Electrical storm treated successfully in a patient with *TANGO2* gene mutation and long QT syndrome: A case report

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Introduction

Long QT syndrome (LQTS) is one of the causes of sudden cardiac death in children[1]; in fact, this condition may lead to severe ventricular arrhythmias (eg, polymorphic ventricular tachycardia, torsades de pointes [TdP]) and subsequent cardiac arrest.[2] Several gene mutations have been related to congenital forms of LQTS, and the number of reports describing new LQTS-related gene mutations is growing.[1,2]

In this context, a newly identified hereditary form of pediatric metabolic myopathy was recently linked to LQTS; more specifically, this novel syndrome is associated to biallelic truncating mutations in the transport and Golgi organization 2 (*TANGO2*) gene. Such condition results in infantile-onset metabolic crises characterized by encephalopathy, hypoglycemia, rhabdomyolysis, and cardiac arrhythmias—mainly LQTS-related.[3,4]

In the present report, we thoroughly describe the case of a patient who developed severe cardiac arrhythmias due to *TANGO2* gene mutation syndrome, as well as acute and chronic treatment for this condition.

KEY TEACHING POINTS

- Recently, investigators linked a hereditary form of pediatric metabolic myopathy to biallelic truncating mutations in the transport and Golgi organization 2 (*TANGO2*) gene. This condition is characterized by a syndrome including encephalopathy, hypoglycemia, and rhabdomyolysis and cardiac arrhythmias.
- *TANGO2* mutation syndrome–related cardiac arrhythmias are associated with long QT interval, which may result in torsades de pointes, ventricular fibrillation, and sudden cardiac death.
- Patients with *TANGO2*-related electrical storm may be successfully treated conventionally, with transvenous pacing and intravenous beta-blockers. Moreover, isoproterenol may also play an important role, serving as a bridge until successful pacing is achieved.

Case report

A 4-year-old Brazilian girl was admitted to our service in July 2018 owing to muscular weakness and lethargy after prolonged fasting. Two months earlier, owing to delay in global neurological development, hypoglycemia, and episodic hearing impairment, she was diagnosed with the syndrome connected to the mutation of the *TANGO2* gene. In particular, approximately 3 months before the current admission, one of her frequent episodes of altered level of consciousness led to vomit-related aspiration pneumonia, which was treated in another facility with a 14-day antibiotic therapy.

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On admission, her laboratory examination showed increased levels of creatine phosphokinase, compatible with rhabdomyolysis. The levels of creatine phosphokinase muscle/brain fraction were also elevated, as well as the ammonia levels. Her laboratory test results are summarized in Supplementary Table 1. An initial treatment with fluid and glucose solution did not stabilize the acute process, whereas the rhabdomyolysis crisis worsened. A therapy for the rhabdomyolysis crisis was then initiated, which comprised alkalinization of urine—aiming at a urinary pH between 7.0 and 7.5—in addition to fluid, electrolyte, and glucose support.

An initial assessment of the cardiovascular system was performed through electrocardiogram (ECG), which showed sinus rhythm with a prolonged QT interval (ie, 520 milliseconds, Figure 1). Moreover, echocardiography was

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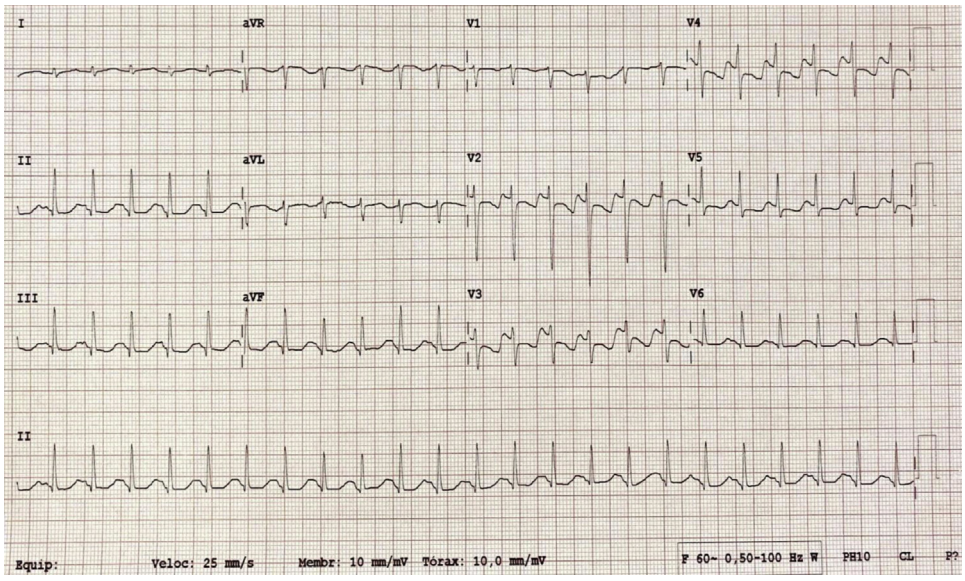

Figure 1 Electrocardiogram on the seventh day of hospitalization showing sinus rhythm and prolonged QT interval (520 ms).

performed, showing normal overall cardiac function and discretely dilated left chambers.

