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Case Report

Molecular Autopsy Implicates Primary Carnitine Deficiency in Sudden Unexplained Death and Reversible Short QT Syndrome

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ABSTRACT

We report a case of sudden unexplained death in a young asymptomatic woman in whom postmortem genetic testing after a negative autopsy identified a homozygous pathogenic mutation in *SLC22A5* which leads clinically to primary carnitine deficiency (PCD). Her brother was subsequently diagnosed clinically with short QT syndrome, received an implantable defibrillator, and was then found to carry the same pathogenic homozygous mutation and critically low levels of carnitine. His QT interval improved with the use of carnitine supplementation, highlighting the close relationship between electrophysiology and biochemistry, and the importance of postmortem genetic testing in the clinical management of surviving relatives.

RÉSUMÉ

Nous décrivons le cas de mort subite inexpliquée d'une jeune femme asymptomatique chez qui les analyses génétiques *post-mortem* effectuées après une autopsie négative ont révélé une mutation homozygote pathogène du gène *SLC22A5* entraînant sur le plan clinique un déficit primaire en carnitine (DPC). Son frère, chez qui un diagnostic clinique de syndrome du QT court a été posé ultérieurement, a reçu un défibrillateur implantable. On a alors constaté qu'il était porteur de la même mutation homozygote pathogène et qu'il présentait des concentrations de carnitine dangereusement faibles. La prise de supplément de carnitine a donné lieu à une amélioration de l'intervalle QT chez le patient, ce qui met en lumière la relation étroite qui existe entre l'électrophysiologie et la biochimie, de même que l'importance des analyses génétiques *post-mortem* dans la prise en charge clinique des proches survivants.

Primary carnitine deficiency (PCD; OMIM:212140) is an autosomal recessive disorder caused by mutations in *SLC22A5* encoding for the organic cation transporter type 2 (OCTN2). Mutant *SLC22A5* leads to increased urinary carnitine excretion and low plasma and intracellular levels of carnitine.[1] PCD can present along a wide clinical spectrum. Metabolic decompensation and severe cardiac manifestations, such as cardiomyopathy, are mostly seen in early childhood; however, adult patients are also at risk of arrhythmia.[1] Here we report a case of sudden unexplained death in a young asymptomatic woman who was diagnosed with PCD based on postmortem genetic testing after a negative autopsy. Her brother, who was diagnosed clinically with short QT syndrome and received an implantable cardioverter defibrillator, was also found to have PCD through family screening.

Case

A previously well 26-year-old Chinese woman (II-2; Fig. 1) died suddenly during sleep. Autopsy investigation did not identify an anatomic or toxicologic cause of death. The decedent's 28-year-old brother (II-1; Fig.1) subsequently underwent cardiac investigations in the Philippines after presenting with near syncope. Echocardiography and cardiac magnetic resonance imaging showed a structurally normal heart. He was found to be bradycardic, with a manually measured corrected QT interval (QTc) of 330-355 ms (Fig. 2A). The proband's brother was diagnosed with short QT syndrome, a condition known to be associated with sudden cardiac death (SCD). He received a primary-prevention implantable cardioverter-defibrillator before returning to Canada. No known history of consanguinity or SCD was reported, except for a maternal second cousin of the proband, who died at 16 years of age from an

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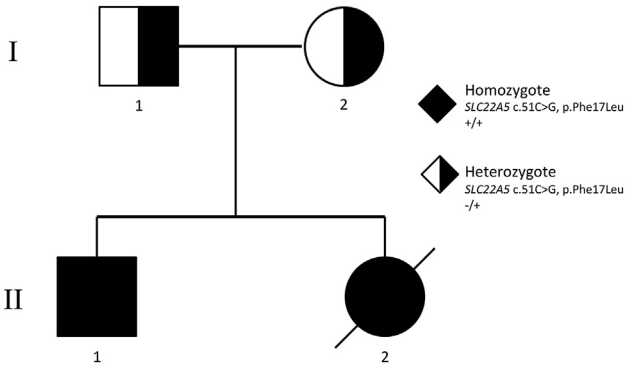

Figure 1. Family pedigree reporting *SLC22A5* genotype status. Male and female are indicated by squares and circles, respectively.

