Recurrent syncope in a patient with Andersen's syndrome

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Introduction

Most common inherited diseases with cardiac involvement are associated with structural abnormalities of the heart and/or great vessels. Discussions of inherited cardiac electrophysiological abnormalities were once limited to Jervell and Lange-Nielsen syndrome and Romano-Ward syndrome. Subsequently, other genetically distinct arrhythmogenic cardiovascular disorders have been discovered.[1] These result from mutations in the fundamental cardiac ion channels that orchestrate the action potential of the human heart. Most of these genetic channelopathies are depicted by marked QT prolongation on the electrocardiogram.

Case report

A 26 year old woman was referred to Castle Hill Hospital for further investigation following recurrent syncope. She had experienced syncope and pre-syncopal symptoms from the age of six years. Prior to her referral the frequency of her syncopal episodes had increased so that they were occurring up to 10 times per week. These episodes were abrupt in onset, with no warning, and on each occasion the patient made a rapid recovery. Symptoms were unwitnessed. There was no associated tongue biting and no history of epilepsy.

From the age of 10 she had also noted periods of upper and lower limb weakness. There were no precipitating events and the weakness would last a number of days on most occasions.

The patient had a long history of asthma requiring treatment with inhaled steroids. After a road traffic accident at the age of 18 she was noted to have frequent ventricular ectopy. Since then the patient had complained of recurrent atypical chest pain and palpitations and had been prescribed disopyramide.

The patient had learning difficulties as a child and had delayed development of her secondary sexual characteristics. Her menstrual cycle had been irregular since it started when she was 19. She was known to have periods of depression and at the age of 24 the patient took an overdose of disopyramide. Consequently she had a cardiac arrest, from which she was successfully resuscitated. Sustained ventricular tachycardia was recorded during this event.

The patient's mother was known to suffer from palpitations and syncopal episodes; she had been diagnosed, some years earlier, as having periodic paralysis based upon intermittent episodes of proximal muscle weakness. The patient's brother and sister apparently had frequent episodes of muscle weakness but no palpitations or syncope. The brother exhibited mild dysmorphic facial features and he had a posterior cleft palate. Two of the patient's other siblings had died, but further details regarding their causes of death were unknown. The patient's father was fit and well. No other family history was available.

Examination revealed that the patient had short stature (152 cm), facial hirsutism, a short neck, low-set and prominent ears, a hypoplastic mandible, hypertelorism, unilateral right-sided partial ptosis and diplopia on right lateral gaze (figure 1). She had poorly developed secondary sexual characteristics. Examination of the cardiovascular system revealed an irregular pulse but no other abnormalities. Further neurological examination was normal and there were no other relevant findings on physical examination.

