



Case Report

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Long QT Syndrome, Epilepsy or Both? A Case-Report of a Family with Heterozygous Mutation in KCNQ1 Gene

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Abstract

Background: In the last few years, there has been an increasing interest in the association between epilepsy channelopathies and cardiac arrhythmias. This includes genetically confirmed congenital long QT syndrome (LQTS), an arrhythmologic syndrome often responsible for sudden cardiac death if left untreated. Sometimes, patients can be affected by both, LQTS and epilepsy caused by channel dysfunction in myocardial and neuronal cells

Case presentation: In this case-report we describe a family with a confirmed mutation in KCNQ1 gene, with a phenotype of both electrocardiographic-evident QTc prolongation and electroencephalographic-documented epilepsy.

Conclusions: Due to possible common genetic loci and presence of similar ion channels also in extra-cardiac tissues, we emphasize the need of raised clinical suspicion, collaborative approach, and comprehensive investigation of patients with a first episode of afebrile seizures or loss of consciousness of undetermined etiology.

Highlights

1. LQTS is associated with syncope, seizures or sudden cardiac death.
2. LQTS and epilepsy often seem to share common pathological pathways.
3. This case report describes a coexistence of epilepsy and LQTS in a family.
4. In the case of epilepsy, an electrocardiogram should always be performed, so that the diagnosis of LQTS will not be missed.
5. Correct identification of this dual pathology may be of vital importance to patients.

Key words: LQT Syndrome; Epilepsy; KCNQ1 Gene; Genetic Channelopathies; Seizures

Background

In the last few years there has been an increasing interest in the association between epilepsy channelopathies and cardiac arrhythmias, including genetically confirmed congenital long QT syndrome. Long QT syndrome is a genetic abnormality of ventricular repolarization, resulting from mutations in cardiac potassium and sodium ion channels. It is associated with prolongation of the QT interval and T-wave abnormalities in the electrocardiogram and occasionally with malignant ventricular tachycardia (torsade de pointes and ventricular fibrillation). The mean age of first cardiac event is 8 years for males and 14 years for female's [1-3]. The clinical manifestations of long QT syndrome range from sudden death in infancy, syncopal episodes, and seizures, to asymptomatic longevity, with phenotypical variability among family members [3-7]. About 75% of clinically long QT syndrome is caused by a mutation in 3 genes. In long QT syndrome type I the mutation is found

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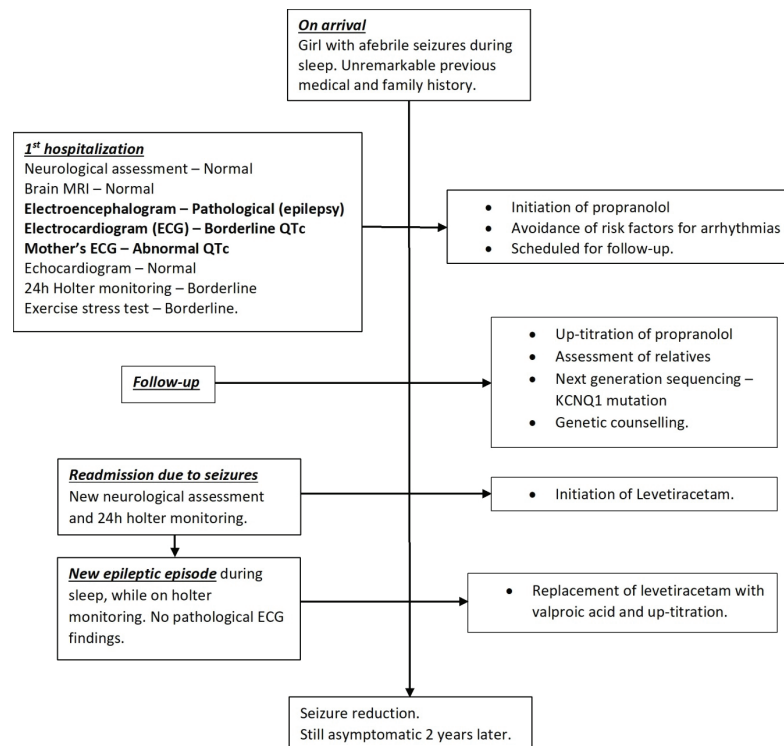


