ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–6
https://doi.org/10.1093/ehjcr/ytad044

CASE REPORT
Electrophysiology

The TANGO2 disease and the therapeutic challenge of acute arrhythmia management: a case report

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Received 30 December 2021; first decision 28 January 2022; accepted 25 January 2023; online publish-ahead-of-print 30 January 2023

Background TANGO2-related metabolic encephalopathy and arrhythmia are a rare, newly recognized, and likely under-diagnosed condition. First described in 2016, it is characterized by developmental delay and recurrent metabolic crisis. During these episodes, patients may present QTc prolongation and ventricular arrhythmias.

Case summary A 13-year-old female, with developmental delay, presented with severe rhabdomyolysis and an initially normal electrocardiogram (ECG). Due to the worsening of rhabdomyolysis, QTc prolongation was identified (QTc 570 ms) and oral β-blocker therapy started. A non-sustained ventricular tachycardia developed, initially managed with magnesium and lidocaine. After a short period, an arrhythmic storm of polymorphic ventricular extrasystoles induced Torsade de Pointes (TdP) was triggered. A temporary percutaneous pacing lead was placed and esmolol infusion started. The electrical instability ran in parallel with the increasing severity of rhabdomyolysis and systolic ventricular function decline. Genetic testing identified a pathogenic variant in homozygosity in the TANGO2 gene. A stable sinus rhythm was achieved with metabolic and serum electrolytes optimization. ECG showed normalization of the QTc interval.

Discussion The full TANGO2-related phenotype emerges over time and the prognosis is linked to the appearance of ECG abnormalities. QT interval prolongation can lead to life-threatening ventricular tachycardias. The arrhythmia mechanism seems to be secondary to metabolite build-up in cardiomyocytes, which can explain the cardiac phenotype during the crisis which subsides after their resolution. In these patients, avoiding bradycardia is fundamental, since long QT-related TdP seems to be triggered by bradycardia and short-long-short ventricular premature beats (VPB). During an acute metabolic crisis, the management of arrhythmias relies on metabolic control.

Keywords Torsade de Pointes • TANGO2 disease • TANGO2-related metabolic encephalopathy and arrhythmias • Arrhythmias • case report

ESC Curriculum 5.6 Ventricular arrhythmia • 7.1 Haemodynamic instability

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Handling Editor: Rami Riziq Yousef Abumuaileq
Peer-reviewers: Fabian Barbieri; Richard Ang
Compliance Editor: Jef Van den Eynde
Supplementary Material Editor: Nida Ahmed

