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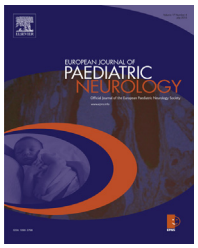

Original article

Mortality and causes of death in children referred to a tertiary epilepsy center

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ABSTRACT

Background: Patients with epilepsy, including children, have an increased mortality rate when compared to the general population. Only few studies on causes of mortality in childhood epilepsy exist and pediatric SUDEP rate is under continuous discussion.
Aim: To describe general mortality, incidence of sudden unexpected death in epilepsy (SUDEP), causes of death and age distribution in a pediatric epilepsy patient population.
Methods: The study retrospectively examined the mortality and causes of death in 1974 patients with childhood-onset epilepsy at a tertiary epilepsy center in Denmark over a period of 9 years. Cases of death were identified through their unique civil registration number. Information from death certificates, autopsy reports and medical notes were collected.
Results: 2.2% ($n = 43$) of the patient cohort died during the study period. This includes 9 patients with SUDEP (8 SUDEP cases per 10,000 patient years). 9 patients died in the course of neurodegenerative disease and 28 children died of various causes. Epilepsy was considered drug resistant in more than 95% of the deceased patients, 90% were diagnosed with intellectual disability. Mortality of patients that underwent dietary epilepsy treatment was slightly higher than in the general cohort. There were no epilepsy-related deaths due to drowning.
Conclusions: This study confirms that SUDEP must not be disregarded in the pediatric age group. The vast majority of SUDEP cases in this study displays numerous risk factors similar to those described in adult epilepsy patients. Including SUDEP, only 30% of the mortality was directly seizure related.

1. Introduction

Mortality in epilepsy patients is about two to three times higher than in the general population with a higher risk in the younger age group. In children with epilepsy, up to 5.3–8.8 times increased risk of death has been reported in population-based cohort studies.[1,2] Most cases of death can be attributed to the underlying neurological disease but some are epilepsy related, including accidents, drowning, status epilepticus, and SUDEP. Long-term mortality in pediatric patient series is

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generally less well studied than in adult cohorts. In childhood-onset epilepsy, general mortality rates were reported to lie between 26 and 69 per 10,000 patient years.[2–7] In the study with the longest follow-up the median age at death was 23 years.[7] The highest risk for death was found in patients without a 5-year terminal remission, patients with remote symptomatic causes of epilepsy that had major neurological abnormalities and/or severe cognitive impairment as well as patients with a history of status epilepticus.[7]

The rate of sudden unexpected death in epilepsy patients (SUDEP) in children continues to be under discussion.[8] Rates reported in the literature range from 1.1 to 4.3 per 10,000 patient years in population-based studies[2,5,6,9,10] and are in general lower than in the adult population. In the study analyzing long-term mortality in childhood-onset epilepsy with a prospective 40 year follow-up 38% of deaths were due to SUDEP. In this prospectively followed, population-based cohort of 245 children with a diagnosis of epilepsy in 1964 the cumulative risk of SUDEP was 7% at 40 years (2.6 cases of SUDEP per 1000 patient years[7]). Mechanisms underlying SUDEP are not well understood. It is hypothesized that dysregulation in cardiac and respiratory physiology, dysfunction in cerebral circulation, and seizure-induced hormonal and metabolic changes all contribute to SUDEP. An individual predisposition to SUDEP is likely to be multifactorial and might include rare genetic predisposition.[11] Currently, SUDEP prevention is mainly based on the avoidance of risk factors, e.g. reduction of seizure frequency, patient information, and increase of compliance to AED treatment. As nocturnal seizures seem to be an independent risk factor for SUDEP, preventive measures might include night supervision for certain patients.[12]

In the present study, we retrospectively examined mortality and causes of death in a cohort of 1974 patients with childhood-onset epilepsy that were followed and treated at a tertiary epilepsy center. We present general mortality, incidence of SUDEP, and give detailed information on causes of death in our pediatric patient population in order to add to the limited knowledge on mortality and causes of death in pediatric epilepsy patients.