Figure 1: Case-report timeline - Diagnostic and therapeutic approach

in the KCNQ1 gene (35%), in type II in KCNH2 (30%), and in type III in SCN5A gene (10%), encoding for potassium (types I and II) and sodium channels (type III) that are critically responsible for the orchestration of the cardiac action potential [5,8,9]. So far, numerous pathogenic variants have been identified in patients suffering from cardiac arrhythmias and epilepsy, mainly in the SCN5A and KCNH2 genes [10.] Long QT syndrome may be misdiagnosed as epilepsy due to seizures triggered by secondary hypoxia during a ventricular arrhythmia [11]. However, some patients can be affected by both, long QT syndrome and epilepsy caused by channel dysfunction in myocardial and neuronal cells [10].

Combined electroencephalogram and electrocardiogram studies confirm the high prevalence (33-44%) of cardiac arrhythmias in individuals with true epileptic seizures, including 12%-22% of those with confirmed long QT type I mutation. On the other hand, 27% of the epilepsy patients who underwent genetic testing were variant-positive for the three genes [12-14]. Despite clinical practice guidelines and established diagnostic criteria (Schwartz Risk Score), the diagnosis of long QT syndrome continues to be missed. An estimated 39% of the patients experience a delay of 2.4 years between initial presentation and diagnosis, after their first episode of seizure or syncope [9,15]. However, those with an initial diagnosis of epilepsy have an average delay of 9.75 years, which can lead to patient and family deaths [1]. It has been suggested that screening electrocardiograms for long QT syndrome are indicated in those presenting with their first afebrile seizure.

We present two family members, a mother and her daughter, featuring long QT syndrome and epilepsy, who carry the same genetic variant in the KCNQ1 gene, with different clinical picture and clinical course. Written informed consent was obtained from the mother for publication.

Case presentation

Patient Information

An 8-years-old girl (30 kg) was referred for the evaluation of her

first episode of afebrile generalized tonic-clonic seizures, during sleep time. She is the third child of healthy and unrelated parents, born after an uneventful pregnancy, with a birth weight of 3kg, at the 37th gestational week. She had no perinatal problems and achieved normal developmental milestones. Her medical history was unremarkable. Family history was also negative for sudden death or epilepsy. Her physical examination did not yield any important clinical findings. The diagnostic and therapeutic approach (timeline) is presented in Figure 1.

Diagnostic Assessment

During her hospitalization, neurological assessment was normal. Brain MRI did not reveal any pathological findings. Electroencephalogram was pathological with high voltage spike-wave complexes at frontal-temporal area, supporting the diagnosis of epileptic seizures (Figure 2A).

Cardiologic assessment demonstrated a borderline corrected QT (QTc) of 472 msec at a heart rate of 80bpm (using the Bazett formula), accompanied by non-specific repolarization abnormalities (Figure 3 online). Her echocardiogram was unremarkable. According to European Society of Cardiology guidelines long QT syndrome is diagnosed with either QTc $\geq$ 480 msec in repeated electrocardiograms or with a long QT Schwartz risk score $>$ 3 or finally in the presence of a known mutation. However, it should also be considered in patients with a QTc $\geq$ 460 msec and an unexplained syncopal episode.

Cardiological assessment was performed to the mother of the child. Her electrocardiogram revealed a QTc of 495 msec with exaggerated repolarization abnormalities. Her echocardiogram was also normal and she only reported a vasovagal syncopal episode after prolonged standing 25 years ago. However, her electrocardiogram raised the clinical suspicion for long QT syndrome with hereditary involvement. Treatment with propranolol was initiated in the mother. In addition, a 24-hour holter monitor was placed at the child, which did not reveal any arrhythmias or low mean heart rate according to age. Throughout the day, her QTc was between 421 and 482 msec.



