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ARTICLE

Natural history of TANGO2 deficiency disorder: Baseline assessment of 73 patients

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ABSTRACT

Purpose: TANGO2 deficiency disorder (TDD), an autosomal recessive disease first reported in 2016, is characterized by neurodevelopmental delay, seizures, intermittent ataxia, hypothyroidism, and life-threatening metabolic and cardiac crises. The purpose of this study was to define the natural history of TDD.

Methods: Data were collected from an ongoing natural history study of patients with TDD enrolled between February 2019 and May 2022. Data were obtained through phone or video based parent interviews and medical record review.

Results: Data were collected from 73 patients (59% male) from 57 unrelated families living in 16 different countries. The median age of participants at the time of data collection was 9.0 years (interquartile range = 5.3-15.9 years, range = fetal to 31.8 years). A total of 24 different *TANGO2* alleles were observed. Patients showed normal development in early infancy, with progressive delay in developmental milestones thereafter. Symptoms included ataxia, dystonia, and speech difficulties, typically starting between the ages of 1 to 3 years. A total of 46/71 (65%) patients suffered metabolic crises, and of those, 30 (65%) developed cardiac crises. Metabolic crises were significantly decreased after the initiation of B-complex or multivitamin supplementation.

Conclusion: We provide the most comprehensive review of natural history of TDD and important observational data suggesting that B-complex or multivitamins may prevent metabolic crises.

Introduction

TANGO2 deficiency disorder (TDD, OMIM 616878) is an autosomal recessive disease caused by biallelic pathogenic variants in the *TANGO2* gene.[1,2] Although the exact functional role of TANGO2 remains unknown, some data suggest TANGO2 deficient cells have secondary mitochondrial dysfunction.[3-6] There are also data showing abnormal protein trafficking between the endoplasmic reticulum and Golgi.[4,5] Clinical symptoms include developmental, cognitive, and speech delay; dystonia, seizures, and hypothyrodism. Metabolic stressors such as illness or prolonged fasting trigger metabolic crises associated with rhabdomyolysis, muscle weakness, ataxia, worsening dysarthria, prolonged QTc and sometimes hypoglycemia or encephalopathy.[1-3,5,7-11] During metabolic crises, patients with TDD can develop life-threatening ventricular arrhythmias and cardiomyopathy, resulting in cardiac arrest, the leading cause of mortality in TDD.[5,7,8,12-14] Our goal was to detail clinical characteristics and disease course using data collected from families and medical records to describe the natural history of TDD.

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Materials and Methods

The TDD natural history study (ClinicalTrials.gov Identifier: NCT05374616) is led by a team of Baylor physicians and is open to any family with a member affected with TDD. Enrollment is advertised at TANGO2 related conferences and information is available on the TANGO2 Research Foundation website. To participate in this study, families provided consent to be contacted directly or via their medical care team. Written informed consent was then obtained from the parents of patients and included patients living in 16 different countries. The study was approved by the Institutional Review Board (IRB, H-43240) of Baylor College of Medicine. Diagnosis was determined on the basis of clinical symptoms and confirmed by genetic testing showing biallelic variants in the *TANGO2* gene. In some instances, patients were deceased before the diagnosis of TDD or genetic testing availability and were included based on confirmatory genetic testing of a sibling or parental carrier status and review of records indicating symptoms consistent with TDD. Data were obtained using questionnaire-based interviews conducted over a video or phone call, with interpreters as necessary. Information regarding race and ethnicity was collected to determine the distribution of *TANGO2* alleles based on the observations made among specific populations. Racial and ethnic status were determined by questioning families during study interviews. Parents were first asked to answer an open-ended question about their child's ancestral background, race, and ethnicity. Answers were recorded as self-reported. In addition to the open-ended question, parents were asked if they identified as Hispanic or non-Hispanic. All self-reported answers were then categorized. Detailed race and ethnicity categorization are provided in the Supplemental Methods. Families who identified as non-Hispanic and Caucasian, White, or European were categorized as non-Hispanic White. Families who identified as Hispanic included participants with ancestors from Mexico, Puerto Rico, and Spain. There were no participants living in Africa at the time of the interview; families self-reporting as either Black or African American were categorized as Black. In total, 8 families identified as more than one race and ethnic background and were categorized as other. These included non-Hispanic White and Native American, non-Hispanic Black and non-Hispanic White, non-Hispanic White and Asian, non-Hispanic Black and Hispanic, and non-Hispanic White and Hispanic. Available medical records were examined for information pertaining to medical history; clinical outpatient and inpatient course; diagnostic studies, including electrocardiograms (ECG), echocardiograms, electroencephalograms, brain magnetic resonance imaging, genetic testing and standard metabolic testing results; medications and treatments; feeding regimens; outcomes; and autopsy reports. Supplemental multivitamins or B-complex intake was recorded and considered only when taken as an additional source outside of diet (eg, gummy, tablet, liquid).

Abbreviations

ACP – acylcarnitine profile
ALT – alanine aminotransferase
AST – aspartate aminotransferase
CK – creatinine kinase
ECG – electrocardiogram
ECMO – extra corporeal membrane oxygenation
DP4 – Developmental Profile 4
IQR – interquartile range
IRR – incident rate ratio
MRI – magnetic resonance imaging
NPO – nil per os
QTc – corrected QT interval
TANGO2 – transport and Golgi organization homolog 2
TDD – TANGO2 deficiency disorder
TPN – total parenteral nutrition
UOA – urine organic acids
VT – ventricular tachycardia

B-complex vitamin was defined as a supplemental vitamin marketed and labeled as "B-complex" including at least 7 of the 8 B vitamins, which must have included B5 and B9. Supplements marketed and labeled as "multivitamins" were considered multivitamins. Metabolic crisis was defined as a hospital admission associated with rhabdomyolysis and elevated creatine kinase (CK) above normal range. Cardiac crisis was defined as the development of ventricular arrhythmias, cardiomyopathy defined as systolic dysfunction, or cardiac arrest during a metabolic crisis. Standard clinical biochemical testing reports for patients with TDD were extracted from available medical records and previously published case series. All biochemical testing was performed at a CLIA-certified laboratory or their equivalent outside the United States and obtained using tandem mass spectrometry techniques. Details regarding clinical laboratory analyses are provided in Supplemental Methods.

