*Case Report*

# Torsades de Pointes: A Rare Complication of an Extra-Adrenal Pheochromocytoma

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**Pheochromocytoma is an infrequent secondary cause of arterial hypertension, often associated with paroxysmal headache, sweating, weight loss, and palpitations. Cardiovascular complications of pheochromocytoma include sudden death, heart failure due to toxic cardiomyopathy, and hypertensive encephalopathy. Here we report the case of a female with an acquired long-QT-syndrome as a rare complication of an extra-adrenal pheochromocytoma. Diagnosis was made after sotalol-induced Torsades de Pointes. (*Hypertens Res* 2007; 30: 1263–1266)**

***Key Words*: pheochromocytoma, long-QT-syndrome, Torsades de Pointes**

## Introduction

Pheochromocytoma is a rare cause of sustained hypertension or hypertensive crisis and many cardiac complications have been reported with this neuroendocrine tumor. Development of long-QT-syndrome (LQTS) due to myocardial hypertrophy in this patient group is an occasional but potentially life-threatening complication increasing the risk for arrhythmias.

## Case Report

A 33-year-old female was referred to our hospital because of syncope. The patient had been well until 2 years earlier, when arterial hypertension was diagnosed and β-blocker treatment (bisoprolol 5 mg once daily) had been initiated by her primary care physician. She also reported loss of weight, paroxysmal sweating, emesis, and non-exertional tremor, yet no further diagnostic procedures were initiated. Because of palpitations, bisoprolol was switched to sotalol. The syncope occurred after a cumulative dose of 320 mg sotalol. On initial examination her blood pressure was 220/90 mmHg and her heart rate was 106 beats per minute. The remaining physical findings were normal, except for a 4/6 pansystolic murmur at Erb. There was no family history of sudden death. Serum electrolytes were as follows: sodium 139 mmol/L, potassium 5.1 mmol/L, calcium 2.7 mmol/L, anorganic phosphorus 4.1 mg/dL, magnesium 1.97 mg/dL. Fasting blood glucose was elevated to 124 mg/dL. Renal, liver and thyroid tests were all normal.

Her baseline ECG showed sinus rhythm and deep T-wave inversion in V2–4. Most remarkably it showed a QTc interval of 480 ms (Fig. 1A). Sotalol-treatment was discontinued immediately but during intensive care unit monitoring, a Torsades de Pointes tachycardia was recorded (Fig. 2), and was terminated by magnesium sulfate (1 g i.v.) infusion. Echocardiography showed hypertrophic cardiomyopathy with marked septal hypertrophy (interventricular septal diameter [IVSd] 21 mm, posterior wall diameter [PWd] 17 mm (physiologic: 6–12 mm; Fig. 3). There were no segmental wall-motion abnormalities and fractional shortening was 58%. Invasive diagnosis revealed patent coronary and renal arteries. Left ventriculography showed homogenous unaffected contractility with a small left ventricular cavity that occluded almost completely late systolic. No ventricular arrhythmia could be induced by programmed ventricular stimulation.

Twenty-four–hour urine metanephrine excretion was 16.1 mg, vanillylmandelic acid 70.4 mg, adrenaline 25.9 μg, nor-

