



SADS FOUNDATION

SUDDEN ARRHYTHMIA DEATH SYNDROMES

Timothy Syndrome

A Guide for Patients and Health Care Providers

by Katherine Timothy, September 28, 2005.

A note from the SADS Foundation.

We provide this information with the hope that informing physicians, other health care providers, and the public will encourage early and correct diagnosis and proper therapy, resulting in the reduction and ultimately elimination of cardiac arrest and sudden death from Timothy Syndrome and other inherited arrhythmias.

What is Timothy Syndrome?

Timothy Syndrome (TS) is a rare and serious genetic disorder characterized by a spectrum of complicated health concerns which include:

- ♥ abnormally prolonged *repolarization* time of the heart (the process of returning heart cells to a resting state in preparation for the next heart beat), as measured by a rate corrected QT interval of >480 to 700 ms, predisposing a child to serious cardiac events including cardiac arrest and sudden death,
- ♥ *syndactyly* (webbing between or apparent fusing) of fingers or toes
- ♥ congenital heart defects (structural heart anomalies present at birth),
- ♥ facial anomalies,
- ♥ weakened immune system,
- ♥ developmental delays and autism.

The genetic discovery of TS was made in 2004 by researchers at Children's Hospital Boston, Howard Hughes Medical Institute and University of Pavia, Italy.

How is Timothy syndrome recognized and diagnosed?

Timothy syndrome can often be suspected in a child before birth when the fetal heart rate is noted to be *bradycardic* (abnormally slow) or the fetus is found to be in distress. At birth or with the first feeding the neonate can suddenly develop *hypoxia* (diminished availability of oxygen) and presents with *cyanosis* (a bluish discoloration of the skin). Upon evaluation of bradycardia and/or cyanosis the TS infant is generally found to be in 2:1 AV block (AV or atrio-ventricular block refers to a functional block due to an extremely prolonged ventricular repolarization rather than an AV conduction abnormality), and always a markedly prolonged QT interval is observed. Within days of birth the TS infant often undergoes pacemaker placement in an effort to stabilize the heart rate and reduce the risk for induction of arrhythmias.

The diagnosis of TS is suspected with the following features:

- A rate corrected QT (QTc) interval of >480 ms-700ms
- Bilateral or singular combination of finger syndactyly and bilateral syndactyly of the 2nd and 3rd toes

These two constant features are often associated with the following additional phenotypes:

- Congenital heart defects (ASD, VSD, PDA, PFO, TOF)
- Facial anomalies including flat bridge nose, low set ears, thin upper lip, or very round, fattish face.

The presence of the de novo G406R mutation in the Ca(v)1.2 Calcium Channel gene, CACNAC1C confirms the TS diagnosis.

What is the genetic basis for Timothy syndrome?

Without exception, all children studied for Timothy syndrome were identified to have a single *de novo* (new or spontaneous) G406R mutation in the Ca(v)1.2 Calcium Channel gene called CACNAC1C, located on chromosome 12. This mutation causes the impairment of a fundamental cell ion channel, found in most tissues and organs, which controls the amount of calcium entering a cell. Ion channel gating closure is affected by this mutation and cells are overwhelmed by a continuous influx of calcium. The affected gene is *expressed* (activated) in cardiac muscle cells as well as tissues of the gastrointestinal system, lungs, immune system, smooth muscle, testes and brain, including regions of the brain which are associated with abnormalities observed in autism.

Is Timothy syndrome an inherited disorder?

Timothy syndrome was identified to arise from a single spontaneous or new mutation in each child and it is not considered to be an inherited disorder from one's parents; however, researchers were perplexed by one identified TS family as having multiple children affected with the syndrome. Further studies of parental DNA from additional tissues (saliva, cheek and sperm cells) in this family revealed *mosaicism* (one tissue differing in genetic presentation from other tissues) in one parent. This parent's spontaneous CACNAC1C mutational change was only identified in reproductive tissue, which during fertilization gave rise to multiple children with the disorder; this explained why no other symptoms or multiple health concerns were observed in the mosaic parent. However, when a child is born with the spontaneous TS mutation, the disorder is considered to be an *autosomal* (males and females are equally

affected) *dominant* (the disorder's expression dominates) characteristic; half of the TS genetic make-up is affected by the disorder while the other half is not. If a TS child survives and is capable of reproducing children, each of his/her offspring would now have a 50/50 chance of inheriting the disorder.