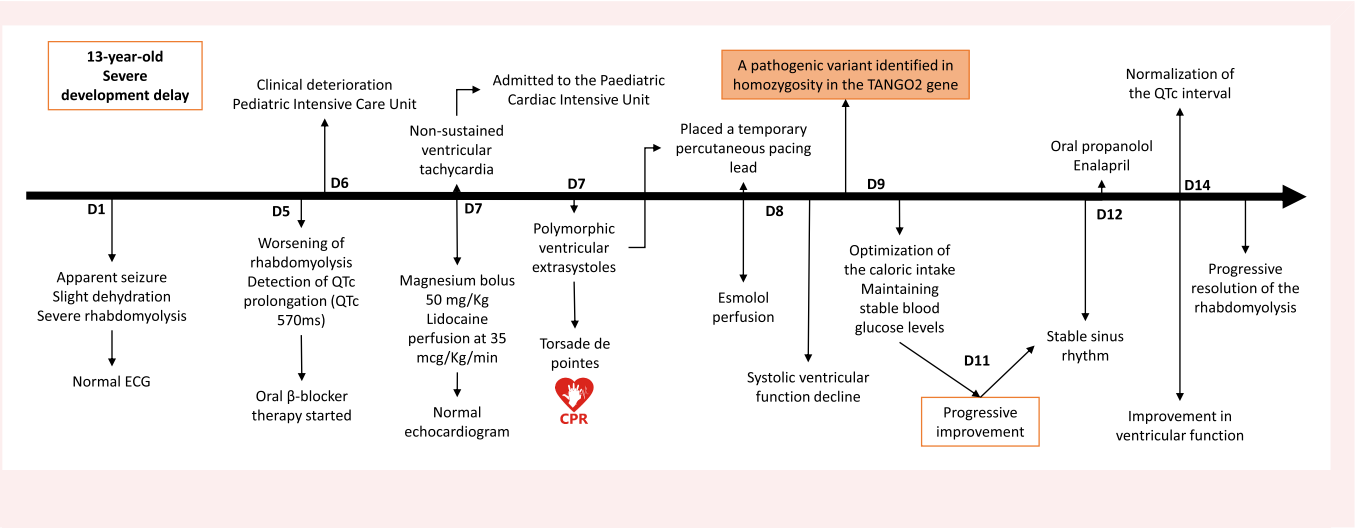
Learning points

- TANGO2-related metabolic encephalopathy and arrhythmia is a rare and newly recognized, likely under-diagnosed condition whose prognosis is closely linked to the appearance of electrocardiogram abnormalities.
- The arrhythmia mechanism seems to be secondary to metabolite build-up in cardiomyocytes, and it relies on metabolic control.
- In this specific population with QT interval prolongation, avoiding bradycardia is fundamental, since long QT-related Torsade de Pointes seem to be triggered by bradycardia and short-long-short ventricular premature beats.

Introduction

TANGO2-related metabolic encephalopathy and arrhythmia (TRMEA), also known as TANGO2 disease, is a newly recognized, rare disorder, first described in 2016.[1,2] It results from biallelic pathogenic variants in the TANGO2 (transport and Golgi organization 2 homolog) gene.[2] Although the role of the TANGO2 gene in cells is still poorly understood, its involvement in human pathology is now certain.[3]

She was admitted to a peripheral hospital in the postictal state of an apparent episode of epilepsy, with the physical examination at admission showing only a slight degree of dehydration. She was haemodynamically stable, in normal sinus rhythm with an average heart rate (HR) of 99 b.p.m., adequate blood pressure and peripheral perfusion, and peripheral oxygen saturation of 99%. The laboratory workup identified severe rhabdomyolysis and elevated cardiac and hepatic cellular lesion biomarkers (Creatine phosphokinase [CPK] 6640 U/L, Troponin I 1156 ng/L, aspartate aminotransferase [AST] 187 U/L, alanine transaminase [ALT]



Timeline

The phenotype is characterized by developmental delay, seizures, and recurrent metabolic spells associated with rhabdomyolysis and hypoglycaemia. During metabolic crises, patients may present with prolongation of QTc interval,[2] leading to ventricular arrhythmias.[4] The diagnosis is often made after the emergence of life-threatening symptoms.[1]

The incidence of TANGO2 disease is unknown,[4] with 76 patients described in the medical literature.[1]

We report a case of a patient who presented with severe ventricular arrhythmias in a rhabdomyolysis setting and the acute management that successfully treated her electrical storm.

Case report

We present a case report of a 13-year-old female diagnosed with severe developmental delay and under investigation for suspected epilepsy due to frequent episodes of brief, sudden loss of consciousness. She was medicated with levetiracetam, despite having multiple normal electroencephalogram (EEG) assessments.

65 U/L). The remaining laboratory assessment was unremarkable, including normal serum electrolyte levels. The initial electrocardiogram (ECG) showed no relevant changes, with a normal QTc interval.

