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Review

Torsade de pointes: the clinical considerations

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Abstract

Torsade de pointes is a form of polymorphic ventricular tachycardia occurring in a setting of prolonged QT interval on surface electrocardiogram. Congenital causes of prolonged QT interval occur in individuals with genetic mutations in genes that control expression of potassium and sodium channels and acquired causes are numerous, predominantly drugs causing prolonged QT interval by blockade of potassium channels. Among the drugs, antiarrhythmic agents most notably quinidine, sotalol, dofetilide and ibutilide have the potential to induce the fatal torsade de pointes. Many non-antiarrhythmic drugs can also cause torsade de pointes. Although it is important to distinguish between the congenital and the acquired forms of long QT syndrome as the later can often be reversed by correction of the underlying disorder or discontinuation of the offending drug, both forms are not mutually exclusive. Clinical considerations and management of torsade de pointes are described.

Keywords: Torsade de pointes; Long QT syndrome; Ventricular tachycardia; Sudden cardiac death; Sudden arrhythmia death syndrome

1. Introduction

In 1966, Dessertenne [1] first reported torsade de pointes arrhythmia. Torsade de pointes is an electrocardiographic pattern of continuously changing morphology of the QRS complexes that seem to twist around an imaginary baseline. It is a form of polymorphic ventricular tachycardia that usually occurs in a setting of prolonged QT interval, T wave abnormalities or increased U wave amplitude. Prolonged QT intervals are based on a corrected QT interval (QTc) of >440 ms; however, the classic configuration of torsade de pointes may be seen in cases without QT interval prolongation [2]. Torsade de pointes, in addition to being polymorphic, differs from sustained monomorphic ventricular tachycardia due to its characteristic pattern of onset and its difficult inducibility with programmed electrical stimulation. Also, it is amenable to suppression by an increase in heart rate [3]. The arrhythmia can range in length from 3 beats of non-sustained ventricular tachycardia up to >100 beats. The intervals between QRS complexes vary and the rate of tachycardia is usually 200–250 beats/min (range: 150–300 beats/min).

In most, but no all, cases torsade de pointes is preceded by a characteristic sequence of a long RR interval of the dominant cycle followed by a short extrasystolic interval with premature depolarization interrupting the preceding repolarization [4]. It can follow severe bradycardia and has been noted to precede ventricular fibrillation [5,6]. Torsade de pointes tends to be less disorganized than ventricular fibrillation and is usually self-terminating but on occasion can degenerate into ventricular fibrillation or end with sinus arrest with a slow ventricular escape rhythm. It usually occurs as episodic paroxysms consisting of two or more cycles. The cycle length of these episodes varies from 200 to 400 ms, and there are usually 5–20 complexes in each cycle. Because of the wide QRS complexes and rapid rate, it is often difficult to distinguish between the QRS and T waves. The QRS configuration changes during the tachycardia and can take several forms, and different QRS patterns can be seen in different torsade de pointes episodes in the same patient. Sometimes, the phasic variation of the polarity and amplitude of the QRS complexes may be apparent only if several electrocardiographic leads are recorded.