What about genetic testing for Timothy syndrome?

Presently prenatal or molecular genetic testing for TS is not commercially available. However, testing may be available for families in which the disease causing mutation has been identified in an affected family member in a research or clinical laboratory.

Because mosaicism in a parent of a TS child may be of concern, when a TS child is born into a family and future additional children are desired, it would be prudent for the parents to be specifically screened for the G406R mutation in blood as well as additional tissues (saliva, cheek and sperm cells).

What is the treatment for Timothy syndrome?

Treatment for Timothy syndrome children is complex, and is dependant upon the severity of affectedness in each child concerning their personal array of health concerns.

Ventricular tachyarrhythmias (ventricular tachycardia and ventricular fibrillation) are present in 80% of TS patients and are the leading cause of death; therefore, treating TS children for cardiac survival is of vital importance. Beta-blocker medications are generally prescribed to treat patients with irregular heartbeats and prolonged QT intervals and as such, have been considered standard medication in the treatment of TS children; however, no available data exists regarding the specific effectiveness of beta-blocker therapy in TS. Since the identification of this syndrome resulting from a Calcium Channel gating abnormality the use of beta-blocker medications is now in question; in an effort to shorten QT repolarization and restore 1:1 AV conduction, additional pharmacological therapies (mexiletine and sodium channel blockers) have been tried without success. Calcium Channel blockers have been shown to be effective in treating this disorder in the animal model, but effectiveness has not been proven to date. Pacemakers are often placed in infants and children for pacing hearts at higher rates, resulting in improved cardiac function. External and internal defibrillators are also considered prudent and should be considered with a confirmed diagnosis, but internally placed devices also put the TS child at increased risk for problems with anesthesia and device site infections.

The TS congenital heart defects are generally treated with standard approaches. However, anesthesia is a known trigger of

arrhythmias in TS, therefore if surgical intervention is required for cardiac repair, extreme care in anesthesia selection and cardiac monitoring is essential to survival.

Table of TS Health Concerns

health concerns - TS children	% affected
syndactyly fingers	100%
syndactyly 2-3 toes	100%
prolonged QT interval	100%
ventricular tachyarrhythmias	80%
congenital heart defects	60%
facial dysmorphism	90%
metabolic (immune responses/hypoglycemia)	50%
Neuro-psychiatric involvement	80%

TS Complications

The TS congenital heart defects are generally treated with standard approaches. However, anesthesia is a known trigger of arrhythmias in TS, therefore if surgical intervention is required for cardiac repair, extreme care in anesthesia selection and cardiac monitoring is essential to survival.

Secondary complications which can further compromise the health of a TS child include:

- severe infections, particularly bronchial and sinus infections (probably due to altered immune response) are frequent and death is reported despite aggressive antibiotic therapy.
- Death due to intractable hypoglycemia has been anecdotally reported. Close monitoring of glucose levels is prudent with prescribed beta-blockers as these drugs may mask hypoglycemic symptoms.

Neuro-psychiatric concerns of the TS child

The current average age of death in TS children is reported as 3.1 years. With great care and vigilance of parents and the health care community, some TS children are known to have survived into their teenage years, the oldest TS individual now being 20 years. TS survival has allowed for neuro-psychiatric evaluations for physical, mental and social developmental abilities. It is now recognized that some TS children have delayed physical development (walking, running, skipping, jumping, etc.). Severe speech delays are observed in all TS children; some children are tested for deafness because of lack of speech response-evaluated hearing ability is found to be normal. Social development is impaired, most children appear to be intensely shy, lack common sense and prefer solidarity. Mild mental retardation has also been observed. Autism has been diagnosed in some TS children, others being diagnosed with an autism spectrum disorder. Early interventions in speech, social integration and physical therapy have proved beneficial.

Leading the Way to Save Lives

The SADS Foundation is a nonprofit organization committed to save the lives and support the families of children and young adults who are genetically predisposed to sudden death due to heart rhythm abnormalities.

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