Due to worsening rhabdomyolysis (CPK >42 670 U/L), levetiracetam was suspended, and she was transferred to a specialized paediatric hospital. At this time, a QTc interval prolongation was identified (QTc 570 ms) (*Figure 1*), and oral β-blocker therapy started (initial dose of propranolol at 1 mg/kg per day). In the following days, her clinical condition deteriorated, leading to the development of hypotension and severe hydro-electrolyte disturbances. She was ultimately admitted into the paediatric intensive care unit. Soon after, a non-sustained ventricular tachycardia developed, with an average HR of 200 b.p.m. (*Figure 2*). A bolus of 50 mg/kg of magnesium was administered, and a loading dose of 1 mg/kg of lidocaine was started, followed by perfusion at 35 mcg/kg/min. The echocardiogram did not identify structural or functional alterations.

She was then transferred to the paediatric cardiac intensive unit. A congenital long QT syndrome management strategy was pursued, as no diagnosis was available. The therapeutic goal was to maintain normal plasma levels of potassium, calcium, and magnesium while keeping lidocaine perfusion.

However, after a short period of normal sinus rhythm, frequent polymorphic ventricular extrasystoles of ventricular premature beats (VPB) in

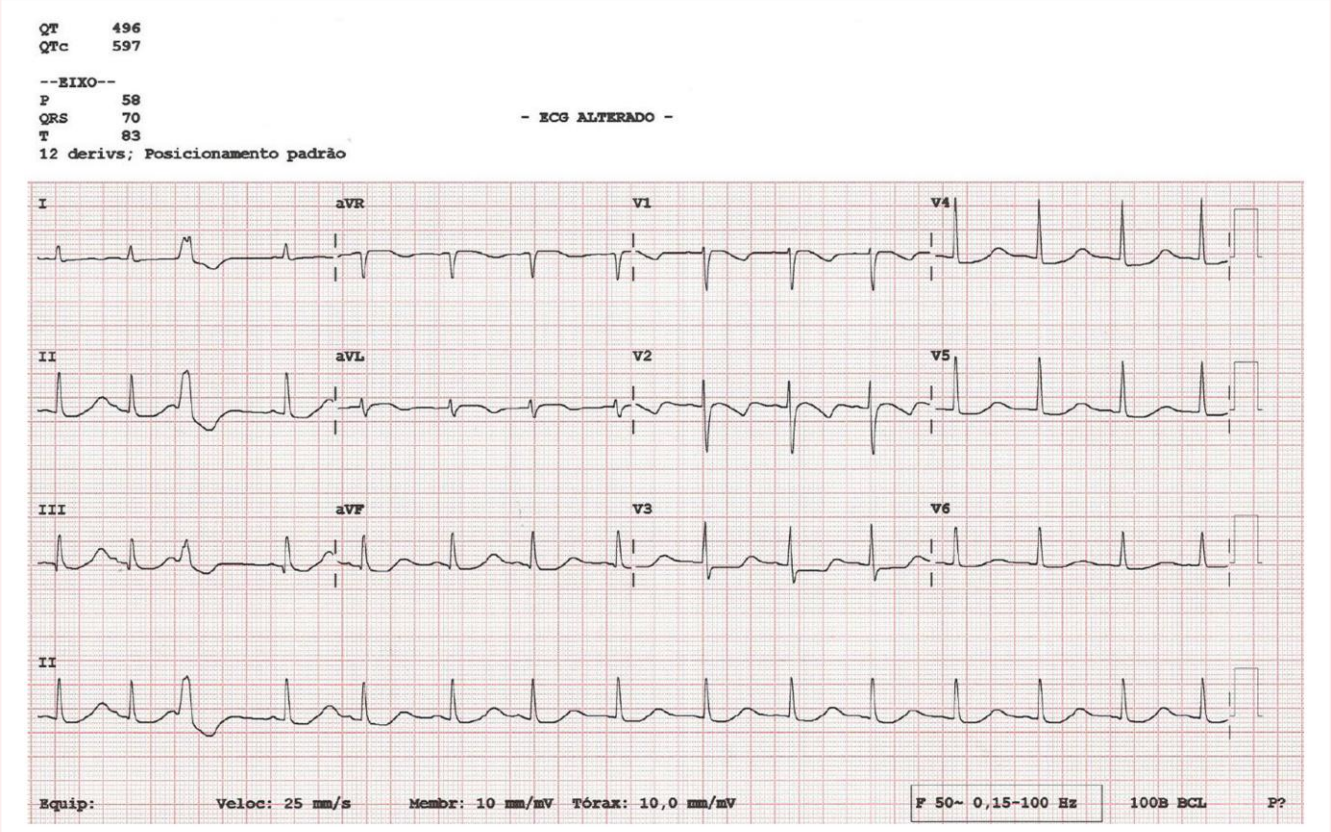


Figure 1 First identification of QT interval prolongation, with a corrected QT of 597 ms. A ventricular premature beat is observed.

short-long-short sequences developed, triggering an arrhythmic storm with polymorphic ventricular tachycardia (Torsade de Pointes—TdP), with some episodes degenerating into ventricular fibrillation and leading to cardiac arrest requiring advanced life support and defibrillation.

Due to the bradycardia-dependent nature of the TdP, a temporary pacemaker lead was inserted for ventricular pacing, and perfusion of esmolol was started at a rate of 25 mcg/kg/min, maintaining lidocaine with transitory rhythm stabilization. Subsequently, two new episodes of TdP developed, requiring defibrillation; the electrical instability ran in parallel with increasing severity of rhabdomyolysis and deterioration of left ventricular systolic function (LVEF 40%).

Genetic testing identified a pathogenic variant in homozygosity in the TANGO2 gene (NM_001322141.1-c.728 + 1G > A).