Figure 2: A). Interictal EEG of the patient at the time of diagnosis, showing high voltage spike-wave complexes mainly recorded from frontal-temporal lobe
 B). EEG 2 years later with the presence of sporadic low-voltage spikes on left frontal-temporal area

Following the Schwartz criteria and since the child was stable, an exercise stress treadmill test was also performed 5 days later which revealed once more a borderline QTc of 477-480 msec at the fourth minute of recovery.

Therapeutic Intervention

So, due to high clinical suspicion (Schwartz Score 3) the child was also initiated on propranolol (1mg/kg/D) and patient and family education for avoidance of provocative factors was offered. Triggers for cardiac events include but are not limited to exercise and emotional stress, swimming and exposure to cold water, exposure to loud noise and alarm clocks, dehydration, and QTc prolonging drugs. In addition, genetic counseling was advised, and the child was scheduled for follow-up accompanied by her siblings.

Follow-up and Outcomes

On her scheduled appointment one month later, she did not complain of any new symptoms and her new electrocardiogram revealed a QTc of 467 msec. Up-titration of propranolol was performed (to 2mg/kg/D). Her siblings were also assessed. Her 18-year-old brother had a QTc of 422 msec, and her 16-year-old sister a QTc of 455 msec. Their echocardiograms were within normal range. The family received genetic counselling and next generation sequencing was performed which revealed the heterozygous mutation c. 724G>A in KCNQ1 gene, in both mother and child, responsible for familial long QT syndrome (Figure 4 online). The mutation was not identified in her siblings. An electroencephalogram was then performed to the mother who did not reveal any pathological findings.

Two months later she was re-admitted due to recurrent episodes of generalized tonic-clonic seizures, during sleep time. Levetiracetam was chosen as antiepileptic treatment. However, because of failure to respond, epileptic episodes were treated with dosage adjustment (40mg/kg/D). The patient was also re-evaluated with a 24-hour holter monitor. During sleep the patient had an epileptic episode but no pathological findings were reported on holter monitoring. Levetiracetam was then replaced with valproic acid, resulting in significant seizure reduction. Upon reaching the maximum dosage on valproic acid (30mg/kg/D), a cardiological reassessment was performed without aggravation of the already existing electrocardiographic findings.

Currently, 2 years after the diagnosis, she remains asymptomatic. She is on antiepileptic treatment with valproic acid (30mg/kg/D) and she is free of seizures. Her inter-ictal electroencephalogram has improved, with the presence of sporadic low-voltage spikes on left frontal-temporal area (Figure 2B). She also continues her medication with propranolol (2mg/kg/D) without any new significant electrocardiographic changes.

Discussion

In 2009, Goldman et al. demonstrated in mice that the potassium channel gene KCNQ1, which was known to encode the cardiac KCNQ1 (KvLQT1) delayed rectifier channel, was also expressed in forebrain neuronal networks and brainstem nuclei, regions in which a defect in the ability of neurons to repolarize after an action potential can produce seizures and dysregulate autonomic control of the heart. Animals carrying a mutation in this gene, displayed episodes of