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2. Etiopathogenesis

Major causes of torsade de pointes are given in Table 1. Congenital long QT syndrome (LQT) is caused by mutations in at least five genes, including KCNQ1 (KVLQT1), HERG, SCN-, KCNE1 (minK) and KCNE2 (MiRP1) [7]. The KCNQ1 (KVLQT1) currently represents more than 50% of the all cases of the congenital LQT [8]. The primary underlying abnormality irrespective of the cause of LQT is of the ionic currents involved in repolarization, resulting in its prolongation. Mutations in KCNQ1 and KCNE1 genes are responsible for defects in I_{Ks}, which is the slowly activating component of the delayed rectifier potassium current, whereas mutations in HERG and KCNE2 genes are responsible for defects in I_{Kr}, which is the rapidly activating component of the delayed rectifier potassium current. Mutations in SCN-gene enhance the function of I_{Na}, a sodium channel. Interestingly, the mutations in the SCN-gene, but of loss in function type, result in Brugada syndrome. The QT interval prolonging drugs do so by affecting I_{Kr} function. The prolonged repolarization, irrespective of the ion channel involved, consequently generates early afterdepolarizations, which subsequently induce trigger beats [9]. The Purkinge network is the predominant site where the early afterdepolarization-induced triggered beats arise. Furthermore, prolonged repolarization is associated with an increased spatial dispersion of repolarization [10]. The focal early afterdepolarization-induced triggered beats infringe on the underlying substrate of inhomogeneous repolarization and initiate a serial reentry phenomenon resulting in initiation and maintenance of torsade pointes [10]. It is not clear why episodes of torsade de pointes frequently stop spontaneously, but this is probably because of a rate related shortening of the refractory period and a reduction in repolarization dispersion. The development of early afterdepolarizations is potentiated by slower heart rates, hypokalemia, hypomagnesemia and many drugs as listed in Table 2. Interestingly, torsade de pointes has been reported in the setting of normal QT interval (short-coupled variant) in patients with syncope and structural heart disease [2]. In such cases, there is an increased dispersion of ventricular repolarization and causing the coupling interval of the first tachycardia complex to be unusually short.

Table 1
Major causes of long QT syndrome and torsade de pointes

Congenital long QT syndrome
Acquired long QT syndrome
Pharmacological agents
Electrolyte abnormalities
Sinus node dysfunction
High-grade atrioventricular block
Myocardial injury and ischemia
Starvation
Anorexia nervosa
Liquid protein diets
Human immunodeficiency virus infection
Intracranial diseases
Cocaine abuse
Organophosphorus poisoning

Table 2
Drugs reported to prolong QT interval and/or induce torsade de pointes

Category	Drugs
Antiarrhythmics	Disopyramide, procainamide, *n*-acetyl-procainamide, quinidine, beperdil, mexiletine, propafenone, flecainide, amiodarone, bretylium, sotalol, ibutilide, dofetilide, azimilide, aprindine, ajmaline, almokalant, mibefradil, clofilium, sematilide
Antimicrobials	Erythromycin, clarithromycin, azithromycin, ampicillin, levofloxacin, moxifloxacin, sparfloxacin, gatifloxacin, grepafloxacin, trimethoprim-sulfamethoxazole, troleandomycin, Pentamidine, quinine, foscarnet, fluconazole, itraconazole, ketoconazole, chloroquine, halofantrine, mefloquine, amantadine, spiramycin
Antihistamines	Astemizole, diphenhydramine, terfenadine, ebastine, hydroxyzine
Antidepressants	Doxepin, fluoxetine, desipramine, imipramine, clomipramine, paroxetine, sertraline, venlafaxine, citalopram, ketanserin
Antipsychotics	Chlorpromazine, prochlorperazine, trifluoperazine, fluphenazine, felbamate, haloperidol, droperidol, mesoridazine, pimozide, quetiapine, risperidone, thioridazine, ziprasidone, lithium, chloral hydrate, pericycline, sertindole, sultopride, zimeldine, maprotiline
Anticonvulsants	Felbamate, fosphenytoin
Anesthetics	Sevoflurane
Antianginal/ vasodilators	Bepridil, lipoflazine, prenylamine, intracoronary papaverine
Antihypertensives	Isradipine, nicardipine, moexipril/ hydrochlorthiazide
Anticancer agents	Arsenic trioxide, tamoxifen
Antilipemic	Probucol
Antimigraine agents	Sumatriptan, zolmitriptan, naratriptan
Diuretics	Indapamide thiazide, furosemide
Endocrine octreotide, vasopressin	
Gastrointestinal stimulants	Cisapride, metoclopramide, domperidone, erythromycin
Others	Arsenic trioxide, tizanidine, tacrolimus, salmeterol, levomethadyl, pinacidil, cromakalin, aconitine, veratridine, batrachotoxin, anthopleurin A, ketanserin, vincamine, terodiline, budipine, cesium chloride, tiapride, levomethadyl acetate, cocaine, organophosphorus compounds

