

# Primary hyperparathyroidism associated with acquired long QT interval and ventricular tachycardia

Emir Muzurović<sup>1,2</sup>, Sanja Medenica<sup>1,2</sup>, Milovan Kalezić<sup>3</sup> and Siniša Pavlović<sup>4</sup>

<sup>1</sup>Department of Internal Medicine, Endocrinology Section, Clinical Center of Montenegro, Podgorica, Montenegro, <sup>2</sup>Faculty of Medicine, University of Montenegro, Podgorica, Montenegro, <sup>3</sup>Department of Cardiology, Clinical Center of Montenegro, Podgorica, Montenegro, and <sup>4</sup>Pacemaker Center, Clinical Center of Serbia, Faculty of Medicine University of Belgrade, Belgrade, Serbia

Correspondence  
should be addressed  
to S Medenica  
**Email**  
[mednicasanja@gmail.com](mailto:mednicasanja@gmail.com)

## Summary

We present a 54-year-old patient admitted to the emergency department due to loss of consciousness. The initial ECG registered monomorphic ventricular extrasystoles and prolonged QT interval (QT corrected (QTc) >500 ms). Sustained ventricular tachycardia (VT) was registered on 24-h Holter ECG monitoring, which clinically was presented as a crisis of consciousness. Coronary angiography and other visualization methods were normal. Implantable cardioverter-defibrillator (ICD) implantation was planned for the purpose of secondary prevention of sudden cardiac death (SCD). Laboratory and hormonal analyzes revealed primary hyperparathyroidism (PHPT), chronic kidney disease, and hypokalemia. Neck ultrasound showed a 25 mm, sharply outlined homogenous tumor mass which was separated from thyroid gland (TG) and exerted a mild impression on lower parts of the left lobe. Dual wash technetium-99m sestamibi parathyroid scintigraphy with single-photon emission CT (SPECT)/CT also showed the uptake of tracer behind the lower half of the left lobe of the TG. Surgical treatment, lower left parathyroidectomy, was performed, and pathohistological analysis verified parathyroid adenoma. The patient was rhythmically and hemodynamically stable for 7 days after surgery, without additional complaints, and was discharged from the hospital. Timely diagnosis of PHPT, correct assessment and surgical treatment, did not lead our patient to unnecessary ICD implantation. Our case suggests an additional intertwining of electrolyte disorders and ventricular arrhythmias in PHPT and more importantly emphasizes the need for caution when indicating ICD, even in patients with the most serious life-threatening arrhythmias.

## Learning points:

- Electrolyte abnormalities in PHPT can have highly malignant consequences, and the occurrence of hypokalemia in the presence of hypercalcemia is underestimated in PHPT, and the consequences can be life-threatening.
- Although hypercalcemia causes shortened QT interval, concomitant severe hypokalemia may overcome hypercalcemia and prolong QT interval, even in the absence of structural heart disease or LQTS.
- Timely diagnosis of PHPT, correct assessment and surgical treatment, do not lead to unnecessary ICD implantation.

## Background

Patients admitted with ventricular tachycardia (VT) or ventricular fibrillation (VF) have high inpatient mortality, with sudden cardiac death (SCD) as their most important

consequence (1). A prospective surveillance study reported a SCD incidence of 53 per 100 000 population, accounting for 5.6% of annual mortality (1). VT is associated with

structural heart diseases but can occur in a wide spectrum of non-cardiovascular (CV) diseases (CVD) (2).

During standard 12-lead ECG evaluation, it is necessary to exclude the existence of an aberrant QT interval due to the consequent risk of VT and SCD (3). Prolongation of the QT interval (QT corrected (QTc) >450 ms males and >460 ms females) may trigger malignant arrhythmias, and QTc interval  $\geq 500$  ms as a life-threatening cardiac arrhythmia syndrome could be a leading cause of SCD in adulthood (4). Long QT syndrome (LQTS) can be congenital or acquired, mainly in those with structural heart diseases (heart failure, myocardial infarction, and left ventricular hypertrophy), electrolyte abnormalities, or drug administration (3). Treatment of malignant arrhythmias is a challenge, and implantable cardioverter-defibrillator (ICD) may be a crucial lifesaving approach in these patients (3). ICD therapy aids not only in the acute termination of ventricular arrhythmia but also in the long-term management of patients with VT (3).