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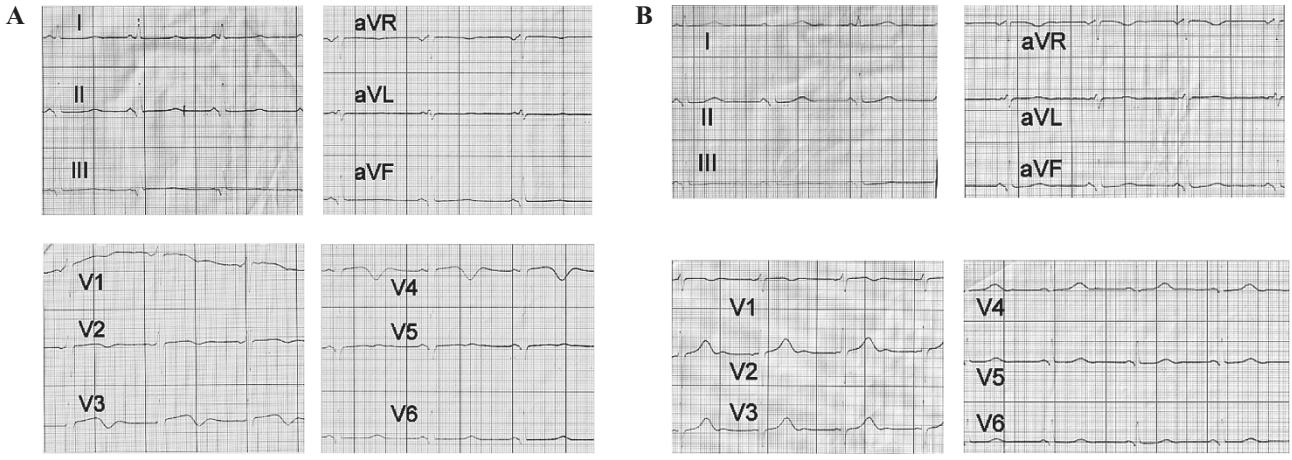


**Fig. 1.** *Electrocardiograms in our patient at baseline (A) revealed QTc prolongation and deep T-wave inversion in V2–4. Six months after tumor extirpation, the QTc interval was within the physiologic range and the electrocardiogram did not show further abnormalities (B).*

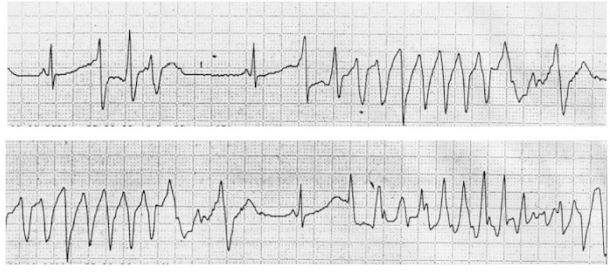

**Fig. 2.** *Intensive care unit monitor tracing of a typical episode of non-sustained polymorphic ventricular tachycardia in our patient under sotalol treatment.*

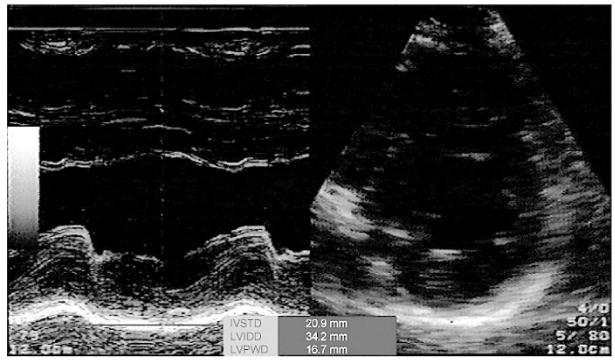


**Fig. 3.** *Baseline echocardiography showed hypertrophic cardiomyopathy with marked septal hypertrophy.*

adrenaline 5,038 μg, homovanillin acid 10.5 μg and dopamine 6,736 μg excretion in 1,400 mL with physiologic values for 5-hydroxyindole-3-acetic acid.

Based on the overall findings we suspected pheochromocytoma with subsequent development of left ventricular hypertrophy as the underlying cause of an acquired LQTS. The patient was started on an α-adrenergic blocker (phenoxybenzamine) and later on, a β-adrenergic blocker therapy was slowly added.

MRI-scan and radioiodinated metaiodobenzylguanidine ($^{131}$I-MIBG) whole-body scintigraphy revealed a left-sided paravertebral retroperitoneal tumor (5.5×4×7 cm) and multiple enlarged lymph nodes in its cranial surrounding. No mutations in exons 10, 11, and 13 of the RET oncogen could be found.

