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A woman in her thirties with seizure relapse after a previous diagnosis of epilepsy

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A girl was diagnosed with epilepsy as a teenager and became seizure-free after treatment was initiated. However, she experienced a relapse when in her thirties. It transpired that a diagnostic re-evaluation was of tantamount importance.

A girl in her teens experienced without warning an abrupt onset of generalised tonic stiffening with consecutive jerking in all extremities. The seizure was accompanied by foaming at the mouth, loss of consciousness and sequential disorientation. At the emergency department, the clinical investigation was normal and she was referred to a specialist.

The attending neurologist assessed the incident as a probable generalised epileptic seizure caused by sleep deprivation. A cerebral contrast CT-scan and EEG investigation were ordered. The CT-scan was normal. The EEG showed two paroxysms, one spontaneously occurring and one during intermittent photic stimulation, which were not interpreted as distinctly epileptiform, thus a follow-up EEG was recommended.

A new seizure occurred in the following month. The neurologist initiated treatment with valproic acid which resulted in seizure freedom. She became somewhat tired from the medication and her next of kin experienced episodes in which she lacked concentration, but she always responded when addressed. The follow-up EEG was interpreted as pathological. Epileptiform activity was found during intermittent photic stimulation, and discomfort as during the previous seizures. She experienced a similar feeling of discomfort during facial sun-exposure. She was diagnosed with primary generalised juvenile epilepsy. A further EEG in the same year was interpreted as slightly pathological in light of the previous registration, but with less prominent changes. This finding could indicate a possible treatment effect of valproic acid. The prognosis was considered to be good as no more seizures had occurred, photosensitivity had disappeared and the EEG findings were less pathological.

Further EEG investigations two and three years later, respectively, showed normal findings. Four years after occurrence of the first seizure, a further EEG could not completely exclude underlying epileptogenic mechanisms, but it was concluded that deviations were most likely attributable to artefacts.

In addition to being followed up at the neurology outpatient clinic, the patient had initially presented at the emergency department after each seizure, with persistent normal clinical status and ECG. After four years of seizure freedom and repeated normal EEG recordings, valproic acid was discontinued without seizure recurrence.

Since her early twenties, the patient had experienced a ten year period with several episodes of prodromal symptoms in the form of dizziness and grogginess. In addition, she experienced clinical photosensitivity - with slight altered awareness when exposed to flickering lights, although with intact consciousness. Further, she sometimes experienced a darkening in front of her eyes although it was simultaneously perceived as light. All these symptoms receded after her first pregnancy, which occurred 11 years after the first seizure. Eighteen years after the first seizure, when the woman was in her thirties, a new episode occurred. She was out for a walk when she lost consciousness, fell to the ground and sustained minor injuries. The duration of her unconsciousness was unknown as there was no collateral information available. She explained that the period prior to this incident had been characterised by considerable stress and inadequate food and liquid intake. Further, she reported several similar episodes in the same period. From time to time, she could experience prodromal dizziness before transient episodes of loss of consciousness. She also reported being groggy and confused for a few minutes thereafter.

At the neurological outpatient clinic – eighteen years after the first consultation – a myriad of differential diagnoses were considered, including convulsive syncope as well as non-epileptiform events (1). In neuro-cardiogenic and vasovagal syncope, prodromal symptoms are typically malaise or discomfort. Loss of consciousness in such instances may be

accompanied by jerking of the extremities. Torsade de pointes usually occurs without prodromal symptoms, thus the patient loses consciousness without any warning.

To exclude structural cardiac disease, the neurologist ordered an echocardiographic examination. Additional investigations requested were a Holter recording to exclude paroxysmal atrioventricular block and sinoatrial block, a tilt test to provoke a vasovagal reaction, and carotid sinus massage to stimulate baroreceptors. A cerebral MRI scan with epilepsy protocol was also performed. None of these investigations revealed any pathology. The patient was nevertheless referred to a cardiologist for further work-up. A cardiologic history revealed several episodes of palpitations that did not cause the patient to contact a doctor. There were no prior ECG recordings available in the patient records prior to her attendance for cardiac assessment. However, ECG had been performed at all previous visits to the emergency department and these ECGs were repeatedly described as normal.

The episodes of palpitations were interpreted as functional tachycardia. The patient usually carried out her work in an upright position, but she did not feel this was unpleasant. She was married and had undergone an uncomplicated pregnancy and childbirth. The recent seizure episode with loss of consciousness occurred during physical activity. She was out for a walk when without warning she lost consciousness with no obvious precipitating factor. She had previously experienced seizures during situations of emotional distress, in the absence of physical exercise. She also reported a seizure while swimming in cold water that had occurred on one occasion. The patient's history revealed no familial cases of sudden cardiac death, which could have raised the suspicion of genetically based primary arrhythmia.