Holter monitoring—performed on the sixth day of hospitalization—revealed frequent nonsustained episodes of TdP. Oral low-dose beta-blocker treatment was subsequently initiated, and the patient's heart rate (HR) was carefully monitored and maintained above 80 beats per minute (bpm). Although the rhabdomyolysis crisis stopped worsening on the ninth day of hospitalization, the nonsustained TdP episodes observed on cardiac monitoring became more frequent. No potassium, magnesium, or any other electrolyte altered levels—which could explain either the longer QT interval or the worsening in TdP episodes frequency—were found (Supplementary Table 1). On the 11th day of hospitalization, the patient went into cardiac arrest, which was aborted after 10 minutes of cardiopulmonary resuscitation and direct-current defibrillations. Figure 2 shows the patient's ECG from the day before the cardiac arrest, whether Figure 3 displays a sustained TdP episode degenerating into ventricular fibrillation, recorded by Holter monitoring performed from the day before to the onset of the cardiac arrest. The HR before the sustained TdP and cardiac arrest episodes was 78 bpm, and the Holter did not show any significant pause. Subsequently, we administered intravenous beta-blockers, magnesium, and lidocaine to prevent another cardiac arrest, as well as to shorten the QT interval. However, the patient developed an electrical storm secondary to further frequent and sustained episodes of TdP, clustered during the evening and night of the same day.

After the second event, the patient was sedated with benzodiazepines and mechanically ventilated. However, the electrical storm persisted and was only controlled after transvenous atrial pacing was achieved, maintaining a HR above 130 bpm, associated with administration of high-dose intravenous esmolol. A total of 60 direct-current defibrillations were applied until crisis control.

Three days later, owing to displacement of the transvenous pacemaker lead, new episodes of TdP started; however, they were promptly suppressed by the use of isoproterenol, until lead replacement.

Thereafter, the patient developed pneumonia, which was subsequently treated with a 14-day course of meropenem and teicoplanin. After the antibiotic treatment, the patient was referred for an implantable cardioverter-defibrillator (ICD), which was successfully implanted on the 25th day of hospitalization and programmed to maintain a high-frequency atrial pacing (HR = 110 bpm). In order to prevent prolonged fasting episodes, a gastrostomy tube was placed at the end of the hospitalization period.

The patient was then prescribed oral propranolol and discharged after 41 days from admission; at that time, she was asymptomatic and had no worsening in neurological status. Furthermore, since hospital discharge—15 months ago—the patient remained asymptomatic, and her parents reported an improvement in her neurological status. The patient's ICD monitor has not recorded any further sustained arrhythmias, and her basal HR progressively slowed down to 90 bpm.

Discussion

In this report, we presented the case of a 4-year-old girl with *TANGO2* gene mutation syndrome–related LQTS, which led to recurrent TdP and electrical storm. To the extent of our knowledge, this report is the first to describe this recently identified syndrome in a Brazilian patient.

Of the 22 previously reported cases of *TANGO2* gene mutation syndrome, the first 12 were described by Lalani and colleagues[4]: in their series, the age at diagnosis ranged from 3.5 to 7 years, and the typical clinical presentation included rhabdomyolysis, hypoglycemia, global neurological development delay, epilepsy, and cardiac arrhythmias.

