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Short communication

Mortality in Dravet syndrome

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ABSTRACT

We measured the mortality rate and the rate of Sudden Unexpected Death in Epilepsy (SUDEP) in Dravet Syndrome (DS). We studied a cohort of 100 consecutively recruited, unrelated patients with DS; 87 had *SCN1A* mutations. Living cases had a median follow-up of 17 years. Seventeen patients died, at a median age of seven years (inter-quartile range 3–11 years) with causes of death: 10 SUDEP, four status epilepticus, two drowning and one asphyxia. The SUDEP classification included three *Definite*, one *Definite Plus* and six *Probable*. The Dravet-specific mortality rate/1000-person-years was 15.84 (98% CI 9.01–27.85). The Dravet-specific SUDEP rate was 9.32/1000-person-years (98% CI 4.46–19.45). The Dravet-specific SUDEP rate is the only documented syndrome-specific SUDEP rate. SUDEP in DS occurs mainly in childhood. It is also the highest SUDEP rate, considerably higher than the recent 5.1 SUDEP rate/1000-person-years for adults with refractory epilepsy.

1. Introduction

Dravet syndrome (DS) is a severe infantile-onset developmental epileptic encephalopathy with intractable seizures and poor outcome. Early death occurs in some individuals. A developmentally normal infant of around six months of age presents with convulsive seizures, which may be hemiclonic or generalised. The infant typically has episodes of status epilepticus (SE) and develops multiple seizure types. By two years, developmental slowing occurs. Intellectual disability, ataxia and refractory seizures are usual (Dravet et al., 2012; Catarino et al., 2011). In DS, >80% patients have a mutation in the voltage-gated sodium channel α1 subunit gene, *SCN1A* (Harkin et al., 2007).

Mortality in DS ranges from 3.7–17.5% with 15–61% deaths attributed to Sudden Unexpected Death in Epilepsy (SUDEP) and to SE in 25–42% cases (Dravet et al., 2012; Skluzacek et al., 2011). Death most commonly occurs in childhood (Dravet et al., 2012).

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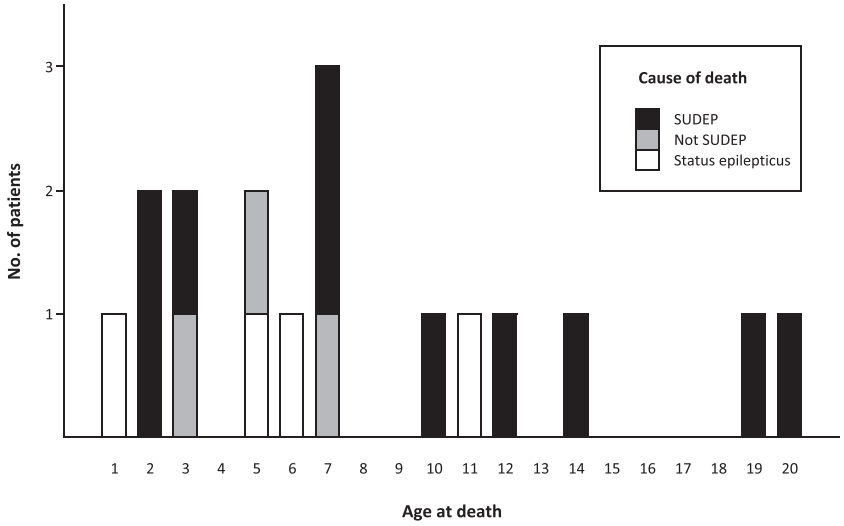

Fig. 1. Causes and Age of Death in Dravet Syndrome. This figure shows that the causes of death are predominantly SUDEP. SUDEP is across the ages of 2–20. The peak ages of death are 2–7 years.