With this new data, optimizing caloric intake and stable blood glucose levels was pursued while keeping hyperhydration and urine alkalinization. The metabolic stabilization made it possible to reduce continuous intravenous ion infusion while maintaining oral calcium, magnesium, and potassium supplementation. After progressive clinical and hydro-electrolytic improvement, normalization of the QTc interval and sinus rhythm stabilization was achieved, allowing for the transition from esmolol infusion to oral propranolol and down-titration and discontinuation of lidocaine. Due to the persistence of left ventricular systolic dysfunction, enalapril was started.

The patient was transferred back to the paediatric hospital. She remained haemodynamically stable during the remaining hospital stay, with a normal ECG.

At 6 months of follow-up, the patient did not experience new episodes of metabolic crisis. She remains without anti-epileptic therapy and has no record of recent seizures. However, she showed signs of neurodevelopmental regression and did not regain all her baseline competencies. A nasopharyngeal tube was placed, maintaining adequate caloric intake and avoiding periods of fasting. Regarding cardiac assessment, she keeps a normal ECG with a corrected QT of 370 ms; however, the echocardiogram still documents a left ventricular systolic function in the low normal range with an LVEF of 51%.

Discussion

The *TANGO2* gene encodes a protein that seems to be involved in transferring Golgi membranes into the endoplasmatic reticulum (ER).[5,6] Furthermore, the data demonstrating the involvement of mitochondrial function and delayed macromolecular trafficking between the Golgi apparatus and the ER suggests an impact on energy metabolism,[1,4] highlighting these processes as relevant for TANGO2-dependent disease manifestation.[5]

The diagnostic criteria for TRMEA have yet to be established.[7] The complete TANGO2-related phenotype often emerges over time.[3,6] The clinical presentation shows a similar neurological phenotype combined with severe recurrent metabolic crises resulting in rhabdomyolysis, severe encephalopathy, and life-threatening arrhythmias.[4,5,8] These episodes of rhabdomyolysis are a striking feature of TRMEA and should prompt consideration of this diagnosis.[1] With a lack of specific cerebral MRI or biomarker abnormalities, the diagnosis is often overlooked until rhabdomyolysis episodes.[3]

When faced with a clinical presentation of rhabdomyolysis, several metabolic disorders, such as mitochondrial diseases, carnitine