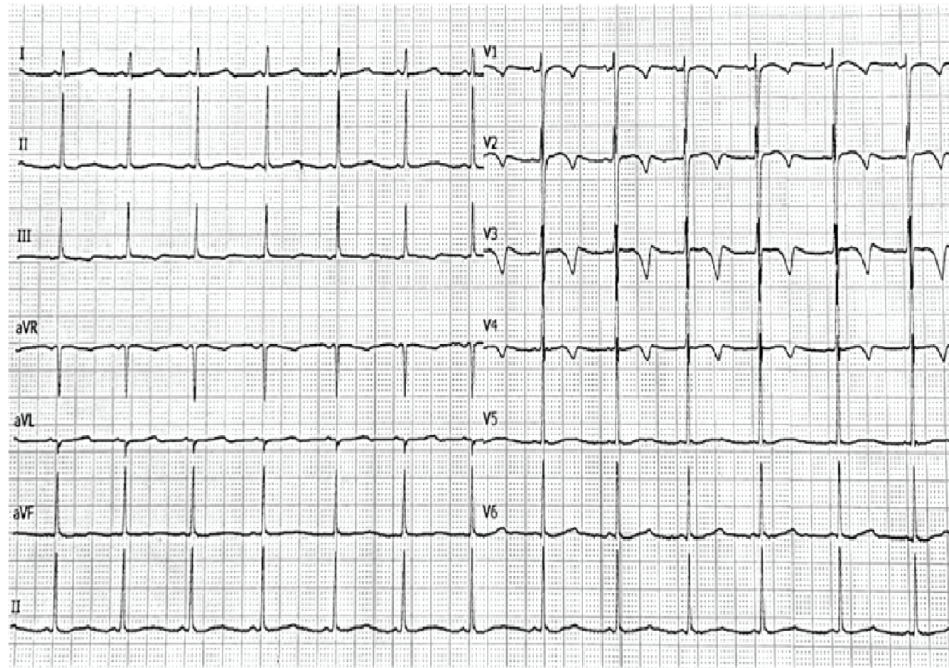


Figure 3: online. Baseline ECG of the girl showing a borderline QTc of 472 msec at a heart rate of 80 bpm, as calculated by the ECG machine. Non-specific ST changes are also noted (subtle flattening of the T-waves in the inferior and lateral leads)

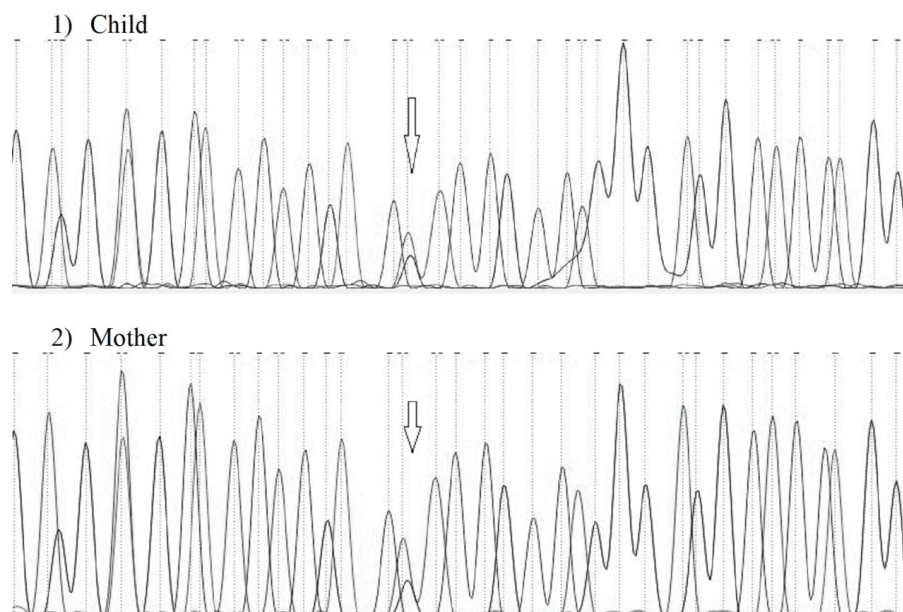


Figure 4: online

Sanger sequencing data

1) Mutation c.724G>A in the KCNQ1 gene in heterozygous state (child)

2) Mutation c.724G>A in the KCNQ1 gene in heterozygous state (mother)

cardiac arrhythmia and epileptic seizures and may have simultaneous epileptogenic activity in the electroencephalogram in the presence of a controlled cardiac rhythm 12.