2. Patients and methods

Patients included all children referred to the Danish Epilepsy Center in Dianalund, Denmark, a tertiary epilepsy center, in the period from January 1, 1999 to August 31, 2008. The Dianalund Epilepsy Center is the only tertiary center of its kind in Denmark with a population of 5.4 million. Patients were included into the study if they received an epilepsy diagnosis after evaluation and were between 1 month and 18 years old at time of enrollment. General information regarding the study population (age, sex, epilepsy diagnosis) were provided by the hospital discharge register. Cases of death were identified in the Danish civil register based on their unique civil registration number by the 1st of June 2009. Because of patients' age at enrollment, deaths were recorded also beyond the age of 18 years. Relevant medical information regarding the circumstances and causes of death were derived from death certificates, autopsy reports and the medical charts of terminal caregiving hospitals and the Epilepsy Center. Clinical details regarding the deceased patient population (antiepileptic treatment, seizure control, absence or presence of intellectual disability, underlying neurometabolic disorder) were supplemented from the Epilepsy Center's medical charts. Frequency of death was expressed in relation to patient years observed in our cohort.

Treatment resistant epilepsy was defined according to ILAE.[13] SUDEP was defined as "Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus where postmortem examination does not reveal a cause of death" according to Nashef and Ryvlin.[11] If an autopsy could not be performed cases are referred to as probable SUDEP.

The study cohort consisted of 1974 epilepsy patients accounting for 11,309 patient years, counted from the time-point of enrollment into the study to the end of the study period. Gender distribution was 1:0.92 (male:female). At the end of the study period (August 31st, 2008) patients were on average 15 years old (median 15). Epilepsy diagnoses (ICD 10) were distributed as follows: 40.3% focal epilepsy with partial seizures, with or without secondary generalized tonic-clonic seizures, 21.7% idiopathic generalized epilepsy, 10.1% epileptic encephalopathies, 4.5% idiopathic focal epilepsy, and 23.4% other and unspecified epilepsy types. 218 patients were treated with classical ketogenic and modified Atkins diet during the study period. Dietary treatment of epilepsy at the Danish Epilepsy Center was started in 2002 and 2007 for classical ketogenic and modified Atkins diet, respectively. 3 patients were treated with a vagus nerve stimulator (VNS[14]).

3. Results

43 of 1974 patients (2.2% of the study cohort) died during the study period (overall mortality 38 cases per 10,000 patient years). Two thirds of the deceased patients were male. Death of 9 patients (0.45% of the study cohort) was classified as definite or probable SUDEP corresponding to 8 SUDEP cases per 10,000 patient years. 9 patients died with progressive neurometabolic diseases (0.45% of the study cohort; 8 cases per 10,000 patient years). 25 remaining patients (1.3% of the study cohort; 22 per 10,000 patient years) died of various other causes. Table 1 displays that 8 of 9 patients with SUDEP had drug resistant epilepsy, all had generalized tonic-clonic seizures (GTCS) among other seizure types, and none of the patients were seizure-free. In one of these patients epilepsy etiology was classified as idiopathic; this patient was diagnosed with juvenile myoclonic epilepsy (JME) and died at age 22 (patient 6). One patient was not on antiepileptic treatment; the remaining patients were treated with 2–3 antiepileptic drugs. Death occurred at 2.5–24 years of age (median 17 years). 4 patients died before the age of 16 years (patients 3, 4, 7, and 9). Of these, patient 3 had symptomatic epilepsy on the background of perinatal asphyxia, seizures were complex partial with secondary generalization. The patient had cerebral palsy and intellectual disability. Patient 4 was diagnosed with multifocal epilepsy and intellectual disability, the etiology remained unknown. Patient 7 had an unclassified