Statistics

Data are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) based on distribution. Patient characteristics were described overall and then compared among those with and without crises using Wilcoxon rank sum for continuous variables and Fischer exact or χ^2 for categorical variables. To describe freedom from metabolic crises, a Kaplan-Meier curve was created with time 0 defined as birth. Patients were censored at first metabolic crisis, death, or last follow-up in the natural history study.

To test the association between multivitamins and B-complex exposure and metabolic crises, we took into account the fact that patients may take supplemental vitamins at different times in their life and patients can have multiple crises events. We calculated the incidence rates of metabolic crises by calculating the number of crisis events over person years while exposed or not exposed to multivitamins or B-complex and other supplemental vitamins.

We then calculated incidence rate ratios with a 95% confidence limit using the exact Poisson method, comparing these incidence rates. A *P* value was calculated using the exact mid-p-double sided *P* value. Prevalence estimates were performed by the Broad Institute of Harvard and MIT (method details in Supplemental Methods).

Results

Demographics

Between February 2019 and May 2022, a total of 73 patients from 57 unrelated families (43 males, 59%) living in 16 different countries (Argentina, Australia, Canada, France, Greece, Hungary, Iran, Italy, Mexico, The Netherlands, Saudi Arabia, Spain, Sweden, United Arab Emirates, United Kingdom, United States) were enrolled. Median age at the time of data collection was 9.0 years (IQR = 5.3-15.9 years, range = 2 months to 31.8 years). A total of 14 (19%) patients were deceased. Most patients reported race and ethnicity as non-Hispanic White (53%), Hispanic (22%), Middle Eastern (12%), or other (more than 1 race and ethnicity, 11%). Patient characteristics are shown in Table 1.

Genetics

In our cohort, 24 different alleles were observed (Table 2, Supplemental Table 1). The median age at TDD genetic diagnosis was 4.8 (IQR = 2.0-12.0, range fetal to 28.0) years. In total, 43 patients (59%) harbored homozygous and 30 (41%) compound heterozygous variants. Consanguinity was reported in 8 families accounting for 14 (19%) patients. The most frequent allele observed was exons 3 to 9 deletion (49.3% of all alleles), followed by c.460G>A (p.(Gly154Arg), 7.5%), and exons 4 to 6 deletion (5.5%). Four patients (2.7%) had 22q11.2 deletion. Because the *TANGO2* gene is located in the 22q11.2 region, all patients with 22q11.2 deletion syndrome have heterozygous deletion of *TANGO2*; those harboring an additional pathogenic variant on the opposite nondeleted allele will be affected by TDD. In addition to having features of velocardiofacial/DiGeorge syndrome, these patients also had features unique to TDD.

Prevalence estimates by the Broad Institute of MIT and Harvard Rare Genomes Project

TDD is suspected to affect ~8000 individuals worldwide with an overall prevalence of approximately 1 in 1 million, based on current estimates. The overall carrier frequency is approximately 1 in 500, with the highest rate among non-Finnish Europeans (1:308), Latino (1:592), and African (1:767) populations. The prevalence of TDD is therefore highest in non-Finnish Europeans (~1:379,000). These data were calculated using 20 *TANGO2* alleles (including 8 of 24 variants reported in this study and excluding 22q11.2 deletion) and may under-represent the true prevalence of TDD (Supplemental Tables 1-3).

Birth and development

Most patients (96%) were born at term after an uncomplicated pregnancy and delivery. Early infancy and feeding were reported by parents to be normal in 77% of patients. Feeding difficulties during infancy were reported in 12 of 62 (19%) patients and poor suck in 8 of 62 (13%) infants. These data excluded 4 patients with 22q11.2 deletion, 3 of whom reported early feeding difficulties. Diagnosis of TDD was made postnatally in all but 1 case, in which prenatal testing was ordered based on family history of TDD in an older sibling. Our data showed no clinical features that would distinguish TDD diagnosis antenatally or at birth. Early developmental milestones were reported by parents to be normal through approximately 4 to 6 months of age followed by progressive delay in later developmental milestones (Figure 1). The median age at which parents first noted developmental delay was 12 (IQR = 8-18) months. Walking was achieved in 56 of 68 (82%) patients at a median age of 16 months (IQR = 12-22 months, range = 9 months to 57 months). Regression in milestones such as walking was common after metabolic crises although most children regained skills eventually over time. In 4 of 68 (6%) patients, ambulation was not achieved even after 10 years of age (ages in years at last follow-up: 10.1 17.6, 21.6, and 22), all of whom had early metabolic crises between the ages 1.3 to 1.5 years. Language delay, dysarthria, and difficulty with speech and articulation were reported in 61 of 63 patients (97%). Cognitive delay was also nearly universal in 64 of 66 patients (97%) and anecdotally, nearly all families reported children had better receptive compared with expressive language abilities.

Patients with TDD did not show a recognizable pattern of craniofacial dysmorphisms although exotropia was commonly reported in 43 of 61 (70%) patients. Several patients, particularly those who had metabolic crises exhibited a characteristic happy/smiling affect. Given their happy demeanor, seizures, gait abnormalities, and spasticity, testing for Angelman syndrome was offered to a few of these patients. Growth measurements for patients were available for height, weight, and head circumference in 74%, 90%, and 52%, respectively. Median height was 30th percentile (IQR = 8th-44th percentile), weight 44th percentile (IQR = 20th-67th percentile), and head circumference 35th percentile (IQR = 4th-57th percentile). Microcephaly has been previously reported as a feature of TDD. Of the 37 patients in whom a head circumference measurement was available, 8 patients (22%) were microcephalic, with a head circumference below the third percentile and 3 (8%) were macrocephalic (above the 97th percentile). Not all patients with microcephaly suffered a