Primary hyperparathyroidism (PHPT) is typically characterized by elevated serum calcium (Ca) associated with elevated or non-suppressed parathyroid hormone (PTH) concentration (5). CV complications occur in patients with PHPT and are associated with an increased risk of death (5). Hypercalcemia in PHPT may induce, in addition to shortening the QT interval, a prolongation of the PR interval and QRS duration, which together increase the risk of arrhythmias and SCD (5). Due to physiological effects of both PTH and Ca on cardiomyocytes, cardiac conduction system, smooth vascular and endothelial cells, the associations between symptomatic and mild PHPT with hypertension, arrhythmias, and CV mortality, are well known (5). This leads to the conclusion that the relationship between arrhythmias and electrolyte disturbances in PHPT is complex and requires further elucidation.

ECG Holter monitoring may allow early detection of arrhythmias in PHPT, and it is also important to monitor those PHPT patients who do not undergo surgery (5). Consequently, an interesting question is whether parathyroidectomy (PTX) in PHPT can resolve malignant arrhythmia (5). The occurrence of supraventricular and ventricular premature beats, mainly related to the short QTc caused by hypercalcemia, is significantly reduced by PTX (5).

Electrolyte testing is indispensable in the examination of cardiac arrhythmias and SCD. In general, hypocalcemia and hypokalemia may lead to prolongation of QT interval and arrhythmias, but the effect of hyperkalemia and

hypercalcemia should not be neglected, because it also predispose to VT and VF by shortening the QT interval (5).

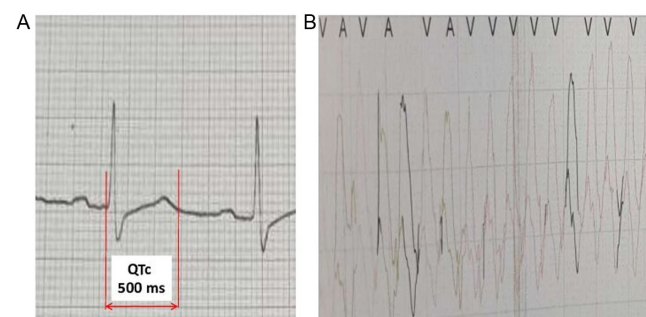
Our case suggests an additional intertwining of these electrolyte disorders and ventricular arrhythmias in PHPT and more importantly emphasizes the need for caution when indicating ICD, even in patients with the most serious life-threatening arrhythmias.

## Case presentation

A 54-year-old patient was admitted to the emergency department due to loss of consciousness. In the last few months, the patient had short-term crises of consciousness four times (lasting few seconds), accompanied by severe weakness. Patient also complained of frequent and excessive urination. Patient had no chest pain or other ailments related to the CV system. Except for the history of dyslipidemia and severe obesity (BMI: 42 kg/m<sup>2</sup>), other atherosclerosis risk factors were not present. There was no family history of multiple endocrine neoplasia. During the physical examination, the cardiac findings (no heart murmurs) and lungs were normal, as was the neurological examination.

## Investigations

The initial ECG registered monomorphic ventricular extrasystoles and prolonged QT interval (QTc 500 ms) (Fig. 1A), and the patient was admitted to the coronary unit. Carotid Doppler ultrasound, multi-slice CT of the endocranium, and echocardiography (showed preserved left ventricular (LV) systolic function, LV ejection fraction (LVEF) >50%, without heart valve abnormalities) were normal. During 24-h Holter ECG monitoring, the patient also had a crisis of consciousness (lasting a few seconds), when sustained VT (250–300 b.p.m) was registered (Fig. 1B).



**Figure 1**  
The initial ECG presenting prolonged QT interval (A) and sustained ventricular tachycardia (B).

Furthermore, coronary angiography, performed to rule out ischemic heart disease, was normal. ICD implantation was planned for the purpose of secondary prevention of SCD.

Baseline laboratory analyses were normal except for higher blood urea nitrogen 11.9 mmol/L (normal range (NR) 3.2–7.4 mmol/L) and creatinine levels 246 µmol/L (NR 62–106 µmol/L) and low potassium levels 3.2 mmol/L (NR 3.5–5.1 mmol/L). Low potassium levels (3.2, 2.8, 3.1, and 3.5 mmol/L) were maintained during hospitalization, and an endocrinologist was consulted (Table 1).

