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'Refractory epilepsy': what lies beneath?

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CASE REPORT

'Refractory epilepsy': what lies beneath?

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SUMMARY

A 30-year-old woman presented to the emergency room with recurrent seizures for 5 days. She had been diagnosed with epilepsy 2 years previously but stopped treatment due to the side effects of her medications. She was now experiencing episodes every 15–30 min. While undergoing a brain MRI to investigate for structural central nervous system pathology, she experienced another episode, preceded by prodromal symptoms. Polymorphic ventricular tachycardia was noted during the event. Further investigation revealed a normal QT interval, normal electrolyte panel, normal coronaries and severe left ventricular systolic dysfunction. Cardiac MRI revealed non-ischaemic cardiomyopathy. The patient was managed with heart failure and antiarrhythmic medications and an implantable cardioverter defibrillator. She remained symptom free at 6-month follow-up. This case highlights the importance of differentiating between cardiogenic syncope and epilepsy and reiterates the importance of re-evaluating a diagnosis of epilepsy when presentation is atypical or symptoms are refractory.

BACKGROUND

This case represents an unusual presentation of a life-threatening condition, namely, ventricular arrhythmia. The patient faced considerable morbidity and potentially, death—before a diagnosis was made. This case highlights the importance of thorough history taking before entertaining a clinical diagnosis such as epilepsy and the consideration of alternative diagnoses when the condition proves resistant to treatment.

CASE PRESENTATION

A 30-year-old woman presented to the emergency room (ER) with recurrent seizures. She had been in her usual state of health 2 years previously, when she experienced one episode of unconsciousness with generalised body stiffness with associated tongue bite and incontinence.

Recovery was rapid and complete but there was some subsequent drowsiness and generalised weakness. She then fell down and experienced trauma to the occipital region. She was taken to a local hospital for evaluation. No central nervous system (CNS) imaging was performed. A diagnosis of epilepsy was made and antiepileptic medication (valproate) prescribed. However, she stopped the medication after 1 month due to excessive drowsiness.

She remained event free for the next 2 years, off all medications.

She now presented with repeated episodes of seizures for the past 5 days.

Each episode was preceded by prodromal symptoms of head heaviness and palpitations and would last 1–2 min. She would recover spontaneously and completely, but would remain sleepy and feel extreme weakness. She would have episodes even while asleep. Her husband had noted that she would turn blue, feel cold to the touch and stop breathing for a few seconds, for which he would apply chest compressions.

She was now experiencing episodes every 15–30 min. With these symptoms, she was taken to a local hospital where she was treated on the lines of refractory epilepsy. Intubation was attempted but she recovered consciousness and became agitated therefore it was deferred.

Owing to the intractable nature of her symptoms, her husband decided to shift her from another town to our tertiary care centre. On the way to the hospital, she had five further episodes for which she was administered intravenous midazolam and brief chest compressions. She was seen in ER where a normal physical examination was documented. An MRI of the brain was planned to investigate for structural CNS pathology.

In the MRI suite, she again had an event of loss of consciousness with up rolling of eyes. The event lasted 2 min with complete recovery. She was moved to the MRI recovery room where she commented that she was having prodromal symptoms. She was then noted to develop up rolling of eyes with generalised body stiffness. Polymorphic ventricular tachycardia (PMVT) was noted on the cardiac monitor.

Chest compressions were initiated. The rhythm terminated spontaneously within 2 min while the staff was preparing to defibrillate her. She was wheeled to the ER where she had another self-terminated event. She was given a loading dose and infusion of lidocaine and shifted to the coronary care unit.

In other significant history, she had completed a course of ciprofloxacin, ibuprofen and pseudoephedrine, a week earlier, for an upper respiratory tract infection. There was no history of sudden cardiac death (SCD) in the family. An ECG (figure 1) revealed some non-specific ST-T segment flattening and infrequent early coupled premature ventricular contractions. Baseline QTc was 426 ms. All subsequent QT interval monitoring continued to reveal QTc within normal limits. No further arrhythmia was noted on lidocaine infusion.

Baseline electrolyte panel was within normal limits.

Echocardiogram was performed to assess for structural heart disease. Severe left ventricular systolic dysfunction was noted with severe global

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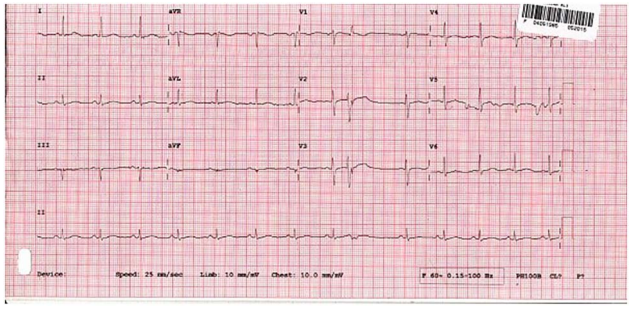


Figure 1 Baseline ECG showing non-specific ST-T segment flattening, infrequent early coupled premature ventricular contractions and corrected QT of 426 ms.

hypokinesia. There was normal right ventricular systolic function but grade II left ventricular diastolic dysfunction with trivial tricuspid regurgitation.

