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Seizure-related death in children with epilepsy

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Abstract: Children with epilepsy have a significantly higher rate of death than the general population. The cause of premature death among epileptics is contributed by the underlying cause, coexisting neurologic compromise and the epilepsy itself. Mortality directly related to seizures in paediatric epilepsy is the subject of this review. Seizure-related deaths in epileptics arise from status epilepticus, aspiration pneumonia, as well as sudden and unexpected death in epilepsy (SUDEP). Epilepsy per se enhances the risks of accidents and suicide. Children with epilepsy who are otherwise neurologically intact and with normal neuroimaging findings have an exceedingly low risk of seizure-related death. Poor compliance to antiepileptic drugs (AED), poorly controlled (intractable and refractory) seizures, impaired cognition, structural/metabolic aetiology and antiepileptic drug polypharmacy tend to carry poor prognosis. Therefore, parents need to be appropriately advised about the risk of seizure-related premature death. Early identification, compliance with AED prescription, and treatment of comorbid conditions can reduce mortality risk and improve health outcomes in children with epilepsy. Children with intractable types of epilepsy may benefit from medical marijuana and neurosurgery.

Key Words: Childhood epilepsy, seizure-related death, prevention

Introduction

Epilepsy is a common childhood neurologic disorder and children with epileptic convulsions have an increased risk of premature death compared with children without epilepsy.[1-5] A multicentre survey in the USA showed that among children with epilepsy in South Carolina during 2000–2011, the overall mortality rate was 8.8 deaths per 1,000 person-years and the annual risk for death was 0.84 percent compared with 0.22 percent among children of the same ages without epilepsy.[4] Children with epilepsy who are otherwise neurologically normal tend to have an exceedingly low risk of seizure-related death. Symptomatic forms of epilepsy - those with a known cause — generally have poorer outcomes than idiopathic forms. The term "cryptogenic" has been used to describe epilepsy believed to be symptomatic but for which the cause is unknown. The prognosis for these cases is poorly understood.
Associated congenital malformations, chromosomal abnormalities, syndromic disorders, cerebral palsy and cardiovascular anomalies do boost the mortality rate in children with epilepsy. Invariably, increased mortality rate may occur due to progression of the underlying disease.

In Nigeria most deaths in individuals with epilepsy occur at home with no documentation.[6] The stigma of epilepsy may dwarf the wish of the parents and the patient to report to hospital hence the statistics of death related to epilepsy are rare in Africa. This communication focuses on the mortality risk due to the direct effect of seizures in children with epilepsy. The rationale is to create an awareness among medical personnel and parents on the dangers posed by every seizure episode. Doctors should not fail to adequately educate parents about the risks of death. Though it is controversial if the child should be told concerning the death aspect, an awareness of the increased risk for premature death associated with epilepsy may enhance patients' and parents' cooperation with therapy.

Death from Status epilepticus

Status epilepticus (SE) is a medical emergency associated with significant morbidity and mortality.[1-5] The duration of a seizure appears to be the single major predictor of mortality.[3-5] Status epilepticus is defined as a continuous seizure lasting more than 30 minutes, or two or more seizures without full recovery of consciousness between any of them. There is the non-convulsive type of status epilepticus (NCSE) whereby the prolonged seizure manifests primarily as altered mental state without convulsive movements.[3-5] GABAergic mechanisms play a crucial role in terminating seizures but in SE the innate inhibitory mechanisms in the brain that put a halt to the seizure are no longer effective. Since only a small fraction of seizures go on to become SE, the probability

that a given seizure will proceed to SE is small at the start of the seizure but increases as the seizure duration increases. Most seizures cease within a minute or two and if the seizure is prolonged beyond a few minutes, it is unlikely to stop by itself. If a seizure lasts > 5 min, clinical experience suggests that the likelihood of spontaneous termination decreases.[5,7,8] Uncontrolled tonic-clonic seizures, especially at night, and children with Dravet syndrome, a rare and catastrophic form of intractable epilepsy, carry a high fatality frequency.[3]
About 9–31% of patients with SE may fail to respond to standard treatment. This subgroup of refractory status epilepticus (RSE) has greater morbidity and mortality.[9] RSE is defined as continuous or repetitive seizures lasting longer than 60 min despite treatment with a benzodiazepine (lorazepam or diazepam) plus another standard anticonvulsant (usually phenytoin/fosphenytoin) in adequate loading dose. Suchis treated with inhalational anaesthetic agents.[9] Regardless of seizure type, isoflurane and desflurane have consistently stopped epileptic discharges with adequate, sustained electrographic burst suppression within minutes of initiation of therapy. Malignant SE is a severe variant of RSE, in which the seizure fails to respond to aggressive treatment even with anaesthetic agents. It commonly occurs in children in the setting of encephalitis.[10]