Despite the opinion about the urgency of ICD implantation, it was postponed by the endocrinologists with the aim of re-evaluating rhythm disorders after normalization of electrolyte levels. Additional laboratory evaluation, PTH concentration 95.7 pmol/L (NR 1.6–8.3 pmol/L), serum Ca 3.55 mmol/L (NR 2.2–2.55 mmol/L), ionized Ca (Ca<sup>++</sup>) 1.75 mmol/L (NR 1.10–1.35 mmol/L), phosphate (Phos) 0.66 mmol/L (NR 0.97–1.45 mmol/L), 24-h urinary Ca 9.92 mmol/L (NR 2.50–7.50 mmol/24 h), and calculated fractional excretion of Ca 3.05% (>1%) were in favor of PHPT. Further examination verified normal bone mineral density and decreased renal function (creatinine clearance 78.6 mL/min/1.73 m<sup>2</sup>) (Table 1).

For preoperative localization of hyperfunctional parathyroid tissue, neck US and nuclear imaging techniques were used. Neck US showed a 25 mm, sharply outlined homogenous tumor mass which was separated from the thyroid gland (TG) and exerted a mild impression on the lower parts of the left lobe. Dual wash technetium-99m sestamibi (99mTc-MIBI) parathyroid scintigraphy with single-photon emission CT (SPECT)/CT also showed the uptake of tracer behind the lower half of the left lobe of the TG (Fig. 2).

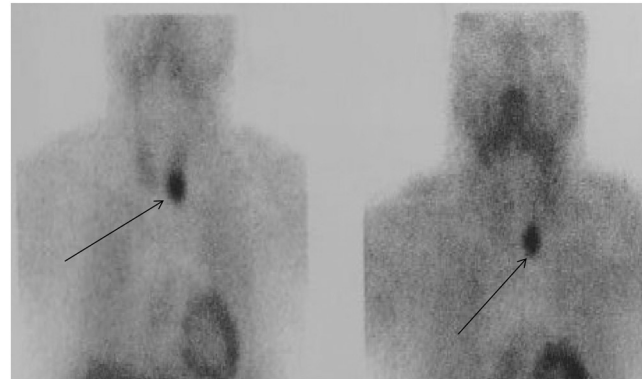
## Treatment

Immediately after the diagnosis of VT, treatment with antiarrhythmics (amiodarone) and beta-blockers

**Table 1** Laboratory analyses.

	Baseline	On discharge	Reference range
BUN (mmol/L)	11.9	8.3	3.2–7.4
Crea (µmol/L)	246	186	62–106
Potassium (mmol/L)	3.2	4.3	3.5–5.1
PTH (pmol/L)	95.7	2.4	1.6–8.3
Serum Ca (mmol/L)	3.55	2.24	2.2–2.55
Ionized Ca (mmol/L)	1.75	1.16	1.10–1.35
Phos (mmol/L)	0.66	1.31	0.97–1.45

BUN, blood urea nitrogen; Ca, calcium; Crea, creatinine; Phos, phosphate; PTH, parathyroid hormone.



**Figure 2** 99mTc-MIBI parathyroid scintigraphy with SPECT/CT showing the uptake of tracer behind the lower half of the left lobe of the thyroid gland.

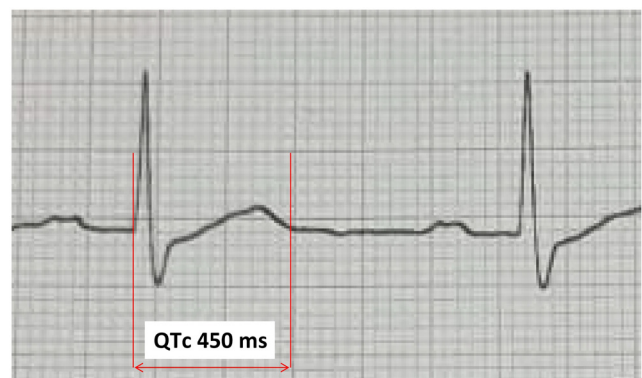
(metoprolol) was initiated, but rare episodes of VT were registered even after the initiation of antiarrhythmic drugs.

