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Torsades de pointes in congenital long qt syndrome following low-dose orphenadrine

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SUMMARY

We report the case of a woman, affected by congenital long QT syndrome (LQTS), who experienced three syncopal episodes shortly after the assumption of a low dose of orphenadrine. The ECG revealed a QT interval of 600 ms, and the corrected QT interval (QTc) was 537 ms. No structural cardiac disease was demonstrated by echocardiography. Orphenadrine treatment was discontinued. During the first 12 h of monitoring, three short-lasting, asymptomatic episodes of torsades de pointes occurred. No other sustained ventricular arrhythmia was revealed at Holter monitoring in the following days. During the ensuing 6 months, the patient remained asymptomatic, and the QTc did not change. Orphenadrine is an analogue of diphenhydramine, an antihistaminic drug that produces sodium channel blockade similar to that caused by quinidine and other Class Ia antiarrhythmic drugs. Our case rises the suspicion that orphenadrine could cause life-threatening arrhythmias in LQTS even at a low dose, and independently from concomitant assumption of potentially QT-prolonging drugs.

Keywords: Orphenadrine; long QT syndrome; syncope; ventricular tachycardia; torsades de pointes

INTRODUCTION

Congenital long QT Syndrome (LQTS) is associated with potentially life-threatening arrhythmias. Ventricular ectopic beats, physical or emotional stress, autonomic nervous system imbalance, particular diets, fasting and drugs may constitute the trigger for ventricular arrhythmias in this particular situation (1).

We report the case of a woman with congenital LQTS in whom life-threatening arrhythmias ensued shortly after orphenadrine assumption.

CASE REPORT

The 12 lead ECG of Figure 1 belongs to a 68-year-old woman admitted to the coronary care unit for recurrent syncopal episodes. The patient had a 10-year history of mild hypertension controlled with ACE inhibitors. In 1996, she underwent coronary angiography because of chest pain associated with abnormal ST segment; the coronary angiogram resulted normal.

Two days before the admission, she complained of myalgia and nuchal tension; for this reason she was advised to take orphenadrine (50 mg once a day). One hour after the second pill the patient experienced a syncope, followed by two further episodes in the ensuing 2 h. Each episode was brief (30–60 s), not preceded by prodromic symptoms and unrelated to any specific event.

On admission, the physical examination was normal, the heart rate was 48 beats per minute (bpm) and the blood pressure measured 145/80 mmHg. Laboratory tests were normal, as well as neurological examination and electroencephalogram. The ECG showed sinus bradycardia with a rate of 48 bpm; the P–R interval and the QRS configuration were normal, while the QT interval measured 600 ms and the corrected QT interval (QTc) [The QTc is calculated, according to Bazzett's formula, by dividing the QT interval (in seconds) by the square root of the R–R interval (in seconds)] was 537 ms (Figure 1). No structural cardiac disease was demonstrated by echocardiography. Orphenadrine treatment was discontinued. During the first 12 h of monitoring, three short-lasting (minimum 4, maximum 6 s) and asymptomatic episodes of torsades de pointes occurred. One of these is shown in Figure 2. In the next 72 h, no further arrhythmias were observed. On days 5 and 8, 24-h Holter recordings did not document any significant arrhythmia. During hospitalisation, the ECG did not change, and the QTc remained stable; laboratory tests were also unchanged. During the ensuing 6 months, the patient continued to take ACE inhibitors and remained asymptomatic; the QTc did not change. Holter recordings at 1, 3 and 6 months did not reveal any rhythm disturbance.

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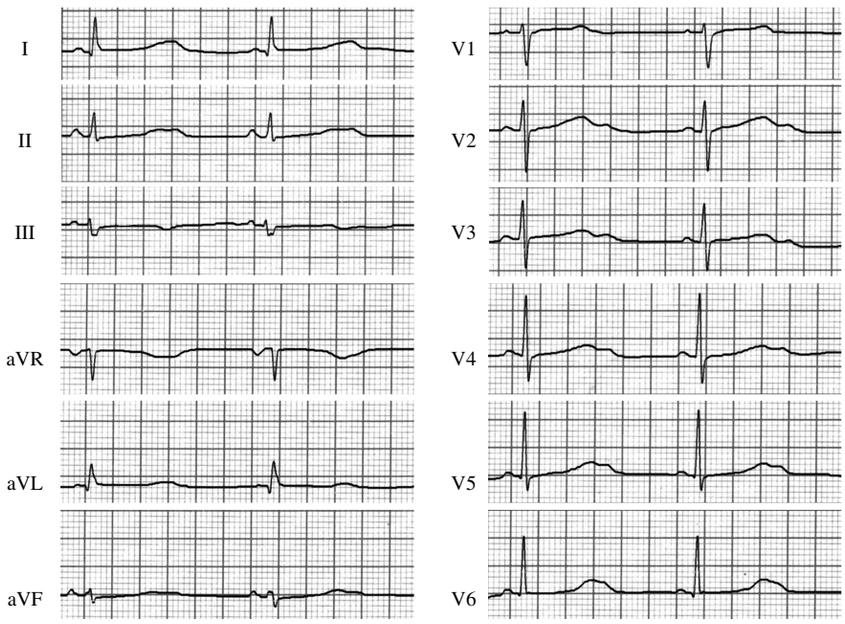

Figure 1 Twelve-lead electrocardiogram recorded on admission

DISCUSSION

Our patient was affected by congenital LQTS: two previous electrocardiograms recorded 8 years before showed a long QT interval; a similar pattern was also documented in her sister and in one out of her two sons.

