

Case Report

Epilepsy in patients with long QT syndrome type 1: A Norwegian family

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ABSTRACT

The congenital long QT syndrome (cLQTS) is an inherited cardiac disorder and is associated with sudden cardiac death. We describe a Norwegian family with mutations within the *KCNQ1* gene causing cLQTS type 1 (LQT1) and epilepsy. The index patient had Jervell and Lange-Nielsen syndrome (JLNS) with deafness and recurrent episodes of cardiac arrhythmia. The mother and the brother have Romano-Ward syndrome (RWS) with recurrent arrhythmias. Whereas the father has focal epilepsy and genetically verified LQT1, the sister has both focal epilepsy and RWS.

Our findings are consistent with the notion that mutations in the *KCNQ1* gene can cause epilepsy.

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1. Introduction

The congenital long QT syndrome (cLQTS) is associated with prolongation of the QT interval and T-wave abnormalities in the ECG, recurrent syncope due to torsade de pointes ventricular tachycardia with a propensity to ventricular fibrillation and sudden cardiac death [1]. It is caused by mutations in genes coding for ion channels. In 75% of cases the mutations are located in the potassium channel genes *KCNQ1* (LQT1) or *KCNH2* (LQT2) or, in a smaller proportion, the sodium channel *SCN5A* (LQT3) [2]. While the majority of individuals with symptomatic cLQTS have the autosomal dominant Romano-Ward syndrome (RWS) and primarily display symptoms of cardiac origin, a minor proportion have the autosomal recessive Jervell and Lange-Nielsen syndrome (JLNS) with both cLQTS and sensorineural hearing loss [3]. Several LQTS genes are expressed not only in the heart but also in the brain [4] and there is increasing scientific interest on the clinical implications of the neuronal co-expression of cardiac arrhythmia genes. It is well known that seizure-like episodes due to cardiac arrhythmia are common in individuals with cLQTS and many patients may have been erroneously diagnosed with epilepsy [5]. However, animal studies [6,7] as well as clinical studies have suggested a possible coexistence of cLQTS and epilepsy; in a cohort of 17 patients with cLQTS, 71% (12/17) had abnormal EEG compared to 13% of the controls ($p < 0.01$) [8] and in a

larger database of 343 patients an association between cLQTS and a seizure phenotype was confirmed [9]. In addition a few case reports have suggested that cLQTS genes may also co-exist with epilepsy [10–14]. However, in the literature there is still a paucity of clinical and electroencephalographic evidence of epilepsy in patients with cLQTS. We present a Norwegian family with genetically verified LQT1, cases of sudden death and individuals with a verified diagnosis of epilepsy.

2. Materials and methods

After the youngest son with JLNS had died at the age of three, the whole family was examined at Department of Cardiology, Oslo University Hospital. Previous diagnoses of epilepsy were reviewed at the Department of Neurology by patient interview and review of medical records.

The considerations made in the diagnostic workup and treatment of the family are reviewed and discussed. The work has been carried out in accordance with the Helsinki Declaration and all participants gave their written informed consent for publication.

3. Results

3.1. The family history

The index patient, the youngest son, had JLNS with biallelic pathogenic variants within the *KCNQ1* gene; Q530X and p.R192Cfs*91. He

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died at the age of three after numerous episodes with cardiac arrhythmia despite management with a pacemaker and beta-blockers.

His older brother has RWS caused by the mutation Q530X and had events with tachycardia and syncope. He is treated with beta-blockers and implantable cardioverter defibrillator (ICD), the latter secondary to episodes with significant arrhythmia.

The sister (see below) is the second of the three siblings and has RWS caused by the mutation p.R192Cfs*91. She has also been diagnosed with epilepsy.

Both parents are heterozygotes and have LQT1. The father (see below) carries the gene Q530X and has epilepsy. The grandfather on the father's side was deaf and died suddenly from unknown reasons at the age of 24. However, JLNS is suspected. In the father's side of the family there are no other cases with epilepsy, deafness or sudden death. The mother has RWS caused by the p.R192Cfs*91 mutation and experienced episodes of syncope during pregnancy and also during exercise. She is currently treated with beta-blockers. On her side of the family there are no cases with epilepsy. The pedigree of the family is shown in Fig. 1.

3.2. Epilepsy

3.2.1. The sister

She had a normal birth and development and had no history of febrile seizures, infection in the central nervous system or severe head trauma.

