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Top Stories on arrhythmias in TANGO2 deficiency disorder

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TANGO2 deficiency disorder (TDD) is a multisystem neurodegenerative disease first discovered by Lalani et al in 2016.[1] This autosomal recessive disorder affects more than 8000 patients worldwide. About 1:500 individuals harbor a pathogenic *TANGO2* variant that, notably, resides within the 22q11.21 locus. Thus, all patients with 22q11.21 deletion (DiGeorge) syndrome who are missing 1 copy of *TANGO2* (transportation and golgi organization homolog 2) are at risk of having both disorders should they harbor a second pathogenic allele. Patients with TDD can present with new-onset arrhythmias from infancy into adulthood and hence its relevance to both pediatric and adult cardiologists/electrophysiologists. Often misdiagnosed as long QT syndrome, TDD may present with marked corrected QT (QTc) prolongation, torsades de pointes, cardiomyopathy, and cardiac arrest. While standard antiarrhythmic treatment is ineffective in most individuals with TDD, disease-specific management may be lifesaving. For this reason, early recognition of the signs and symptoms of TDD is critical.

Recognizing symptoms of TDD

The natural history of patients with TDD was described in 2023.[2] This study provided the complex phenotypic spectrum that includes global developmental and cognitive delays, seizures, abnormal gait, speech difficulties, and hypothyroidism. The most common presentation is an otherwise healthy infant who demonstrates developmental delays by the end of the first year of life. Between 1 and 3 years of age, toddlers develop TANGO2 "spell" symptoms (Figure 1). Children are described as ataxic, leaning to one side, and falling over to the point they cannot get back up (Figure 1). Lethargy, drooling, and worsening speech often accompany these abnormal movements, which can last minutes to hours. Under states of metabolic stress (eg, febrile illness and poor oral nutritional intake), TANGO2 spells can evolve into metabolic crises. Metabolic crises are life-threatening episodes identified by the presence of rhabdomyolysis (elevated creatine kinase, alanine transferase, or aspartate transferase) and prolonged QTc interval (Figure 1). Troponin is elevated, and profound hypoglycemia and encephalopathy can also occur.[2]

Cardiac crisis—Electrocardiographic changes, cardiac arrhythmias, and cardiomyopathy

Multiple early case series reported high rates of ventricular arrhythmias and death in patients with TDD. In 2022, a more in-depth description of the cardiac manifestations of TDD was published.[3] While there are no signs of cardiac abnormalities during baseline health, during metabolic crises, all patients develop QTc prolongation (often between 500 and 600 ms) and some develop a type I Brugada pattern (Figure 1). A history of developmental and speech delays should distinguish TDD from congenital long QT syndrome (notably, TANGO2 is not on long QT genetic panel tests). Of those in *metabolic crisis*, approximately 50% evolve into a *cardiac crisis*, defined by the development of arrhythmias or cardiomyopathy (Figure 1). Premature ventricular contractions can rapidly progress to torsades de pointes and polymorphic ventricular tachycardia (VT), and 50% develop cardiac arrest. About 40% develop systolic dysfunction ranging from mild to severe. TDD-related VT is generally worse when the heart rate is slower and is recalcitrant to standard antiarrhythmic treatment including β-blockers (including nadolol), flecainide, lidocaine, verapamil, amiodarone, and sympathetic denervation. The most effective

