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Clinical Spectrum, Diagnosis, and Management of TANGO2 Deficiency Disorder: A Comprehensive Review

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Abstract

TANGO2 deficiency disorder is an autosomal recessive disease caused by biallelic pathogenic variants in the TANGO2 gene. First described in 2016, the disorder is characterized by acute metabolic crises, neurological dysfunctions, developmental delays, and intellectual disabilities. Laboratory findings indicate a mitochondrial fatty acid oxidation defect, with metabolic crises often triggered by stressors such as illness or fasting. The TANGO2 protein, implicated in lipid metabolism, membrane trafficking, and cellular homeostasis, is critical for maintaining lipid droplets, regulating phospholipid levels, and facilitating protein and lipid transport between cellular compartments. Symptoms of TANGO2 deficiency are diverse, including psychomotor delays, intellectual impairments, seizures, ataxia, and episodic neurological symptoms known as TANGO2 spells. Diagnosis involves genetic testing, with several pathogenic variants identified. During metabolic crises, patients may experience severe cardiac and metabolic disturbances. No curative treatment exists; management includes B-vitamin supplementation, antiepileptic drugs, and interventions for spasticity, dystonia, thyroid dysfunction, and arrhythmias. TANGO2 deficiency disorder can co-occur with DiGeorge syndrome, complicating diagnosis due to overlapping symptoms. Improved awareness and diagnostic strategies are crucial for effective management of this underrecognized condition.

Keywords: TANGO2, TANGO2 deficiency disorder, genetic testing, rare genetic disorder, neurological impairment

Abbreviations

TANGO2 - Transport and Golgi Organization Homolog 2
OCR - Oxygen Consumption Rate
mtDNA - Mitochondrial DNA
CK - Creatine Kinase
PMR - Plasma Metabolomics Residual
EEG - Electroencephalogram
MRI - Magnetic Resonance Imaging
FLAIR - Fluid-Attenuated Inversion Recovery
VT - Ventricular Tachycardia
ECMO - Extracorporeal Membrane Oxygenation

Introduction

TANGO2 deficiency disorder is an autosomal recessive disease resulting from the presence of biallelic pathogenic variants in the TANGO2 (Transport and Golgi Organization Homolog 2) gene [1]. It was first described in 2016 [2]. The disease is characterized by, among other things, acute metabolic crises, neurological disorders, developmental delay, and intellectual disability [3]. Furthermore, laboratory test results in patients with mutations in the TANGO2 gene suggest a defect in the oxidation of mitochondrial fatty acids [4]. Individuals who have concurrent metabolic stressors like illness or extended periods of fasting may undergo metabolic crises, characterized by symptoms such as encephalopathy, hypoglycemia, ataxia, rhabdomyolysis, and muscle weakness [1]. During these episodes, prolonged QTc interval and ventricular cardiac rhythm disturbances may occur [5]. The age of onset ranges from 4 months to 8 years, with neurological disorders usually preceding the first metabolic crisis [6]. The worldwide prevalence of TANGO2 deficiency is estimated to be 1 in 1,000,000 with approximately 8,000 affected individuals [7].

TANGO2 Protein: Functions and Mechanisms

TANGO2, encoded by the TANGO2 gene, stands for ‘Transport and Golgi Organization 2 Homolog’ and plays a crucial role in various cellular processes, particularly lipid metabolism,

membrane trafficking, and maintaining cellular homeostasis. It lacks a transmembrane domain and is reported as cytosolic, as well as localized in the mitochondria. Although the exact mechanisms of TANGO2 are not entirely understood, several key functions and interactions have been identified [4,8]

TANGO2 is implicated in the regulation of lipid metabolism, especially in the synthesis and distribution of lipids within the cell. It helps maintain lipid droplets and regulate phospholipid levels, essential for membrane integrity and cellular signaling. Its function in lipid homeostasis occurs at the level of acyl-CoA metabolism. Defects in lipid metabolism are the main cause of acute rhabdomyolysis, cardiomyopathy, and starvation-induced arrhythmias, which directly translates into motor disturbances, often appearing as the first symptoms of the disease [9].

This protein is also involved in the transport of proteins and lipids between the endoplasmic reticulum (ER) and the Golgi apparatus, as well as other intracellular compartments. It plays a critical role in vesicle formation and trafficking, ensuring that proteins and lipids are correctly sorted and delivered to their appropriate destinations within the cell. This function is vital for maintaining the proper functioning of cellular organelles and the overall cellular architecture [6,10].

Maintaining cellular homeostasis is another critical function of TANGO2, including the regulation of mitochondrial function and energy metabolism, as demonstrated in the fibroblasts of patients with a defect in this protein [10]. TANGO2 may also be involved in responding to cellular stress, particularly oxidative stress, by modulating the levels of reactive oxygen species (ROS) and maintaining redox balance. This role is crucial for preventing cellular damage and ensuring the survival of cells under stress conditions [9].