The ECG obtained at the cardiology department raised the suspicion of long QT syndrome (LQTS) with corrected QT interval (QTc) of 0.48 seconds (pathological if ≥ 0.48 sec) and the typical morphological sign, T-wave alternans, which is characteristic of the condition (2). Long QT syndrome was therefore suspected as the cause of the episodes of loss of consciousness, triggered by torsade de pointes. Possible secondary causes that may prolong the QT interval (electrolyte disturbances, use of pharmaceutical or certain narcotic drugs, or specific dietary habits) were not present. Cycle ergometer exercise testing did not provoke arrhythmia or any other symptoms.

In this patient group, T-wave alternans may be found during exercise as well as prolonged QTc after exercise testing, but this was not the case for this particular patient. Genetic testing was requested.

One year later (19 years after the first seizure), in connection with a combined cardiologic and neurologic work-up, a further cerebral MRI scan with angiography and epilepsy protocol was performed. As an incidental finding, a small aneurysm was found on the left middle cerebral artery (M1). There was no evidence of cortical dysplasia, neuronal migration disorder or other pathological findings.

The patient was diagnosed with long QT syndrome type 2 after confirmation of a heterozygous mutation in the *KCNH2* gene, HERG. Risk stratification was performed after the condition was determined, and a high risk of sudden death was assumed. Because she did not receive drug treatment during her previous seizures, which were assumed to be self-limiting torsade de pointes, no indication was initially found for an implantable cardiac device. She started on metoprolol tablets, 50 mg, twice daily and was especially advised to refrain from drugs that may prolong the QT interval. This turned out to be particularly relevant on a later occasion, as the patient fell ill with a disease where knowledge of the arrhythmia risk had implications for the choice of therapy.

The patient has been followed up at the department of cardiology since the diagnosis was made, and she has not experienced either syncope or loss of consciousness. QTc has varied from 0.48 and 0.53 on automatic recordings, and between 0.48 and 0.52 on manual recordings. If she were to experience cardiogenic loss of consciousness during treatment

with a beta blocker, implantation of an implantable cardiac device is recommended (3). The family has been investigated for the same mutation.

Discussion

The patient was initially thought to have a generalised epilepsy that responded to treatment. EEG supported the diagnosis. Follow-up EEGs were normal, and it was presumed that the epilepsy had receded with time. On renewed plenary evaluation of the original EEGs from the year of the first seizure, the previously described photoparoxysmal response was no longer interpreted as significant. These previous recordings only provided eight channels, and not 25 as today, thus the coverage of brain activity was less. There was no description of torsade de pointes in the accompanying one-channel ECG in relation to the pathological changes described or her subjective symptoms. Repeated ECGs taken at the emergency department were also described as normal.

Long QT syndrome is most commonly a genetic channelopathy caused by a mutation in genes coding for proteins in ion channels of the heart. At least 12 genes are currently known to cause long QT syndrome, as well as more than 35 genes where a mutation leads to prolonged QT interval (4). The most studied mutations are in the genes *KCNQ1*, *KCNH2* and *SCN5A*, which are related to potassium and sodium channels. The mutations cause repolarisation disturbances, resulting in prolonged QT interval.

Symptoms are syncope due to ventricular arrhythmias, typically torsade de pointes, but may also be bradycardia and deafness, as in Jervell and Lange-Nielsen syndrome. A certain degree of correlation between genotype and phenotype is often seen (5). In some cases, the manifestation may present as sudden unexpected cardiac death. Due to their hereditary nature, these cases require molecular autopsy to locate family members with the disease who may be amenable to treatment (6). Disease history, family history and ECG are the pillars of diagnosis.

The QT interval is corrected for heart frequency by using Bazett's formula: $QT_c = QT / \sqrt{RR}$ (c = corrected). Normal QT_c values are < 0.44, with a considerable overlap between normally prolonged QT_c and pathologically prolonged QT interval. The 99th percentile for men is 0.47 seconds and for women 0.48 seconds, but there are also variations with age (7). Diagnosing long QT syndrome may be difficult (8).

There are both European and international guidelines that advise on the diagnosis of long QT syndrome (3, 9). The guidelines differ slightly in details, but diagnosis is mainly based on the presence of a known pathogenic mutation (in the majority) or QT_c > 500 ms on repeated measurements or a LQTS-risk score of > 3. The diagnosis may be considered if a LQTS score = 2–3 (10). Table 1 (2) shows the criteria for calculation of such a score, which have been tested in a large population of children (Schwartz criteria) (11). The Schwartz criteria have since been modified. The criteria are especially important in the absence of genetic testing or when genetic testing is negative (2). An important aspect of these criteria, is that long QT syndrome may be diagnosed with QT_c as low as 450 ms in men (Table 1).