Prolonged SE can lead to cerebral oedema, cardiac dysrhythmia, autonomic dysfunction, and neurogenic pulmonary oedema. Excessive muscular activities during generalised tonic-clonic seizure result in hyperthermia, metabolic acidosis, hypoglycaemia, and hyperkalaemia all of which can grossly compromise cardiorespiratory functions. In developing countries, poverty and ignorance play a delaying role whereby even the very sick children report late for hospital care. It is not uncommon to encounter children who have convulsed all night at home, and some have gone through alternative source of treatment for hours before reporting to hospital as a last resort. Such cases obviously have very slim chance of survival. The goal of pharmacologic therapy is to achieve rapid and safe termination of the seizure and to prevent its recurrence, without adverse effects on the cardiovascular and respiratory systems or alteration of the level of consciousness. Based on this recent understanding of the pathophysiology, it is now considered that any seizure that lasts more than 5 minutes probably needs to be treated as SE.[5,8]

Airway obstruction and Pneumonia

The possibility of aspiration during a seizure is a well-recognized cause of death in epilepsy and tends to occur in children with coexistent neurological compromise.[4] The combination of dysphagia, gastroesophageal reflux, poor airway protection, renders the patients vulnerable.
It can also be dangerous if a child has a seizure with food in his mouth. Such a child may choke as the food can go down the airway instead of the stomach. It is not uncommon to observe adults force liquid concoctions down the throat of children who are actively convulsing. Native herbs, palm kernel oil, olive oil including human and cow urine are common native concoctions for convulsions in some Nigerian communities. Bacterial pneumonia, lipoid pneumonia and chemical pneumonitis are the expected consequences of such unorthodox and undesirable treatment. Being in the prone position is a risk factor for aspiration pneumonia. Turning into the prone position after a convulsive seizure can definitely be a contributing factor in aspiration. This is probably why sleep is considered a risk factor in children with epilepsy.

Sudden unexpected death in epilepsy (SUDEP)

SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in a patient with epilepsy, with or without evidence of a seizure and excluding status epilepticus. Autopsy in this condition does not reveal an anatomical or toxicological cause for the death. This condition is not rare; it contributes 8-17 percent of deaths in people with epilepsy.[11] The average age for SUDEP is 28- 35 years but this condition has also been reported in children.[11,12] A Finnish study followed 245 children with epilepsy for 40 years and found that 24 percent of them died and that 38 percent of the deaths were due to SUDEP.[1]

Various pathophysiologic events contribute to SUDEP. Evaluation of autonomic cardiovascular reflexes in patients with epilepsies indicates a dysfunction of both the sympathetic and parasympathetic components. These include central apnoea, neurogenic pulmonary oedema and airway obstruction; others are cardiac arrhythmias leading to acute cardiac failure and arrest.[13-17]Cardiac arrhythmias, during the ictal and interictal periods, leading to acute cardiac failure may contribute significantly to SUDEP. The death is not usually as a direct result of a seizure or status epilepticus but occurs suddenly during normal or benign circumstances. In a majority of cases, patients had had a seizure immediately before death. In all witnessed deaths, seizure had stopped before death, and in many cases, the patient had even regained full consciousness before he dies. In SUDEP the victim may succumb through a single, brief attack.[15,18]
Repetitive exposure to catecholamines during fits is known to cause myocardial fibrosis. These fibrotic areas act as foci for cardiac arrhythmias. Autopsies following death from SUDEP have demonstrated fibrosis of the cardiac conducting system in some patients.[18]
Frequent and potentially fatal asystole is an indication for a permanent pacemaker insertion to avoid sudden unexpected death.