In the further course, in addition to intensive rehydration, forced diuresis with furosemide and aggressive potassium supplementation (orally and parenterally), the patient was also treated with denosumab. Denosumab treatment led to the normalization of Ca (2.54 mmol/L), Phos (0.90 mmol/L), and potassium (4.2 mmol/L) during the next 72 h. After stabilization of serum electrolytes, the patient was rhythmically stable, and the length of the QT interval on the ECG was normalized (Fig. 3); 24-h Holter ECG monitoring preoperatively did not register episodes of VT.

Surgical treatment, lower left PTX, was performed, and pathohistological analysis verified parathyroid adenoma.

## Outcome and follow-up

After PTX, PTH concentration (2.4 pmol/L), Ca (2.24 mmol/L), Phos (1.31 mmol/L), and potassium (4.3 mmol/L)



**Figure 3** The ECG showing normalized length of the QT interval.



values were maintained in the NR, without consequent hypocalcemia. In addition, after PTX creatinine clearance was 82.6 mL/min/1.73 m<sup>2</sup>. The ECG was normal, no arrhythmias or changes in QT interval were recorded. The patient was rhythmically and hemodynamically stable for 7 days after surgery, without additional complaints and was discharged from the hospital.

In the further period, the clinical status of the patient was monitored, electrolytes and ECG were performed every 3 months; 24-h Holter ECG monitoring was performed after 6 months and after 1 year. Electrolyte levels were maintained in the NR, ECG was normal (without changes in QT interval duration), and 24-h Holter ECG monitoring did not register arrhythmias other than rare supraventricular premature beats.

## Discussion

Increasing use of ICDs leads to the uncritical implementation of these systems in clinical practice nowadays. This view is already somewhat uncritically indicating the implantation of such a large number of defibrillators, but discussions are underway regarding the primary and secondary prevention of SDC.

Based on the European Society of Cardiology (ESC) recommendations, the ICD is an option in treatment (among others), in patients with documented VF or hemodynamically not tolerated VT in the absence of reversible causes (IA), in patients with recurrent sustained VT who are receiving chronic optimal medical therapy (normal LVEF, reasonable expectation of survival with good functional status for  $\geq 1$  year) (IIa C) and in addition to beta-blockers in LQTS patients who experienced syncope and/or VT while receiving an adequate dose of beta-blockers (IIa B) (6). Given the inadequate assessment and uncritical approach, a large number of patients are recognized in these recommendations, which in some cases lead to unnecessary ICD implantation (7). Therefore, the question of the necessity of using defibrillators in non-ischemic cardiomyopathy must be kept open.

For example, PHPT is rare, but it is the important cause of cardiac arrhythmias and had a direct influence on cardiac structural abnormalities such as left ventricular hypertrophy. Serum Ca levels were found to be significantly correlated to the QRS amplitude, ST-segment duration, QT interval, and T wave duration (8). Since hypercalcemia predominantly shortens phase 2 of the action potential, this cellular change most commonly correlates with a short QT interval (ST-segment portion) (8). Hyperparathyroid crisis, electrolyte disturbances,

and consequent shortening of the QT interval could create the potential for cardiac arrhythmia, as described in the literature (9). To our knowledge, we described the first patient with PHPT, prolonged QT interval, and consequent sustained VT. However, a similar patient with severe hypercalcemia and PHPT had an unexpected long QT interval (but not sustained VT as in our case), secondary to multifactorial polyuria (causing extreme hypokalemia and hypomagnesemia), was also reported (10). Hypokalemia-induced electrophysiological changes, such as prolonged QT interval, generate a range of arrhythmic triggers including early and delayed after-depolarizations, as well as oscillatory prepotentials in Purkinje fibers (11).