From the age of 10 years she experienced different types of episodes of loss of consciousness (LOC) with or without convulsions. They included confusion lasting up to a minute preceding loss of muscle tone and LOC. A second type was characterized by a brief moment of confusion, then collapse and involuntary movements described as twists and turns. She also had episodes of up to 2-minute duration with vertigo and sensation of loss of muscle tone in the lower extremities followed by collapse and LOC. These three types of episodes were all reported to be followed by a short period of postictal confusion. No palpitations or other symptoms suggesting cardiac etiology were present. A fourth type was characterized by rapid collapse and LOC for only a few seconds without any warning or associated postictal confusion.

Cerebral MRI on two occasions was normal. The electroencephalogram showed bilateral 4–5 Hz theta activity mainly in the temporo-occipital region. In addition, epileptiform activity with spikes and spike-

wave complexes was found on the left side, mostly in the temporal region, but also evident in the frontal and occipital regions (Fig. 2).

At the age of 11 she was finally diagnosed with focal epilepsy. Initial treatment with carbamazepine was withdrawn due to weight gain and replaced with lamotrigine in increasing dosage until satisfactory seizure control was achieved. She still uses lamotrigine and has not experienced seizures for at least 3 years.

After her younger brother was diagnosed with JLNS it was confirmed that she had inherited the mutation p.R192Cfs*91. The ECG showed a minimal prolongation of the corrected QT interval (QTc) up to 0.46 s. At the age of 11 she started treatment with beta-blockers, but despite treatment, she suffered with convulsions. Telemetry studies after the episode did not show signs of ventricular tachycardia. She had low levels of lamotrigine and the cardiologist concluded that the etiology was noncardiac and probably epileptic. Despite treatment with beta-blocker and lamotrigine she still had a few episodes with LOC. However, these were semiologically clearly vasovagal or circumstantial. A cardiac loop recorder was implanted and she was then asymptomatic for at least 2 years before she had a short episode with discomfort followed by LOC for at least 10 s. No postictal confusion, urination or tongue bite was described. The patient insisted that this episode did not resemble her previous episodes associated with LOC. Recordings from the loop recorder showed an episode of bradycardia and pauses up to 9 s. Due to her family history and psychological reasons, we implanted the patient with an ICD. At this point the lamotrigine levels were within the reference range.

The patient has now been long term asymptomatic relative to both syncope and seizures with treatment composed of a beta-blocker and a stable dosage of lamotrigine.

3.2.2. The father

He was diagnosed with epilepsy at the age of 13. No head trauma or complications at birth were documented. His primary seizure type was focal to bilateral generalized tonic-clonic seizures (GTCS) starting with jerks in one side of the face, possibly the right side, followed by LOC and GTCS. The GTCS-phase usually lasted from 2–3 min followed by a postictal phase with confusion of at least 10 min; sometimes prolonged postictal states lasting up to 1 h. Occasionally tongue or lip bite was reported. In addition, he had short episodes with reduced consciousness without loss of muscle tone most pronounced during the first years after diagnosis. The third type of event was characterized by small jerks in the extremities without LOC occurring also when standing in upright position. Seizure precipitating factors were lack of sleep and alcohol intake.

At the age of 13 he was treated initially with phenobarbital becoming seizure-free for one year, and later switched to carbamazepine due to periods with seizures, becoming again free from seizures for about 14 years. After seizure recurrence with a focal to bilateral GTCS lamotrigine was added and seizure control was re-established. Two years later, he discontinued lamotrigine and the seizures returned with up to eight GTCS per month. Valproate was then added to carbamazepine, and he has now been seizure-free for about 15 years.

The EEG has on several occasions shown focal slow wave activity in the frontotemporal regions with right-sided predominance. No definite epileptogenic activity has been found.

The cerebral MRI was normal.

When his younger son was diagnosed with JLNS, it was revealed that the father was carrier of the mutation Q530X. His QT interval was normal, no arrhythmias could be detected, and his seizures were considered not to be cardiogenic. Beta-blocker treatment was therefore not started, but he has been followed up regularly by the cardiologist.

4. Discussion

To our knowledge this is the first report documenting epilepsy in a patient with LQT1 and epileptogenic activity in the EEG.