Table 1 Patient demographics and characteristics

Characteristic	Total, *N* (%)	Patients With Crises, *n* (%)[a]	Patients Without Crises, *n* (%)[a]	*P* value
Total number of individuals[b]	73	46 (63)	25 (34)	—
Total number of families[b]	57	37	18	—
Males	43 (59)	28/46 (61)	15/25 (60)	0.81
Race/ethnicity				0.45
Non-Hispanic White	39 (53)	21 (46)	17 (68)	
Hispanic	16 (22)	11 (24)	5 (20)	
Middle Eastern	9 (12)	6 (13)	2 (8)	
Non-Hispanic Black	1 (1)	1 (2)	0 (0)	
Other	8 (11)	7 (15)	1 (4)	
Non-Hispanic Black/Hispanic	2 (3)	2 (4)	0 (0)	
Non-Hispanic Black/non-Hispanic White	1 (1)	1 (2)	0 (0)	
Non-Hispanic White/Asian	2 (3)	1 (2)	1 (4)	
Non-Hispanic White/Hispanic	1 (1)	1 (2)	0 (0)	
Non-Hispanic White/Native American	2 (3)	2 (4)	0 (0)	
Median age (IQR), y				
Age at first symptoms	1.2 (0.8-1.6)	1.3 (0.8-1.7)	1.2 (0.8-1.5)	0.91
Age at genetic diagnosis	5.4 (2.5-12.3)	5.5 (2.5-12.0)	3.0 (2.0-8.0)	0.14
Age at last study follow-up	9.1 (5.6-16.0)	10.6 (7.0-16.9)	5.9 (3.4-11.0)	0.11
Symptoms				
Developmental delay	68/72 (94)	45/45 (100)	21/25 (83)	**0.01**
Cognitive delay	64/66 (97)	41/42 (98)	21/22 (95)	1.00
Speech delay	51/67 (76)	33/41 (80)	18/25 (72)	0.37
Speech difficulties/dysarthria	61/63 (97)	39/39 (100)	20/22 (90)	0.12
Hypothyroidism	31/65 (48)	24/46 (52)	6/25 (24)	**0.01**
Seizures	31/73 (42)	23/46 (50)	7/25 (28)	0.08
TANGO2 spells	59/63 (94)	35/37 (95)	22/24 (92)	0.36
Ataxia/balance problems	65/69 (94)	39/42 (93)	24/25 (96)	1.00
Head lag	56/68 (82)	34/41 (83)	20/25 (80)	0.75
Drooling	41/59 (68)	24/34 (71)	15/24 (63)	0.58
Strabismus/exotropia	43/61 (70)	23/34 (68)	18/24 (75)	0.58
Constipation	37/68 (54)	27/41 (66)	8/25 (32)	**<0.01**
Deceased	14/73 (19)	13/47 (28)	1/23 (4)	
Posthumously diagnosed	9	8	1	0.15
Median age at death (IQR), y	6.5 (4.2-7.5)	7.0 (4.3-7.6)	3.3	
Cause of death				
Ventricular arrhythmias	6 (43)	6	0	
Cardiovascular collapse	6 (43)	6	0	
Unknown	2 (14)	1	1	

Boldfaced values represent statistical significance at $P < .05$ level. Denominators indicate the number of individuals for whom data was available.
IQR, interquartile range.

[a]In 2 patients, who were admitted for a crisis-like event, laboratory testing was not sent, and thus rhabdomyolysis and metabolic crises could not be confirmed. Numbers therefore may differ from total (*N*) column.

[b]Supplements may have been initiated after a crisis.

metabolic crisis, however a trend toward more severe symptoms (eg, nonambulatory, noncommunicative) was seen among patients with microcephaly.

Neurologic

The most prevalent feature of TDD is neurologic involvement in all patients. Delays included gross and fine motor skills, speech, and varying degrees of cognitive impairment ranging from mild to severe. Dysarthria was nearly universal and drooling common. Hearing loss was reported in 2 patients. All parents reported cognitive impairment, with the exception of 1 female who was 6 years at the time of data collection. Formal cognitive intelligence quotient (IQ) evaluations were available in 12 patients. Median full IQ score was 65 (range = 36-76). Cognitive delay was assessed as borderline (3 patients), mild (3 patients), mild-moderate (1 patient), moderate (4 patients), and severe (1 patient). In addition, 7 patients underwent cognitive evaluation using the Developmental Profile 4 (DP-4) assessment. DP-4 cognitive assessment provides standardized scores: above average, average, below average, or delayed. For these 7 patients, DP-4 cognitive assessment was scored as average (1 patient), below average (2 patients), and delayed

Table 2 Genetic variant data of 73 patients

Characteristic	*n* (%)	Variant Classification
Inheritance pattern	Number of patients *n* (%)	
Consanguinity	14 (19.2)	
Homozygous	43 (58.9)	
Compound heterozygous	30 (41.1)	
TANGO2 variant type	Number of alleles *n* (%)	
Intragenic deletion	85 (58.2)	
Splice site	22 (15.1)	
Nonsense	17 (11.6)	
Missense	14 (9.6)	
Frameshift	4 (2.7)	
Contiguous gene deletion	4 (2.7)	
TANGO2 variant	Number of alleles *n* (%)	
Exon 3-9 deletion	72 (49.3)	Pathogenic
Exon 4-6 deletion	8 (5.5)	Pathogenic
Exon 4-9 deletion	2 (1.4)	Pathogenic
Exon 3-5 deletion	2 (1.4)	Pathogenic
Exon 1-2 deletion	1 (0.7)	Pathogenic
22q11.2 deletion	4 (2.7)	Pathogenic
c.460G>A p.(Gly154Arg)	11 (7.5)	Pathogenic
c.57-1G>C	6 (4.1)	Pathogenic
c.728+1G>A	6 (4.1)	Pathogenic
c.605+1G>A	5 (3.4)	Pathogenic
22q11.2 contiguous gene deletion	4 (2.7)	Pathogenic
c.120G>A p.(Trp40*)	4 (2.7)	Pathogenic
c.94C>T p.(Glu32*)	4 (2.7)	Pathogenic
c.711-3C>G	3 (2.1)	Pathogenic
c.262C>T (p.Arg88*)	3 (2.1)	Pathogenic
c.280delC (p.His94Thrfs*3)	2 (1.4)	Pathogenic
c.256C>T (p.Arg86*)	2 (1.4)	Pathogenic
c.338delG p.(Gly113Alafs*10)[a]	2 (1.4)	Pathogenic
c.451+2T>A	2 (1.4)	Pathogenic
c.385C>T p.(Arg129*)	2 (1.4)	Pathogenic
c.119G>A p.(Trp40*)	1 (0.7)	Pathogenic
c.217C>T p.(Arg73*)	1 (0.7)	Pathogenic
c.149T>C p.(Leu50Pro)	1 (0.7)	Likely pathogenic
c.496A>G p.(Lys166Glu)	1 (0.7)	VUS
c.77G>A p.(Arg26Lys)	1 (0.7)	Pathogenic