First, and perhaps most important, when considering arrhythmias in PHPT, the possibility of developing hypokalemia, as in our case, in PHPT must be emphasized. Although the presence of hypokalemia in PHPT is often forgotten and underestimated nowadays, much earlier Aldinger *et al.* have shown that hypokalemia occurs in about one-sixth of patients with PHPT (prevalence 16.9%) (12). The link between hypercalcemia and hypokalemia is explainable. Hypercalcemia has been shown to activate the Ca-sensing receptor in the thick ascending limb of Henle and inactivate the sodium-potassium-2 chloride cotransporter, and induce a hypokalemic metabolic alkalosis, under the effect of aldosterone, an effect similar to that of the loop diuretic furosemide (13). Furthermore, hypokalemia is probably a result of proximal (type II) and, to a lesser extent, type I renal tubular acidosis (14). Secondary hyperaldosteronism resulting from intravascular volume depletion can also occur and exacerbate hypokalemia (14). Although, hypercalcemia shortens the plateau phase of the action potential, leading to a shorter QT interval (14), the additional presence of hypokalemia may overcome concomitant hypercalcemia and lead to QT interval prolongation.

There is also evidence that PTH alone may affect cardiac physiology independent of its effects on serum Ca (15). Palmeri *et al.* found that elevated PTH concentrations were associated with longer QTc interval independent of serum Ca levels, and suggested that PTH could affect cardiac repolarization in acute coronary syndrome survivors.

The prevalence of acquired LQTS is high in patients with chronic kidney disease (CKD) (16). LQTS is responsible for SCD, one of the leading causes of death in CKD patients (16). In our case, CKD (apparently a consequence of PHPT) also was partly responsible for the more pronounced electrolyte disturbances that gave the above sequence of events. This also requires further clarification.



Despite the acute threat to the patient, an adequate order of diagnostic steps is very important with the aim of detecting reversible disorders that could be the cause of malignant arrhythmias. The benefits of unnecessary implantations of antiarrhythmic devices are clear. It has been reported that only surgical resection of the parathyroid adenoma can resolve malignant recurrent ventricular arrhythmias in a case of a patient with an automatic ICD, all due to PHPT and hypercalcemia (17). In our case, after parathyroidectomy, the length of QT interval was normal and VT did not recur, leading to the conclusion that prolonged QT in PHPT may be reversible and ICD implantation may be redundant in these situations.

Timely diagnosis of PHPT, correct assessment and surgical treatment, did not lead our patient to unnecessary ICD implantation.

In conclusion, we presented a case with PHPT, profound hypercalcemia, and hypokalemia, which led to prolonged QTc interval and sustained VT resolved by PTX. To the best of our knowledge, this case is unique in the literature so far.

The recognition of the association between the underlying electrolyte abnormalities and ventricular arrhythmias is crucial. In patients with malignant arrhythmias, due to the threat to life, for cardiologists, the ICD is very often the most urgent and the only treatment option. Comorbidities are often neglected but their presence could directly lead to an increased risk of malignant heart rhythm disorders, independently of the genetic predisposition.

Electrolyte abnormalities in PHPT can have highly malignant consequences. The occurrence of hypokalemia in the presence of hypercalcemia is underestimated in PHPT, and the consequences can be life-threatening. Although hypercalcemia causes shortened QT interval, concomitant severe hypokalemia may overcome hypercalcemia and prolong QT interval, even in the absence of structural heart disease or LQTS. In patients with severe PHPT, Ca levels must be rapidly lowered, but the presence of hypokalemia must be considered because vigorous use of diuretics may result in profound hypokalemia and VT.

Given this risk, arrhythmias in PHPT require much more attention in the future, especially when their solution could be permanent by surgical treatment instead of ICD implantation.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

#### Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

#### Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

#### Author contribution statement

E M – conceptualization, writing, investigation, visualization, validation; S M – writing, investigation, visualization, validation; M K – writing, investigation, visualization, validation; S P – review and editing, supervision, validation.

