Long QT syndrome masquerading as epilepsy

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ABSTRACT

The diagnosis of epilepsy is incorrect in up to 20% of cases so should be revisited if attacks are not responding to treatment. We present a case of long QT syndrome that remained undiagnosed in the epilepsy clinic for 15 years until a near-fatal arrhythmia revealed the diagnosis and allowed effective treatment of her attacks. We hope this near miss raises awareness of long QT syndrome as a potentially fatal, rare but treatable condition that neurologists must consider in people with a label of refractory epilepsy. We provide practical pointers to increase the chance of early diagnosis and explore the impact of a late diagnosis for the patient and her family.

CASE REPORT

A 16-year-old girl presented with sleep-related events. In January 2001 on a school skiing holiday, her friends heard her making noises at night. While sleeping upright on a coach, she fell into the aisle unresponsive with her eyes wide open, but with no abnormal movements. She awoke within 2 min and was confused for 5–10 minutes. Later that night she was witnessed to shake in her sleep; her friends could not rouse her but on waking she recovered quickly. Her mother witnessed five further episodes over the following week, all in sleep and usually in the early morning. Her parents heard her whimpering with either shaking of her upper body or thrashing movements of all limbs lasting for 2–3 minutes. She was unresponsive during the episodes and would go back to sleep and sleep until morning. The following day she had only a vague feeling that something had happened. Her neurological and cardiovascular examinations were normal.

The exact nature of her episodes was not clear. The history did not suggest generalised tonic-clonic seizures, and possible diagnoses of frontal lobe seizures or sleep disturbance were considered. CT scan of head and EEG were normal. The EEG included a single-lead ECG, showing sinus rhythm at 54–90 beats per minute. Her blood test results were normal.

We prescribed lamotrigine for presumed frontal lobe epilepsy and her attack frequency decreased. In 2003, 2005, 2008 and 2010, she re-presented with further attacks on waking suddenly in the morning (figure 1). On one occasion on her honeymoon, an alarm at 06:00 triggered a seizure. By 2010, she was taking lamotrigine 300 mg daily. A family history emerged that two of her father's cousins had died in their early 20–30s in their sleep of an unknown cause.

In March 2012, she had a seizure post partum that was described as stereotypical tonic-clonic seizure lasting 2–3 minutes, followed by confusion and sleeping for 2 hours. In August 2012, she has a further generalised convulsive seizure with urinary incontinence. In 2014, during her second pregnancy, she had two further generalised seizures in the first trimester that were described as '*she wakes up, calls her husband's name, appears panicky, hyperventilates and then comes round*'. At this stage, the attacks were described as focal epilepsy with no EEG localisation to suggest frontal lobe seizures. We increased the dose of lamotrigine to 350 mg daily. After the birth of her second child in May 2015, she reduced the dose of lamotrigine to 325 mg daily. At the end of July 2015, she experienced increased seizure activity where she would startle from sleep with heavy breathing, become rigid but not cyanotic, with no limb jerking for 10–15 s with eyes closed and irregular breathing and then relaxed and was clammy with confusion for a few minutes, followed by a deep sleep. Lamotrigine was increased to 400 mg daily (figure 1). In June and July 2015, she had four to six seizures per month, all from sleep. In December 2015, a repeat MR scan of brain was normal. In December 2015, we added levetiracetam and increased this to 750 mg twice a day.

