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Perspective Open Access

Timothy Syndrome: A Rare Multi System Disorder

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Perspective

Timothy Syndrome (TS) is a rare, multi-system disorder caused by genetic changes in the L-type calcium channel gene, *CACNA1C*. The "classic" TS form can be specifically noted at the birth of an infant having a dramatically prolonged QT interval (longer than normal time duration between the onset of the QRS complex to the end of the T wave as measured on an electrocardiogram), and an associated varying degree of syndactyly of fingers and toes. This Timothy Syndrome Type One (TS1) was originally discovered as an identical *de novo* G406R change in exon 8A of *CACNA1C* [1]. A secondary TS form, or Timothy Syndrome Type Two (TS2) was identified at the exact same G406R location of *CACNA1C*, but in exon 8 [2]. This TS2 type also presents at birth with a prolonged QT, but without syndactyly. During the past 15 years since the original discovery of TS in 2004, other atypical forms of TS (ATS) have been identified in the *CACNA1C* gene, some presenting with greater system-wide abnormalities and a reduced life expectancy, while others are reportedly to be affected with a prolonged QT (LQT) only [3-5]. Those individuals seemingly only affected by a heritable form of LQT (LQT8) will not be considered in this review.

Throughout 25 years of data collection, (author's database compiled of physician or parental patient referrals, and periodical reported individuals), TS numbers are increasing annually, however, an updated TS demographics has not been reported, thus the reason for this general and abbreviated review.

Currently, 65 TS1 and TS2 individuals have been genetically identified, all having the exact same G406R change in the *CACNA1C* gene, either in exon 8A or exon 8, (exon 8A being the most common, presumably due to the recognizable presentation of syndactyly with a prolonged QT interval at birth.) Male births out number female in TS1, whereas females marginally out number males in TS2. Timothy syndrome type 1 female deaths generally occur earlier than male deaths; currently all known TS2 males are thriving, however females are not as fortunate, most having passed before their fourth birthday. With improved medical recognition and clinical treatment, TS1 currently has five older individuals thriving, ages 18-27 years. The oldest of the TS2 individuals is 13 years of age.

Multi-system abnormalities are included in Atypical TS (ATS) changes which have been identified sprinkled throughout the *CACNA1C* gene in 16 individuals. Male birth numbers are greater than female births. Mosaicism in ATS may account for some individuals having severe system-wide abnormalities but lack the noted cardiac involvement.

Once the recognizable cardiac challenges of TS (bradycardia, 2:1 atrioventricular block, severely prolonged QT interval, various congenital heart defects and cardiomyopathies) are stabilized by recognized paediatric cardiac standards (beta adrenergic blockers, Mexiletine, pacemaker and ICD placement and reparative surgeries), and survival is enhanced, other significant health issues become problematic. Most notably is a sudden and life-threatening hypoglycaemic condition, exact origin of this sporadic beta cell dysfunction is currently unknown. Hypoglycaemia is noted in all types of TS and affects both males and females. Medical records indicated hypoglycaemia was specifically the cause of death or contributed to the demise of some TS children.

Frequent and reoccurring pneumonia and upper respiratory infections are prevalent in TS, particularly challenging for TS males. Treatment proves troublesome as most pharmaceutical interventions exacerbate cardiac QT prolongation and the propensity to initiate arrhythmias.

Of surviving TS children gastrointestinal problems exist in all types and in both genders. Problems include acid reflux, severe gag reflex and problematic constipation. Severe gastric pain is also noted in TS children.

Fetal programmed cell death is impaired in TS1, causing congenital heart abnormalities and an atypical form of finger syndactyly. Surgical cardiac repairs and conjoined finger separation under anaesthesia is worrisome for TS1 children as anaesthetic paralytics have proven problematic for causal factors in initiating life-threatening arrhythmias. Although syndactyly is not common in TS2, other bone developmental problems are noted such as congenital hip dysplasia and foot disorders. Same anaesthetic concerns apply to TS2 children.

Muscular hypotonia is problematic in all types of TS, attributing to significant delays in physical development: sitting, standing, walking, running, jumping, skipping are all delayed or impaired.

Significant speech delays are prevalent and require long term speech therapy. Learning disabilities are frequent with ADD, ADHD and autism being recognized by standard school testing modalities. All TS children require additional special developmental aids for educational success.

Social problems are also noted and can include extreme shyness to being overly friendly. Aggressive behaviour/anger issues are problematic. Phobias are noted mainly in TS1. Schizophrenia is clinically diagnosed in an older TS1 individual. Other organ issues of concern involve the eyes, ears, skin and circulatory problems. Significant dental issues can be severe and require surgical measures for multiple tooth extractions resulting from gum infections.

This perspective is not intended to be in depth, but is reported to be a general and wide- reaching indication of the numerous significant health concerns associated with the rare and little understood disorder of Timothy syndrome, and is written in the hope that further

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research will be undertaken into the multiple health concerns which the overwhelming expression of calcium exhibits in most cells of the diagnosed TS individual. Almost every cellular function is adversely affected by the increased influx of calcium, causing the often-severe abnormalities as observed in TS due to mutational changes in the *CACNA1C* gene.

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