Symptoms of TANGO2 deficiency disorder

The disease presents with diverse symptoms. Patients exhibit psychomotor developmental delay, intellectual impairment, cognitive disorders, speech difficulties such as dysarthria, increased deep reflexes, spasticity, balance disturbances, and movement difficulties including gait disorders such as wide-based gait, toe walking, unilateral paralysis of upper and lower extremities [1,2,6,7,11]. Neurological disorders such as seizures, including generalized myoclonic seizures (sometimes resistant to treatment), epilepsy, and progressive ataxia, pyramid and/or cerebellar symptoms, optic nerve atrophy, and hearing impairment are common in affected individuals [1,4,6]. Some patients may experience gastrointestinal symptoms such

as drooling, constipation, and intestinal motility disorders [1]. Occasionally, signs of thyroid dysfunction are observed [1]. Microcephaly, facial dysmorphism, and synophrys are spontaneously diagnosed, along with co-occurrence of TANGO2 deficiency and DiGeorge syndrome, which may present with developmental delay, dysmorphia, and cleft palate [12].

Patients may experience episodic and transient neurological symptoms known as TANGO2 spells, including transient ataxia, weakness, sudden falls, balance disturbances, paroxysmal dyskinesias, dystonia, unilateral or bilateral exotropia, speech disturbances, and lethargy [1,7]. These symptoms typically occur upon waking, mostly in the morning but can occur at any time of day [1]. Increased TANGO2 spells are noted with physical activity, elevated ambient temperature, and reduced food intake [1]. Symptoms typically last from minutes to hours and resolve spontaneously [1].

During TANGO2 deficiency, metabolic crises occur, characterized by rhabdomyolysis accompanied by muscle pain and weakness, ataxia, or even coma [7]. These crises may be triggered by elevated body temperature, infectious diseases, heat, or disturbances in food intake [1].

Diagnosis

The TANGO2 gene is located in the 22qq11.2 region [1]. Studies have identified 24 alleles responsible for the disease [1]. Homozygous variants predominate, with deletions of exons 3 to 9 being the most prevalent [2]. Various pathogenic variants responsible for the disease have been identified, including: a splicing site variant (c.711-3C>G), a recurrent nonsense variant (c.94C>T, p.R32*, n = 3), a single-exon 6 deletion (arr[GRCh37] 22q11.21[chr22:20 042 250-20 048 850]), missense variants (c.77G>A, p.R26K; c.265G>T, p.G89C), single-base deletion: c.280delC resulting in (His94Thrfs3), missense variant: c.59T>G, resulting in a leucine to arginine exchange at position 20 (p.[Leu20Arg]), recently also described variant c.711-3C>G impairing splicing to exon 9, and a case of substitution: c.262C>T, resulting in premature stop codon at position 88 p.(Arg88*) [2,8]. Homozygosity in the TANGO2 gene (NM_001322141.1-c.728 + 1G > A) has also been described [5]. One study described 9 cases with the following mutations: Hom. c.262C>T, p.Arg88*, Hemizygous c.11_13delTCT, p.Phe5del, Hom. c.380+1G>A, Hom. c.220A>C, p.Thr74Pro, Hemizygous exon 3–9 deletion, Hom. c.6_9del, p.Phe6del, Hom. exon 3–9 deletion [6].

TANGO2 protein can be identified in Western blot analysis of whole cells and mitochondrial extracts from fibroblasts, with appropriate signals detected in patient fibroblast

analysis [10]. TANGO2 protein may also be present outside mitochondria, as indicated by a less intense signal in mitochondrial extract analysis [10]. Patient fibroblast analysis reveals mitochondrial respiratory dysfunction (reduced OCR), decreased ATP content, reduced flow through mitochondrial fatty acid oxidation [10]. Possibly, patients exhibit increased mitochondrial number and volume, increased overall mtDNA content, elevated levels of DRP1 protein (particularly P2), probably increased levels of IP3R protein [10]. Reduced mRNA expression of mitochondrial protein genes, including some involved in mitochondrial fatty acid oxidation and mitochondrial oxidative phosphorylation system is observed in patients [10]. Immunofluorescence staining shows reduced signals for medium chain acyl-CoA dehydrogenase (MCAD), isovaleric acid-CoA dehydrogenase (IVD), and electron-transferring-flavoprotein dehydrogenase (ETFDH) [10]. Sometimes reduced activity of complex II is observed [8].