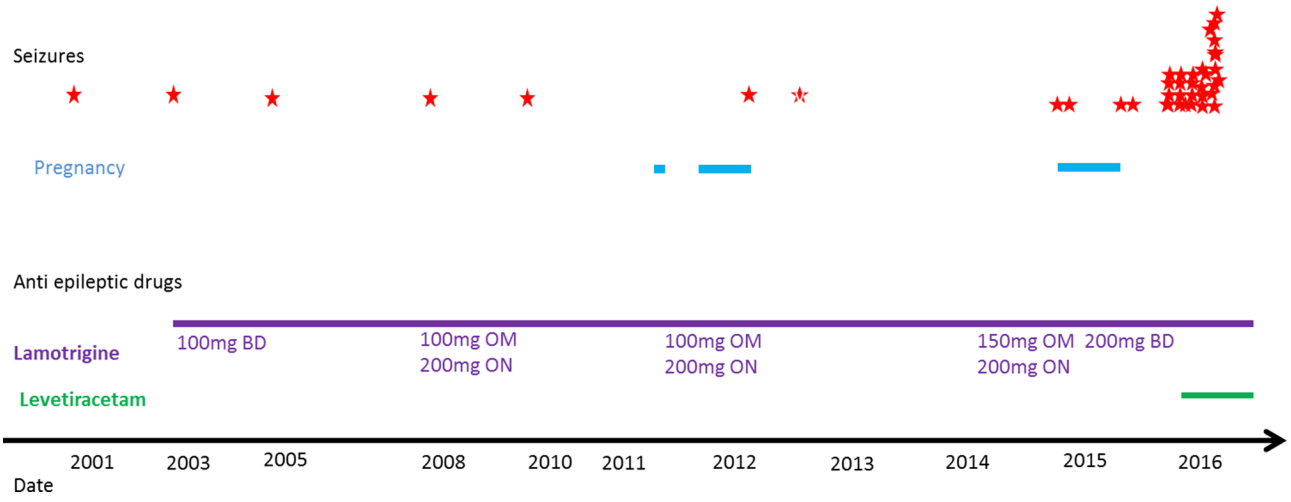

Figure 1 Timeline of seizure frequency, antiepileptic medication and pregnancy. Individual seizures represented by red stars show the increased frequency associated with pregnancy (blue) and the effect of medication lamotrigine (purple) and levetiracetam (green). BD, twice a day; OM, once a day in morning; ON, once a day at night.

In January 2016, she had five seizures, and in February 2016, she had 11 seizures.

On 28 April 2016, she had a seizure in bed at 04:45 that lasted over 5 min: she was found to be in ventricular fibrillation and received defibrillation. ECG in emergency department showed bigeminy (figure 2A). A subsequent 12-lead ECG showed prolonged QT 600–630 ms (figure 2B). She had further episodes of ventricular fibrillation in intensive care (figure 2C). She had a pacing wire and implantable cardioverter–defibrillator fitted. The levetiracetam was switched to zonisamide. She then had a genetically confirmed