Figure 1. Facial features of the patient

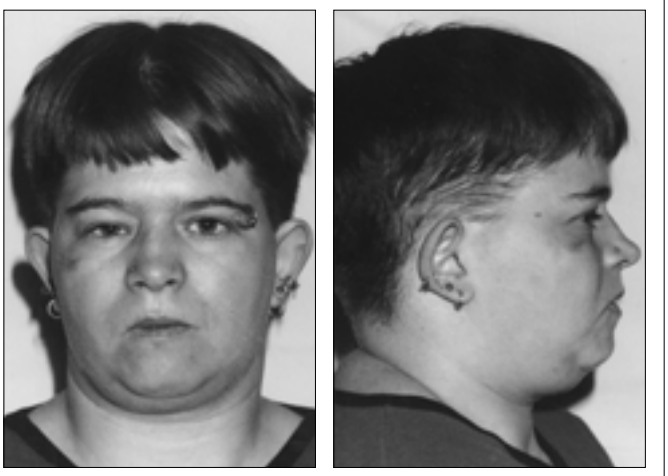

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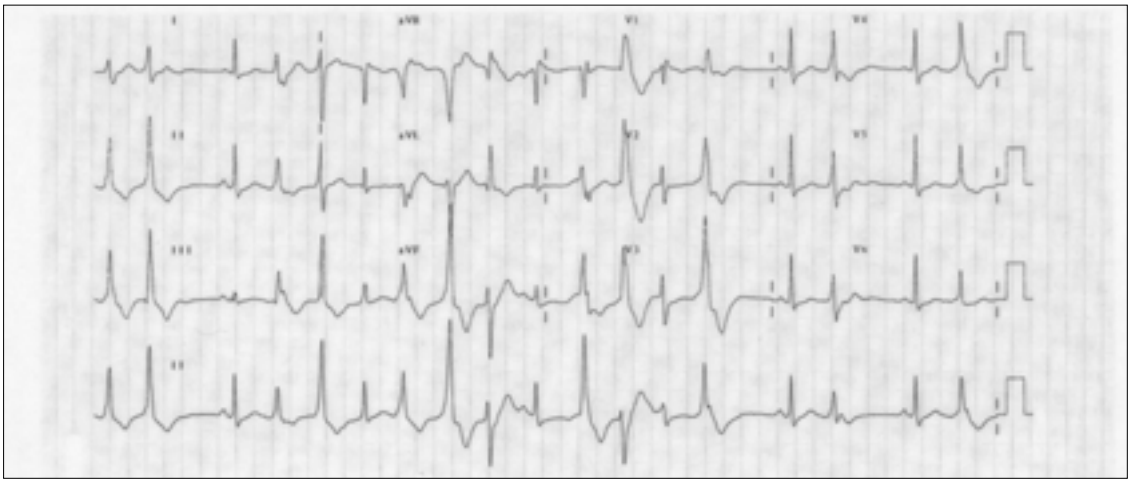
Figure 2. Twelve-lead electrocardiogram (ECG), showing ventricular ectopy



Investigations

A 12-lead electrocardiogram showed frequent multimorphic ventricular ectopic beats, a normal QRS axis, an RR interval of 580 ms and a QT interval of 320 ms (corrected QT [QTc]=420 ms) (figure 2). Her chest X-ray was normal. Holter monitoring revealed sinus rhythm interspersed with frequent multimorphic ventricular extrasystoles, runs of ventricular bigemini and non-sustained ventricular tachycardia. A transthoracic echocardiogram revealed no systolic or diastolic dysfunction, no chamber enlargement and no valvular pathology. Doppler and colour flow studies were normal. The patient completed six minutes of a Bruce protocol exercise stress test, attaining a heart rate of 160 beats per minute. During this test her ventricular ectopy was suppressed. The patient had no syncopal or pre-syncopal symptoms during or immediately following the treadmill test.

Routine biochemistry, in particular serum potassium, magnesium and calcium were all normal. A random creatine kinase level was within the normal range. Despite documented episodes of weakness, review of this woman's referring hospital notes revealed only one episode of hypokalaemia (serum potassium 3.1 mmol/L), recorded at the time of her cardiac arrest. Thyroid stimulating hormone, follicle stimulating hormone and luteinizing hormone levels were within normal limits. An electroencephalogram was normal.

The patient had prolonged telemetric ECG monitoring as an in-patient. No significant sustained arrhythmias were recorded although the patient did experience one syncopal episode. During the stay in hospital disopyramide was withdrawn, with no change in rhythm disturbance. Since the patient complained of persistent chest pains she went on to have coronary angiography: this revealed normal coronary arteries. An electrophysiological study was performed, which demonstrated parameters within the normal range.[2] Table 1 shows the conduction times and table 2 the refractory periods obtained at electrophysiological study. The patient did not exhibit ventriculoatrial conduction.

Table 1. Conduction times found at electrophysiological study

Conduction times (ms)	
Basic cycle length	580
PA interval	35
AH interval	68
HV interval	45
QRS interval	80
QT interval	320
Corrected QT interval	420
Anterograde Wenckebach cycle length	320
Sinus node recovery time (DCL 400 ms)	720

Key: DCL = drive cycle length

Table 2. Refractory periods fund at electrophysiological study

	Effective refractory period (ms)	**Functional refractory period (ms)**
Atrium	250	280
AV node	260	330
Ventricle	230	240

Drive cycle length = 400 ms

Sustained ventricular tachycardia could not be induced using three extra stimuli delivered from the right ventricular apex and right ventricular outflow tract.