Congenital LQTS is a familial disorder caused by mutations in sodium or potassium channels producing genes. These mutations result in alteration and prolongation of ventricular repolarisation, giving rise to early after depolarisations leading to torsades de pointes (2). This term refers to a particular form of ventricular tachycardia, characterised by ventricular complexes with progressive polarity modification, in such a way that the QRS configuration gradually changes from positive to negative and vice versa. The arrhythmia typically occurs in non-sustained, self-terminating runs; at times, however, degeneration into ventricular fibrillation can ensue. Whenever the heart rate is high and/or the episode is relatively prolonged, this ventricular tachycardia is poorly tolerated and can result in syncopal attacks. Patients with congenital LQTS can experience either syncope or sudden

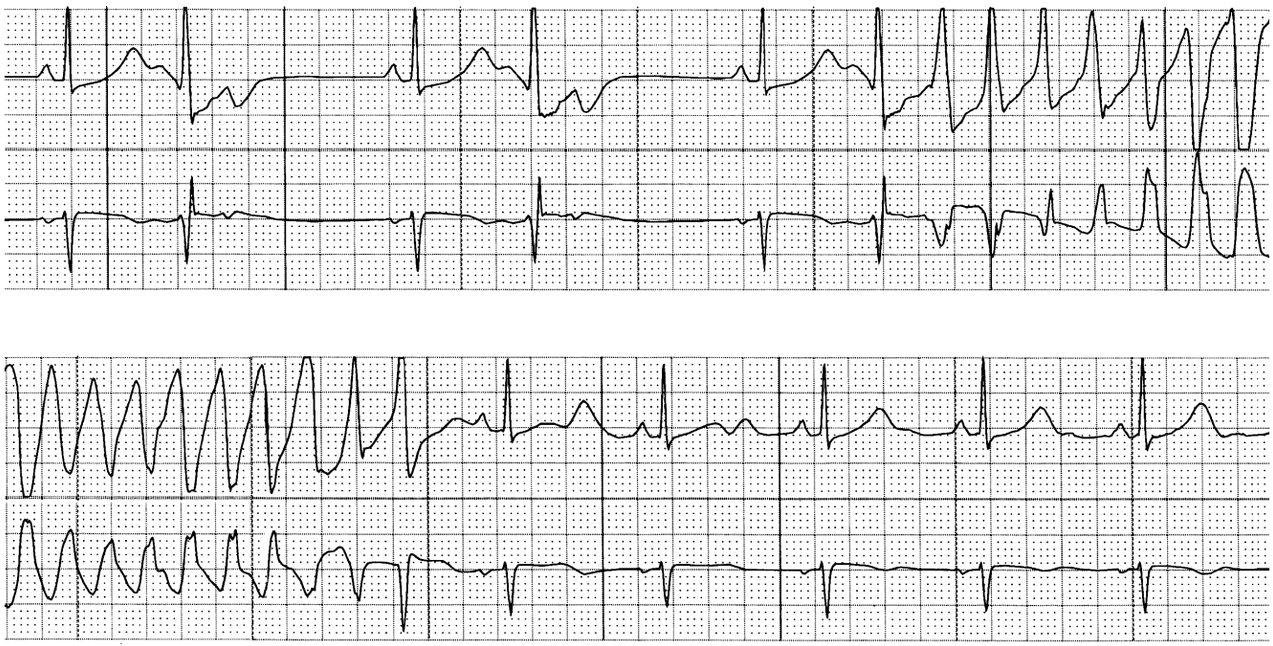

Figure 2 Monitor strip demonstrating atrial extrasystoles in bigeminal rhythm, followed by a short phase of torsades de pointes tachycardia

cardiac death due to torsades de pointes. The arrhythmia can be triggered by physical exercise, auditory stimuli, emotional stress and QT-prolonging drugs (3).

Several drugs are potentially responsible for torsades de pointes in LQTS, particularly some antiarrhythmic drugs such as quinidine, proicainamide, sotalol, ibutilide, some antibiotics like erythromycine, claritromycine, ampicillin, ciprofloxacin, several antidepressive agents like amitriptyline and imipramine and a long list of other drugs (4). Orphenadrine, an anticholinergic agent mainly used in the treatment of Parkinson's disease, is not included in the list of these drugs. As an analogue of diphenhydramine, an antihistaminic drug, it could be expected to exert the same type of cardiotoxicity; diphenhydramine, indeed, is known to produce sodium channel blockade similar to that caused by tryciclic antidepressants, Quinidine and other Class Ia antiarrhythmic drugs (5,6). It is, therefore, conceivable that, in patients with LQTS, orphenadrine can decrease the 'repolarisation reserve' (7), thereby enhancing the risk of the life-threatening arrhythmias. Previous papers have pointed out the risk of cardiotoxicity, and especially of dangerous ventricular arrhythmias, after orphenadrine assumption (8–10). To the best of our knowledge, there is just one case of ventricular arrhythmias induced by low-dose orphenadrine; in that case, there was neither QT prolongation nor hypokaliemia, and the authors hypothesised that the combination of the drug with a sodium channel-blocking agent (propafenone) was probably responsible for the ventricular tachycardia (10).

Our case rises the suspicion that orphenadrine could cause life-threatening arrhythmias in LQTS even at a low dose and independently from concomitant assumption of potentially QT-prolonging drugs.

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