The sister displayed a mixture of episodes of cardiac and cerebral origin. However, the episodes with impaired consciousness preceding loss

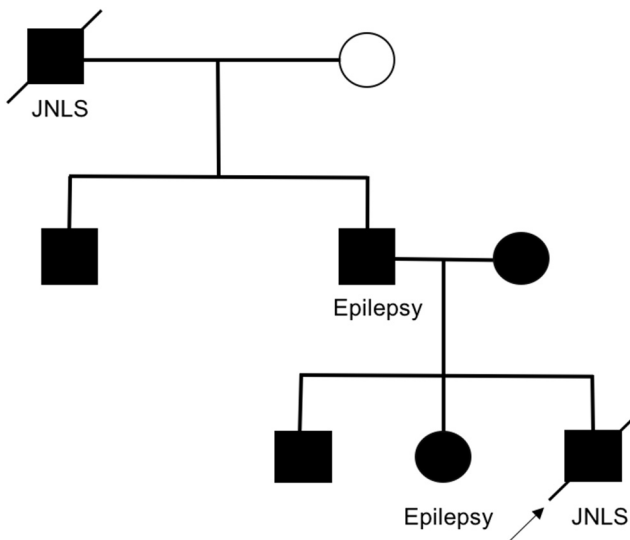


Fig. 1. Pedigree of the family. The index patient is indicated by an arrow. Female gender — circles; male gender — squares; filled squares and circles — individuals with cLQTS. Slashes — individuals with sudden cardiac death. JLNS — Jervell and Lange-Nielsen syndrome.