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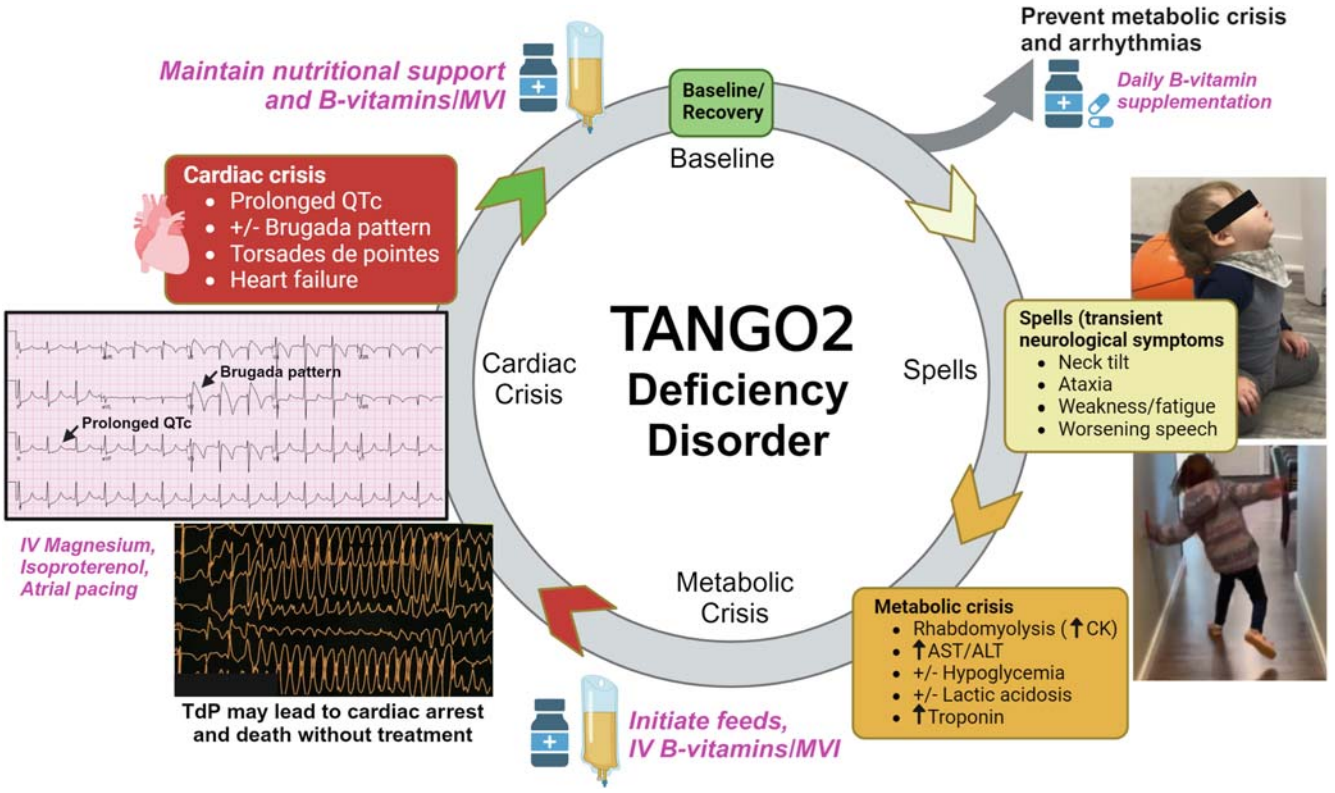

Figure 1
TANGO2 deficiency disorder (TDD) spectrum of disease. At baseline, patients have neurocognitive delays but have normal electrocardiograms and normal systolic function. Metabolic stressors trigger crises that can evolve into life-threatening ventricular arrhythmias, systolic dysfunction, and cardiac arrest. No single antiarrhythmic medication or treatment uniformly terminates ventricular tachycardia. Treatment is aimed at the early initiation of nutrition and B vitamins (including intravenous multivitamins for inpatients). ALT = alanine transferase; AST = aspartate transferase CK = creatine kinase; QTc = corrected QT; IV = intravenous; MVI = multivitamin.

acute antiarrhythmic for treatment is continuous magnesium infusion, isoproterenol, and atrial pacing; however, even these have not been effective in all patients. Importantly, vitamins are emerging as an alternative strategy (Figure 1). If VT is recalcitrant, extracorporeal membrane oxygenation can be successfully used. Prolonged QTc interval, Brugada pattern, arrhythmias, and systolic function resolve with adequate continuous maintenance of nutrition and B-vitamin supplementation (Figure 1). Outpatient treatment to prevent cardiac crisis is daily B-vitamin administration (Figure 1). β-Adrenergic blocking agents and implantable cardioverter-defibrillators are not necessary.

New insights into the role of B vitamins in TDD

While the exact functional role of TANGO2 remains unknown, recent publications reveal an emerging and potentially critical role of B vitamins in TDD. The natural history study demonstrated that patients taking B complex or multivitamins (containing all B vitamins) never developed metabolic crisis.[2] Among hospitalized patients in active metabolic crisis, early initiation of nutritional support and B vitamins reduced the development of cardiac crises.[2,3] The use of B vitamins as an antiarrhythmic strategy is of interest. In a case report by Yılmaz-Gümüş et al,[4] acute administration of B vitamins was associated with the normalization of QTc interval, Brugada pattern, and resolution of crisis. In another recent case report, early initiation of B vitamins in infancy, before symptoms develop, may ameliorate major TDD manifestations.[5] These clinical findings are supported by a study by Asadi et al,[6] demonstrating that fruit flies deficient in Tango2 show reduced movement and higher risk of seizures and mortality. All these features normalized after treatment with vitamin B5 (pantothenic acid), emerging as one of the critical B vitamins in TDD.

In the 8 years since TDD was first identified, these and many other studies have contributed substantially to our understanding of this severe disease, changing the course and saving the lives of patients with TDD. Research is ongoing to discover the functional role of TANGO2 and provide further insight into how specific B vitamins may help prevent cardiac dysfunction due to TANGO2 deficiency.

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Corrigendum

In the editorial commentary titled "Is more, "more" when it-comes to pacing in heart transplant patients?" by J. Rod Gimbel published in February 2024 (2024;21;161-162) in *Heart Rhythm*, the surname of the related article's first author, Zain Gowani, is incorrectly referred to as Gowali. This has been corrected in the online journal. The author regrets this error.