Rapid genetic testing facilitating the diagnosis of short QT syndrome

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Short QT syndrome (SQTs) is a rare genetic disease with a risk of sudden cardiac death. The present report describes syncope in a young man that resulted in a motor vehicle accident. An electrocardiogram and initial investigations were unremarkable, but treadmill testing showed a lack of adaptation of the QT interval, which has been described in SQTs. To evaluate the possible diagnosis of SQTs, DNA sequencing of genes known to be associated with SQTs was performed and identified a novel mutation in the *KCNH2* gene. Consequently, the patient was diagnosed with SQTs and the recommendation of implantable cardioverter defibrillator implantation was accepted by the patient before discharge from the hospital.

Key Words: Genetic testing; Primary electrical disease; Short QT syndrome; Sudden cardiac death; Syncope

Sudden cardiac death (SCD) remains a major public health challenge, often presenting in the young as a sentinel event in the absence of structural heart disease. Published estimates suggest that up to 15% of patients surviving SCD suffer from primary electrical disease (PED), resulting in a substantial cohort of young patients at high risk for recurrent arrhythmic events (1). Short QT syndrome (SQTs) is a rare, inherited PED that has only recently been recognized and is associated with atrial and/or ventricular fibrillation, resulting in SCD in the absence of structural heart disease at any age (2). The diagnosis of SQTs is challenging in light of the wide range of QT intervals in healthy subjects and the potential overlap with idiopathic ventricular fibrillation and early repolarization (2). Genetically heterogeneous, three specific channelopathies characterized by gain of function of the rapid, inward and slow delayed rectifier potassium currents, and more recently, a fourth channelopathy characterized by three loss of function mutations in two genes encoding subunits of the L-type calcium channel, have been demonstrated as a genetic basis for the condition (3,4). To date, seven genetic mutations associated with rate-corrected QT (QTc) intervals of less than 360 ms in affected probands have been identified. A correlation between genotype and phenotype does not yet exist due to the relatively few cases described and genetically confirmed. We describe a clinical presentation of unheralded syncope in a previously healthy 22-year-old man with suspiciously short but nondiagnostic QTc intervals (381 ms). Rapid genetic testing (less than 72 h) provided additional information supportive of a diagnosis of the SQT1 form of SQTs, assisting with in-patient decision making

Test génétique rapide pour faciliter le diagnostic de syndrome du QT court

Le syndrome du QT court (SQTc) est une maladie génétique rare qui s'accompagne d'un risque de mort subite d'origine cardiaque. Le présent rapport décrit, chez un jeune homme, une syncope ayant occasionné un accident de la route. L'électrocardiogramme et les analyses initiales n'ont révélé aucune particularité, mais l'épreuve d'effort a montré une absence d'adaptation de l'intervalle QT qui a été décrite dans le SQTc. Pour évaluer un diagnostic possible de SQTc, le séquençage de l'ADN des gènes reconnus pour leur lien avec le SQTc a permis de reconnaître une nouvelle mutation au niveau du gène *KCNH2*. Par conséquent, le patient a reçu un diagnostic de SQTc et il a accepté de suivre notre recommandation de se faire implanter un cardioverseur-défibrillateur avant de quitter l'hôpital.

and implantable cardioverter defibrillator (ICD) recommendation for a potentially fatal genetic syndrome.

CASE PRESENTATION

A previously healthy 22-year-old man experienced unheralded syncope for the first time while driving, resulting in a motor vehicle accident. No resuscitation was required by the attending paramedics. Physically unharmed, he was transferred to the University of Ottawa Heart Institute (Ottawa, Ontario) for assessment. The patient had no history of previous chest pain, palpitations or syncope. He denied using supplements, smoking cigarettes, prescription or recreational drug use, and intercurrent illness. Although physically active, he did not participate in competitive sports. There was no family history of SCD, atrial fibrillation or syncope. The physical examination of the patient was unremarkable. The initial electrocardiogram (ECG) demonstrated normal sinus rhythm at 60 beats/min, with QT and QTc intervals of 364 ms and 381 ms, respectively. No abnormalities were detected on electrolyte testing, echocardiography, myocardial perfusion scintigraphy or cardiac magnetic resonance imaging. Holter monitoring and repeated ECGs were performed throughout the patient's hospitalization because surface ECG abnormalities can be intermittent. However, his minimal QT and QTc intervals during observation were 334 ms and 366 ms, respectively, which were well beyond the length of QTc intervals described in SQTs (less than 360 ms) (Figure 1). Tilt testing was not considered due to the atypical nature of his syncopal event. Electrophysiological testing was not