Please see Supplemental Table 1 for reference sequence information. Variants and variant classification are listed as stated in the molecular reports of patients from different countries with the one exception[a] where sequencing was performed at Texas Children's Hospital, Baylor College of Medicine.

VUS, variant of uncertain significance.

(4 patients). Spasticity and gait abnormalities (eg, wide based gait, toe-walking) were nearly universal, ranging from mild to severe and showed an overall worsening with age. Although many patients were able to walk independently, some required walkers or wheelchairs. Most common treatments for hypertonicity and spasticity included local botulinum toxin injections as well as systemic medications including baclofen and clonazepam.

Clinical symptoms—transient episodes not associated with metabolic crises

Between the ages 1 to 3 years (median = 18 months, IQR = 12.5-24 months, range = 4-36 months), 94% of parents (59/63) reported their children exhibiting similar episodic and transient symptoms. These symptoms are often the first symptoms of TDD but can continue over time. Symptoms were characterized by one or more of the following: (1) transient ataxia or weakness in which children were described as "walking like a drunk sailor" or suddenly falling over while walking or sitting, sometimes unable to upright themselves (Supplemental Videos 1-2), (2) tilting of the head to the side or back (Supplemental Video 3) or tilting of the body to the side (Supplemental Video 1), (3) moderate to extreme lethargy, (4) a seemingly unresponsive child who seems to be "spacing out" or "in a fog," (5) slurring of speech, (6) drooling, (7) unilateral or bilateral exotropia, and (8) paroxysmal dyskinesia, which are recurrent attacks of involuntary movements without loss of consciousness. Most symptoms appear to be related to transient muscle weakness or focal dystonia. These

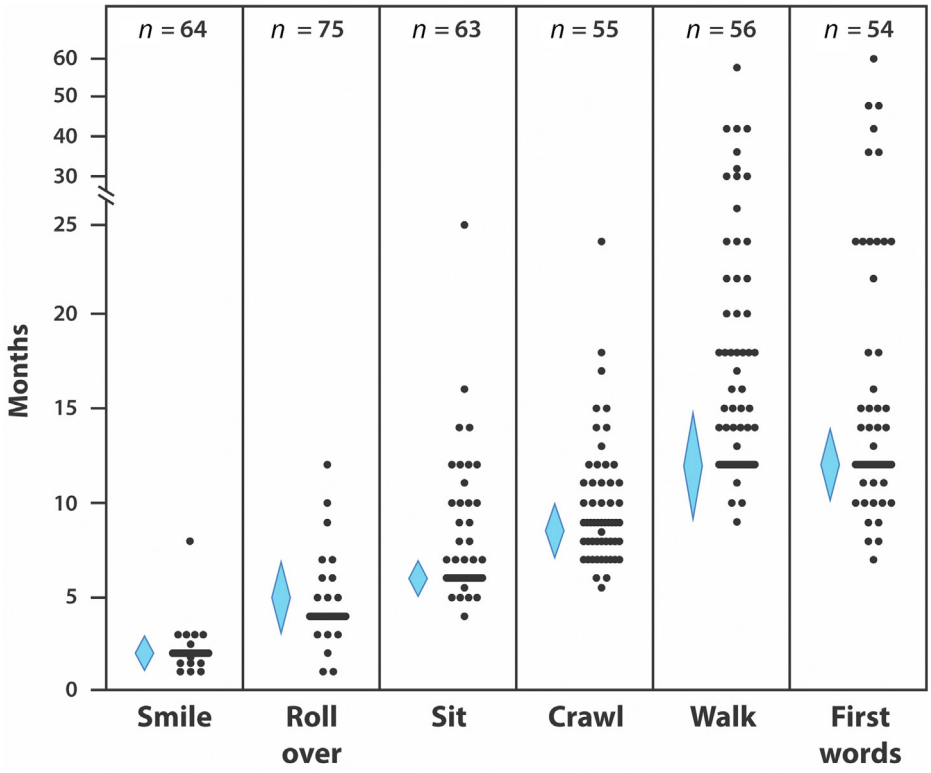

Figure 1 Developmental milestones in patients with TANGO deficiency compared with average. Major developmental milestones in early development showed a progressive delay in the age at which TANGO2-deficient children meet milestones in comparison with national averages. Diamonds represent age range for average expected normal development.

symptoms most commonly occur in early morning hours after waking from sleep but can occur anytime and are often triggered by warm weather, exertion, decreased oral intake, and disruptions to daily routines, particularly when these changes (eg, vacations, new schools) result in longer periods between snacks or meals. Symptoms can last anywhere from minutes to hours and resolve spontaneously. Parents reported that rest/naps and snacks help alleviate symptoms and constipation may worsen symptoms. Episodes may cluster together, occurring multiple times a day for weeks, or they may be sporadic with months in-between episodes; however, they can continue throughout the lifetime. These transient symptoms should be differentiated from baseline neurodevelopmental and endocrine dysfunction, which include baseline cognitive delay, seizures, spasticity, difficulty with walking (Supplemental Video 4), dysarthria (Supplemental Video 5), and hypothyroidism. Importantly, although these symptoms can be transient, they are also associated with metabolic crises albeit symptoms are often worse during crises. The important difference is the association of laboratory abnormalities (elevated CK and transaminases [ALT/AST]) and QTc prolongation during metabolic crises. To help distinguish symptoms that are noncrises from metabolic crises, the TANGO2 community refers to these noncrises symptoms and transient episodes as "TANGO2 spells." If symptoms are associated with laboratory derangements with QTc prolongation this would be termed a metabolic crisis. Certain age periods appear to be associated with higher frequency and intensity of TANGO2 spells including toddler and adolescent years particularly surrounding puberty. Interestingly, some children have fewer TANGO2 spells than others. The reason for this remains unclear but is currently under investigation.

