Journal of Clinical Neuroscience 22 (2015) 1594–1600

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Sudden unexpected death, epilepsy and familial cardiac pathology

A.J. Eastaugh [a], T. Thompson [a], J.K. Vohra [a], T.J. O'Brien [a,b], I. Winship [a,b,*]

[a] The Royal Melbourne Hospital, Grattan Street, Parkville, VIC 3050, Australia
[b] The University of Melbourne, Parkville, VIC, Australia

ARTICLE INFO

Article history:
Received 22 April 2015
Accepted 2 May 2015

Keywords:
Arrhythmia
Brugada syndrome
Channelopathy
Long QT syndrome
Sudden unexpected death in epilepsy

ABSTRACT

We evaluated the prevalence of epilepsy in a cohort of patients who suffered a sudden unexpected death (SUDEP), and determined the proportion of the deaths that were related to an identifiable underlying familial cardiac pathology. Epilepsy is common in people who experience a sudden unexpected death, with approximately a quarter having identifiable familial electrophysiological abnormalities. Familial cardiac pathology may be an important cause of SUDEP. A retrospective evaluation was performed of 74 families that were referred to the Royal Melbourne Hospital Cardiac Genetic Clinic over a 5 year period for investigation following a family member's sudden, presumed cardiac, death. This state-wide referral clinic includes all patients who have died from a sudden unexpected death in whom the cause of death is unascertained. An epilepsy diagnosis was categorised as either definite, probable, possible or unlikely. The family members underwent comprehensive clinical evaluations and investigations in an attempt to identify a familial cardiac cause for the sudden unexpected death. Our findings suggest that systematic referral to a cardiac genetics service is warranted for the first degree relatives of people with epilepsy who experience a sudden unexplained death, for further evaluation and to identify those who are at higher risk for sudden death. Interventions may then be instituted to potentially reduce this risk.

1. Introduction

People with epilepsy have an increased risk of death compared to the general population [1–4]. One of the most important groups of deaths in people with epilepsy is sudden unexpected death (SUDEP) [5]. SUDEP refers to the sudden and unexpected death in a person with epilepsy who is otherwise well, whereby the death cannot be attributed to trauma, status epilepticus, toxins or drowning [6].

The reported incidence of SUDEP varies according to the populations examined [4,7–8]. In community samples, the incidence of SUDEP has been estimated at 0.09–2.65 per 1000 patient years [7]. By contrast, the incidence of SUDEP is estimated at 4 in 1000 patient years in patients being treated in specialised epilepsy centres [9], whilst the rate can be as high as 9.3 per 1000 patient years in those who have undergone epilepsy surgery but continued to experience uncontrolled seizures [7]. SUDEP may be the overall cause of as many as 18–30% of deaths in people with epilepsy [10–11], and is believed to be the leading cause of death in children and young adults with epilepsy [12].

The aetiology of SUDEP remains uncertain. The two most commonly implicated mechanisms are cardiac, due to a seizure induced malignant cardiac arrhythmia, or respiratory, due to post seizure apnoea or airway obstruction [7,9]. A third mechanism is cerebral hypoperfusion and brain shut down, which may occur in combination with respiratory or cardiac mechanisms [7].

Mutations in voltage-gated ion channel genes involved in regulating cardiac electrical conductivity are increasingly being recognised as important causes of sudden unexpected death in young people in a non-epilepsy context [13], frequently on a familial basis [14]. As a number of ion channels expressed in the heart are also expressed in the brain [15,16], it is possible that mutations in these ion channels predispose to the dual phenotype of epilepsy and sudden cardiac death [17]. There is increasing evidence to suggest that in patients with sudden unexplained death and negative autopsy findings, there may be a degree of overlap between channelopathies in familial cardiac arrhythmias and SUDEP [15].

This study aimed to evaluate data from a cohort of people who had experienced a sudden and unexpected, presumed cardiac, death to determine what proportion had a personal or family history of epilepsy, and identify what proportion had evidence of a familial cardiac pathology, specifically electrophysiological abnormalities that may predispose to sudden death. The information was collected and evaluated from the audit of a state-wide cardiac

* Corresponding author at: The Royal Melbourne Hospital, Grattan Street, Parkville, VIC 3050, Australia. Tel.: +61 3 9342 7151; fax: +61 3 9342 4267.
E-mail address: Ingrid.winship@mh.org.au (I. Winship).

http://dx.doi.org/10.1016/j.jocn.2015.05.002
0967-5868/

genetics clinic comprising autopsy reports, investigations of family members and collateral information.

2. Methods

2.1. Setting and study cohort

A retrospective analysis was undertaken of the families referred to the Royal Melbourne Hospital Cardiac Genetic Clinic from July 2007 to July 2012 for investigation following a family member's sudden death. This is a state-wide referral clinic from the Victoria Institute of Forensic Medicine (VIFM) for the families of all of those who have died from a sudden unexpected death where the cause of death is unascertained, leading the pathologist to query a possible inherited arrhythmia. Mostly, the deaths had occurred in a young person (<40 years of age), but the cohort included people up to 65-years-old who had no obvious cause of death. The clinic also receives referrals where a cardiac cause of death is found, however, these individuals were excluded from this study. Approval was given by the Melbourne Health Human Research Ethics Committee for this audit.

