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Sudden unexpected death in GEFS+ families with sodium channel pathogenic variants

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ABSTRACT

We aimed to describe families with genetic epilepsy with febrile seizures plus (GEFS+) in which individuals suffered sudden unexpected death. The Epilepsy Pharmacogenomics Research Database was reviewed for GEFS + families in which at least one individual had suffered sudden death, and two families were identified. In Family A, five males had febrile seizures and one girl had febrile seizures plus. The latter died at 22 months of age and was classified as definite SUDEP. Molecular genetic testing identified a pathogenic *SCN1B* variant. In Family B, two brothers had recurrent focal status epilepticus with fever, and were classified as having atypical multifocal Dravet syndrome. The elder brother died suddenly at seven years of age, but was not classified SUDEP because the event occurred following status epilepticus. *SCN1A* sequencing in the surviving brother identified a likely pathogenic variant. These two cases of sudden death in GEFS + families with likely pathogenic variants in sodium channel genes demonstrate that sudden death may occur in GEFS+, even with mild phenotypes. The presence of sodium channel variants may have further increased the sudden death risk, particularly in the case of *SCN1B*, a gene which has also been associated with cardiac conditions including Brugada syndrome and long QT.

1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is a devastating occurrence, in which individuals with epilepsy die suddenly without an identifiable cause (Nashef et al., 2012). Of course, sudden unexpected death also occurs in individuals without epilepsy, and SUDEP occurs in only a small percentage of people with seizures (Bagnall et al., 2016). SUDEP researchers have investigated whether an aspect of the underlying etiology of epilepsy predisposes certain individuals to sudden death, or whether individuals suffering SUDEP carry other genetic factors that increase their risk of unexpected early mortality (Bagnall et al., 2016).

Two genes of interest in epilepsy and sudden death are *SCN1B* and *SCN1A (OMIM 600235 and 182* (OMIM 600,235 and 182,389), encoding the β-1 and α-1 subunits of the voltage-gated sodium channel, respectively (Escayg et al., 2000; McClatchey et al., 1993). Variants in *SCN1B* are associated with a specific familial epilepsy syndrome, genetic epilepsy with febrile seizures plus (GEFS+), in which members of the same family may have different phenotypes, the most common being febrile seizures (FS) and febrile seizures plus (FS+) (Scheffer and Berkovic, 1997; Wallace et al., 1998; Zhang et al., 2017). However, *SCN1B* variants have also been linked to non-epilepsy sudden death, with associations demonstrated with Brugada syndrome, sudden infant death syndrome and long QT syndrome (Hu et al., 2012; Riuró et al., 2014; Watanabe et al., 2008).

SCN1A pathogenic variants can cause multiple epilepsy phenotypes, including milder GEFS + phenotypes, Dravet syndrome, and other early-onset developmental and epileptic encephalopathies (Claes et al., 2001; Harkin et al., 2007; Wallace et al., 2001). *SCN1A* variants have not been clearly associated with non-epilepsy sudden death; however, SUDEP incidence is especially high in Dravet syndrome, in which ~90% of patients have *SCN1A* pathogenic variants (De Jonghe, 2011).

The link between sodium channel variants and SUDEP has been much discussed but remains unclear. Here, we report two GEFS + families with sodium channel gene variants, in which affected children suffered sudden unexpected death.

2. Methods

We reviewed the Epilepsy Pharmacogenomics Research Database at the Montreal Children's Hospital for cases of sudden death in GEFS + families. Informed written consent was obtained from parents