In order to evaluate the pathogenic mechanism of QT-prolongation in this patient, a provocative i.v. sotalol test (2 mg/kg i.v. over 20 min) was performed to reveal an intrinsic myocardial predisposition to disproportional QT-prolongation and cardiac arrhythmias upon extrinsic triggers (*1*). With marked left ventricular hypertrophy but sustained cardiac function, serum potassium within reference limits and in the absence of any other QT-prolonging medication, the patient displayed a marked increase in QTc-interval upon challenge with *dl*-sotalol (from 461 ms at baseline to 512 ms), which is consistent with an abnormal repolarization reserve (Fig. 4A). Genetic analysis revealed no mutations in five of the major genes predisposing to LQTS (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2). These genes account for approximately 80% of all congenital LQTS (*2*).

The tumor that had locally invaded the aorta, vena cava, and the left v. iliaca could not be curatively resected. Postoperative palliative irradiation therapy was initiated (total of 55.8 GY). Biopsy confirmed the diagnosis of an extra-adrenal pheochromocytoma with positive staining for synaptophysin and neuron-specific enolase. Urine catecholamine levels and blood pressure returned to normal within 7 days. A second provocative i.v. sotalol test 6 months after extirpation demarked a persistent disproportional increase in QTc-inter-

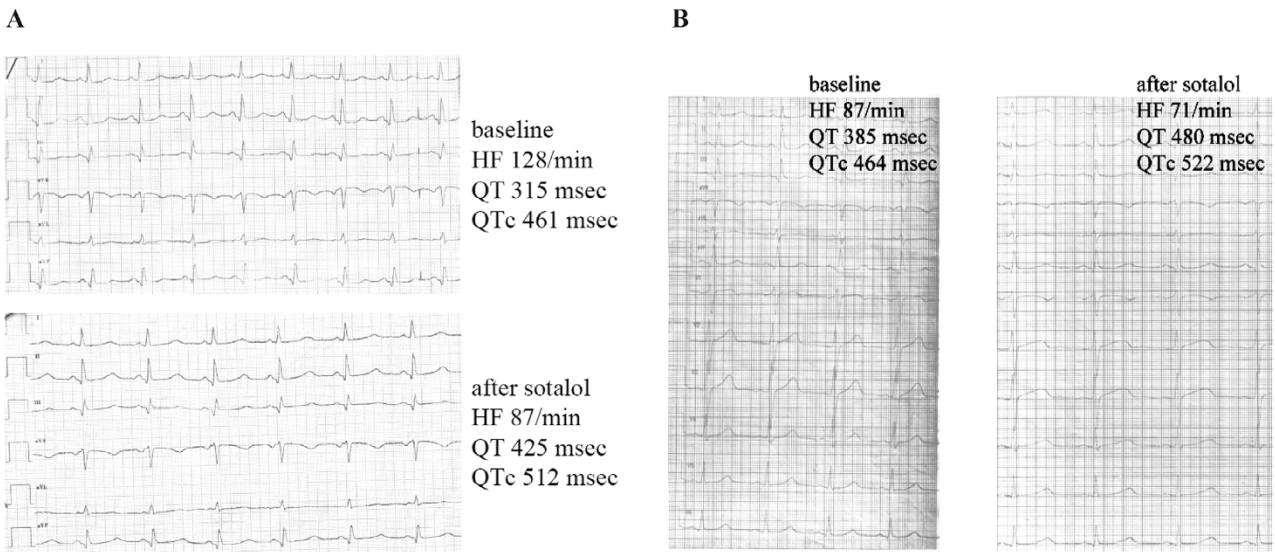


**Fig. 4.** *Upon exposure to i.v. dl-sotalol (2 mg/kg), the patient presented with a marked increase in QTc-interval revealing an abnormal repolarization reserve. A: Before tumor extirpation (treated with phenoxybenzamine). B: Six months after tumor extirpation (without concomitant treatment).*

val upon challenge (from 464 ms to 522 ms; Fig. 4B), whereas echocardiography revealed a reduction in left ventricular hypertrophy, although some degree of hypertrophy was still present (IVSd 14 mm, PWd 13 mm). Echocardiography 20 months after surgery showed normalization of the left ventricular wall index with sustained ejection fraction. During follow-up no further tachycardia occurred and the QTc-interval normalized (Fig. 1B).