The drug-induced torsade de pointes is a relatively rare event but its incidence can be as high as 2–3% with some drugs [11]. More than 25% prolongation of QTc interval from the baseline or a QTc interval longer than 500 ms increases the risk of precipitation of drug-induced torsade de pointes, which is true for both the antiarrhythmic and the non-antiarrhythmic drugs [12,13]. More than 90% of incidences of drug-induced torsade de pointes occur with QTc values of more than 500 ms. Women are two to three times more prone to develop drug-induced torsade de pointes [12,13]. The higher incidence in women is not simply

Table 3
Risk factors for drug-induced torsade de pointes

Congenital long QT
Female gender
Electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia)
Diuretic use
Bradycardia
Cardiac hypertrophy
Myocardial fibrosis
Congestive heart failure
Renal and liver insufficiency
Co-administration of drugs blocking P450 isoenzyme CYP3A4
High doses or rapid intravenous infusion of the drug
Baseline electrocardiographic abnormalities (prolonged QT, T wave lability)

related to their smaller body size and the dose of the drug, the baseline QT interval is longer in women and varies with the menstrual cycle, being longest during menses and ovulation. Many clinically available or still investigational cardiovascular and non-cardiovascular drugs have been implicated to provoke torsade de pointes (Table 2), and a number of drugs have been withdrawn from the market or have had their sale restricted. Only about 1% of serious adverse drug effects are reported to the agencies, so it can be assumed that there is far less information about the drug-induced torsade de pointes. Of further concern is the interval, usually measured in years, from the marketing of a drug to the initial recognition of its association with prolonged QT interval, torsade de pointes or both. Although the incidence of torsade de pointes usually does not correlate well with the plasma concentrations of the drugs known to precipitate it, a number of risk factors for drug-induced precipitation of torsade de pointes have been recognized including clinically significant bradycardia or heart disease, electrolyte imbalance, impaired hepatic or renal function, concomitant treatment with other drugs with known potential for pharmacokinetic or pharmacodynamic interactions, and congenital long QT syndrome, as the congenital and the acquired forms of long QT syndrome are not mutually exclusive [14–16] (Table 3).

Besides drugs, the risk of torsade de pointes is increased with hypokalemia, hypomagnesemia, hypocalcemia, severe bradycardia, high-grade atrioventricular block and impaired ventricular function [17–20]. The other clinical conditions known to predispose to torsade de pointes include poisoning with organophosphorus compounds, intracranial hemorrhage, air encephalography, hypothyroidism and anorexia nervosa, [21–25]. The rare causes are fad weight reducing diets, therapeutic starvation, ionic contrast injections into the coronary artery and pheochromocytoma [26–30]. In addition, torsade de pointes has also been reported in few patients with chronic stable angina, variant angina, myocarditis and rarely in mitral valve prolapse [31–33]. In patients with human immunodeficiency virus infection, prolonged QT interval and torsade de pointes have been reported even in the absence of pentamidine or drug therapy [34]. Postulated mechanisms for torsade de pointes in such patients include myocarditis, a subclinical cardiomyopathy, and autonomic neuropathy [35]. In a number of cases, it is a combination of multiple predisposing factors that leads to the clinical syndrome of torsade de pointes [36,37].

3. Presentation and diagnosis

Symptoms begin usually in preteen to early teenage years, but can occur as early as the first day of life or as late as 40–50 years of age. Syncope occurs in approximately two-thirds of the congenital LQT gene carriers [38–41]. Sudden death can be the first presenting feature in up to 30–40% of congenital LQT patients emphasizing the importance of an early diagnosis and treatment [10]. Patients with frequent syncope or resuscitated cardiac arrest carry higher risk for sudden death. Syncope and sudden death most often occur during exercise or emotional stress (KCNQ1), with sudden auditory stimuli (HERG), and during sleep (SCN-). The use of QT prolonging drugs and the hypokalemia, which in turn is commonly secondary to diuretics use, may precipitate symptomatic events in patients with congenital LQT [42].

The electrocardiographic rhythm strip of torsade de pointes depicts a polymorphic ventricular tachycardia associated with QT interval prolongation (Fig. 1). There is a short, pre-initiating RR interval due to a ventricular premature beat, which is followed by a long initiating cycle resulting from the compensatory pause after the ventricular premature beat [43]. In addition to the electrocardiographic features, a careful clinical and family history is essential.

