

## **WHAT IS SUDDEN/UNEXPLAINED DEATH IN EPILEPSY**

Sudden unexplained death in epilepsy or SUDEP is the term used to describe when a person with epilepsy dies unexpectedly without a clear cause. The condition was first observed in 1854, however, a formal definition is still being debated today. Nashif (1997) presented one of the most widely accepted definitions within the scientific community, which is “the sudden, unexpected, witnessed or un witnessed, non-traumatic, and non-drowning death in patients with epilepsy with or without evidence for a seizure, and excluding documented status epilepticus (a seizure lasting more than 30 minutes), in which post mortem examination does not reveal a structural or toxicological cause for death”.<sup>1,2</sup> The main problem with this definition is that it requires a post-mortem autopsy, whose quality and timing vary considerably among countries. Furthermore, this definition may not be useful in epidemiological or statistical studies that attempt to understand why the condition occurs and identify risks for SUDEP. Therefore, the Annegers (1997) criteria are used in the absence of an autopsy for these types of studies. These are 1) a patient with epilepsy dies suddenly while in a reasonable state of health; 2) the death occurred within minutes; 3) the death occurred while performing normal, everyday duties; 4) no obvious cause of death was found; and 5) the death was not directly caused by a seizure or status epilepticus.<sup>3,4</sup> Regardless of the definition, many who have epilepsy, their friends and family are not aware of the possibility of SUDEP until it is too late. Furthermore, the word “unexplained” in the definition points to the multitude of unknown factors surrounding this devastating event.

## **RISK FACTORS FOR SUDDEN UNEXPLAINED DEATH IN EPILEPSY**

The reality is that epilepsy appears to be associated with a two-to-three fold increase in SUDEP compared to the general population and is the most common direct epilepsy-related cause of death.<sup>5</sup> Incidence rates are difficult to accurately ascertain because of a lack of post-mortem examinations, however, cohort studies, or a statistical study of a group of people who share common characteristics, have shown that SUDEP occurs in a range from approximately 1:100 person per year in intractable epilepsy surgery cohorts to 0.35/1,000 persons-years in an epilepsy population-based study.<sup>6</sup> From these studies, a number of risk factors have been observed.

### **I. Treatment with Anti-Epileptic Drugs (AEDs)**

There are a number of factors involving AEDs that have been shown to increase the risk for SUDEP. One of the more apparent risks is the use of more than one medication at a time (polytherapy versus monotherapy) and frequent changes in medication.<sup>6,7</sup> It is believed that this can affect the postictal state (the state of consciousness after a seizure) or cause a dysfunction in the body's autonomic system.<sup>6</sup> Another study showed that the number of AEDs taken over a lifetime or no treatment at all can also increase the risk for SUDEP.<sup>8</sup>

Lack of patient compliance to treatment protocols has been proposed as a risk factor, however the results of studies have been mostly contradictory. This risk cannot be completely dismissed because accurate information about how medications were taken are not always available after death and post-mortem blood analysis may not accurately portray AED levels making it difficult to determine whether the patient was compliant.<sup>6,9</sup> That being said, analysis of hair samples using high-performance liquid chromatography (HPLC), showed that there was an increased variability in AED concentrations in SUDEP patients.<sup>10</sup> In addition, almost all of these studies attempting to resolve this issue have been based on three AEDs — phenytoin, carbamazepine and lamotrigine. Despite this controversy, patient compliance is important to overall patient health, especially those living with epilepsy. Subtherapeutic drug levels, or

taking doses that are too low to be therapeutic, is one of the strongest risk factors for SUDEP.

