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Short communication

New SCN5A mutation in a SUDEP victim with idiopathic epilepsy

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ABSTRACT

Many idiopathic epilepsies have been shown to be caused by ion channel dysfunction. Channelopathies also cause the long QT syndrome (LQTS) which is associated with syncopes and sudden cardiac death. It has been postulated that the same channelopathy may be associated with both epilepsy and LQTS. We report a patient with idiopathic epilepsy who died in sudden unexpected death in epilepsy (SUDEP) at the age of 25. A post mortem DNA sequencing of the LQTS-associated genes revealed a novel missense mutation in the SCN5A gene coding for the cardiac sodium channel, voltage gated, type V, alpha subunit. The possibility that the mutation may explain both the epilepsy and the sudden death is discussed. However, the patient was treated with lamotrigine which may interfere with cardiac ion channels and may also have played a part in inducing a terminal cardiac arrhythmia.

1. Introduction

Many idiopathic epilepsies have been connected to channelopathies.[1] Likewise the congenital long QT syndrome (LQTS) which is associated with syncope and sudden cardiac death has been shown to be caused by ion channel dysfunction.[2] Most of the more than 400 different mutations that have been found to cause LQTS involve the potassium or sodium channel.[3]

It has been postulated that the same channelopathy may be associated with both familial long QT syndrome and epilepsy,[4] but so far there is little clinical evidence that connects cardiac ion channel dysfunction with epilepsy.

Recently, we reported four SUDEP victims with idiopathic epilepsy that were all young females treated with lamotrigine in monotherapy.[5] The deaths occurred during the 10 years period 1995–2005, and after the common denominators were recognized our hypothesis was that a genetic predisposition to cardiac arrhythmia may have played a part to their deaths. We therefore performed a post mortem analysis of the LQTS genes in these four patients. In three of the victims no abnormalities were found. In one (case one in our previous report) a novel mutation was detected.

2. Patient and methods

This previously healthy woman had her first seizure at the age of 17 years. The seizures started with a feeling of déjà vu, followed by a feeling of fear and a sensation down her chest which she described as being similar to an electrical current. She also felt flushed and had palpitations. The seizures lasted only a few seconds. Sometimes the patient's consciousness was reduced during these episodes. She also had generalized convulsive seizures and a few myoclonias.

After she was diagnosed with epilepsy at the age of 24 she was initially treated with carbamazepine (CBZ) in monotherapy. Because of insufficient effect the treatment was switched to valproate (VPA) which also had an unsatisfactory effect. After lamotrigine (LTG) was added to VPA 7 months ante mortem the seizure frequency was reduced, but the patient experienced side effects like hand tremor and tiredness. VPA was then tapered down and withdrawn 4 weeks ante mortem. At the time of SUDEP she was treated with lamotrigine 100 mg/day in monotherapy with no concurrent medication.

Her standard EEG showed frequent bursts of bilateral synchronous spikes followed by slow waves with side shift dominance with duration up to 2–3 s. A concurrent cardiac abnormality was not suspected ante mortem and unfortunately, an ECG was not conducted. The cerebral MRI was normal.

At the age of 25 she was found dead lying prone in her bed. Diagnosis after autopsy was SUDEP.[5]

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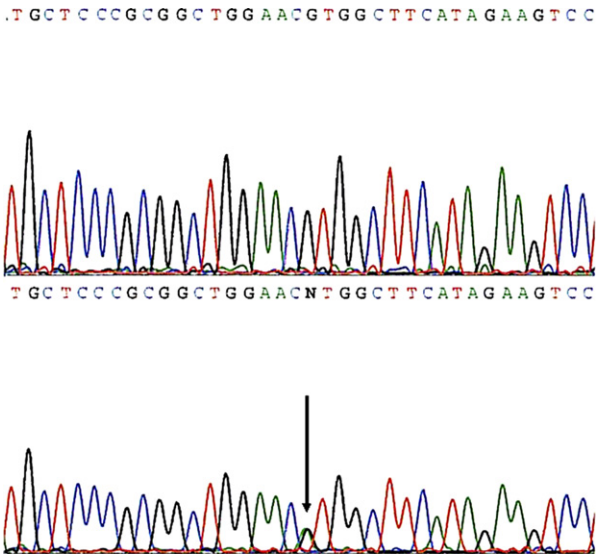

Fig. 1. Identification of mutation R523C in the SCN5A gene by DNA sequencing. The figure shows the DNA sequence of the anti-sense strand of nucleotides 1548–1585 of the SCN5A gene in a normal subject (upper panel) and in the SUDEP victim (lower panel). Above the electropherograms are shown the nucleotide compositions (A = adenosine; C = cytosine; G = guanosine; T = thymidine). Heterozygosity for an adenosine at nucleotide 1567 in the SUDEP victim is indicated by the arrow. This mutation changes codon 523 from CGT (arginine, R) to TGT (cysteine, C).