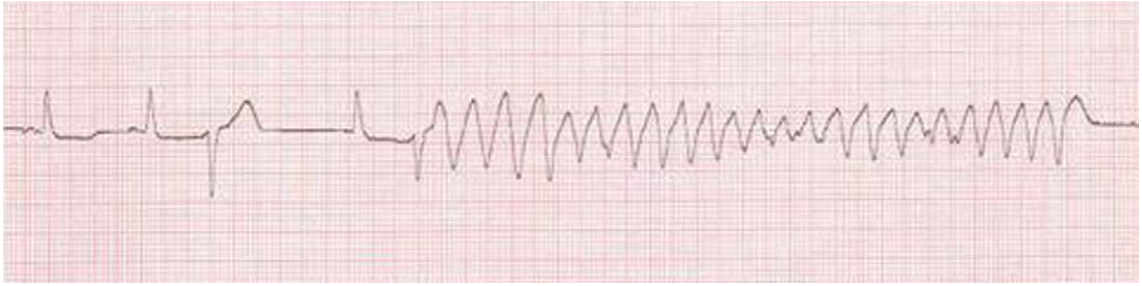

Fig. 1. An electrocardiographic rhythm strip demonstrates a short-long-short cycle initiating an episode of torsade de pointes.

Patients presenting with presyncope, syncope or sudden death should be carefully evaluated to exclude secondary causes. In case of a congenital LQT, an exercise test could be performed to demonstrate a lack of an appropriate shortening of QT interval (KCNQ1), super-shortening of QT interval (SCN-) or to un-mask an abnormal T wave morphology (KCNQ1), but there is much overlap with normal. Genetic studies are offered in investigational labs.

4. Management

4.1. Short-term treatment

Treatment of torsade de pointes is summarized in Table 4. The pathophysiological differences between the congenital and acquired forms of torsade de pointes attribute to certain apparent differences in the treatment [44]. Immediate administration of intravenous magnesium sulfate is indicated as the first line therapy for long QT interval related ventricular ectopic beats and torsade de pointes [45]. It is administered as a 2 g intravenous bolus over 1–2 min and a repeat dose in 15 min if necessary. In cases not responding to intravenous magnesium sulfate or those with bradycardia, temporary atrial or ventricular pacing is used at rates of >90 beats/min. In the out-of-hospital setting, treatment of torsade de pointes with percutaneous overdrive pacing has been found as an effective bridge before the definitive therapy is available [46]. Isoproterenol and atropine have been used to increase the sinus rate and decrease the QT interval, and both of these drugs have been successful in suppressing the torsade de pointes. Isoproterenol is contraindicated in presence of ischemic heart disease and in congenital LQT. Recently, it has been demonstrated that, compared to isoproterenol, atropine is associated with a relatively more QT interval shortening in normal individuals [47]. This may make a case, albeit weak as the observation was not made in individuals with long QT interval, in favor of atropine use in the acute settings, especially considering the scarce availability of isoproterenol. Lidocaine and phenytoin have been occasionally used for torsade de pointes with variable success. Alkalinization of plasma to enhance protein binding of quinidine by giving sodium bicarbonate is important in the treatment of quinidine-induced torsade de pointes. Intravenous potassium supplementation may be beneficial even when potassium levels are normal; however, at this time, it is uncertain whether it is an effective method to prevent torsade de pointes [48].

Table 4
Summary of the treatment of torsade de pointes and long QT syndrome

	Pharmacological	Nonpharmacological
Congenital	Magnesium sulfate	Permanent cardiac pacemaker
	β-Blockers	Cardiothoracic sympathectomy
	Mexiletine[a]	Implantable cardioverter defibrillator
Acquired	Magnesium sulfate	Removal of the cause
	Isoproterenol	Temporary cardiac pacing
	Atropine	
	Lidocaine	
	Phenytoin	
	Sodium bicarbonate[b]	

[a] For SCN5A mutations-induced torsade de pointes.
[b] For quinidine-induced torsade de pointes.