Finally, whether certain AEDs provide a higher risk for SUDEP has also been evaluated. Some studies have shown that there is no AED in particular that increases the SUDEP risk, while others have implicated higher than normal levels of certain drugs may elevate risk.<sup>6,7,8, 17, 18,18,28</sup> All in all, the studies have been largely contradictory. That being said, it is obviously important that using AEDs aggressively causing blood concentrations to be above therapeutic levels (as well as below) should be generally avoided regardless of the AED used. It is clearly important to follow prescription schedules

## **II. Age, Gender and Ethnicity**

The age at the highest risk for SUDEP appears to be between the ages of 20 and 40 years old.<sup>11,12,13</sup> Ficker *et. al.* (1998) reported that 7 out of the 9 SUDEP cases assessed were within the ages of 15 and 44.<sup>13</sup> However, there are reported SUDEP cases of people from anywhere between the ages of 8 months to 83 years.<sup>9</sup> Unfortunately, many of these cohort studies are fraught with bias, but the accepted wisdom appears to be that people are at a higher risk for SUDEP within the ages of 20-to-40, especially those with poor seizure control.<sup>11,12</sup> SUDEP in children is often overlooked, however an important Ontario study assessing 27 cases under 15 years of age showed an incidence of 1-2 deaths per 10,000 patients-years.<sup>14,15</sup>

Conclusions about gender and ethnicity as it relates to SUDEP risk are equally biased. Some cohorts reveal that men are more susceptible, others reveal that women are more susceptible, but most show that gender does not contribute to risk.<sup>8,9,14,16</sup> Finally, a number of studies have demonstrated that people of African descent have a higher incidence of SUDEP, however, the selection of patients within the cohort is biased as well as a number of confounding factors were ignored.<sup>9</sup>

### **III. Types of Seizures, Remission and age of onset**

Patients who have refractory seizures have the highest risk for SUDEP.<sup>11,17,19</sup> It is believed that 10-50% of SUDEP cases are within this category.<sup>9</sup> Refractory epilepsy is a multi-faceted condition and experts tend to group individuals who have not had seizure control for over 18 months and whose treatment regimens with 2 or more different AEDs have failed.<sup>20,21</sup> This would help to explain some of the risks related to AED treatment discussed earlier. Many studies have shown that the incidence of SUDEP is inversely related to remission of epilepsy and the MRC Antiepileptic drug withdrawal study has confirmed that the SUDEP is rare in patients in remission.<sup>9,22</sup> This means that proper seizure control is key and it is imperative to find proper medication as soon as possible in order to reduce the risk of SUDEP. In addition, it appears that people who experience generalized tonic-clonic (sometimes called “grand mal seizures”) seizures especially if experienced within the past year.<sup>6,8,9,11,23</sup> Seizure frequency, especially generalized tonic clonic seizures, is probably the strongest risk factor for SUDEP and deaths have occurred in patients with as little as 1-3 seizures within a year.<sup>7,16</sup> Finally, it appears that all types of epilepsy (idiopathic, cryptogenic, symptomatic and unclassified) experience deaths from SUDEP, however, the symptomatic epilepsy group (those with an identifiable cause for epilepsy) had the most deaths within 10 years from diagnosis.<sup>12</sup>

Those diagnosed with chronic epilepsy in childhood are at the highest risk for SUDEP, especially under the age of 20.<sup>9,12</sup> Furthermore, the statistical models showed increased mortality with rising age in patients with chronic epilepsy, especially those living with epilepsy for 15-20 years.<sup>9,12</sup> Another at risk group appears to be those newly diagnosed in adulthood (median age of 29 years).<sup>12</sup> The SUDEP cases within this group occurred mostly between the ages of 31-40.<sup>12</sup> The studies showed that the incidence of SUDEP increased more than 42% in patients with newly diagnosed epilepsy where in any of the AEDs prescribed were unable to control seizures.<sup>12</sup> This is yet another reason why seizure control is incredibly important.

#### **IV. Epilepsy with other Neurological Problems**

Mental retardation (IQ<70) along with a seizure disorder accounts for up to 45% of SUDEP cases.<sup>9</sup> However, again, studies have been contradictory, but it is still considered a risk factor even after adjusting for seizure frequency.<sup>9,16</sup> Regardless, the evidence is weak. Other neurological disorders that have also shown contradictory results include the use of psychotropic drugs along with AEDs and the development of brain lesions. The concurrent use of psychotropic drugs has a very weak relationship to SUDEP.<sup>16</sup> One study showed that focal CNS lesions were reported in 35-50% of SUDEP cases within a study group, however, these are not supported by other case-controlled studies.<sup>9</sup>