"enlarged heart." The family is of Chinese Fookien origin, a population from the southern province in China, who immigrated to the Philippine, where II-1 and II-2 were born.

Postmortem genetic testing of patient II-2 was performed at a commercial genetic testing laboratory with the use of retained frozen heart tissue. A broad panel of 184 genes known to be associated with inherited arrhythmia or cardiomyopathy conditions (Supplemental Table S1) was tested and revealed a homozygous missense variant (c.51C>G) in *SLC22A5* resulting in a phenylalanine-to-leucine substitution in position 17 (p.Phe17Leu). This variant was classified as pathogenic for PCD by the American College of Medical Genetics Standards and Guidelines[2] (Supplemental Table S2). Targeted variant testing was undertaken in the decedent's brother who was also found to be homozygous (Fig. 1). Both parents, who had normal ECGs (Supplemental Fig. S1), were confirmed heterozygote carriers (Fig. 1). The decedent's brother demonstrated critically low levels of free and total carnitine on adult dry blood spot testing (Supplemental Table S3). He was started on high-dose carnitine therapy, 146 mg/kg/d, and 12-week follow-up showed improvements in his carnitine levels (Supplemental Table S3) and QT measurement (Fig. 2B). Subsequently the carnitine dose was reduced to 82 mg/kg/d, and carnitine levels are now being monitored every 6 months.

Discussion

OCTN2 (encoded by *SLC22A5*) is an Na^+-dependent bifunctional transporter of carnitine. Its dysfunction causes PCD and limits fatty acid oxidation (Supplemental Fig. S2). Functional studies have shown that *SLC22A5* p.Phe17Leu is associated with altered OCTN2 trafficking to the plasma membrane resulting in < 20% of wild-type OCTN2 activity.[3] Reversible QT shortening has been observed in patients with PCD and in a mouse model of carnitine deficiency.[4] However, to the best of our knowledge, this is the first case of PCD presenting with SCD during adulthood in the absence of other cardiac manifestations. Caution should be exercised, however, when implicating *SLC22A5* in cases of shortened QT interval or SCD because other determinants must also be considered.

This report strengthens the link between metabolic disorders and arrhythmias, and broadens the discussion regarding genetic testing in SCD and gene-elusive inherited arrhythmia syndromes. Metabolic investigation may therefore be considered in the presence of unexplained atrial and ventricular arrhythmias and cardiomyopathies, and may provide an opportunity for disease-modifying therapy.

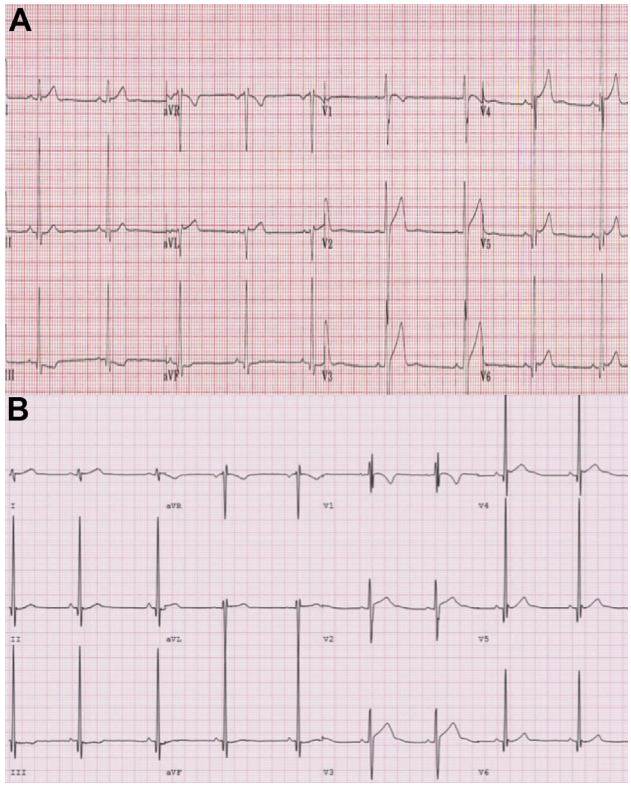

Figure 2. Electrocardiograms of patient II-1 (**A**) at first presentation in Canada (QTc = 320 ms) and (**B**) after carnitine replacement (QTc = 433 ms).

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.05.014.