## References

- 1 Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, Ilias N, Vickers C, Dogra V, Daya M, *et al*. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *Journal of the American College of Cardiology* 2004 **44** 1268–1275. (<https://doi.org/10.1016/j.jacc.2004.06.029>)
- 2 Koplan BA & Stevenson WG. Ventricular tachycardia and sudden cardiac death. *Mayo Clinic Proceedings* 2009 **84** 289–297. ([https://doi.org/10.1016/S0025-6196\(11\)61149-X](https://doi.org/10.1016/S0025-6196(11)61149-X))
- 3 Dresen WF & Ferguson JD. Ventricular arrhythmias. *Cardiology Clinics* 2018 **36** 129–139. (<https://doi.org/10.1016/j.ccl.2017.08.007>)
- 4 Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, *et al*. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *Journal of the American College of Cardiology* 2009 **53** 982–991. (<https://doi.org/10.1016/j.jacc.2008.12.014>)
- 5 Pepe J, Curione M, Morelli S, Varrenti M, Cammarota C, Cilli M, Piemonte S, Cipriani C, Savoriti C, Raimo O, *et al*. Parathyroidectomy eliminates arrhythmic risk in primary hyperparathyroidism, as evaluated by exercise test. *European Journal of Endocrinology* 2013 **169** 255–261. (<https://doi.org/10.1530/EJE-13-0293>)
- 6 Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, *et al*. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *European Heart Journal* 2015 **36** 2793–2867. (<https://doi.org/10.1093/eurheartj/ehv316>)
- 7 Silverstein JR, Katritsis DG & Josephson ME. Use and abuse of internal cardioverter defibrillators for primary prevention. *Arrhythmia and Electrophysiology Review* 2012 **1** 46–50. (<https://doi.org/10.15420/aer.2012.1.46>)
- 8 Lind L & Ljunghall S. Serum calcium and the ECG in patients with primary hyperparathyroidism. *Journal of Electrocardiology* 1994 **27** 99–103. ([https://doi.org/10.1016/s0022-0736\(05\)80092-5](https://doi.org/10.1016/s0022-0736(05)80092-5))
- 9 Vázquez-Díaz O, Castillo-Martínez L, Orea-Tejada A, Orozco-Gutiérrez JJ, Asensio-Lafuente E, Reza-Albarrán A, Silva-Tinoco R & Rebollar-González V. Reversible changes of electrocardiographic abnormalities after parathyroidectomy in patients with primary hyperparathyroidism. *Cardiology Journal* 2009 **16** 241–245.
- 10 Ortega-Carnicer J, Ceres F & Sanabria C. Long QT interval in severe hypercalcaemia. *Resuscitation* 2004 **61** 242–243. (<https://doi.org/10.1016/j.resuscitation.2004.01.023>)



- 11 Osadchii OE. Mechanisms of hypokalemia-induced ventricular arrhythmogenicity. *Fundamental and Clinical Pharmacology* 2010 **24** 547–559. (<https://doi.org/10.1111/j.1472-8206.2010.00835.x>)
- 12 Aldinger KA & Samaan NA. Hypokalemia with hypercalcemia. Prevalence and significance in treatment. *Annals of Internal Medicine* 1977 **87** 571–573. (<https://doi.org/10.7326/0003-4819-87-5-571>)
- 13 Reiser IW, Ali S, Gotlieb V & Spitalowitz S. Hypercalcemia-induced hypokalemic metabolic alkalosis in a multiple myeloma patient: the risk of furosemide use. *Case Reports in Oncology* 2015 **8** 389–393. (<https://doi.org/10.1159/000439377>)
- 14 Kearney P, Reardon M & O'Hare J. Primary hyperparathyroidism presenting as torsades de pointes. *British Heart Journal* 1993 **70** 473. (<https://doi.org/10.1136/hrt.70.5.473>)
- 15 Palmeri NO, Davidson KW, Whang W, Kronish IM, Edmondson D & Walker MD. Parathyroid hormone is related to QT interval independent of serum calcium in patients with coronary artery disease. *Annals of Noninvasive Electrocardiology* 2018 **23** e12496. (<https://doi.org/10.1111/anec.12496>)
- 16 Liu P, Wang L, Han D, Sun C, Xue X & Li G. Acquired long QT syndrome in chronic kidney disease patients. *Renal Failure* 2020 **42** 54–65. (<https://doi.org/10.1080/0886022X.2019.1707098>)
- 17 Occhetta E, Bortnik M, Magnani A, Francalacci G & Vassanelli C. Primary hyperparathyroidism and arrhythmic storm in a patient with an implantable cardioverter defibrillator for primary prevention of sudden death. *Europace* 2004 **6** 184–188. (<https://doi.org/10.1016/j.eupc.2004.01.005>)

---

Received in final form 19 May 2021

Accepted 13 July 2021