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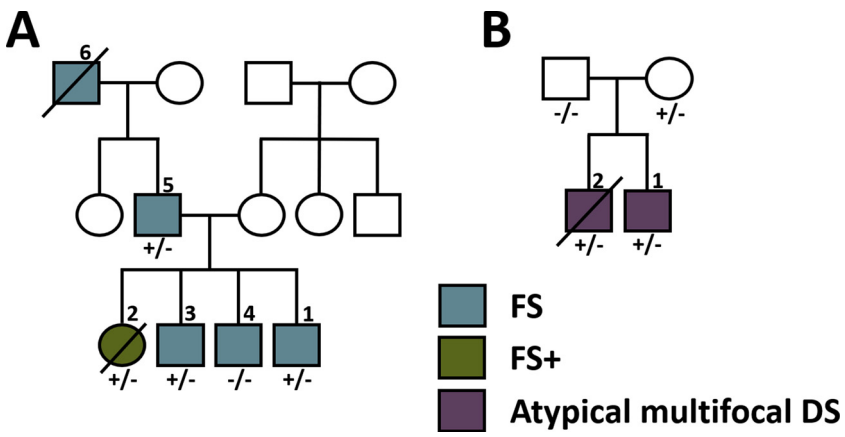

Fig. 1. Pedigrees of the two families. FS = Febrile seizures, FS+ = Febrile seizures plus.

in all cases. This study was approved by the McGill University Health Centre Research Ethics Board (2018–3937). Variant pathogenicity was classified by American College of Medical Genetics and Genomics Guidelines (Richards et al., 2015).

3. Results

Two families meeting criteria were identified.

3.1. Family A

3.1.1. Patient A1 (19 months)

A boy had two febrile convulsions at 11 and 12 months of age, with the latter lasting ˜25 min. He was prescribed clobazam to be taken while ill and has had no further events. Early developmental milestones were normal, with no history of regression. EEG at 12 months was normal, as were echocardiogram, ECG and Holter monitor study.

A five-gene GEFS + panel (*SCN1A*, *SCN1B*, *GABRG2*, *SCN2A*, *SCN9A*) revealed a paternally-inherited c.1 A > T, p.Met1? *SCN1B* pathogenic variant (Fig. 1A) which results in removal of the start codon. The change is predicted damaging, resulting in activation of a potential downstream translation initiation site with new reading frame. The variant is not present in the Genome Aggregation Database (gnomAD) (Lek et al., 2016).

3.1.2. Patient A2 (died at 22 months)

The older sister of A1 was born following uncomplicated pregnancy and delivery. She had three febrile convulsions between 12 and 16 months of age, all approximately five minutes. At 18 months, she had a 5-minute afebrile generalized tonic-clonic seizure. She was developmentally normal.

She was found dead following a nap at daycare at 22 months of age. On autopsy, periventricular leukomalacia was noted. Mild left ventricular cardiac hypertrophy was also noted; however, a 15-gene hypertrophic cardiomyopathy panel and 23-gene fatty acid oxidation panel did not reveal pathogenic variants.

Following A1′s genetic diagnosis, her DNA was tested, and she was found to also carry the *SCN1B* variant.

3.1.3. Patient A3 (5 years)

An older brother of A1; at four years of age he had an episode with fever with which he lost tone, became unresponsive, and had rhythmic jerking for five minutes. He is developmentally normal. EEG showed multifocal spikes over the left centroparietal, right centroparietal and right frontal regions. An echocardiogram and three ECGs were all normal.

Following A1′s genetic diagnosis, he was tested, and was found to also carry the *SCN1B* variant.

3.1.4. Patient A4 (7 years)

The eldest brother of A1, had two febrile convulsions between 2 and 3 years of age. He is developmentally normal. EEG at two years of age was normal. An echocardiogram and three ECGs were all normal.

Following his brother, A1′s genetic diagnosis, he was tested, and was found not to carry the *SCN1B* variant.

3.1.5. Patient A5 (44 years)

The father of A1 had febrile convulsions before six years of age (exact ages and number of seizures unknown). He did not have afebrile seizures and development was normal. He was found to carry the *SCN1B* variant on routine parental testing following identification in A1.

3.1.6. Patient A6 (died at ˜58 years)

Paternal grandfather of A1; had febrile convulsions as a child. Not known to have had afebrile seizures. He died at age ˜58 years of alcoholic cirrhosis (unavailable for genetic testing).

There was no other known family history of seizures or early sudden unexpected death. The parents were both of Romanian ancestry.