Discussion

This patient's findings, coupled with her developmental delay and dysmorphic features, would suggest a common pathogenetic aetiology. A number of patients with cardiac dysrhyth-

Key messages

- Andersen's syndrome consists of episodic muscular weakness, ventricular dysrhythmias and dysmorphic features
- It is a rare, genetically unique, channelopathy affecting cardiac and skeletal muscle membrane excitability
- The most consistent cardiac manifestation is a prolonged corrected QT interval
- In patients who present with syncope, particularly those with a dysmorphic appearance, calculation of the QTc should be a routine part of their ECG assessment

mias associated with periodic paralysis have been reported since 1963.[3-5] Cardiac dysrhythmias independent of serum potassium levels are a primary manifestation of some forms of periodic paralysis.[4] Andersen first described a syndrome characterised by episodic muscular weakness, ventricular dysrhythmias and dysmorphic features in 1971.[6] It is a rare, genetically unique, channelopathy affecting cardiac and skeletal muscle membrane excitability. Since that time, 10 patients with the full distinctive clinical triad and five first-degree relatives with varying features of the syndrome have been described in the literature.[4,7]

There is intrafamilial phenotypic variability within kindreds of those with Andersen's syndrome (AS). The most common dysmorphic features found in AS are clindactyly, low-set ears, a small mandible, short stature and hypertelorism.[4] A prolonged corrected QT interval (QTc) is the most consistent cardiac manifestation, being found in eight out of 10 of those with the full syndrome.[4,7] Grandparents and parents of documented index cases have been found who have isolated asymptomatic QTc prolongation but no history of arrhythmias or weakness and no dysmorphic features.

Genetic linkage studies have shown that AS is not linked to other distinct loci responsible for the more common long QT syndromes. Neither is there any linkage to the common genetic defects causing hypo- or hyperkalaemic periodic paralysis.[4,7] Candidate loci for AS would include genes coding for ion channel isoforms common to skeletal and cardiac muscle or genes coding for regulatory proteins needed for the stable functioning of these ion channels. The complex and variable physical findings in persons with AS would suggest the possibility of genetic and mutational heterogeneity. The autosomal dominant nature of AS and its variable expression is highlighted by our patient's family history and is confirmed in the literature.[4,7]

Our patient had episodes of weakness which tended to last longer than more typical cases of periodic paralysis. Similar variants have previously been described in AS and periodic paralysis associated with arrhythmias.[4,5] Periodic paralysis associated with AS can be hyper-, hypo-, or normokalaemic.[4] It has, in the past, been routine practice to provoke changes in serum potassium in order to aid classification[7] but such provocation, especially hypokalaemic challenges, should be avoided in those with ventricular arrhythmias. Rapid shifts in serum potassium may exacerbate the arrhythmia and potentiate a prolonged QTc interval.

Sudden death has been documented in at least two patients with cardiac arrhythmias and periodic paralysis.[5,8] Two patients with AS have had non-fatal cardiac arrests, both of them were found to have a prolonged QTc interval. Other patients with AS have been free from syncope.

Our patient is of interest because, despite her normal QTc interval, her frequent ventricular ectopy made a cardiac cause the leading contender as the reason for her syncopal episodes. Following detailed investigation this young woman's episodes of syncope diminished and it was felt that a non-organic cause was primarily responsible for her presenting symptom. The therapy with disopyramide was successfully discontinued without adverse sequelae. It has been found that the arrhythmias in AS respond poorly to antiarrhythmic agents[6,8,9] and that these agents may even make paralysis worse.[9]

Conclusion

Given the predisposition for potentially fatal cardiac dysrhythmias, it is important that clinical recognition of this syndrome occurs. Those with proven symptomatic sustained ventricular tachycardia may be candidates for implantation of a cardioverter defibrillator. The presence of distinctive physical features in a patient with periodic paralysis should particularly alert the clinician to the diagnosis of Andersen's syndrome. Provocation of hypo- or hyperkalaemia, in an attempt to differentiate potassium-sensitive from hypokalaemic periodic paralysis, should be avoided in those with cardiac arrhythmias. Although it was not prolonged in this particular case, calculation of the QTc interval should be a routine part of the electrocardiographic assessment of patients presenting with syncope.

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