Seizures

Seizures were present in 42% (31/73) of patients, approximately one-third of whom had drug-resistant epilepsy (12/31). The majority of seizures occurred independently from crises events. In 6 individuals, seizures occurred in the setting of hypoglycemia. Median age of seizure onset was 1.8 years (IQR = 1-3.6 years, range = 2.5 months to 23 years). The most common seizure types reported were generalized myoclonic (9/31, 29%) and tonic-clonic (7/31, 23%) events. Generalized tonic (5/31, 16%), atonic (4/31, 13%), and focal motor (1/31, 3%) seizures were also reported. Infantile spasms were reported in 3 patients (3/31, 10%). The most common antiseizure medications used were levetiracetam (8/31, 26%) and valproic acid (7/31, 23%). Other reported medications included carbamazepine, clobazam, clonazepam, felbamate, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, prednisone, rufinamide, topiramate, vigabatrin, and zonisamide. One patient was also treated with a vagus nerve stimulator, which significantly reduced the frequency of

atonic seizures. Electroencephalography abnormalities included both generalized and multifocal epileptiform activity in the form of generalized spike-wave and polyspike-wave discharges as well as focal and regional spikes and sharp waves. Generalized background slowing was often present and regional slowing was also observed. Myoclonic seizures as well as nonepileptic myoclonic jerks were documented on EEG, the latter of which were often startle-induced. A total of 19 patients reported significant reactions to loud noises, 8 of whom exhibited hyperekplexia, an exaggerated startle response to unexpected sensory stimuli.

Neuroimaging

Brain magnetic resonance imaging (MRI) was abnormal in 62% (31/50) of patients who had undergone advanced neuroimaging. Those with abnormal MRIs typically had nonspecific findings such as mild diffuse ventriculomegaly, cerebral volume loss, and diminished white matter (14/31, 45%). Two of these patients exhibited mild progression in their degree of cerebral atrophy when examined between 4-to-8-year intervals. In 4 patients who underwent imaging in the acute and subacute settings of metabolic crises, including those with severe hypoglycemia, cardiac arrest, and/or extracorporeal membrane oxygenation treatment (ECMO), MRIs showed evidence of hypoxic ischemic encephalopathy or focal infarcts. Findings consistent with hypoxic ischemic encephalopathy included diffusion restriction and increased T2 signal in the subcortical white matter and increased T2 signal in the brainstem. Magnetic resonance spectroscopy in the acute setting revealed significantly elevated lactate peaks in the basal ganglia. In nonacute settings, magnetic resonance spectroscopy was normal or showed nonspecific mildly elevated cerebrospinal fluid lactate. Pars intermedia cysts and Chiari I malformation were incidentally noted in 4 and 1 patients, respectively.

Ophthalmologic

Optic nerve atrophy has been described in TDD.[8,11] In this cohort, optic nerve involvement was reported in 4 (6%). Exotropia was reported in 70% (43/61) with worsening of disconjugate gaze when fatigued or during spells or metabolic crises. Outcomes of 4 patients who underwent attempted surgical repair of exotropia include 2 with reported improvement, 1 with transient improvement, and 1 with no improvement.

Gastrointestinal

Gastrointestinal complaints were common with constipation being the most frequently reported (37/68, 54%). Nearly half (18/37, 49%) reported exacerbation of other symptoms, particularly TANGO2 spell symptoms, when constipation was worse. Gut dysmotility, particularly during metabolic crises, was commonly reported, making it difficult to advance or continue oral or enteral tube feeds during hospitalization. A total of 18 patients (25%) had gastrointestinal tubes. Eosinophilic esophagitis was reported in 2 patients.

Endocrine

In this cohort, about half of the patients who underwent an evaluation had a diagnosis of hypothyroidism (31/65, 48%) at a median age of 4 years (IQR = 2-8 years, range = 2 months to 17 years). Hypothyroidism was more common among patients with a history of metabolic crises ($P = .01$, Table 1). All patients were treated with oral levothyroxine replacement. For patients with available data, biochemical tests confirmed primary hypothyroidism with elevated thyroid-stimulating hormone level with low or low-normal free T4 levels. In a subset of patients ($n = 4$) with available data on etiology of thyroid disease, one had autoimmune thyroid disease (positive antithyroglobulin antibody), one had post-thyroidectomy hypothyroidism (thyroidectomy was performed because of papillary thyroid carcinoma), and the remaining 2 patients had nonautoimmune thyroid disease of unknown etiology. Hypoglycemia was a common feature during acute metabolic crises and 37 patients were evaluated for adrenal insufficiency, only 1 (3%) of whom was ultimately diagnosed with adrenal insufficiency. Details regarding this patient are provided in the supplement. With the exception of 1 patient, hypoglycemia was not reported outside of metabolic crises.