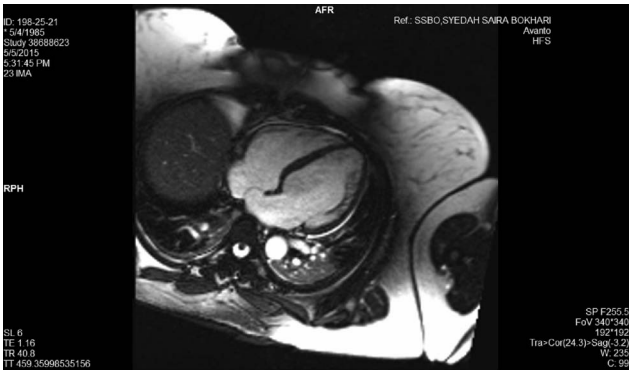
Coronary angiogram was then performed to rule out coronary artery disease. A normal coronary angiogram was documented.

A provisional diagnosis of non-ischaemic cardiomyopathy of unknown aetiology was made. To delineate the nature of the cardiomyopathy, a cardiac MRI was performed, which revealed severe left ventricular systolic dysfunction (video 1). In addition, late gadolinium imaging revealed mid-myocardial enhancement at the level of the basal interventricular septum, suggestive of non-ischaemic aetiology of the cardiomyopathy (figure 2). Additionally, no evidence of myocarditis was noted.

This was followed by brain MRI to rule out structural CNS pathology, which did not reveal any abnormality.

A detailed retrospective history revealed that the patient had experienced an eventful pregnancy 6 years previously with disproportionate dyspnoea on exertion and pedal swelling. These symptoms had begun in the last trimester and had not been investigated. It was postulated that she may have been suffering from undiagnosed peripartum cardiomyopathy. Long-standing untreated cardiomyopathy can manifest with malignant ventricular arrhythmias, which can be monomorphic or polymorphic.

Cardiomyopathy is associated with scar formation, usually associated with monomorphic ventricular tachycardia. The cardiac MRI (CMR) demonstrated no scarring, which may explain why the patient presented with polymorphic rather than monomorphic ventricular tachycardia. She was reviewed by an electrophysiologist. Electrophysiology study was not undertaken



Video 1 Cardiac MRI cine image showing severe left ventricle systolic dysfunction.

due to the high burden of arrhythmia with poor haemodynamic tolerance and concomitant severe left ventricular systolic dysfunction.

Unfortunately, genetic testing for inherited channelopathies could not be offered as it is unavailable in our country and difficult and expensive to arrange from elsewhere.

The patient was discharged on heart failure medications, single antiepileptic, amiodarone and an implantable cardioverter defibrillator (ICD).

INVESTIGATIONS

Echocardiogram was performed to assess for structural heart disease. Severe left ventricular systolic dysfunction was noted with severe global hypokinesia. There was normal right ventricular systolic function but grade II left ventricular diastolic dysfunction with trivial tricuspid regurgitation.

Coronary angiogram was then performed to rule out coronary artery disease. A normal coronary angiogram was documented.

To delineate the nature of the cardiomyopathy, a cardiac MRI was performed, which revealed severe left ventricular systolic dysfunction (video 1). In addition, late gadolinium imaging revealed mid-myocardial enhancement at the level of the basal interventricular septum, suggestive of non-ischaemic aetiology of the cardiomyopathy (figure 2). Additionally, no evidence of myocarditis was noted.

This was followed by brain MRI to rule out structural CNS pathology, which did not reveal any abnormality.

DIFFERENTIAL DIAGNOSIS

This case invites the question as to whether the patient had purely cardiogenic syncope that was misdiagnosed as epilepsy or a seizure that was secondarily complicated by arrhythmia.

TREATMENT

The patient was given lidocaine loading and infusion. She was discharged on heart failure medications, single antiepileptic, oral amiodarone and an ICD. The decision to continue antiepileptic treatment for the short term was made after discussion between two neurologists, the primary cardiologist and an electrophysiologist. The patient lives far from our tertiary care centre and would have difficulty in accessing specialist healthcare in case of an event. Since rare channelopathies, which affect the heart and brain, could not be excluded due to unavailability of testing, the antiepileptic was tapered and discontinued over 4 weeks.

OUTCOME AND FOLLOW-UP

The patient remained symptom free and arrhythmia free at 6-month follow-up. She is now off antiepileptic drugs and is New York Heart Association I.