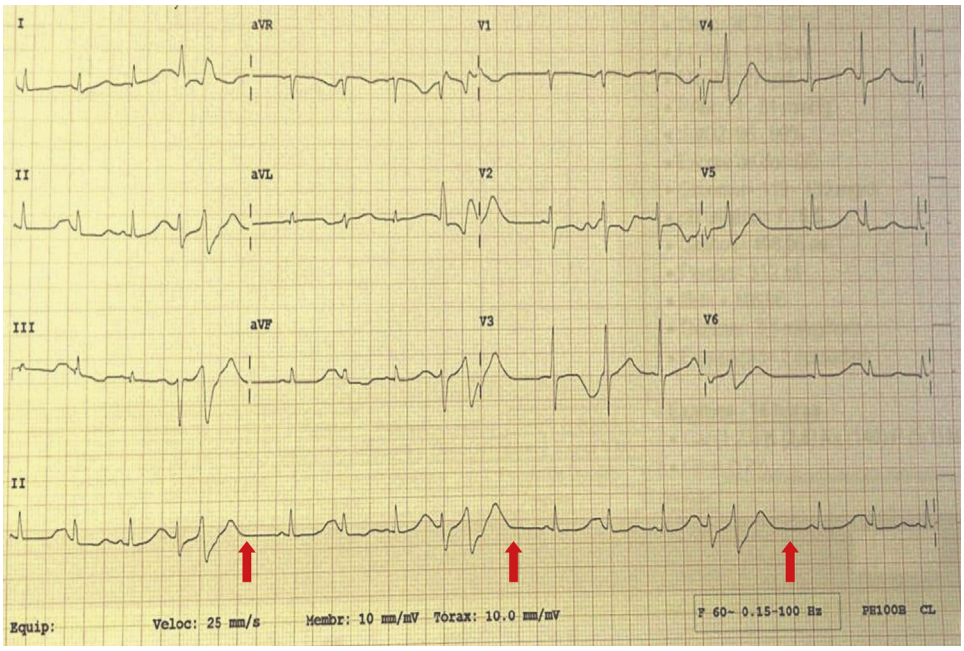

Figure 2 Electrocardiogram on 10th day of hospitalization, showing the presence of pauses (*red arrows*) after the paired premature ventricular contractions, but not long enough to trigger a torsades de pointes episode.

More specifically, 6 of their patients (ie, 50%) presented with a long QT interval, 4 developed severe ventricular tachycardia or TdP, and 3 required an ICD (33% and 25% of all patients, respectively). Surprisingly, 1 patient with ventricular tachycardia was successfully treated with amiodarone,[4] which is a rather controversial treatment for ventricular tachycardia and TdP associated with LQTS, since it might lengthen the QT interval.[5]

The treatment for pediatric LQTS-related electrical storms often involves multiple interventions, such as intravenous beta-blockers, magnesium replacement, class IB antiarrhythmic agents (eg, lidocaine), sedation, and overdrive pacing. In addition, selective cardiac sympathectomy may be required in case of medical treatment failure.[5]

Isoproterenol is indicated for the treatment of Brugada syndrome–related and acquired LQTS–related electrical storms. Nonetheless, it is a second-line treatment in patients with congenital LQTS, since adrenergic stimulation may trigger premature afterdepolarizations, which in turn could initiate TdP, as demonstrated by Shimizu and colleagues.[6,7]

Interestingly, Suarez and colleagues[8] recently reported the case of a 19-year-old woman with type 2 congenital LQTS where isoproterenol completely suppressed frequent TdP episodes, suggesting that it could act as a temporizing agent in similar settings.

The evidence supporting the use of isoproterenol in *TANGO2* gene mutation syndrome–related electrical storm is also related to the description of Brugada ECG pattern alternating with long QT interval.[4] Therefore, the recommendation for isoproterenol use may be even stronger, especially in cases of TdP associated with low HR and frequent pauses, in which isoproterenol could serve as a bridge to successful temporary high-frequency pacing. However, our patient only showed a prolonged QT interval; in fact, both her ECG and cardiac monitoring did not show alternating Brugada pattern during hospitalization, although isoproterenol proved to be effective in suppressing new TdP episodes triggered by the decrease in HR owing to pacing lead displacement.

Even though HR was carefully monitored to be maintained above 80 bpm, the TdP episodes persisted; one of the possible reasons for that is the presence of pauses following premature ventricular contractions, as shown in Figure 2 following the paired premature ventricular contraction. In this case, however, the pause was not long enough to trigger a TdP episode.

In this setting, avoiding not only bradycardia but also prolonged pauses is fundamental to prevent harmful arrhythmias occurring because of bradycardia-dependent triggered activity,[9] such as LQTS-related TdP. In our case, the electrical storm crisis was controlled only after atrial transvenous pacing and appropriate HR increase. In fact, avoidance of both long pauses and bradycardia through pacing has been considered as a reliable way to prevent as well as stop TdP episodes by several experienced centers and authors.[10–13]

Interestingly, Viskin and colleagues[14] have described that pediatric TdP is not always pause-dependent, although this is still the major mechanism. Their article reports that TdP, which is not pause-dependent, is present especially in patients with severe forms of LQTS.[14] Looking back to the present case, the TdP episode that triggered the ventricular fibrillation and cardiac arrest episode was not pause-dependent—as shown in Figure 3 — possibly reflecting a more severe form of LQTS, as described by Viskin