#### **V. Lifestyle Factors**

Drinking alcohol is often an issue with treatment of many neurological disorders. This is because alcohol can easily cross the blood brain barrier and possibly disrupt the passage of AEDs leading to poor seizure control. Although this appears to be a simple explanation, in reality is a very complex and the relation between alcoholism and SUDEP is very weak.<sup>9,24</sup>

There is a perpetuating myth that physical activity can induce seizures and increase their frequency.<sup>25</sup> In fact, exercise-related seizures are rare and better fitness can improve cardiovascular and psychological health.<sup>25</sup> A surprising case study of a 33 year old active Duty soldier who survived the events leading to SUDEP, collapsed in the midst of rigorous training.<sup>26</sup> Although this could be construed as a risk factor, it may be more likely due to dehydration, electrolyte imbalance, hyperventilation, and hyperthermia that can occur during exercise and are known to increase the likelihood of seizures.<sup>26</sup> What can be learned from this is that physical activity should be within normal levels and that care should be taken to minimize the above during physical activity.

#### **VI. Respiratory, Cardiac and Genetic Mechanisms**

Pulmonary edema or the fluid build-up in the lungs that can lead to respiratory failure has been found in a large number of SUDEP cases.<sup>6</sup> Most un-witnessed SUDEP cases occur in bed and 71% are found in the prone sleeping position.<sup>6</sup> This position, a common cause of Sudden Infant Death Syndrome (SIDS), results in respiratory obstruction. In addition, sleep apnoea or snoring is associated with seizures, which may attribute to respiratory issues that can lead to SUDEP.<sup>27</sup>

Possible cardiac mechanisms in SUDEP are hypothetical and include possible primary or secondary cardiac mechanisms.<sup>6</sup> There may be certain people who are mildly predisposed to SUDEP because of various cardiac disorders and uncontrolled seizure control could heighten the risk.<sup>6</sup> Genetic susceptibility is currently being studied. In particular, defects in potassium channel genes, sodium channel genes, genes that cause long-QT syndrome, H-Channel genes and calcium signaling genes may have roles in causing SUDEP.<sup>6</sup>

## **VII. Other Possible Preventive Measures**

Obviously, the main goal to reduce the likelihood of SUDEP is proper seizure control, however the AEDs have limited clinical efficacy in about one third of patients.<sup>5</sup> Since genetic, environmental and social factors could contribute to the lack of efficacy, non-medical and surgical preventative measures may reduce the risk of SUDEP.<sup>5</sup> First, increased omega-3 fatty acids (3000-to 4,000 mg of daily fish oil supplements or 2-3 servings of fish) have a number of health benefits, but it is the prevention of cardiac arrhythmias and sudden cardiac death that make it interesting in reducing the SUDEP risk. Another suggestion would be to increase physical activity to improve overall cardiovascular health. This is because some of the mechanisms behind SUDEP that have been proposed include autonomic effects such as cardiovascular disturbances.<sup>5</sup> Physical activity is also considered to have anticonvulsant effects. The risk of SUDEP appears to increase in very cold winter seasons.<sup>5,14</sup>

## SUMMARY AND CONCLUSION

These studies showed a number of risk factors that may lead to SUDEP. Some of the risks mentioned were weakly correlated with SUDEP while others were very strongly correlated and provide substantial motivation for those with epilepsy to reduce the possibility of SUDEP. Seizure control is of utmost importance and there needs to be more research in developing future AEDS to control seizures, especially generalized tonic clonic seizures. Another element that needs to be addressed is better screening for determining what kind of AEDS would be effective right away rather than approaching treatment in a trial and error fashion thereby minimizing the overall number of AEDs used. The population most affected (i.e. chronic epilepsy diagnosed in childhood and newly diagnosed in adulthood [mean age of 29]) need to be especially cautious. Finally, lifestyle choices play a role because reducing sleep apnoea, avoiding the prone sleeping position, eating plenty of healthy fats versus a diet high in saturated fats (i.e. Omega-3 fatty acids) and exercise could also substantially reduce SUDEP cases.

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