Seizure severity is a risk factor because intractable epileptics have a higher rate of SUDEP than patients with well-controlled epilepsy do. Epilepsy is said to be intractable when a patient requires at least two or three AEDs taken simultaneously to control the attacks. Poor control of epilepsy, and polytherapy in the management of patients, render some epileptics vulnerable to SUDEP.[16,17] Epileptic children with severe cognitive impairment tend to have an increased risk of sudden, unexplained death.[3] The most likely explanation for this

association is that the more mentally deranged epileptic children are more likely are they to have intractable seizures.[3,5]

Seizure-related injury and death

Epilepsy enhances the risks of accidents, such as falls from heights, burns, traffic injuries and drowning.[19,20,21] The kitchen, with its ovens, burners, and sharp knives is a potential danger zone. Adjusting how food is prepared, cooked, and cleaned up may make the kitchen safer for children with seizures. Catastrophic burns may occur if a seizure throws a patient into an open fire. This may be common in poor socioeconomic settings where families cook with firewood or kerosene stove in the open on ground level where children may be playing around.

In some superstitious communities, it is a taboo to touch an actively convulsing person for fear of contagion hence should a convulsing child fall into a burning furnace, such may be left to perish.[22] If an epileptic experiences an attack while walking across a busy street or while riding a bicycle, instant death may be the outcome. Likewise, drowning episodes have been reported in streams, swimming pool and even in bathtubs within the house.[21]

Suicide

It is important to assess the psychological status of adolescents with epilepsy. Epilepsy is often complicated by depression, impulsivity, psychosis, and substance abuse, all of which increase the risk for suicide among epileptics.[22,23, 24] The authors of this communication have encountered a 14-year old female who had made repeated attempts to cut into her radial artery. On interrogation, she confessed it was a deliberate effort to terminate her life so as to end the embarrassment from frequent fits which she had suffered in front of her mates at school. The patient was referred for psychiatric evaluation and follow up. Some medication used as AED such as Levetiracetam has been associated with suicidal tendencies.[25]

Treatment-related causes

Poor compliance with prescribed antiepileptic drug (AED) and antiepileptic polytherapy, constitute risk factors for premature death in epilepsy.[1-5,16,17] Non-compliance to appropriate medication is one of the most common causes of status epilepticus among children with epilepsy. In known epileptics the most common cause is a change in medication, This may involve the use of substandard drugs; the change may be directed by the clinician, or may be due to an abrupt cessation on the parent's part whether intentional or unintentional.-[26] Over-dosage and overzealous administration of an anticonvulsant by intravenous route during the active phase of a seizure, can compromise cardiorespiratory functions with a fatal outcome.

Recommendations

Health care and social service providers, advocacy groups and others interested in improving outcomes for children with epilepsy can work together to assess whether coordinated care for these children can prevent complications associated with epilepsy and reduce their risk for premature death. Taking AED medications as prescribed is the key factor in reducing the number of seizures and therefore the risk of premature death. Parents of epileptic children have the right to know the mortality risks associated with epilepsy. Once the parents or intelligent teenagers know and accept the risks, they should be able to decide for themselves what precautions to take. Ensuring appropriate and timely health care and social services for children with epilepsy, especially those with complications, might reduce the risk for premature death. Patients who have persistent generalized seizures beyond 5 minutes deserve to be treated as SE. It is a recent knowledge that some children with intractable epilepsy types such as Dravet, Doose and Lennox-Gaustat syndromes, have benefitted from Cannabidiol extract from Cannabis.[27,28]It is equally important to attend to the general medical condition of the patient, even as the AEDs are being administered.

Achieving complete seizure control with epilepsy surgery in intractable patients, who are good surgical candidates, reduces the risk of death to a level indistinguishable from that of the general population.
Some dogs have been trained to bark or otherwise alert families when a child has a seizure while playing outside or in another room. Public interest in seizure assistance dogs has fuelled demand for dogs with these skills.[29] The term "seizure dog" covers a variety of activities associated with a service dog's response to an epilepsy seizure. Some dogs learn to lie next to someone having a seizure to prevent injury. Others are said to be able to activate alarm systems. Seizure dogs therefore trigger securing speedy assistance when a seizure occurs or alerting others for help.

Conclusion

Seizure per se can contribute to mortality in childhood epilepsy. Parents, and perhaps the adolescent child, should be enlightened regarding this possibility. Poorly controlled (intractable and refractory) seizure frequency constitute a major risk factor. It is pertinent that clinicians should enlighten and warn the parents concerning medication. Strict compliance with antiepileptic drugs and other adjunct preventive measures is the key in reducing premature death in children with epilepsy.
Regarding under-reporting of seizure-related deaths, the use of verbal autopsy is being strongly advocated especially in developing countries.[30] This involves a standardized method of collecting data retrospectively from parents and siblings of an epileptic who died suddenly and unexpectedly. The data, when analysed can help in determining the diagnosis of SUDEP hence its preva-

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