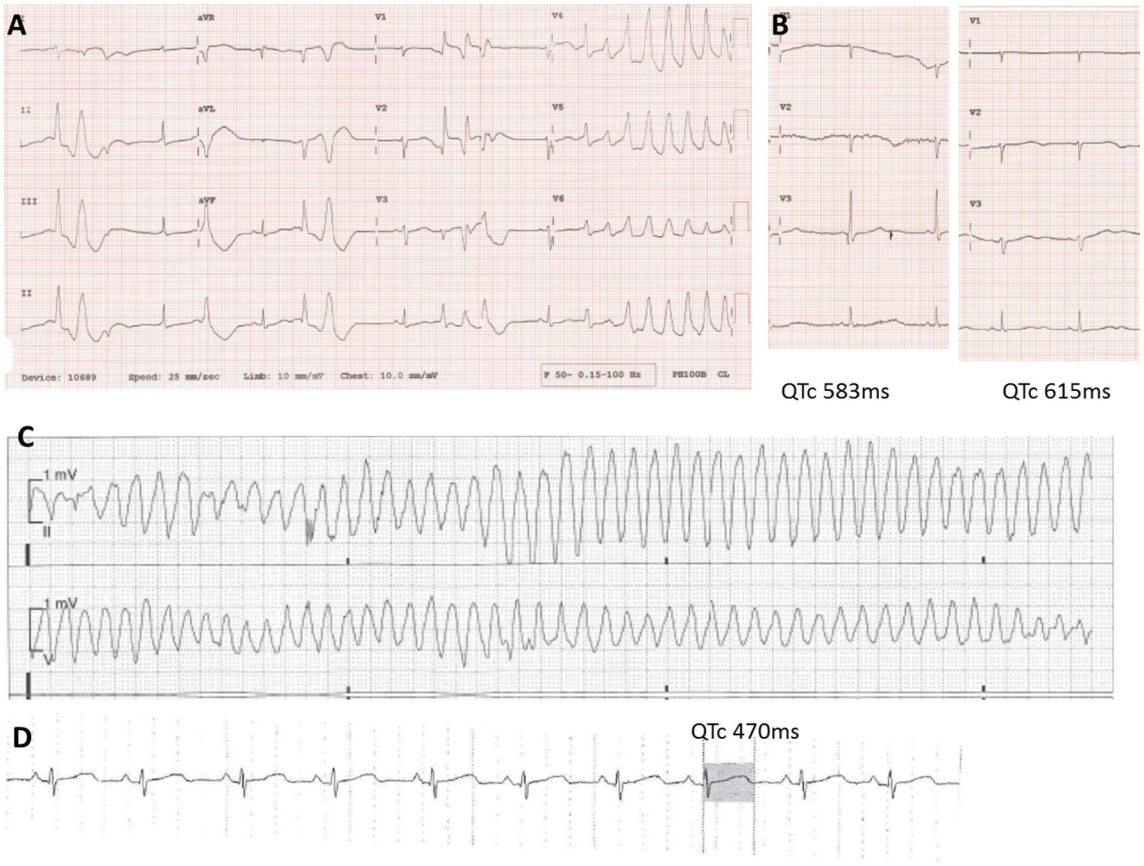

Figure 2 ECG abnormalities. ECG in emergency department showed bigeminy (A). Subsequent ECG showed prolonged QT 600–630 ms (B). She had further episodes of ventricular fibrillation in intensive care (C). Retrospective analysis of single-lead ECG from her EEG at diagnosis showed a heart rate of 75 per minute, QT interval of 419 ms and corrected QT interval (QTc) of 470 ms (D).

diagnosis of long QT syndrome type 2 (LQTS2) with a pathogenic mutation in *KCNH2*. She was treated with propranolol, and the zonisamide and lamotrigine were slowly withdrawn. She has not had any further attacks.

Our retrospective analysis of the single-lead ECG performed during her EEG at diagnosis in 2001 showed a rate of 75 beats per minute, QT interval of 419 ms and corrected QT interval (QTc) of 470 ms (normal up to 460ms) (figure 2D).

Reflection

This is a case of long QT syndrome that remained undiagnosed in epilepsy clinic for over 15 years and was diagnosed after a near-fatal cardiac arrhythmia. Unfortunately, such delayed diagnosis is not uncommon. Thirty-nine per cent of patients with long QT syndrome are diagnosed on average 2.4 years after their first seizure or syncope. 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] The question is how can we avoid missing similar cases in our epilepsy clinics? Clearly, awareness of long QT syndrome is key, but it is also worth considering what this syndrome is and how to diagnose it. Also, there is the possibility that proarrhythmic effects of her antiepileptic drug treatment worsened the situation, We will consider the possible interactions between the arrhythmia and the epileptic drugs. Finally, the patient describes the effect of the new diagnosis on her (box 1).

Box 1. Patient perspective: effect of late diagnosis

'I don't recall being particularly upset or alarmed by my original diagnosis of epilepsy, perhaps because of my young age—the daily medication and very occasional seizure became part of my life. It wasn't until years later when I became pregnant that it concerned me because of the possible effect taking antiepileptic medication could have on either of my unborn children. I try not to think about the 'what ifs' since my change in diagnosis to long QT syndrome, but I know that the pregnancies would have been completely different had I known I had long QT syndrome, given the 50/50 chance each of the children inheriting it and the higher risk to me post partum. It has taken a lengthy course of counselling since my cardiac arrest and long QT syndrome diagnosis to live with this new normal for me and my daughter and come to terms with my ICU stay and how close the children came to losing their mother at 11 months and 4 years old'.

DISCUSSION

What is Long QT Syndrome?

Long QT syndrome (LQTS) is a rare, life threatening channelopathy with an incidence of 1 in 2500. There is 20% mortality in the first year after presentation and 50% in the next 10 years(1). It is a disease of the young with mean age of first cardiac event 8 years for males and 14 years for females; 90% have their first cardiac event before the age of 40 years. The high risk period is in puberty for males and in adulthood for females. It is caused by a mutation in either potassium or sodium channels that result in prolonged and unstable repolarisation with dispersion of refractoriness between cardiac cells which results in triggered activity resulting in a characteristic form of polymorphic ventricular tachycardia called Torsade de Pointes which the QRS axis rotates through 360 degrees. Greater than 90% are explained by a mutation in 3 genes (table 1). Each of these mutations have different channelopathic changes, ECG changes and arrhythmia precipitants. LQTS can be treated with beta adrenergic blocking agents, left cardiac sympathetic denervation and implantable cardioverter- defibrillator. Beta blockers, specifically propranolol, the first line choice for symptomatic patients combined with avoidance of QT prolonging medication is associated with a 97% reduction in risk of cardiac events in these patients.