## Discussion

We report here a rare case of LQTS and Torsades de Pointes in a female patient with pheochromocytoma. Pheochromocytomas are catecholamine-producing neuroendocrine tumors arising from chromaffin cells of the adrenal medulla (in 80–85% of cases) or extra-adrenal paraganglia (15–20%) (*3*, *4*). In general outpatient clinics, the prevalence of pheochromocytoma in patients with hypertension is 0.1–0.6% (*5*–*7*). Malignancy of pheochromocytomas is currently only based on the presence of metastases of chromaffin tissue at sites where no chromaffin tissue should be expected. The most common metastatic sites are the bones, lungs, liver, and lymph nodes (*8*). In general, tumors that are large (>5 cm) or have an extra-adrenal location have a higher risk for malignant disease than tumors that are small or have an adrenal location (*9*). When malignant disease is confirmed, the natural clinical course is highly variable, with a 5-year survival rate of 50% (*10*).

Whereas 50–70% of all pheochromocytoma patients complain about palpitations, only a small number develop ventricular tachycardia, and only a very few of these cases have been reported to be due to QT interval prolongations and Torsades de Pointes (*11*–*14*). However, Stenström and Swedberg described a significant decrease in QTc interval in a retrospective study of patients with pheochromocytoma after surgical removal (*15*).

LQTS (defined as prolongation of the QT interval corrected for heart rate, to >440 ms in adult males and children, or >460 ms in women) is a primary electrical disease characterized by mutations found in genes encoding various subunits of the potassium, sodium and calcium channels or membrane adapter. They cause ion channel dysfunctions and lead to cardiac arrhythmias by altered depolarization or repolarization, resulting in prolonged action potential, increased heterogeneity of repolarization, and cardiac arrhythmia typically presenting as Torsades de Pointes (*2*). Eight forms of autosomal dominant disease (LQTS1–8) and two autosomal recessive diseases (Jervell-Lange-Nielsen) have been described so far (*2*).

On the other hand, acquired LQTS has been postulated to be the result of a combined block of the rapid cardiac calcium-modulated potassium channel for the cardiac delayed rectifier ($I_{Kr}$) and of the delayed cardiac potassium channel ($I_{Ks}$) components of the potassium current (*16*). Acquired LQTS is far more common, and affected subjects have either a subclinical abnormality in some of the channels (forme fruste of the syndrome) (*16*), and/or a reduced repolarization reserve (*17*). In two-thirds of cases, acquired LQTS affects female gender. Major risk factors are bradycardia or hypokalemia in the presence of medications that prolong the QT-interval or under conditions that predispose to electrical remodeling, such as ventricular hypertrophy, myocardial

ischemia, and heart failure.

Accordingly, a multivariate analysis in hypertensive patients revealed significant relationships between QT dispersion and both systolic blood pressure and left ventricular mass index (*13*). It is widely accepted that prolongation of action potential duration is the most consistent electrophysiological abnormality in myocardium and myocytes from hypertrophied hearts, which is in most cases due to a decrease in outward potassium currents (*18*). Enhanced susceptibility for acquired Torsades de Pointes arrhythmias has also been demonstrated in a dog model with experimentally induced cardiac hypertrophy (*19*). The reduction of outward delayed rectifier potassium currents ($I_{Kr}$) may also be involved in the enhanced sensitivity to triggering factors such as hypokalemia, ischemia, and antiarrhythmic agents with class III effects, as evident in our patient.

Therefore, assessing the individual repolarization reserve and thereby unmasking a latent repolarization disorder (*e.g.*, by provocative drug-testing using i.v. sotalol) is helpful in identifying patients with pheochromocytoma at risk for arrhythmias in the context of QT-prolonging drugs. Interestingly, we detected a persistent increase in QTc-interval upon i.v. sotalol challenge despite a decrease in the extent of left ventricular hypertrophy 6 months after resection of the extra-adrenal pheochromocytoma in our patient with this form of neuroendocrine disease.

In conclusion, pharmacological tests for repolarization abnormalities might be useful tools to identify patients with pheochromocytoma at risk for ventricular arrhythmias.

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