JACC: CLINICAL ELECTROPHYSIOLOGY VOL. ■, NO. ■, 2017

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2017.08.007

Clinical Outcomes and Modes of Death in Timothy Syndrome

A Multicenter International Study of a Rare Disorder

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ABSTRACT

OBJECTIVES The objective of this study was to evaluate contemporary clinical outcomes and identify triggers for arrhythmias or sudden death in an international cohort of Timothy Syndrome (TS) patients including those with novel TS-associated CACNA1C mutations.

BACKGROUND TS is an extremely rare genetic disorder of the L-type cardiac channel $Ca_v1.2$ encoded by *CACNA1C*. The syndrome is characterized by multisystem abnormalities consisting of QT prolongation, congenital heart defects, syndactyly, facial dysmorphism, and neurological symptoms.

METHODS Patients diagnosed with TS between January 1, 1994, and April 1, 2016, from 12 international tertiary care pediatric centers were included in this retrospective study. Data were gathered via survey from the patients' electrophysiologists.

RESULTS Seventeen patients diagnosed with TS were identified. Length of follow-up was 4.9 years (range: 3.0 to 19.0 years). Mean QTc was 640 ms (range: 500 to 976 ms). All patients were treated with beta-blockers; 13 patients (76%) were also treated with an implantable defibrillator. Eleven patients experienced an episode of aborted cardiac arrest, 6 associated with general anesthesia and 2 with hypoglycemia. Four patients died suddenly due to ventricular fibrillation, 2 of whom had associated hypoglycemia.

CONCLUSIONS This study shows that mortality in TS patients is due to multifactorial mechanisms, which include ventricular arrhythmias, pulseless electrical activity, and hypoglycemia. A simple nomenclature for ongoing studies of TS and related syndromes is described. A worldwide prospective registry is needed for continued exploration of this syndrome. (J Am Coll Cardiol EP 2017;■:■–■) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACA = aborted cardiac arrest

AED = automatic external defibrillator

AV = atrioventricular

CHD = congenital heart disease

CIED = cardiac implantable electronic device

ECG = electrocardiogram

GA = general anesthesia

ICD = implantable cardioverter-defibrillator

LCSD = left cervical sympathetic denervation

LQTS = long QT syndrome

SCD = sudden cardiac death

TdP = torsades de pointes

TS = Timothy syndrome

TWA = T-wave alternans

VF = ventricular fibrillation

VT = ventricular tachycardia

Timothy syndrome (TS) is an extremely rare genetic disorder characterized by myriad multisystem abnormalities, consisting of a cardiac phenotype that universally includes QT prolongation and potentially congenital heart disease (CHD) and/or cardiac hypertrophy, syndactyly, facial dysmorphism, and a neurological phenotype that can include autism, seizures, and intellectual disability. The original genetic discovery attributed the predominant cause to a recurrent de novo heterozygous missense mutation, p.Gly406Arg, in the alternatively spliced exon 8A of *CACNA1C* (1). Subsequently, 2 additional mutations were identified in exon 8 (p.Gly402Ser and p.Gly406Arg) associated with a slightly different phenotype than the original exon 8A-localizing missense mutation (2–4). With the advent of whole exome sequencing, other novel *CACNA1C* mutations have emerged, leading to an elucidation of phenotypic variants (5–11). Extreme QT prolongation is typical in TS and predisposes to ventricular fibrillation (VF), cardiac arrest (ACA), and sudden cardiac death (SCD). According to previous reports, most patients die before the third year of life despite medical treatment with beta-blockers (1). However, clinical outcome data reflecting current management strategies of this high-risk cohort have not been reported in the past decade.

We evaluated clinical outcomes and triggers for arrhythmia or sudden death in an international cohort of patients with TS, including those with novel TS-associated *CACNA1C* mutations. This case series provides a contemporary report of clinical course and outcomes in TS patients, along with updated management strategies and prognostic findings.

METHODS

STUDY COHORT. Patients diagnosed with TS from January 1, 1994, to April 1, 2016, from 12 international tertiary care pediatric centers were included in this retrospective study. De-identified data of TS patients from participating institutions were transferred electronically to the coordinating center and included baseline demographics, clinical characteristics, electrocardiogram (ECG) findings, genetic test results, treatment strategies, and outcomes. Additionally, hospitalization records including types of procedures and anesthetics were evaluated, along with the response and complications related to therapy.

Specific clinical characteristics evaluated included syndactyly, facial anomalies, abnormal dentition, baldness at birth, neurodevelopmental delay, CHD, suspected immune disorders, and hypoglycemia. The diagnosis of noncardiac manifestations, such as neurodevelopmental delay, suspected immune disorders, and hypoglycemia, were made based on the assessment by the patient's treating clinician (12,13).

INCLUSION CRITERIA. Patients were included in this study if they met the clinical criteria for TS with or without a confirmed genetic diagnosis as follows (1): QTc ≥480 ms and 1 or more of the following clinical features: 1) unilateral or bilateral cutaneous syndactyly; 2) typical TS facial and dental anomalies; 3) neurological symptoms including autism, seizures, intellectual disability, and hypotonia; and 4) CHD.

ECG AND RHYTHM ABNORMALITIES. The standard pediatric ECG was reviewed for measurements and rhythm analysis. QTc was calculated according to the Bazett formula on a standard pediatric ECG. Maximum QTc recorded was used for analysis in this study. The T waves were analyzed for the presence of T-wave alternans (TWA). Bradyarrhythmias were defined as 1) pauses in the rhythm >3 s and 2) atrioventricular (AV) block. Tachyarrhythmias were classified as 1) torsades de pointes (TdP); 2) ventricular tachycardia (VT); 3) VF; and 4) atrial tachycardia/atrial fibrillation. Rhythm abnormalities data were obtained from documentation in medical charts, implantable cardioverter-defibrillator (ICD) analysis, and automatic external defibrillator (AED) rhythm analysis.

GENETIC TESTING. Genetic testing approaches included: 1) targeted analysis for pathogenic variants of *CACNA1C*, followed by whole gene sequence analysis if no pathogenic variant is found; 2) sequence analysis of *CACNA1C* followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found; 3) use of a multigene panel that includes *CACNA1C* and other genes of interest; and

presented in this manuscript from Medtronic, Inc. Dr. Temple has served as a consultant for St. Jude Medical. All other authors have reported that they have no relationships relevant to this paper to disclose.

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received January 31, 2017; revised manuscript received August 21, 2017, accepted August 22, 2017.