In the family reported in our case, diagnostic workup revealed a heterozygous mutation in KCNQ1 gene. Whereas the mother carrying the same mutation has asymptomatic long QT syndrome and no sign of epilepsy, her daughter with the same mutation

has both epilepsy (with seizures and epileptogenic activity in the electroencephalogram) and asymptomatic electrocardiographically evident long QT syndrome. In our opinion, this is likely co-expression of cardiac arrhythmia genes in the brain, as shown in animals. The differences in phenotypes between family members carrying the same mutation reflects the well-known phenotypic heterogeneity that is often seen in channelopathies [16].

Epileptic seizures are common in patients with long QT syndrome and frequently appear independent of cardiac symptoms. The brain expresses KCNQ1 and it has been found that approximately a 25% reduction in KCNQ channel activity due to impaired expression or function, can lead to a loss of control over neuronal excitability in the brain, resulting in a seizure predisposition [17,18]. Proposed mechanisms include direct stimulation of the central autonomic network (i.e., cingulate gyrus, amygdala, or insular cortex) and seizure-induced catecholamine release leading to vasovagal responses [19]. The manifestation of epileptic seizures without precedent cardiac arrhythmias in all patients with long QT syndrome and the absence of family members with epileptic seizures without long QT syndrome implicate the involvement of a genetic modifier [14]. Video-electroencephalographic monitoring in mutant animals, detected two types of seizures; generalized and partial motor seizures, consisting the most common type [12]. In our patient, all epileptic episodes presented with generalized tonic-clonic seizures during sleep, lasting less than 2 minutes. If we consider that in one of the episodes, concomitant holter monitoring did not record any arrhythmias, this could support the evidence showing that episodes appear independently of cardiac symptoms. We cannot provide a scientific explanation why the mother did not report any seizures. It may be explained by a possible age-dependent expression/appearance of epilepsy and/or by the influence of additional genetic or environmental modifiers.

Long QT syndrome, predisposes patients to ventricular arrhythmias that can lead to syncope and sudden cardiac death [10]. In a recent review, Bleakley et al. (2020), highlight that variants in known cardiac genes, and in several other cardiac and long QT syndrome genes, have been identified in sudden unexpected death in epilepsy cases [8]. The heart-brain potassium channel gene, KCNQ1, was identified as the first ion channel gene for sudden unexpected death in epilepsy, associated with the most common form of cardiac long QT syndrome (LQT1). Patients with this gene exhibit spontaneous, unprovoked seizures that can lead to lethal cardiac arrhythmias [12]. In a separate postmortem study of 68 cases, mutations in genes associated with LQTS were found in 13% of patients. A leading explanation for sudden unexplained death in epilepsy, which affects up to 17% of those with idiopathic epilepsy and accounts for 7.5%-20% of patients' deaths, is that seizures initiate pathogenic neural signalling between the brain and heart, leading to lethal cardiac arrhythmias [10,17]. Although our patient's family history was free of sudden and unexpected death, the risk of sudden death is present and increased, especially with recurrent seizure activity. Adrenergic β -blockade, as it has already been added, may reduce the likelihood of fatal arrhythmia.

Conclusions

Here we report two family members with heterozygous mutation in KCNQ1 gene and variable clinical expression. This family further supports the view that coexistence of epilepsy with long QT syndrome may not be as rare as we believe and that KCNQ1 genetic variations may be expressed in a different way even in the same family. In case of diagnosis of the syndrome in a family member, an electrocardiogram should be obtained in all first-degree family members to determine whether others are affected. Up to approximately 50% of family members will be gene carriers and potentially at risk [11]. Future increased attention on the possibility of a coexisting long QT syndrome in patients with epilepsy may hopefully contribute to a reduction in the occurrence of sudden unexplained death in epilepsy.

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