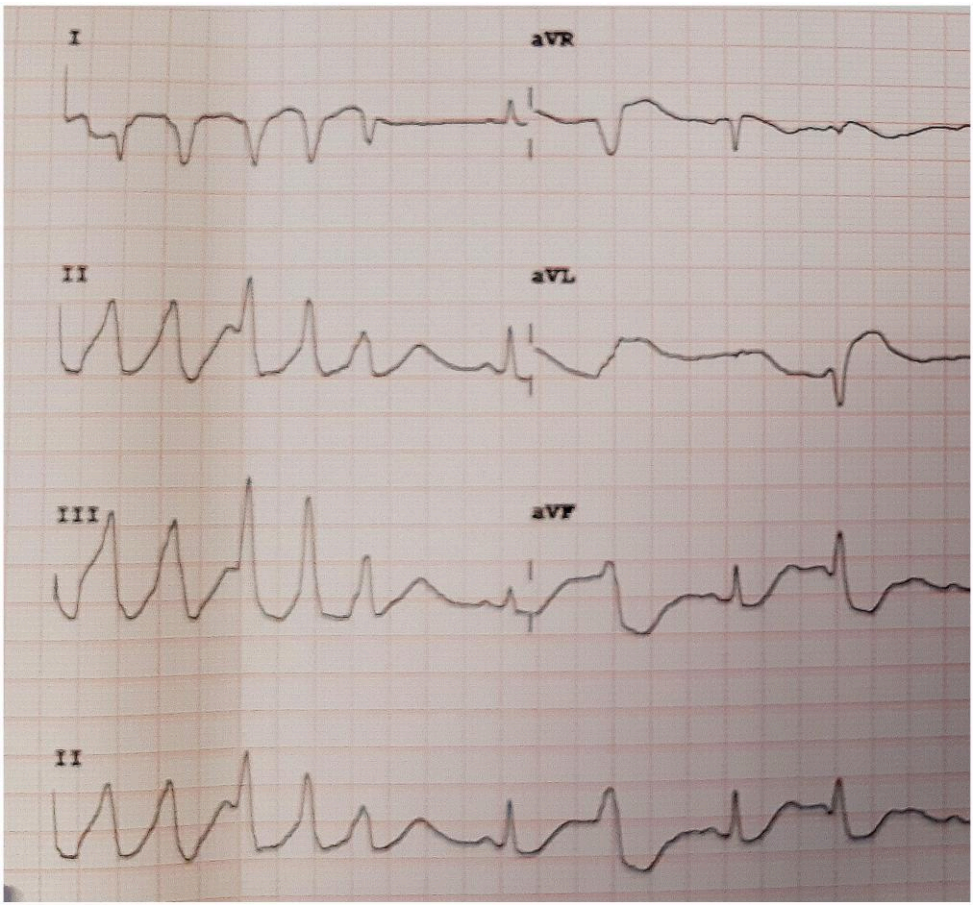


Figure 2 Non-sustained polymorphic ventricular tachycardia and ventricular premature beats in bigeminy pattern.

palmitoyltransferase II, carnitine acylcarnitine translocase, and very-long-chain acyl-CoA dehydrogenase deficiency, acute recurrent myoglobinuria, and glycogen storage disease, should be included in the differential diagnosis of TRMEA.[2,4,7] QT interval prolongation is not usually part of the clinical features at presentation.[7] As indicated in *Figure 3*, the diagnostic approach to QT prolongation should consider the iatrogenic, congenital, and acquired variants.[9–11]

The prognosis is closely linked to the appearance of ECG abnormalities.[3] The most common ECG finding, observed exclusively during metabolic crises, is marked QT interval prolongation (>500 ms)[4] and, more rarely, intermittent Brugada type I pattern.[4,7,8] Life-threatening ventricular tachycardias (TdP being the most common) can occur during metabolic crises and may lead to sudden cardiac death.[2,5,6] Ventricular dysfunction can be transient, with normalization of function after resolving these crises.[2,6]