The aim was to analyse the deceased patient population where a death remained undetermined or unascertained after autopsy (with or without a history of epilepsy), by investigating family members. During the 5 year period, 196 separate families comprising 442 people were assessed in the clinic, and 122 families were excluded; 19 because of underlying preexisting conditions or a cause of death identified at autopsy, 35 because the deceased persons were found to have structural cardiac pathology on autopsy, 31 because an alternate cause of death was found or there was insufficient information, and 37 because no death had occurred (either a diagnosis had already been established or an out of hospital cardiac arrest with successful resuscitation had occurred). This left 74 families (comprising 184 people) where a death had occurred and the cause of death on autopsy was unascertained or considered to be SUDEP (n = 6).

2.2. Clinical data collection

Information regarding the deceased person's history of epilepsy was abstracted from the family files, which were obtained as standard practice at the clinic. The available data included the full autopsy report outlining the examination findings, circumstances surrounding the death and toxicology reports from the VIFM. A detailed history including the deceased person's medical history was obtained from collateral sources (family members and medical professionals after consent had been provided). The standard data collection included the family history, verified medical record including personal history, previous investigations including, where available, electroencephalogram and MRI. Based on this information, the deceased person was categorised as having a definite, probable, possible or unlikely history of epilepsy. The criteria for classifying a person as having a definite history of epilepsy was based on a combination of a prior diagnosis (as determined by correspondence from neurologists), and supporting information including positive imaging results, hospital admissions, treatment with antiepileptic drugs (AED) and a history of seizure activity. A 'probable' classification was when an individual had not necessarily been diagnosed with epilepsy, but there was a history of seizure-like events (with evidence of postictal confusion, tongue biting or incontinence) and treatment with AED. A 'possible' epilepsy classification was given if the deceased did not have a prior diagnosis but there was evidence of at least two episodes that were suspicious for seizure activity during their life. If there was evidence of seizure activity at the time of death, this information would support, but not alter, the classification of a deceased person. This 'possible' category was given to deceased individuals where there was seizure activity, but either due to age constraints or limited accessible information, a likely history of epilepsy could not be made. Where there was no history of seizure activity during life, nor correspondence, investigations or the use of AED, a classification of 'unlikely' was given.

2.3. Cardiac investigations

Information regarding their own medical history and investigations was collected for the surviving family members who were seen in the clinic. During the initial assessments an electrocardiogram (ECG) and transthoracic echocardiogram was performed on those who attended. Further cardiac investigations included exercise stress testing (Sprint protocol) and, where relevant, a flecainide or adrenaline challenge [18]. Genetic testing was undertaken if there was strong evidence of Brugada syndrome or long QT syndrome (LQTS) [18].The results of an audit of the full clinic cohort which analyzed the sudden cardiac deaths and arrests over a 6 year period have been published previously [18]. Of the 74 families that were included in this audit during July 2007 to July 2012, all had a minimum of one family member who underwent an ECG, of which 12 (16.2%) showed some anomaly (Brugada Syndrome or LQTS).

2.4. Genetic testing

Genetic testing was carried out in 15 (20.3%) of the families. Typically, six genes that are commonly associated with significant cardiac electrophysiological anomalies and risk of sudden death were analysed: potassium channel voltage gated KQT-like subfamily Q member 1 (KCNQ1; LQT1), potassium channel voltage gated EAG related subfamily H member 2 (KCNH2; LQT2), sodium channel voltage gated type V alpha subunit (SCN5A; LQT3), potassium channel voltage gated subfamily E regulatory beta subunit 1 (KCNE1; LQT5), potassium channel voltage gated subfamily E regulatory beta subunit 2 (KCNE2; LQT6), potassium channel inwardly rectifying subfamily J member 2 (KCNJ2; LQT7). In two of these families, testing of the cardiac ryanodine receptor 2 gene (RyR2) for catecholaminergic polymorphic ventricular tachycardia (CPVT) was performed.

3. Results

3.1. Personal or family histories of epilepsy

Of the 74 families studied, 15 (20.3%) of the deceased were identified as having a personal history of epilepsy; six categorised as definite, four as probable and five as possible (Fig. 1; Table 1). The details of these are given in Table 2. Of these 15 people, two (13.3%) had a family history of sudden death and four (26.7%) were identified as having an underlying familial cardiac cause of death (excluding one individual with an equivocal diagnosis of either CPVT or SUDEP).

Eleven (14.9%) families had a family history of epilepsy, seven of whom had a deceased member with no personal history of epilepsy (Table 3). There were 52 (70.3%) families in which there was neither a personal nor family history of epilepsy.

3.2. Cause of death

Of the 74 families in the study cohort, 12 (16.2%) were found to have an underlying cardiac history (eight with LQTS, two with borderline LQTS, and two with Brugada Syndrome). A diagnosis of