Metabolic crisis

The hallmark of TDD is susceptibility to metabolic crises, defined by the presence of clinical symptoms along with laboratory derangements (rhabdomyolysis with elevated CK, AST, and ALT). During crisis, CK values ranged between mildly elevated (6.3 μkat/L, 377 U/L) to extreme elevation (>4175 μkat/L; >250,000 U/L), progressively increasing during most admissions before returning to normal in those whose crises resolved without demise. In this cohort, the status of whether a metabolic crises occurred or not was known for 71 patients. In 2 patients, crises status could not be confirmed because of the lack of confirmatory laboratory testing. Of the 71 patients, 46 (65%) experienced a total of 115 metabolic crises. The median age at first metabolic crisis was 3.0 (IQR = 1.0-5.9) years with patients presenting with first crises as young as 4 months and as old as 20 years. In this cohort, 50% of patients had a first crisis by 5.6 years (Figure 2A). Hypoglycemia was common during crises (52%) but not always seen. Lactic acidosis, hyperammonemia, and troponin leak were observed but not uniformly. Metabolic crises were triggered by viral illness, fever, and poor oral intake or prolonged fasting. Extreme heat and infections (eg, unrecognized tooth abscess) that are not necessarily easily recognizable in a child could also trigger crises. A total of 35% of the 71 patients had never suffered crises. The median current age among patients who

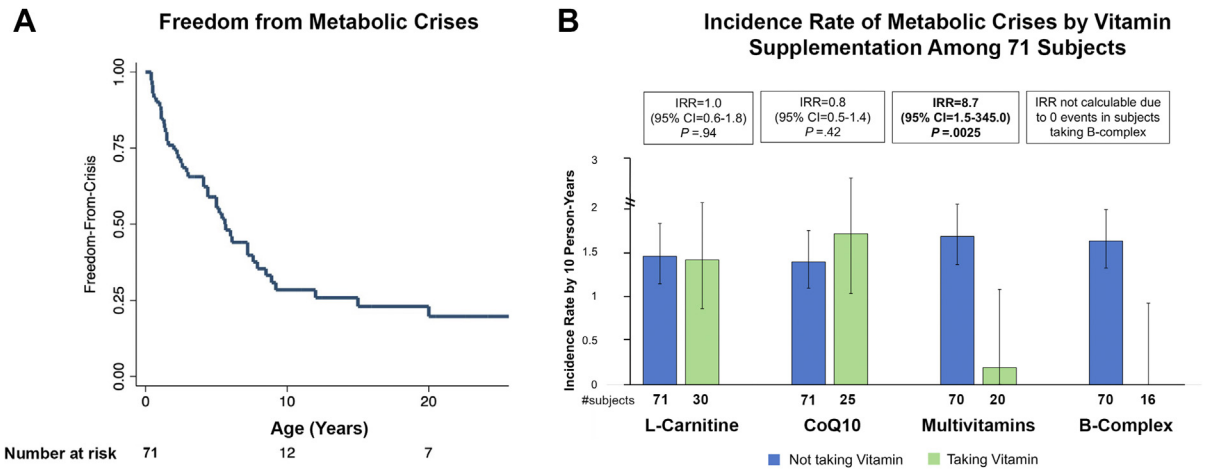

Figure 2 Metabolic crisis and vitamin supplementation. A. Kaplan-Meier curve freedom from metabolic crises. The time to first metabolic crisis is shown. In this cohort, 50% of patients had suffered a crisis by age 5.6 years. B. Supplemental use of multivitamins or B-complex significantly decreased metabolic crises. Blue bars indicate incident rate of crises when patients were not taking supplement, and green bars indicate incident rate of events when taking the supplement. The incident rate ratio (IRR) is the rate of metabolic crises per 10 patient years when patients were not taking B-complex vitamin or multivitamins compared with the rate of metabolic crises per patient years when patients were taking each vitamin. There was a significant decrease in the rate of events by 8-fold when taking multivitamins. This difference was not seen with supplemental carnitine or CoQ10. There were no events when patients were taking B-complex, and thus IRR was not calculable.

have never experienced a metabolic crisis was 7.2 years (IQR = 4.4-12.1 years, range = 1 month to 26.8 years).

Following hospital admission for metabolic crises, patients' hospital courses varied widely, with some patients being discharged within a few days and others requiring several months. Normalization of CK varied and, in some patients, took weeks. Rare complications during hospitalization included pancreatitis, adrenal insufficiency, and bowel ischemia. Marked gut dysmotility resulting in difficulty with advancing or tolerating feeds was common. Rhabdomyolysis did not result in any major renal complications among patients and for the vast majority, despite the severity of the illness, significant issues with maintaining electrolyte levels were not reported. After recovery from crisis, 2 patients were diagnosed with nephrocalcinosis.

Metabolic diagnostic evaluation

A total of 98 standard biochemical testing reports from 22 patients were collected for review. Of these, 38 samples were plasma amino acid analysis: 53% (20/38) at baseline and 47% (18/38) during crises. In total, data of 28 acylcarnitine profile (ACP) assays were extracted from medical records, and in addition, 5 patients' data in this study were extracted from previously published reports:[11] 58% (19/33) at baseline and 42% (14/33) during a crisis. A total of 17 urine organic acid reports were reviewed: 65% (11/17) at baseline and 35% (6/17) during a crisis. Diagnostic metabolic testing data for both crisis and baseline data were only available for 6% (6/98).

Individual comparisons were performed for amino acids involved in the urea cycle, along with branched-chain amino acids and alanine. Plasma amino acid profiles revealed a slight decrease in branched amino acids during times of crisis. These changes are nonspecific and were not statistically significant. These changes are commonly observed in patients who are fasting or those with poor nutritional intake. Although lactic acidosis can be observed in TDD crisis, alanine levels were only slightly increased in our cohort and this difference did not reach statistical significance (Supplemental Table 4).

Acylcarnitine profiles showed elevations in C2 at baseline and crisis, likely reflecting levocarnitine supplementation. Long-chain acylcarnitine species did not show statistically significant elevations in baseline samples or crisis samples. Significant differences were not seen in the 6 patients in whom baseline and crisis ACP were available. Disruption of ACP ratios (short-chain, middle-chain, and long-chain species) was also not observed in this cohort. Urine organic acids and urine amino acid samples did not reveal specific abnormalities or statistically significant differences when comparing baseline vs crisis samples (Supplemental Table 4). Although hyperammonemia has been reported as one of the features of TDD metabolic crisis, few patients within our cohort had this analyte measured during crises. In those in whom levels were measured ($N = 9$), ammonia levels were largely within normal limits (mean = 55.1 μmol/L ± 41 μmol/L, range = <9-148 μmol/L; mean = 77.2 μg/dL ±57.4, range = <12.6-207.3 μg/dL) and no patients required specific treatment for these levels.