Acute treatment and long-term management are still unclear, as the pathogenic mechanism of arrhythmias has not yet been defined.[7] Meisner et al.[2] compared the TRMEA features to those seen in long-chain fatty acid oxidation disorders, in which the arrhythmia-associated mechanism is believed to be secondary to metabolite build-up in cardiomyocytes, being able to explain the cardiac alterations that appear during these crises and that cease to exist after their resolution. Given the multifactorial nature of this patient's cardiac arrhythmias, it's impossible to rule out the possibility that, in addition to the impact of metabolic changes and the not negligible influence of the anti-epileptic drugs in QT prolongation, the initial therapeutic approach aimed at a congenital long QT may have resulted in decompensation, culminating in the arrhythmic storm.

Isoprenaline is indicated to treat electrical storms associated with Brugada syndrome and acquired long QT syndrome.[8,9] In the TRMEA patients, the long QT-related TdP seems to be triggered due to the presence of severe bradycardia and short-long-short VPB.[8] Therefore, avoiding bradycardia to prevent harmful arrhythmias is fundamental,[8] achieved by administering isoprenaline or with temporary pacing.

During acute metabolic crises, the management of arrhythmias relies on metabolic control.[2,4] Therefore, beyond the tailored antiarrhythmic treatment, magnesium levels should be maintained at >2.2 mg/dL, and potassium and glucose levels should be kept in the normal range.[7]

The primary preventive and symptomatic treatment is the limitation of fasting, glucose infusion upon illness,[4] and the avoidance of medications that prolong the QT interval.[7] Given QT prolongation during crises, long-term treatment with cardio-selective beta-blockers has been proposed.[4] Implantable cardioverter-defibrillator (ICD) implantation could be discussed, but its systematic indication as secondary prevention in TANGO2 patients is probably not conceivable.[4] Bearing in mind that ICDs are associated with complications,[4,9] such as inappropriate shocks and lead failure,[9] in this patient, whose QT remains normal outside of metabolic crises, ICD implantation was associated with an unfavourable risk to benefit balance.