Table 1

Schwartz criteria for diagnosing long QT syndrome, after Schwartz PJ, Crotti L. QT_c Behavior During Exercise and Genetic Testing for the Long-QT Syndrome (2). Score: ≤ 1 low probability of LQTS, 1.5–3 intermediate probability of LQTS, ≥ 3.5 high probability of LQTS. In the absence of medications or disorders known to affect these electrocardiographic features. ₂QT_c calculated using Bazett's formula where $QT_c = QT / \sqrt{RR}$. ₃Mutually exclusive. ₄Resting heart rate below the 2nd percentile for age. ₅The same family member cannot be

counted in both A and B.

ECG findings ¹	Points
A QTc ²	
≥ 480 ms	3
460–479 ms	2
450–459 ms (men)	1
QTc ≥ 480 ms in minute 4 after completed stress test	1
C Torsade de pointes ³	2
D T-wave alternans	1
E Jagged T-wave in 3 leads	1
F Low cardiac frequency for age ⁴	0.5
Disease history	
A Syncope ³	
With stress	2
Without stress	1
B Congenital deafness	0.5
Family history	
A Family members with confirmed LQTS ⁵	1
B Sudden unexplained cardiac death in close family members under the age of 30 ⁵	0.5

Typically the inheritance in long QT syndrome is autosomal dominant. The incidence is probably between 1: 2 000 and 1: 2 500 (11, 12). In recent years, genetic testing has become more easily accessible and has become an important tool in diagnosing genetic causes of sudden cardiac death.

Indications for genetic testing of long QT syndrome are first of all a strong clinical suspicion based on clinical findings or family history, in addition to prolonged QT interval in ECG. Furthermore, it may be suspected in asymptomatic individuals with an obviously prolonged QTc (> 0.50 sec) where no other cause is present. The third group that should be investigated is first degree relatives in families where a distinct pathogenic mutation is proven (10).

Clinical manifestations may occur at any time of life, but are most common before the age of 30. Depending on subtype, several different triggers are known – physical exercise and especially swimming in long QT syndrome type 1, emotional triggers and especially auditory stimulating factors in type 2, rest and sleep in type 3 (5).

The clinical background for the assumption of a common pathophysiological substrate between epilepsy and long QT syndrome has mainly been limited to case reports (13–16). The proteins that are coded in the *KCNH2* gene are also found in ion channels in the astrocyte membrane of the hippocampus. This association is postulated as a possible explanation for the link between long QT syndrome and epilepsy (14–17). Further, it is shown that patients with long QT syndrome type 2 more often have a history that includes epileptic seizures and are more often treated with antiepileptic drugs than patients with long QT syndrome types 1 and 3 (17).

In a prevalence study of patients with long QT syndrome, it was found that 15 % of those with clinical seizures or seizure-like episodes had epileptiform activity in EEG recordings (18). Exome sequencing of patients with sudden unexpected death in epilepsy have shown mutations in clinically relevant genes coding for arrhythmia and epilepsy (19).

Animal studies have also described mutations in the *KCNQ1* gene causing epileptic seizures with concomitant epileptiform activity in EEG, and in addition malignant cardiac arrhythmia (20). In a large-scale study of genetic biomarkers and the risk of seizures in long QT syndrome, it was found that LQTS2 mutations in the *KCNH2* pore region were positive predictors of both arrhythmias and seizures. In contrast, mutations in the cyclic nucleotide-binding domain (cNBD) of *KCNH2* gave a negative risk of seizures but not arrhythmias. LQTS2, *KCNH2*-pore, *KCNH2*-cNBD, QTc and sex were independent predictors of seizures (21).

Furthermore, the literature describes a patient with presumed long QT syndrome whose ICD required explantation and who is now treated by an epileptologist (22).

It is important to diagnose long QT syndrome and investigate close family members due to the availability of good and effective ways to prevent serious events. Drugs that prolong the QT interval must be avoided in patients with a proven mutation and in all patients diagnosed with long QT syndrome. In cases where these drugs are given, proper follow-up must be provided. Web pages are available with updated lists of the relevant drugs (23).

Whether our patient originally had genuine epilepsy that was outgrown is uncertain, but incidental presence of both diseases is of course possible. However, epileptiform activity was only determined in a single EEG recording in the year of her first seizure. This was more or less refuted in the retrospective plenary assessment, but that took place in a new and different EEG era. The fact that long QT syndrome was diagnosed in adulthood does not exclude the diagnosis of epilepsy in her teenage years.

When the episodes of loss of consciousness returned and a plausible cause presented itself in the patient history, reinitiation of antiepileptic medication would have been an easy step to take. In this particular case, such an approach could have brought about serious consequences by exacerbating the existing arrhythmia and increasing the risk of sudden death associated with torsade de pointes. The risk associated with antiepileptic drugs, either alone or in combination, has been described (24).

This patient case is a reminder of the importance of a constant re-evaluation of any diagnosis in a patient at any time in the course of disease. Additionally, it underlines the importance of measuring the corrected QT interval in loss of consciousness that is not obviously explained by the circumstances. In the case of recurring seizures that are not unequivocally consistent with a cardiac aetiology, a control EEG should be performed with repeated intermittent photic stimulation.

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