During metabolic crises, prolonged QTc interval with possible onset of type 1 Brugada syndrome may be noted [1,7]. Patients may experience various arrhythmias, with torsades de pointes resistant to treatment being most common, but ventricular tachycardia is also frequent [1,2]. Metabolic crises may be accompanied by heart failure and dilated cardiomyopathy [2]. Echocardiography may reveal left ventricular hypertrophy and impaired function [2]. Increased CK and aminotransferase activity, metabolic acidosis, hyperammonemia, troponin leak, hypoglycemia, and abnormalities in TSH and/or FT4 levels are observed during metabolic crises [1,2,6]. Increased urinary excretion of dicarboxylic acids, ketonuria, and abnormalities in acylcarnitine profiles may be noted [6,8]. PMR examination may show increased lactate levels [8].

Brain MRI may detect diffuse ventriculomegaly, cerebral volume loss, and diminished white matter [7]. Occasionally, subacute or acute brain infarctions or progressive generalized cerebral atrophy, thinning of the corpus callosum, delayed myelination, and prominent subarachnoid space may be diagnosed [2,8]. FLAIR imaging may reveal hyperintensities in the posterior pons, deep, and subcortical white matter [11]. Patients who experience metabolic breakthroughs may be diagnosed with hypoxic ischemic encephalopathy or focal infarctions [1].

EEG may show generalized and multifocal epileptiform activity. Sometimes background slowing or regional slowing is observed. EEG may also show myoclonic seizures and non-epileptic myoclonic jerks provoked, for example, by startle [1].

Histological examination may reveal small changes in fiber diameter, regenerative and degenerative changes, and sometimes necrosis [6].

Impaired Golgi apparatus-endoplasmic reticulum retrograde vesicle transport may be observed in patients [6].

Treatment

There is no known curative treatment. Some studies support the use of B-group vitamin supplementation, significantly reducing the risk of metabolic crises in patients [1]. Treatment of seizures involves the use of antiepileptic drugs such as levetiracetam or valproic acid [1]. Local botulinum toxin injections and medications such as baclofen or clonazepam are used in the therapy of spasticity and dystonia [1,2,13]. Thyroid dysfunction is treated with L-thyroxine, for example [6]. For arrhythmias, interventions such as isoproterenol, magnesium, esmolol, lidocaine, isoproterenol, and atrial pacing may be used [14]. Persistent VT may require defibrillation, but often, refractory VT requires ECMO [14]. Treatment of cardiomyopathy in heart failure includes milrinone, epinephrine, dopamine, vasopressin, and oral medications such as diuretics, angiotensin-converting enzyme inhibitors, carvedilol, and digoxin [14].

TANGO2 deficiency disorder and DiGeorge Syndrome

TANGO2 deficiency disorder (TDD) can occur in patients with DiGeorge syndrome, as both conditions are associated with genetic abnormalities within the same chromosomal region. TANGO2 gene is located in the 22q11.2 region, which is commonly deleted in DiGeorge syndrome (22q11.2DS). Despite the increased risk of TDD in individuals with 22q11.2DS, the disorder often remains underdiagnosed. This diagnostic challenge is largely due to overlapping symptomatology between TDD and 22q11.2DS, coupled with a general lack of awareness about TDD. The complexity of distinguishing TDD amidst the broad spectrum of symptoms associated with 22q11.2DS makes accurate diagnosis difficult. Effective screening methods are crucial, as highlighted by a study that employed different screening techniques to identify comorbid TDD in patients with 22q11.2DS. Although the study identified several patients meeting criteria for TANGO2 testing, none of those tested ultimately received a TDD diagnosis, emphasizing the need for improved diagnostic strategies and better awareness to address this potentially overlooked condition [15].

Conclusions

TANGO2 deficiency disorder is a complex, multisystemic disease characterized by severe metabolic and neurological manifestations due to defects in the TANGO2 gene. Despite advancements in understanding its pathophysiology and genetic underpinnings, the disorder remains challenging to diagnose and manage, particularly in the presence of comorbid conditions like DiGeorge syndrome. Current treatments focus on symptomatic relief and managing metabolic crises, with no curative options available. Increased awareness, improved diagnostic techniques, and further research into the molecular mechanisms of TANGO2 are essential for developing targeted therapies and improving patient outcomes. Addressing these challenges will pave the way for better management strategies and potentially curative interventions for those affected by TANGO2 deficiency disorder.

Disclosure

Author's Contribution:

Conceptualization, MD, PG and OD; methodology, MD and PG; check, MD; formal analysis, MD, PG, JG and AS; resources, MD, PG, OD and JM; data curation, PG; writing - rough preparation, MD, PG and OD; writing - review and editing, MD, PG, OD, JG, JM and AS; visualization, PG and JM; supervision, MD; project administration, MD; All authors have read and agreed with the published version of the manuscript.

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