3.2. Family B

3.2.1. Patient B1 (13 years)

A 13-year-old boy had recurrent focal status epilepticus from 11 months of age. His events initially involved loss of awareness and hemiclonic movements, lasting up to 90 min. He subsequently had events that only involved impaired awareness. His events were initially with fever, but subsequently occurred without fever. Events were always prolonged, requiring emergency medication to abort. He has had an estimated seven events in total.

From a developmental perspective, he has mild global impairment. He walked at 18 months and is able to run and jump, but with more difficulty than age-matched peers. He also struggles with fine motor tasks. His first word was around one year; he speaks in sentences but language is delayed. He has attention deficit hyperactivity disorder, obsessive-compulsive and aggressive behaviours, and anxiety. He has not had clear developmental regression. His epilepsy phenotype appears most consistent with atypical multifocal Dravet syndrome (Kim et al., 2014).

He was trialed on valproate, nitrazepam and clonazepam; effectiveness was difficult to assess given the relatively low frequency of events. Interictal EEGs have all been normal. CT head was normal at 11 months, and again at 11 years. MRI brain at 13 months was also normal. Clinical sequencing of *SCN1A* identified a maternally-inherited c.973 T > C (p.325Tyr > His) missense variant, which is not present in gnomAD (Fig. 1B). Polyphen-2 predicts the change to be probably damaging (0.997) and Grantham score is 83. The variant is classified as

"of uncertain significance."

3.2.2. Patient B2 (died at 7 years)

From age three years, the proband's older brother also had recurrent focal status epilepticus that always required rescue medication to stop. He was treated with valproate, and carbamazepine was subsequently added. Initial EEG was normal, but at 6 years showed multifocal and generalized epileptiform discharges, with photoparoxysmal response. Development was normal. CT head was normal.

He died at seven years, following an episode of status epilepticus. Autopsy showed mild cerebral edema likely related to the prolonged seizure; the death was not classified as SUDEP by 2012 criteria because it occurred following status epilepticus (Nashef et al., 2012). He died years before his younger brother's genetic diagnosis, so *SCN1A* testing was not possible to confirm whether he carried the variant.

The two brothers were the only children of their non-consanguineous parents, both of southern Italian descent. There were no other known family members with seizures or febrile convulsions. After his brother's death, patient B1 had a 12-lead ECG and Holter monitor, both of which were normal.

4. Discussion

In these two GEFS + families, two children suffered sudden death, and both carried variants in sodium channel genes. The girl in family A represents the first description of SUDEP in a GEFS + family with *SCN1B* pathogenic variant, though there is one report of a possibly pathogenic *SCN1B* variant in an individual with "GEFS + " who suffered SUDEP (Bagnall et al., 2016). Her autopsy was reported as showing periventricular leukomalacia and mild cardiac hypertrophy; these findings are not typically reported in patients with *SCN1B* pathogenic variants, and their clinical significance is unclear in this case.

The boy in family B is the second report of sudden unexpected death in *SCN1A* -associated GEFS + (Hindocha et al., 2008). These cases are notable as pediatric SUDEP is rare, particularly in milder epilepsy phenotypes (Harden et al., 2017). In the children described, the sodium channel variant likely increased their risk of sudden death, though this cannot be stated with absolute certainty. Supportive evidence comes from the observation that when post-mortem genetic screening is performed in patients suffering SUDEP, there is a relatively high rate of pathogenic or possibly pathogenic variants in sodium channel genes (Bagnall et al., 2016).

These findings suggest there is additional utility in genetic testing in GEFS +, as a sodium channel variant may indicate increased SUDEP risk. In addition, the identification of sodium channel variants may lead clinicians to avoid the use of sodium channel antagonist drugs. This is especially pertinent in the case of the boy in the *SCN1A* family, who was taking carbamazepine at the time of death.

Genetic testing in GEFS + has been a topic of some debate in recent years. A 2013 statement recommended against *SCN1A* testing in GEFS + (Hirose et al., 2013); this was subsequently challenged by a report that de novo *SCN1A* variants can cause GEFS + phenotypes (Myers et al., 2017). A gene panel approach may be most appropriate in GEFS +, particularly as the cost of such testing continues to decrease.

Declarations of interest

None.

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