DNA sequencing of the translated exons with flanking intron sequences of the LQTS-associated genes KCNQ1, HERG, SCN5A, minK and MiRP1 was performed as described by Berge et al.[6] to study whether the patient actually had a channelopathy.

3. Results

The molecular genetic analyses revealed that the patient was heterozygous for the novel missense mutation R523C in exon 12 of the SCN5A gene (accession number XP_001131636) coding for the cardiac sodium channel, voltage gated, type V, alpha subunit (Fig. 1). This mutation was not identified in 315 unrelated Norwegian subjects referred for genetic testing with respect to LQTS. The mutation changes codon 523 from arginine to cysteine. Arginine is a polar and strongly basic residue, whereas cysteine is polar and neutral. Thus, there will be a change in charge. The amino acid substitution is located in a highly conserved region of the protein. It was predicted to be pathogenic by the use of the prediction program PolyPhen which is a bioinformatics tool that takes several parameters into account—like changes in charge of the amino acid substitution, sequence homology between species and effect on three-dimensional structure. More detailed information about Polyphen can be found on http://coot.embl.de/PolyPhen/

4. Discussion

In a recent review Nashef et al.[7] discussed a possible genetic predisposition to cardiac arrhythmia in SUDEP victims. However, the authors concluded that bridging evidence between cardiac inherited gene determinants and SUDEP is lacking.

The novel mutation we have detected is to our knowledge the first example described of a LQTS mutation in a SUDEP victim. Although the lack of an ECG precludes a firm clinical diagnosis of LQTS it is difficult to believe that the mutation is just a coincidence with no relation to the SUDEP.

Mutations in the SCN5A gene is associated with Brugada syndrome and the congenital LQTS type 3.[8] In addition to sudden cardiac death such mutations may cause syncopes and seizures.[9] In the literature there are several reports on patients with seizures that after a previous incorrect diagnosis of epilepsy eventually turned out to represent convulsive syncopes due to LQTS.[9–11]

We are not aware of convincing clinical evidence that mutations in the SCN5A gene may cause genuine epilepsy. However, the SCN5A gene has been shown to be selectively expressed in limbic regions of rat brain,[4] and the authors suggest that arrhythmias of heart and brain may be related and implicate SCN5A in some forms of primary inherited epilepsy. This may be relevant in explaining the seizures of our patient since they started with a déjà vu which is associated with the limbic system.[12]

Based on the ictal semiology the clinical episodes were considered to represent simple, complex partial and generalized tonic clonic epileptic seizures. However, the classification of the epilepsy syndrome was not unequivocal since the patient in addition to partial seizures also reported myoclonias and had an EEG with bilateral synchronous epileptogenic activity indicating generalized seizures.

Although the diagnosis of epilepsy seemed obvious with the epileptogenic activity in the EEG one might ask whether the diagnosis of epilepsy was incorrect and whether the clinical episodes could be explained as episodes of cardiac arrhythmias and syncopes which sometimes were convulsive. When the EEG was done the patient was treated with the tricyclic antidepressant clomipramine 10 mg t.i.d. because the symptoms were initially considered to be of psychogenic origin. It has been reported that high doses of tricyclic antidepressants may elicit epileptogenic activity in the EEG.[13] However, the drug dose was moderate and the epileptogenic activity very prominent and we therefore find this explanation unlikely.

Cardiac arrhythmia and respiratory arrest have been regarded as the two most probable pathophysiological mechanisms in SUDEP.[14] However, cardiac arrhythmias may result from a combination of predisposing factors and in epilepsy an arrhythmia may be more likely in a susceptible individual in the presence of apnoe/hypoxia.[7] SUDEP may therefore not necessarily be caused by a single factor but rather a combination of factors causing the terminal event. The cardiac SCN5A mutation that we have detected may have been of major importance in explaining the death of this young woman. Nevertheless a terminal epileptic seizure as well as a possible arrhythmogenic effect from the drug may also have been involved. LTG exerts its effect through blockade of sodium channels which has been claimed to cause widening of the QRS complex and right-axis deviation in the ECG.[15] A blockade of the cardiac potassium channel Ikr may also have played a part.[16]

5. Conclusion

The new SCN5A mutation that we have detected may support the notion that an ion channel mutation may be expressed both in brain and heart and give rise to both a tendency to epileptic seizures and a predisposition to cardiac arrhythmias. However, we have so far no evidence for a causative relationship between the mutation and the epilepsy in this patient.

More research is needed to reveal whether certain patients with epilepsy are genetically predisposed to cardiac arrhythmias due to expression of the same mutation in both brain and heart. This may be of particular importance in the choice of antiepileptic treatment to avoid drugs that may increase the tendency to potentially life threatening cardiac arrhythmias.

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