DISCUSSION

Misdiagnosis of epilepsy is an increasingly appreciated problem. It is estimated that up to 20% of patients being treated in epilepsy outpatient clinics do not have epilepsy.[1] Cardiovascular syncope is the most frequent underlying condition. The confusion arises due to the association of abnormal motor movements with loss of consciousness, most often seen in reflex mediated syncope, namely, neurocardiogenic syncope.[1] One such instance has been reported by Asadi-Pooya *et al*,[2] who describe a case of a 22-year-old woman who had been treated as a case of refractory epilepsy since the age of 6 years and who subsequently demonstrated profound cardioinhibitory neurocardiogenic

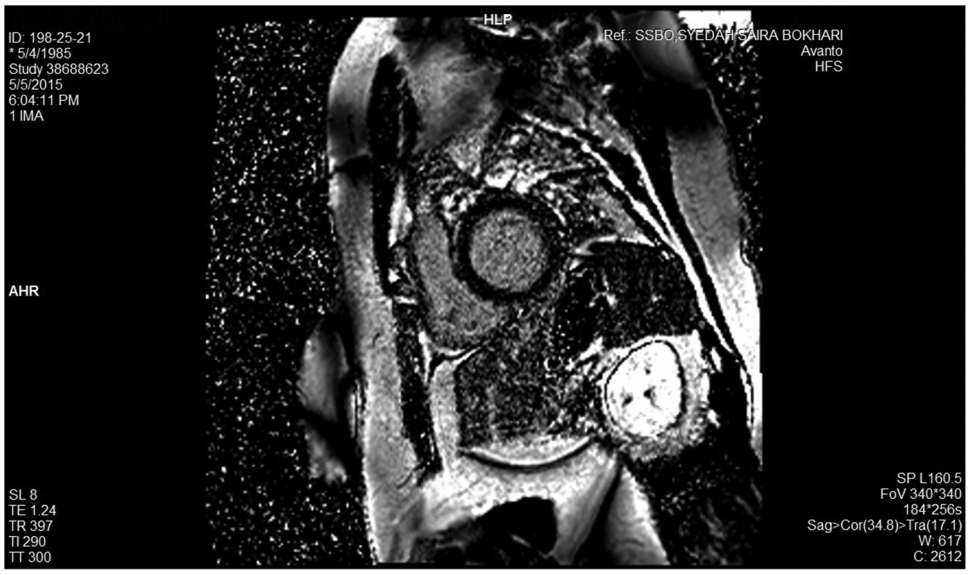


Figure 2 Late cardiac MRI gadolinium image showing midmyocardial enhancement of the basal interventricular septum, suggestive of non-ischaemic cardiomyopathy.

syncope during provocative testing with tonic–clonic movements.

Other rarer causes of cardiogenic syncope that may be misdiagnosed as epilepsy include bradyarrhythmias and tachyarrhythmias.

There are other reasons for the apparent association or confusion between syncope and seizures. Antiepileptic drugs that act on ion channels, for example, phenytoin, may precipitate cardiac arrhythmias. Some forms of epilepsy, specifically temporal lobe epilepsy, are associated with 'ictal bradycardia'.[3] Rarely, epilepsy and cardiac arrhythmias may coexist in the form of 'neurocardiac channelopathies' (Long QT, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia).[4]

Our patient represents one such case, experiencing significant morbidity and risk of mortality due to her misdiagnosis. She presented with seizure-like activity associated with PMVT.

PMVT is considered to be an unusual malignant ventricular arrhythmia that is a frequent cause of SCD. Episodes associated with slower tachycardia rates may be self-limited and present with presyncope, syncope or seizure-like activity due to transient cerebral hypoperfusion.[5]

PMVT is associated with normal or abnormal QT interval and normal or abnormal cardiac structure and function. Our patient had undiagnosed structural heart disease, normal QT interval and evidence of non-ischaemic cardiomyopathy diagnosed by echocardiogram, coronary angiogram and cardiac MRI. After receiving appropriate treatment for arrhythmia and heart failure, she has remained symptom and arrhythmia free. Considering the frequency of her symptoms, she was at very high risk of SCD.

This case highlights the importance of re-evaluating a diagnosis of epilepsy if: sudden loss of consciousness is followed by myoclonic jerks, if symptoms are refractory to epilepsy medications, when EEG is non-diagnostic, when there are atypical premonitory symptoms or when symptoms worsen after initiation of an ion channel active antiepileptic drug.[2]

Learning points

- An estimated 20% of epilepsy cases are misdiagnosed and the commonest underlying diagnosis is cardiogenic syncope.
- For all clinical diagnoses, for example, epilepsy, thorough history-taking and physical examination are warranted.
- It is essential to re-evaluate diagnosis of epilepsy if seizures prove refractory to treatment or worsen with antiepileptic drugs that act on ion channels.

Contributors SH was involved in conceptualising, drafting and reviewing the manuscript. SSB was the primary cardiologist of the patient and was responsible for the concept and main write-up of the case report.

Competing interests None declared.

Patient consent Obtained.

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Reminder of important clinical lesson