Cardiac

With exception of patients with 22q11.2 deletion associated congenital heart defects, patients with TDD had structurally normal hearts with normal systolic function and normal electrocardiograms (ECGs) (including normal QTc) at baseline.

Table 3 Hospitalizations and crises data

Characteristic	*N* (%)
Median number of any hospitalizations per person (IQR)	3 (1-5)
Metabolic crises data (*N* = 71 patients with available data)	
Total number with metabolic crisis	46 (65)
Median age of first metabolic crisis (IQR), y	3.0 (1.0-5.9) (range = 4 months to 20 years)
Median number of metabolic crises per person (IQR)	1 (1-3)
Total number without metabolic crisis	25 (35)
Current median age without crises (IQR), y	7.2 (4.4-12.1) (range = 1 month to 26.8 years)
Cardiac crises data (*N* = 71 patients)	
Total number of patients with cardiac crises	30 (42)
Median age at first cardiac crisis (IQR), y	4.7 (1.4-7.2) (range = 4.8 months to 20 years)
Median number of cardiac crises per person (IQR)	1 (1-3)
Prolonged QTc (ECGs performed in 24 patients)	24 (100)
Median longest QTc (IQR), ms	552 (509-613)
Concomitant type 1 Brugada pattern (ECGs performed in 24 patients)	8 (33)
Arrhythmias and cardiomyopathy among 30 patients with cardiac crises	
Total number with arrhythmias	23 (77)
Total number of patients with ventricular tachycardia	22 (73)
Total number of patients with supraventricular tachycardia	4 (13)
Total number ot patients with heart block	1 (3)
Total number of patients with cardiac arrest	21 (70)
Total number of patients with VT and cardiomyopathy	11 (37)
Cardiomyopathy recovery data (*N* = 19 patients, 29 hospitalizations)	
Total number of crises hospitalizations with function recovery	25/25 (100)
Number of hospitalizations where function recovery unknown	2
Number of patients with dysfunction, deceased	2
Median lowest EF (%) per crisis (IQR)	21 (28-46)
Median number of days to recovery of function (IQR)	42 (10-150)
Median number of days to normalization of function before discharge (IQR)	17 (7-24)
Median number of days to normalization of function after discharge (IQR)	153 (112-168)

EF, ejection fraction; *IQR*, interquartile range; *QTc*, corrected QT; *VT*, ventricular tachycardia.

Severe changes, however, occurred during metabolic crises. During crises, all patients in whom an ECG was obtained demonstrated QTc prolongation and 33% reported simultaneous intermittent type 1 Brugada pattern (Supplemental Figure 2). The predominant arrhythmia was torsade de pointes (Supplemental Figure 2), which was typically unresponsive to standard antiarrhythmic treatment. In this cohort, 30 patients (41% of total cohort, 65% of patients who had a metabolic crisis) were admitted for a total of 49 cardiac crises events (Table 3). Median age at first cardiac crisis was 4.7-years (IQR = 1.4-7.2 years, range = 4.8 months to 20 years). Details regarding 27 patients have been previously published.[14] A total of 21patients (70%) suffered a cardiac arrest, and of 12 deaths during cardiac crises, 6 (50%) were directly related to uncontrolled arrhythmias. In 5 patients, arrhythmias were controlled after extracorporeal membrane oxygenation (ECMO) support, 4 of whom survived. Most successful treatment of arrhythmias included isoproterenol, IV magnesium, and atrial pacing.

Of the 30 patients with cardiac crisis, systolic dysfunction (ranging from mild to severely depressed) was documented in 19 (63%) patients during 29 admissions. Although left ventricular dilation was reported during crisis and ultimately resolved, hypertrophic changes were not. Systolic function fully recovered in all at a median time of 42 (IQR = 10-150) days; 52% recovered function at the time of discharge, whereas 48% recovered after discharge.

Observations related to vitamin supplementation

Of 73 patients in this cohort, 46 had a metabolic crisis and 25 had no metabolic crisis. Two patients were admitted with symptoms consistent with metabolic crisis; however, laboratory testing was not performed, and thus a metabolic crisis could not be confirmed. Based on parental interviews, we made a striking observation: not only did patients who initiated multivitamins or B-complex at a young age never develop a lifetime crisis but patients who initiated either supplement after crises had taken place did not experience additional crises. The single exception to a metabolic crisis after initiation of multivitamins was a patient with total parenteral nutrition (TPN) dependency who developed a crisis when multivitamins were discontinued from TPN and administered enterally instead of intravenously. One patient who started B-complex between 13-16 months of age has never had a crisis and reports no TDD symptoms at age 6 years.

To evaluate our observations regarding B-complex and multivitamin supplementation, we calculated the incident rate ratios (IRRs) of crisis events by vitamin supplementation. We

Table 4 Supplemental vitamin intake and crises events: Total number of patients taking supplements, cumulative patient years, and number of crises events when patients were taking or not taking each supplement

Supplement	Total Number of Patients[a]	Total Number of Patient Years	Number of Crises Events
Carnitine			
Not taking carnitine	71	518.0	75
Taking carnitine	30	141.6	20
CoQ10			
Not taking CoQ10	71	548.1	76
Taking CoQ10	25	111.5	19
Multivitamins			
Not taking multivitamins	70	586.2	98
Taking multivitamins	20	51.7	1
B-complex			
Not taking B-complex	70	610.3	99
Taking B-complex	16	40.1	0

[a]Data regarding multivitamins and B-complex usage was not available for 1 subject.

assessed the incident rate of crises when patients were taking multivitamins and B-complex and compared this with the incident rate of crises when patients were not taking each supplement. We then compared these (IRRs) with 2 other commonly prescribed supplements, carnitine and co-enzyme Q10 (Table 4, Figure 2B). Although we cannot confirm compliance, there were no crises when patients reported consistently taking B-complex vitamins. With the exception of the single patient with TPN dependency mentioned before, there were also no crises when patients were taking multivitamins. Even among patients who suffered multiple crises, no further crises were noted once the patient was consistently taking B-complex or multivitamins. The IRRs for carnitine (IRR = 1.0, 95% CI = 0.6-1.8, $P = .94$) and coenzyme Q10 (IRR = 0.8, 95% CI = 0.5-1.4, $P = .42$) showed crises rates are no different with or without these supplements suggesting that these supplements do not prevent crises. There were insufficient number of patients taking thiamine (B1) and riboflavin (B2) to make accurate assessments; however, notably, patients on both thiamine and riboflavin continued to have crises despite these vitamins.