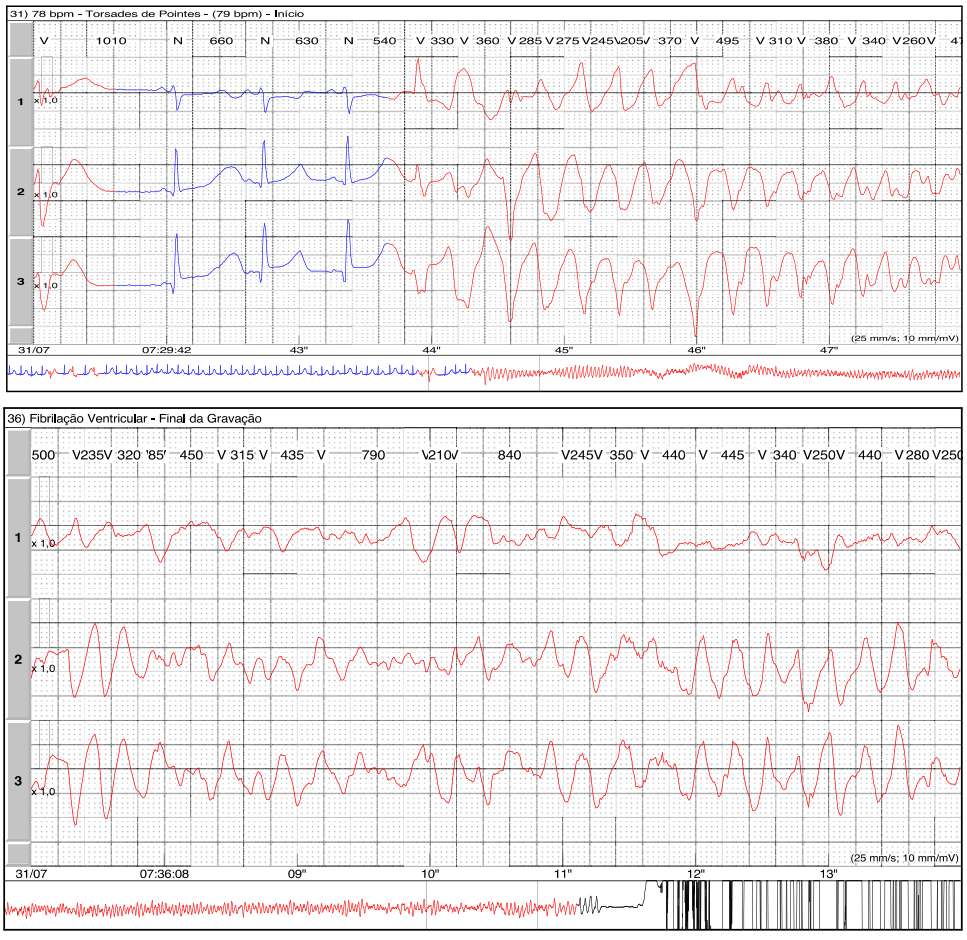

Figure 3 Holter tracing on the 11th day of hospitalization, showing that the torsades de pointes episode that degenerates into ventricular fibrillation was not pause-dependent.

and colleagues.[14] This may be the case, since *TANGO2* gene mutation syndrome–related LQTS is not a channelopathy form of LQTS per se, thus having a different pathophysiological basis.[4]

However, raising HR has shown efficacy to prevent and refrain TdP episodes not only in acute settings—using transvenous pacing—but also in chronic settings—using definitive pacing, suggesting an overlap of mechanisms for TdP occurrence in this newly discovered syndrome.

Once the crisis is controlled, prevention of new episodes is crucial. The whole crisis started with prolonged fasting, probably owing to the patient's altered level of consciousness and inability to feed. Given these circumstances, the patient had a gastrostomy tube placed at the end of the hospitalization period, in order to be fed at regular intervals. Moreover, the family was clearly instructed to present the patient to the emergency department again in case of onset of symptoms and/or signs that might resemble previous crises.

Conclusions

The present manuscript describes a challenging case of arrhythmia management, with a very rare cause of QT prolongation and its associated life-threatening arrhythmias, which is the recently discovered *TANGO2* gene mutation syndrome. Awareness of this condition is important because of the repertoire of acute and preventive management strategies required, since this syndrome is not a channelopathy form of LQTS per se, having different mechanisms for arrhythmia arising, as well as some specific aspects for management and prevention of arrhythmic episodes.

In our case, the patient presented with recurrent episodes of TdP and electrical storm despite a normal HR and absence of pauses; moreover, she was successfully treated using a conventional approach based upon transvenous atrial pacing and intravenous beta-blockers. Nonetheless, isoproterenol may also play an important role in this context, serving as a bridge until transvenous pacing is achieved.

It is also important to point out that our patient developed arrhythmias in a hospital setting, subsequently allowing for prompt treatment of her electrical storm. Thus, education of both parents and the general population about the signs and symptoms of the *TANGO2* gene mutation syndrome is critical, since early recognition and effective treatment of its associated life-threatening arrhythmias may play a crucial role in the prevention of sudden cardiac death in affected children.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2020.01.007.

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