SUDEP has been classified according to the evidence surrounding death, in part to capture cases with uncertainty around the diagnosis. *Definite* SUDEP refers to a presumed epilepsy-related death, unrelated to trauma, without identifiable structural cause on post-mortem examination. Non-specific findings include cerebral edema, hypoxia, neuronal and Purkinje cell loss, and gliosis. *Definite* SUDEP *Plus* means there is an additional potentially contributing condition, such as pneumonia. *Probable* SUDEP refers to likely SUDEP where no post-mortem was conducted. Other causes of death are defined as *Not-SUDEP* (Nashef et al., 2012). Known SUDEP risk factors include frequent generalized tonic-clonic seizures, early seizure onset, developmental delay and polytherapy (Silanpaa and Shinnar, 2010); features all common in DS.

We evaluated the incidence and cause of death in DS and analysed variables that could influence the mortality and SUDEP risk. We measured the Dravet-specific mortality rate and the Dravet-SUDEP rate.

2. Methods

We studied the first 100 unrelated participants recruited to the Epilepsy Genetics Research Program from our cohort of 277 patients with the typical electroclinical phenotype of DS (Harkin et al., 2007). Sixty-one lived in Australia and 39 overseas. Consent for participation was provided by parents or legal guardians. This study was approved by the Austin Health Human Research Ethics Committee.

Each patient's physician was contacted to determine whether their patient had died and, if so, the age, circumstances and cause of death. Post-mortem reports were ascertained where available. Sex, age of seizure onset, MRI and genotype were obtained.

The general mortality rate and Dravet-specific SUDEP rate (including *Definite, Definite-Plus and Probable* SUDEP) (Ryvlin et al., 2013) were calculated for the number of person-years measured. Analysis began from either February 2001 or from when the child turned one year-of-age, whichever was later. This age was chosen as DS is usually not diagnosed until at least one year-of-age. The exit date was set as the date of death or the last date the patient was confirmed alive. The end of follow-up was designated as February 2015.

Survival without death from SUDEP and without death from *Not*-SUDEP causes (such as SE, drowning and asphyxia) are compared on a Kaplan-Meier curve. Factors that could influence mortality or SUDEP risk were analysed. Categorical data were compared using the Chi-square test (or Fisher's exact test when there were <5 subjects). Age related variables were not normally distributed and were compared using a Mann-Whitney *U* Test.

3. Results

The cohort comprised 100 patients with DS (61 girls); 87 had a *SCN1A* mutation. Median age at seizure onset was 5 months (IQR 4-7). 17/100 patients died at median age seven years (interquartile range (IQR) 3–11 years). The eight available post-mortem findings are presented in the Table.

SUDEP was the most common cause of death occurring in 10/17 (59%) deaths, at ages 2-20 years. SUDEP was *Definite* in 3 and *Probable* in 6 patients. Patient 10 had *Definite* SUDEP *Plus* with early signs of pneumonia. Toxicology did not show the prescribed antiepileptic medications. Four patients (1, 6, 8, 13) died from SE at age 13 months to 11 years with hypoxic encephalopathy and multi-organ failure. Three had fever and all had preceding viral infection. Two patients (5, 11) had a history suggestive of drowning. Patient 5, who drowned in the bath, had been unobserved for only a few moments, without evidence of a large amount of fluid in her lungs. Patient 7 had a witnessed seizure, with signs of asphyxia and aspiration of stomach contents on post-mortem. Sex, age of seizure onset, MRI abnormality and presence and type of *SCN1A* mutation were not associated with an increased risk of death or SUDEP (Table 1, Supp. Table 1). There was no correlation between the severity of the cognitive impairment and the risk of death.

The Dravet mortality rate, calculated over a total of 1073 person-years was 15.84 per 1000 person-years (98% CI 9.01–27.85). The Dravet-specific SUDEP rate was 9.32 per 1000 person-years (98% CI 4.46–19.45). The median age of those alive was 17 years (IQR 14–25) with median follow-up 10 years (IQR 8–13 years).

4. Discussion

We report a Dravet-specific mortality rate of 15.84 per 1000-person years which translates to an almost 15% risk of death after 10 years of follow-up post diagnosis of DS. This substantiates previous observations of a high mortality in DS, varying from 17.5% in medical series to 3.75% in a parent-led database (Dravet et al., 2012; Skluzacek et al., 2011; Sakauchi et al., 2011). The reason for this marked variation is multifactorial and includes ascertainment bias