Discontinuation of the offending agent and correction of the metabolic abnormalities remains the cornerstone of the therapy for the acquired torsade de pointes. In patients with drug-induced torsade de pointes, the management strategies, in addition to identifying and withdrawing the offending agent include supplementing potassium to keep the serum level between 4.5 and 5 mEq/l and infusing 1–2 g of intravenous magnesium sulfate. In resistant cases with bradycardia and pauses, isoproterenol, atropine or temporary cardiac pacing may be needed to increase the heart rate and the shorten QT interval. The adverse effects of QT interval prolonging drugs can be minimized by not exceeding the recommended dose, dose restrictions in patients with preexisting heart disease, and avoiding the drugs that inhibit metabolism or excretion of QT interval prolonging drugs and those which produce hypokalemia. The potassium level should be checked regularly in patients on potassium wasting diuretics.

4.2. Long-term treatment

For long-term treatment, interruption of the sympathetic input to the heart either by a pharmacological (β-blockers) or surgical (left cervicothoracic sympathectomy) approach is undertaken for the treatment of the congenital forms of torsade de pointes. β-Blocker drugs have been proven to be beneficial in decreasing syncope and sudden cardiac death in these patients. These drugs decrease the ventricular ectopy and shorten the QT interval and QT dispersion by decreasing the sympathetic activation from left stellate ganglion. The QT dispersion is a measure of risk for sudden death in these patients and failure of β-blockers to reduce QT dispersion may identify a group at particular risk. The effect of β-blockers is related to genotype. They are more effective in patients with KCNQ1 and HERG mutations than in those with SCN-mutations. It has been recently observed that the peak sympathetic stimulation prolongs QTc interval markedly in patients with KCNQ1 and HERG mutations than in those with KCNQ1 mutations, but once a steady state of the sympathetic stimulation is reached, the QTc interval prolongation persists only in patients with KCNQ1 mutations [49]. This observation may explain the rationale of β-blockers' genotype-dependent efficacy, which is highest in the patients with KCNQ1 mutations.

Cardiac pacing is performed to prevent bradycardia and pauses and to reduce both the early afterdepolarizations and the dispersion of repolarization. Long-term pacing is used along with the β-blocker drugs in patients who do not tolerate β-blockers because of excessive bradycardia or atrioventricular block or have clear evidence of pause-dependent malignant arrhythmias, especially in those with

SCN-mutations [50]. Although the combination of β-blockers and pacing is an effective therapy in resistant cases, a possibility of noncompliance may justify the use of backup implantable cardioverter defibrillator in high-risk individuals [51]. In addition, implantable cardioverter defibrillator should be considered for recurrent symptoms in patients who are already on β-blockers and pacing. Nonetheless, the majority of the currently available implantable cardioverter defibrillators have an added pacer function. Although cardioverter defibrillator implantation may prove lifesaving for patients with continuing episodes of torsade de pointes despite being on conventional therapy, it does not seem to decrease the rates of cardiac events except of the potential fatal arrhythmias.

Treatment of congenital forms of LQT is primarily based on the presence or absence of symptoms. If patient is asymptomatic or has no clear history of syncope related to torsade de pointes, treatment consists of a β-blocker drug alone. However, if the patient is symptomatic with presyncope or syncope, the treatment consists of a β-blocker drug and a dual chamber pacemaker in demand mode programmed to effectively shorten the QTc interval to <440 ms. Implantable cardioverter defibrillator should be considered if symptoms recur, or in those who had an aborted sudden death. For pregnant women with congenital forms of LQT, β-blockers should be continued during pregnancy and postpartum period. Research is continuing to explore the electrophysiological mechanisms of LQT and torsade de pointes and to develop the channel specific therapies. Increasing serum potassium level by administration of potassium plus spironolactone has been shown to shorten the QT interval in cases with HERG mutations [52]. Similarly, the use of potassium channel openers, such as nicorandil, has been shown to effectively shorten the QT interval in patients with KCNQ1 and HERG mutations, and use of sodium channel blockers, such as mexiletine, lidocaine and flecainide, in those with SCN-mutations [53–55]. With continuing research, future therapeutic measures will be more based on the better understanding of the genetics and the ionic basis of the aberrant repolarization and the development of torsade de pointes.

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