Diagnosis of long QT syndrome

The diagnosis of long QT syndrome starts with awareness of specific features in the history of the attacks.[2] These can be sudden syncope, near syncope or prolonged syncope with seizures. The loss of

Table 1

	LQT1	LQT2	LQT3
Disease-associated gene	KCNQ1	KCNH2 (hERG)	SCN5A
Channel	α subunit Kv7.1 potassium channel and slow delayed rectifier potassium channel	α subunit Kv11.1 and rapid delayed rectifier potassium channel	α subunit Na v1.5 sodium channel and voltage-gated sodium channel
Resting ECG	Broad T wave	Low amplitude T wave, bifid/ notched T wave	Long isoelectric ST segment, bradycardia
Arrhythmia precipitants	Physical or emotional stress, swimming	Acoustic stimuli/startle, physical or emotional stress, rest	Rest, sleep
ECG at start arrhythmia	No pause	Pause common	Not known
Clinical response to beta blockers	Yes	Yes (less than LQT1)	Insufficient data ? Less effect

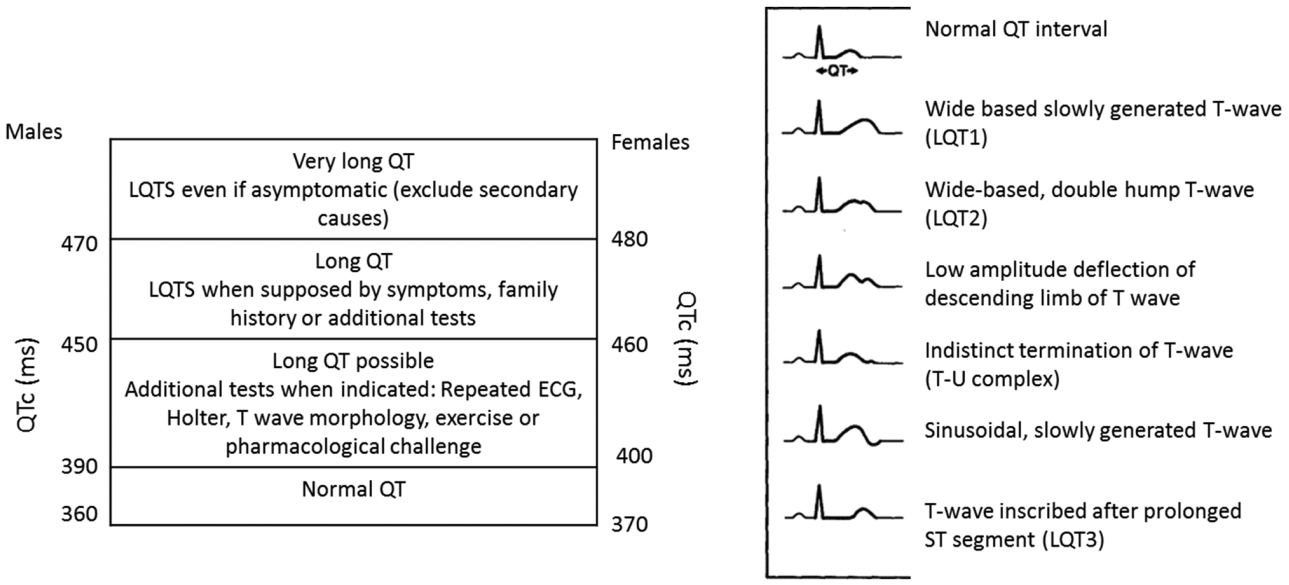

Figure 3 Diagnosis of long QT syndrome. Interpretation of the ECG is important in the diagnosis of long QT syndrome. The normal range of the QTc varies in males and females (A). The ECG can be normal and it is important to check for the presence of T-wave abnormalities (B).

consciousness is due to aborted episodes of *torsade de pointes*, and so occur suddenly as slumping with no warning; they can cause injury, near drowning, vehicle accidents and fainting in bed. Specific triggers include exertion, fever (especially in LQTS2, which could be reported as febrile convulsions), startle and sudden noises (such as the alarm clock in this case). The peripartum period is dangerous for women with long QT syndrome again as shown here. Family history should take in the wider family especially sudden, unexplained death, drowning and sudden infant death syndrome.

ECG interpretation is the next crucial step. The National Institute for Health and Care Excellence (NICE) epilepsy guideline (CG20, 2004) states that all patients with epilepsy should have a full 12-lead ECG. The normal range of the QTc varies in males and females (figure 3A). However, manual measurement of QT interval is difficult and most physicians, including many cardiologists, cannot accurately calculate a QTc and cannot correctly identify a long QT interval.[3] To avoid these interpretation errors, the NICE Transient Loss Of Consciousness guideline (CG109, 2010) states that all patients should have a 12-lead ECG using automated interpretation; a long QT interval is treated as a red flag if reported on the ECG printout. If a 12-lead ECG with automated interpretation is not available, take a manual 12-lead ECG reading and have this reviewed by a healthcare professional trained and competent in identifying long QT (corrected QT>450 ms). Therefore, the advice to neurologists is to use an automated ECG, and if concerned then ask a cardiologist, rather than to try to analyse the QT interval. It is important for neurologists to maintain skills in ECG interpretation.[4]