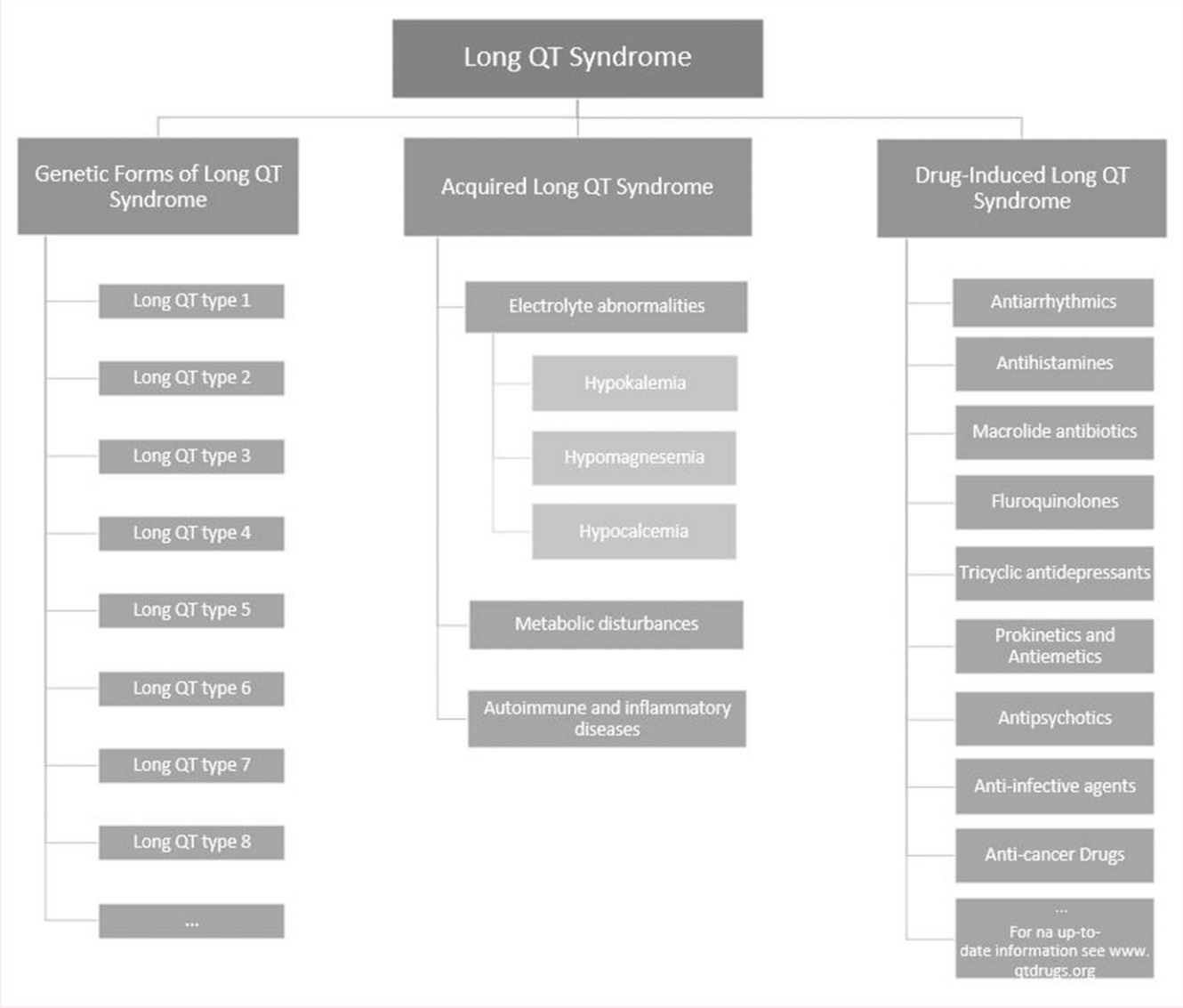


Figure 3 Diagnostic flowchart with the main etiologic groups of QT prolongation.[9–11]

The long-term management of TRMEA patients remains purely symptomatic and preventive,[3] with typical management recommendations including avoidance of triggers for acute metabolic crises (prolonged fasting and dehydration, with many children requiring gastrostomy or postpyloric tubes) and surveillance for signs and symptoms of decompensation during infectious complications or acute illness, as well as regular follow-up with a cardiologist, periodic assessment of thyroid hormones and neurological follow-up for the treatment of epilepsy.[1,3,7] There is still debate about the therapeutic approach, particularly regarding the chronic use of beta-blockers in an outpatient setting on a case-by-case basis.[4,7,8]

As a newly recognized disease, additional clinical and molecular information is needed to identify and comprehend the phenotypic spectrum of this disease.[6]

Although this is not a clinical case that differs phenotypically from others previously described, it does provide a necessary description of the challenging therapeutic approach to the disease before and after the diagnosis of TRMEA. Likewise, it reviews the physiological mechanisms by which the classic therapeutic approach to a newly identified long QT could amplify an arrhythmic storm in the setting of the characteristic pathological features of this rare disease.

Lead author biography

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Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Acknowledgements

The authors want to acknowledge the staff from our Paediatric Cardiology Department and ICU and the Paediatric Neurology Department of Hospital Dona Estefânia for their essential contributions to the outcome of this case.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: According to COPE guidelines, the authors confirm that written consent for the submission and publication of this case report including imagesand associated text has been obtained from the patient's parents.

Conflict of interest: None declared.

Funding: This work was not supported by any sponsorship or grant.

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