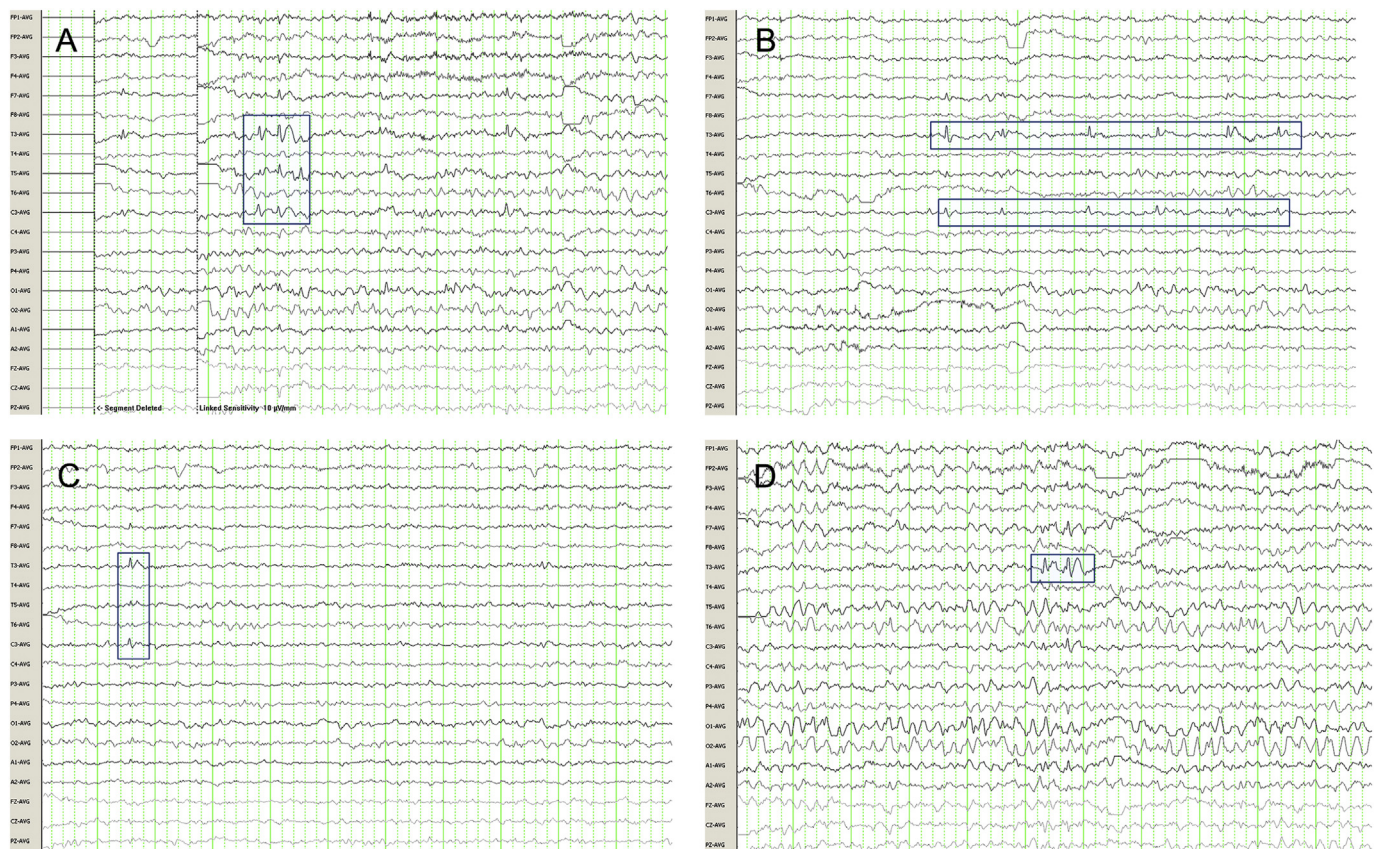


Fig. 2. EEG in the sister with Romano-Ward Syndrome and epilepsy. A–D: Epileptiform activity with single spikes and spike-wave complexes was found on the left side, mostly in the temporal region, but also evident in the frontal and occipital regions.

of muscle tone and focal epileptiform discharges on EEG provide strong support for a clinical diagnosis of epilepsy. After her younger brother was diagnosed with JLNS a cardiologic workup revealed that she also had LQT1.

The father is also a carrier of a LQT1 mutation, but has no sign of cardiac disease. Although his EEG never showed definite epileptogenic activity, the ictal semiology involving focal to bilateral GTCS is consistent with the diagnosis of focal epilepsy.

In 2009, Goldman et al. demonstrated that the potassium channel gene.

KCNQ1 is expressed in the forebrain and brainstem of mice. Animals carrying a mutation in this gene displayed episodes of cardiac arrhythmia and epileptic seizures may have simultaneous epileptogenic activity in the EEG in the presence of a controlled cardiac rhythm [6]. In our two patients with epilepsy, a thorough diagnostic workup did not reveal any other possible etiology other than the finding of a LQT1 mutation. In our opinion this is likely an illustration of the co-expression of cardiac arrhythmia genes in the brain. Furthermore, the differences in phenotypes between family members carrying the same mutation reflects the well-known phenotypic heterogeneity that is often seen in channelopathies [15]: Whereas the father carrying the mutation Q530X has epilepsy and is free from cardiac disease, his oldest son with the same mutation had recurrent episodes with cardiac arrhythmia, but no sign of epilepsy. Similarly, the mother carrying the mutation p.R192Cfs*91 had recurrent cardiac arrhythmia episodes without signs of epilepsy whereas her daughter with the same mutation has both epilepsy and symptomatic cLQTS.

Sudden unexpected death in epilepsy (SUDEP) affects around 1.2 individuals per 1000 patient-years in the general epilepsy population [16]. The majority of observed cases have occurred in relation to a GTCS [17,18]. Cardiac arrhythmias, ranging from insignificant to potentially life threatening, have been shown to occur in a significant

proportion of seizures [19–22] and are believed to represent a possible pathophysiological mechanism in the causation of SUDEP [23]. Consequently, individuals with both epilepsy and cLQTS may be at a particularly high risk of a fatal seizure-related arrhythmia. Interestingly, in a recent study including 61 SUDEP victims 7% had mutations in LQTS genes and 15% in other cardiac arrhythmia genes [24]. In the family we have presented the two cases of sudden death occurred in individuals with cLQTS without evidence of a coexisting epilepsy. Nevertheless, diagnosing cLQTS in the family members with epilepsy and initiating correct anti-arrhythmic treatment is of potentially vital importance.

Our experience supports that individual patients with a correct diagnosis of epilepsy may have co-existing cLQTS. In the epilepsy clinic, patients with this dual pathology may be challenging to identify among the majority of epilepsy patients. However, information about sudden death in the family of a patient with uncommon seizure types should prompt a thorough cardiologic workup. Future increased attention on the possibility of a coexisting cLQTS in patients with epilepsy may hopefully contribute to a reduction in the occurrence of SUDEP.

5. Conclusions

This case report describes a coexistence of epilepsy and symptomatic cLQTS in a family with LQT1. It reinforces the notion that mutations in genes coding for cardiac ion channels may be associated with abnormal brain function manifest as epileptic seizures.

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