This case has many parallels to a case of sudden death from long QT syndrome reported in *Practical Neurology* in 2010[5]; at that time, the authors recommended 12-lead ECG in all people with a diagnosis of epilepsy, having an EEG record a channel of ECG with reporting of QT and QTc interval, and to ensure there are local arrangements for joint working with

Table 2 Diagnosis of long QT syndrome: Schwartz score

Measurements	Points
ECG findings	
QTc interval	
≥480 ms	3
460–479 ms	2
450–459 ms (male)	1
4 min recovery QTc after exercise ≥480 ms	1
Torsade de pointes	2
T-wave alternance	1
Notched T wave	1
Low heart rate for age	0.5
Clinical findings	
Syncope	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history	
Family member with long QT syndrome	1
Unexpected sudden cardiac death age <30 years in family members	0.5

≥3.5 points: diagnosed as long QT syndrome; 1.5–3 points: suspected long QT syndrome; ≤1 point: unlikely long QT syndrome.

Table 3 Antiepileptic drugs that can cause arrhythmias

Drug	Mechanism of action	Arrhythmia
Carbamazepine	Sodium channel blocker	Atrioventricular (AV) conduction blocks
Phenytoin	Sodium channel blocker	Sinus arrest and hypotension
Lacosamide	Slow inactivation of voltage-gated sodium channels	PR prolongation Atrial flutter AV conduction blocks

cardiology. In this case, clearly a review of the ECG channel of her EEG initially might have prompted a 12-lead ECG and cardiac investigations. The NICE guidelines for Transient Loss Of Consciousness guideline (CG109, 2010) were published nine years after our patient's first presentation. As this case reflects, there are a large number of patients in epilepsy clinics that were investigated before 2010, and if their epilepsy is not well controlled, they should also be periodically reinvestigated.

The ECG can be normal and it is important to check for the presence of T-wave abnormalities (figure 3B). Holter monitoring can help with calculation of average QTc interval; provocative testing with exercise or stress can show abnormalities that were not present in the resting ECG. If the diagnosis is not clear, there is a clinical scoring system, the Schwartz score, that is based on personal and family history, symptoms and ECG (table 2).

EFFECT OF ANTIEPILEPTIC DRUGS ON ARRHYTHMIA

There was a temporal association between the introduction and dose escalation of levetiracetam and the precipitation of QT prolongation and arrhythmia. Several antiepileptic drugs can trigger conduction abnormalities or arrhythmias. Atrioventricular conduction block is the most frequent reported complication. ST changes, Brugada-like patterns, atrial fibrillation and QTc prolongation have also been reported. The most common drugs responsible for this are phenytoin, carbamazepine and lacosamide (table 3). This patient was not taking any of these medications. Lamotrigine is a sodium channel blocker that shows significant Ikr inhibition in vitro but no increase in QTc interval in clinical studies. Levetiracetam is a modulator of the presynaptic SV2A protein. In clinical studies in healthy adults, levetiracetam had no effect on QTc interval. However, there have been case reports of QTc interval prolongation with levetiracetam in a 24-year-old woman with a seizure disorder and previously undiagnosed long QT syndrome[6] and an elderly patient with acquired long QT syndrome secondary to levetiracetam.[7]

It is interesting to consider the connection between the seizures and arrhythmias. While the arrhythmias probably directly caused the seizures by brain hypoperfusion, it is possible that the mutation in the potassium channel increases the risk of both arrhythmia in the heart and seizures in the brain. The prevalence of epilepsy in long QT syndrome is low (1.6%) but is higher in LQT2 (3.7%) compared with other long QT syndromes (0.7%), which may be due to the *KCNH2*-encoded potassium channel being expressed in both the heart and the brain.[8]

Key points

- Always check a standard 12-lead ECG in patients with transient loss of consciousness and epilepsy at diagnosis, and also if seizures fail to response to antiepileptic medication.
- Use automated interpretation of 12-lead ECG to calculate the QTc interval; if in doubt, seek advice from a cardiologist.
- When sudden loss of consciousness is followed by myoclonic jerks, consider arrhythmia such as bradycardia or *torsade de pointes* ventricular tachycardia.
- Many antiepileptic drugs also affect cardiac conduction; if attacks increase or change after starting ion-channel-active antiepileptic treatment, repeat 12-lead ECG and cardiac investigations.

Correction notice This article has been updated since it was published Online First. The author name Viva Levee was incorrectly spelt as Viva Lee.

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