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Figure 1) Electrocardiogram from the proband at presentation demonstrating tall abnormal T waves in the precordial leads and an abbreviated QT interval of 366 ms (rate-corrected QT interval of 383 ms at 66 beats/min)

Figure 2) Precordial electrocardiogram showing the onset of a QRS complex to the peak of a T wave in lead V3 in the proband (horizontal bar) (A) and a 30-year-old male control subject (B) at an identical heart rate of 120 beats/min during recovery following exercise tolerance testing

performed because the clinical usefulness of such testing in genetically mediated ventricular arrhythmia remains controversial. Treadmill testing did not result in ventricular arrhythmia but did reveal a lack of adaptation of the QT interval to increasing heart rate during exercise and a failure to adapt to decreasing heart rate during recovery (Figures 2 and 3). These observations have been ascribed to the SQTS due to *KCNH2* mutations (5), raising concern that the patient harboured this condition. To further evaluate the possible diagnosis of SQTS, rapid genetic testing was performed within 72 h at the University of Ottawa Heart Institute's Arrhythmia Genetics Laboratory following written informed consent. Direct DNA sequencing of the *KCNQ1* and *KCNH2* genes, which are implicated in causing SQTS, identified a novel mutation of a highly conserved residue, Glu50Asp, in *KCNH2*. Following this genetic information, a recommendation of ICD implantation was accepted by the patient before discharge.

DISCUSSION

A previously healthy young man presented with unheralded syncope, and initial investigations failed to identify an obvious diagnosis. During in-patient ECG monitoring, further shortening of the QT interval was noted intermittently. An exercise treadmill test was performed to assess QT dynamics and ventricular arrhythmia. ECG analysis demonstrated minimal adaptation of the QT interval during exercise or recovery – a phenomenon that has been described in patients with SQTS due to the *KCNH2* mutations (5). However, despite this, the shortest recorded QT and QTc intervals did not allow for a diagnosis of SQTS to be made with sufficient confidence to recommend an ICD.

SQTS is a genetically based disease, and there is no universally accepted threshold of QT interval diagnostic of SQTS. To date, all genetically defined probands have an observed QTc interval of less than 360 ms. We performed candidate genetic testing during inpatient

Figure 3) Relative lack of adaptation of the QT interval (onset of a QRS complex to the peak of a T wave in a precordial electrocardiogram of lead V3 [QTpV3]) to accelerated heart rate during exercise and lack of adaptation of the QT interval during decelerated heart rate in the recovery of the present patient compared with the average of 10 age- and sex-matched controls from the Ottawa Heart Institute in Ottawa, Ontario

evaluation in less than 72 h. The finding of a novel missense mutation in *KCNH2* (Glu50Asp) provided supportive clinical evidence to diagnose the patient with SQTs, leading to a recommendation of ICD implantation before he was discharged from the hospital. Of note, the patient's mother was subsequently identified as carrying the mutation; however, serial ECGs demonstrated normal QT intervals. This observation is consistent with the incomplete clinical penetrance of SQTs described in other pedigrees (3). In view of normal ECGs, no treatment is currently recommended.

In the presence of an abnormal but nondiagnostic postevent ECG, and the absence of ECG documentation of an arrhythmia, the management strategy is unclear, with a spectrum ranging from potentially no therapy to medical therapy or, at the extreme, implantation of an ICD. The decision to implant an ICD in a young individual requires a high degree of confidence in the diagnosis of a life-threatening condition because the physical and psychological consequences are considerable. Currently, unlike the long QT syndrome, the diagnostic criteria are not known and cases reported in the literature are sparse. Rapid genetic testing may facilitate appropriate in-patient decision making and minimize the risks to patients of SCD while awaiting results of genetic testing over the ensuing months.

CONCLUSION

The diagnosis of rare PED syndromes is difficult yet crucial if SCD is to be prevented. A short period of in-patient monitoring and investigation

with simultaneous rapid genetic analysis can assist in the expeditious diagnosis and management of patients with clinical features suggestive of difficult to diagnose and potentially fatal genetic arrhythmia syndromes. To date, the availability of rapid genetic testing does not exist outside of specialized research laboratories.

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