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Sudden unexplained death in epilepsy: Epidemiology and risk factors

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Abstract

The risk of sudden unexplained death in epilepsy (SUDEP) is in general about 1 in 3,000 person-years, but the risk is disturbingly high at 1 in about 100 person-years if epilepsy is poorly controlled. The type of epilepsy does influence the degree of SUDEP risk, as it has been consistently shown by many studies that generalized convulsive seizures carry the highest risk, and higher frequency of generalized convulsive seizures is associated with greater SUDEP risk. The underlying mechanism of the sudden death is still unknown. Peri-ictal cardio-respiratory dysfunction has been a prime suspect in causing the sudden death, but autonomic dysfunction and genetic factors may in the future be shown to predispose some persons to SUDEP. Recent animal studies suggest that insufficient brainstem serotonergic activity may play a role in causing SUDEP. This finding raises the potential role of SSRI medications in preventing SUDEP. For now, SUDEP prevention should focus on patient and family education and counseling about the nature of the condition and its currently known risk factors. Persons with epilepsy should be encouraged to strive for the best seizure control possible, especially when their seizures are generalized convulsive in type.

INTRODUCTION

Over the last half-century, the phenomenon of sudden unexplained death in epilepsy (SUDEP) steadily gained the attention of epileptologists, but it was only in the last decade that SUDEP has captured the attention of the public worldwide. The operational definition of SUDEP is best understood in terms of the following components to the definition: 1) the person had epilepsy; 2) death occurred suddenly; 3) the person died unexpectedly while in reasonable health; 4) death occurred during normal activities; 5) cause of death remained unknown after autopsy; 6) death is not the result of status epilepticus. If all six components are fulfilled, the term "definite SUDEP" can be used.[1] If autopsy was not performed but there is no other plausible explanation for the death, the death could be termed "probable SUDEP." The term "possible SUDEP" has been used in cases when the death suggests SUDEP, but autopsy was not performed and there is a possible explanation for the death.

RATE OF SUDEP

The standard mortality ratio of persons with epilepsy is twice that of the general population. However, most of the increased mortality is due to underlying acute or progressive medical or neurological disorders with which the epilepsy is associated as a symptom or consequence. SUDEP has been reported to account for 10% to 67% of the deaths in persons with intractable epilepsy.[2] The higher rates were observed in young adult persons with intractable epilepsy (age of about 20 to 40 years). It should be noted that these high rates of SUDEP were determined in cohorts of intractable epilepsy persons. The rate for SUDEP has been typically determined in cohorts of patient with intractable epilepsy in the settings of referral practice or residential homes for chronic epilepsy patient with disabilities. In population-based studies involving both controlled epilepsy and intractable epilepsy persons, the proportion of deaths due to SUDEP was found to be much lower at about 2% only.[3] Whereas the risk of SUDEP in cohorts of intractable epilepsy persons has been reported to be as high as 1 in 100 person-years, the risk is only 1 in 3,000 person-years in population-based studies that include all epilepsy persons.[3,4]

SUDEP RISK FACTORS AND POTENTIAL MECHANISMS

Marked differences in SUDEP rates and risks between intractable epilepsy cohorts and community-wide epilepsy persons suggest

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the relevance of poor seizure control as a risk factor for SUDEP. However, this potential risk factor was not readily observed in case-series of SUDEP, even when the cases were prospectively collected.[5] In contrast, case-control studies of SUDEP consistently demonstrated poor seizure control as a SUDEP risk factor. The type of epilepsy does influence the degree of SUDEP risk, as it has been consistently shown by many studies that generalized convulsive seizures carry the highest risk, and that higher frequency of generalized convulsive seizures is associated with greater SUDEP risk. In one study, persons with 1 to 3 generalized tonic-clonic seizures per year had a 2.5 times greater SUDEP rate than those with no generalized tonic-clonic seizures.[6] The rate was 8 times higher in those with more than 3 generalized tonic-clonic seizures per year. Further data to support the important role of generalized tonic-clonic seizures in SUDEP lies in the observation that 90% to 100% of SUDEP persons had a history of generalized tonic-clinic seizures. Moreover, there is circumstantial evidence that a generalized tonic-clonic seizure episode commonly precedes the death. Although SUDEP events are infrequently witnessed, 50% to 100% of witnessed SUDEP incidents were preceded by a generalized tonic-clonic seizure episode in the minutes to hours before the sudden death event.[7,8] Also, unwitnessed SUDEP cases bear signs suggestive of recent generalized convulsions, such as tongue-biting or urinary incontinence.

Other risk factors identified in case-control series of SUDEP were young adults, long duration of epilepsy, early epilepsy onset, antiepileptic drug (AED) polytherapy, frequent AED adjustments, IQ less than 70, and subtherapeutic AED serum concentrations.[2,9,10] Although these factors are associated with poor seizure control, they have been determined in the studies to be independent of seizure frequency. Nonetheless, seizure frequency may not be the sole determinant of epilepsy or seizure severity. Therefore, more research is needed to further investigate and eventually trace these risk factors to the mechanism underlying SUDEP. The underlying mechanism of the sudden death is still unknown.[11] Peri-ictal cardio-respiratory dysfunction has been a prime suspect in causing the sudden death, but autonomic dysfunction and genetic factors may be shown in the near future to predispose some persons to SUDEP. Recent animal studies suggest that insufficient brainstem serotonergic activity may play a role in causing SUDEP.[12] This finding raises the potential role of SSRI medications in preventing SUDEP. A recent study found that potassium ion channelopathy due to mutations involving the KvLQT1 channel, is co-expressed in the brain and the heart of a mouse model of seizure and cardiac death, and of humans.[13] Mutations in the gene KCNQ1 that encodes the KvLQT1 channel is found in most long QT syndrome patients, and this mutation in mice is associated with spontaneous seizures and potential for cardiac arrest associated with the seizure.

RISK-MODIFYING MEASURES

The beneficial role of supervision in preventing SUDEP was suggested by an observation that nighttime supervision reduces SUDEP risk by 60%.[14] Nighttime supervision was defined as presence of a person with normal intelligence and at least age 10 years, in the same room as the epilepsy person. More definitive evidence is needed before nighttime supervision can be advised as a SUDEP preventive measure. The burden of the responsibility of the supervising person is tremendous, especially if SUDEP were to occur despite the supervision. For now, SUDEP prevention should focus on patient and family education and counseling about the nature of the condition and its currently known risk factors.[15] Persons with epilepsy should be encouraged to strive for the best seizure control possible, especially when their seizures are generalized convulsive in type. Advanced epilepsy treatments such as epilepsy surgery should be considered when seizures remain intractable. One study showed that SUDEP did not occur in 199 persons who had successful epilepsy surgery, but 6 of 194 persons with persistent seizures eventually had SUDEP.

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