In addition to our observational data that B-complex and multivitamins may prevent crises, we have previously reported that during a metabolic crisis, patients who remained nil per os (NPO) for prolonged periods of time with minimal nutritional support (eg, intravenous glucose containing fluids only) appeared to experience progressive clinical deterioration and worse outcomes.[14] Earlier initiation of nutritional support (either enteral or parenteral that included B-complex or multivitamins) appeared to reduce evolvement into cardiac crises.[14] The reduction of metabolic crises with vitamin supplementation is shown in Figure 2B.

Deaths

There were a total of 14 deaths (19%) at a median age of 6.5 years (IQR = 4.2-7.5 years, range = 5.5 months to 20 years). Six deaths were directly related to inability to control ventricular arrhythmias. In 6 other patients, death occurred during hospitalization (diagnosis of TDD was unknown in 4 at the time of death), which was not directly related to arrhythmias. Cardiovascular collapse with hypotension and bradycardia was reported although the exact nature or reason for these deaths was unclear. In an additional 2 patients, death occurred at home from unknown causes. One of these deaths was during sleep and outside of metabolic crisis in an 18-year-old patient with history of seizures.

Discussion

TDD may affect more than 8000 individuals worldwide. This ongoing natural history study expands upon existing literature as the largest report of individuals affected with TDD thus far. Although the exact function of TANGO2 remains unknown, our natural history data contribute to the understanding of this disease and may help prevent crises events.

An important aspect of this disease is the devastating consequence of metabolic crises. Patients who suffer metabolic crises may fare worse from a clinical standpoint than those who never have a crisis. Evaluation of neurodevelopmental differences among patients with TDD is an active and ongoing area of investigation. We believe that early recognition and diagnosis of TDD is critical in providing appropriate counseling to families for crises prevention. Signs and symptoms of TDD begin in late infancy, with delayed developmental milestones followed by a variety of transient and episodic symptoms that include balance and coordination difficulties, ataxia, movement disorders, dystonia (head or body tilt), exotropia, slurred speech, and fatigue. These episodes can be quite frightening to watch, prompting medical evaluation, which can be frustrating because symptoms may entirely resolve before the patient is medically evaluated. Because most physicians are not familiar with these transient but markedly abnormal symptoms as part of the clinical spectrum of TDD, delays in diagnosis are common. Recognizing these symptoms may help aid in earlier diagnosis of TDD. Thus, TDD should be included in the differential of any child with developmental

delay and speech difficulties presenting with these transient TANGO2 spell symptoms.

Metabolic analysis in this cohort did not show obvious abnormalities in intermediary metabolism processes at baseline or during crises including branched-chain amino acid metabolism disturbances, urea cycle defects, or abnormal organic acid metabolism. This is the first statistical analysis of patients with TDD during times of crisis. This analysis does not show a specific pattern suggestive of specific enzymatic deficiency in the fatty-acid beta-oxidation pathway in contrast to previously published reports.[1,5,11] TANGO2 may thus not be involved in 1 specific enzymatic pathway but rather may act in a more complex multitargeted manner, resulting in a unique biochemical signature.

Perhaps most importantly, data from our study sheds light onto the potential treatment and management of TDD. Based on 71 patients in this study, we observed that patients supplemented with B-complex or multivitamins were significantly less likely to have a metabolic crisis. Because multivitamins typically contain B vitamins, we believe one or more of the B vitamins is important in preventing metabolic crises and reducing symptoms. Intrafamial phenotypic variability is well recognized in TDD; we believe that administration of B-complex or multivitamins at earlier ages may be associated with less symptoms and could explain differences seen among patients and even siblings with TDD. The reason for B-complex/multivitamins in crisis reduction is not clear although B vitamins are critical cofactors for metabolic pathways and hence may be important when TANGO2 is deficient. Although we do not have sufficient prospective data to definitively prove these vitamin observations, given the minimal risk of multivitamins or B-complex supplementation and the potential profound therapeutic effect, we believe that these observational data warrant discussion and consideration. The striking reduction of crisis events among those taking B-complex or multivitamins in our cohort could be life-saving and warrants further investigation.

In summary, although data collection from our natural history study are ongoing, we believe that collective information from this larger cohort provides invaluable information to the patients, their families, and the medical community caring for these patients. We have characterized the developmental, neurologic, metabolic, cardiac, endocrine, and crises events in detail. Although, our data regarding B-complex and multivitamin use is observational in nature, supplementation with multivitamins (containing a full complement of B vitamins) or B-complex vitamin should be considered in patients with TDD. The exact dosing required is not known but all patients were meeting recommended daily allowance. Close supervision by a metabolic geneticist and a metabolic dietitian should be considered to avoid hypervitaminosis from dietary sources and external supplementation, particularly vitamin B6 which can lead to adverse effects at high levels. Further prospective studies are needed to understand the functional role of TANGO2, which to date remains unknown. These data from our study may shed light into the mechanism of TANGO2 and initiate further research studies, which can lead to more effective treatment of this disease.

Data Availability

Qualified researchers may request access to patient-level study de-identified data that underlie the results reported in this publication. Data requests can be made via email to the corresponding author and will be pending data use agreements.

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Ethics Declaration

Patient clinical and genetic (de-identified and identifiable) data were obtained from multiple institutions and approved under a single Institutional Review Board (H-43240) of Baylor College of Medicine. Written consent was obtained from parents/legal guardians of participants.

Conflict of Interest

The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from clinical laboratory testing conducted at Baylor Genetics. S.A.M. serves as Scientific Advisor and consultant for Aytu BioPharma, Inc for the AR101 Enzastaurin Clinical Trial. All other authors declare no conflicts of interest.

Additional Information

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