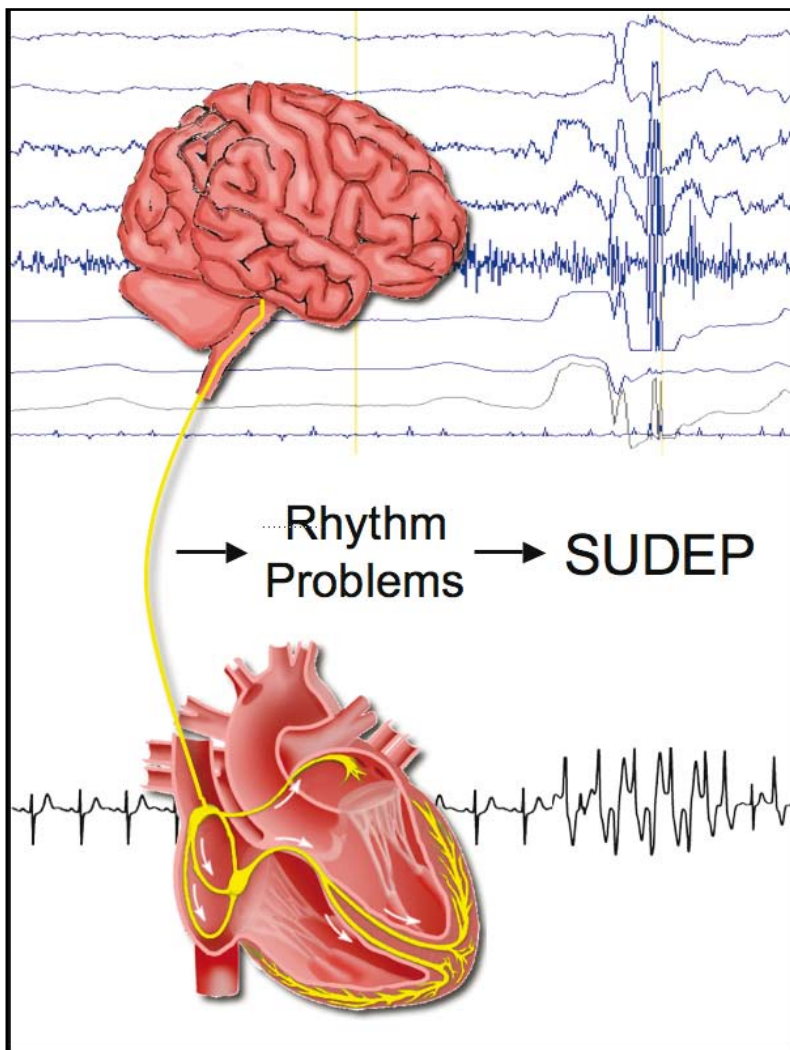
What are the clinical features of SUDEP?

Although the official definition permits diagnosis without evidence of a seizure, SUDEP is widely considered to be a seizure-related event⁴. Clinical and pathological findings indicate that most cases of SUDEP occur during, or shortly after a tonic-clonic seizure⁸ with most deaths believed to be triggered by such a seizure⁴. Thus, the risk of SUDEP increases with escalating frequency of

tonic-clonic seizures and occurs most frequently in chronic, uncontrolled epilepsy⁴. However, in support of the hypothesis that SUDEP is caused by a cardiac rhythm malfunction, at post-mortem there is no obvious cause of death. Diagnosis of SUDEP is not based on the presence of a pathological cause; rather it is diagnosed in the absence of any other cause of death. The patient must have suffered from epilepsy, and then based upon the knowledge gathered surrounding the death, a diagnosis can be given regarding the probability of SUDEP. Cases that fulfill all parts of the SUDEP definition are categorised as ‘definite SUDEP’; sudden death in a person with epilepsy in which there is no post-mortem performed but there are no known competing causes for death are defined as ‘probable SUDEP’; and cases in which SUDEP can not be excluded but there is limited information available are defined as ‘possible SUDEP’⁵.

What is the underlying cause of SUDEP?

Although the pathogenic mechanisms behind SUDEP are unknown, respiratory and cardiac factors are often associated and death usually results just after a tonic-clonic seizure⁵. Also unknown is what causes one seizure to result in death when the epilepsy sufferer has had previous non-fatal seizures⁵. It has been hypothesised that cardiac arrhythmias during and between seizures or transmission of epileptic activity from the brain to the heart via the autonomic nervous system could potentially play a role in SUDEP³. Cardiac factors associated with SUDEP include alteration to cardiac repolarisation, bradyarrhythmias



(slow heart rate), asystole ('flatlining') and occasionally tachyarrhythmias (fast heart rate)⁴. It has been hypothesised that these abnormal rhythms could be caused by malfunctioning depolarisation or repolarization mechanisms within the voltage-gated ion channels of the heart⁹,¹⁰ or voltage-gated ion channels that are present in both the heart and brain and are encoded by the same gene⁷. This suggests a possible link between the brain and heart in SUDEP.

Management of Patients


As there is very little known about the causes and mechanisms of SUDEP there is no definitive preventative treatment available. However, as there is a strong correlation between severe, uncontrolled epilepsy and a high risk of SUDEP⁴ and as 70% of epilepsy sufferers become seizure-free with the use of anti-epileptic drugs (AEDs)¹, the correct use of AEDs could theoretically provide greater protection against SUDEP than leaving epilepsy untreated. In addition to good seizure control, avoiding potential seizure

triggers is important. This may include avoiding triggers such as alcohol, as well as taking precautions with activities such as swimming. Finally, education about epilepsy, and specifically SUDEP, amongst family friends and relatives, as well as raising awareness in the community, are important measures which could potentially improve the management and care of epilepsy sufferers at risk of SUDEP.

Current and Future Research

Generally speaking, very little is known about why SUDEP occurs, and how one can predict who is at risk of developing SUDEP. Our research team at the Centenary Institute and University of Sydney have a specific interest in all causes of sudden death in the young¹¹. We have recently begun a pilot study looking at the possibility that there may be a link between the brain and heart in people who die from SUDEP. We believe people who die from SUDEP ultimately have a terminal heart rhythm problem which leads to their death. We

already know that genetic faults in the ion channels (which allow sodium and potassium in and out of cells) can lead to heart diseases which can cause sudden death. One possibility is that some patients with epilepsy may have gene faults which affect these ion channels both in the heart and brain which could place those people at risk of SUDEP. We are currently reviewing SUDEP cases over the last 15 years in Sydney to determine whether such gene/DNA faults exist and whether these may be the underlying trigger for SUDEP. Our findings will most likely shed light on the mechanisms underlying SUDEP, with the ultimate goal to prevent this tragedy in epilepsy sufferers in the future.

 <http://www.centenary.org.au/ourresearch/cardiovascular/molecularcardiology/>
<http://sydney.edu.au/medicine/people/academics/profiles/c.semsarian.php>

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