An enigmatic case of cardiac death in an 18-years old girl

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Abstract. – We report a case of unusual and unexplained cardiac death in an 18-years old female patient with congenital neurosensorial deafness. The fatal event was characterized by an initial syncopal episode, associated with a wide QRS tachycardia (around 110 bpm) but stable hemodynamic conditions. The patient, however, subsequently developed severe hypotension and progressive bradyarrhythmias until asystole and lack of cardiac response to resuscitation maneuvers and ventricular pacing.

Key Words:
   Cardiac death, Tachyarrhythmias, Bradyarrhythmias, Syncope.

Introduction

Unexpected (sudden) death in young people is a dramatic event which is usually related to cardiac arrhythmias, mainly ventricular tachycardia/fibrillation[1]. Ventricular tachyarrhythmias in some subjects are related to the presence of channelopathy (mainly, long QT syndromes [LQTS] and Brugada syndrome [BS])[2,3], whereas, in others, heart diseases associated with increased arrhythmic risk (e.g., right ventricle cardiomyopathy, hypertrophic cardiomyopathy)[1,4] are responsible. In a number of cases, however, no clear mechanism and cause of sudden death can be found[4]. In this article we report an unusual case of death related to severe abnormalities of the electrical activation of the heart, eventually resulting in hemodynamic compromise and death.

Clinical Case

An 18-years old girl was referred to the Emergency Department (ED) of a hospital in Rome, Italy, after a syncopal episode, occurring while she was at school. Syncope was preceded by subjective dizziness, blurred vision and chest pain, lasted, as referred by witnesses, about 20 minutes and was associated with paleness and sweating.

Clinical history revealed that the patient was born prematurely, with a Caesarean delivery, at 34 weeks of pregnancy due to the detection of fetal "tachycardia". During delivery she suffered from asphyxia needing orotracheal intubation. After birth a diagnosis of paroxysmal supraventricular tachycardia related to a Wolff-Parkinson-White syndrome was done. She was effectively treated with sotalol up to 2 years of age, when the drug was stopped. She referred sporadic episodes of dizziness and some short episodes of syncope in the previous years, but cardiological controls always showed normal clinical and electrocardiographic findings. An electrophysiologic study was proposed several times, but her parents always declined their consensus.

When the patient was 2 years old a bilateral deep neurosensory deafness was diagnosed, following the evidence of speech disorders. At age

of 17, she suffered from a diffuse bullous and erosive dermatitis, but no specific diagnosis was achieved despite skin biopsy and immunologic screening. The patient was only taking cetirizine di-chloro-hydrate because of pruritus related to the persistence of mild skin lesions at limb extremities.

On admission, the patient was conscious and only declared difficulty in image focusing. Neurologic examination revealed a mild motor deficit in her left limbs, and a rotatory nystagmus. Blood pressure (BP) was 120/80 mmHg. Routine haemato-chemical exams, including electrolyte levels, were normal. Brain computed tomography (CT), cerebral CT angiography and electroencephalogram also showed normal findings. A transient reduction of her consciousness state, associated with stereotyped movements of the arms, paleness and sweating, lasting a few minutes, was noticed after cerebral CT angiography.

Echocardiography showed normal structures and function of the heart, except for an atrial septal aneurysm without any apparent interatrial shunt, which was confirmed by transesophageal echocardiography.

The electrocardiogram (ECG), however, showed a wide QRS tachycardia (rate 120 bpm; QRS duration 160 ms) with a right bundle branch block (RBBB) pattern and right axis deviation (RAD) (Figure 1, left). An ECG performed after a few hours showed a faster tachycardia (135 bpm) with a further widening of QRS complexes (200 ms), resulting in a sinusoidal aspect of QRS-ST/T wave complexes in some leads (Figure 1, right).

In the following hours, the patient showed frequent changes in morphology and duration of QRS complexes, as well as heart rate (HR) (Figure 2), with phases of bradycardia up to 30 bpm. When visible, P waves most often appeared dissociated from QRSs, but short phases of apparent sinus rhythm, with episodes of 2nd degree atrio-ventricular (AV) block and wide QRS were noticed. A temporary pacemaker (VVI 40 bpm) was inserted with the electro-catheter in the right ventricle. The patient was transferred to the intensive care unit, where, due to the detection of hypotension (BP up to 70/40 mmHg), intravenous norepinephrine was started. BP normalized after 3-4 hour and the drug was withdrawn. In the following 12 hours the patient remained stable. The ECG showed restoration of sinus rhythm with a 1st degree AV block and an RBBB with RAD QRS pattern (Figure 3, left).

On the day after admission, the patient was transferred to another hospital in Rome, Italy, specialized in the treatment of rhythm disorders. There she maintained stable clinical conditions. Telemetric ECG monitoring showed only nocturnal phases of sinus bradycardia (up to 35 bpm) and the temporary electrode catheter was removed. The ECG continued to improve and
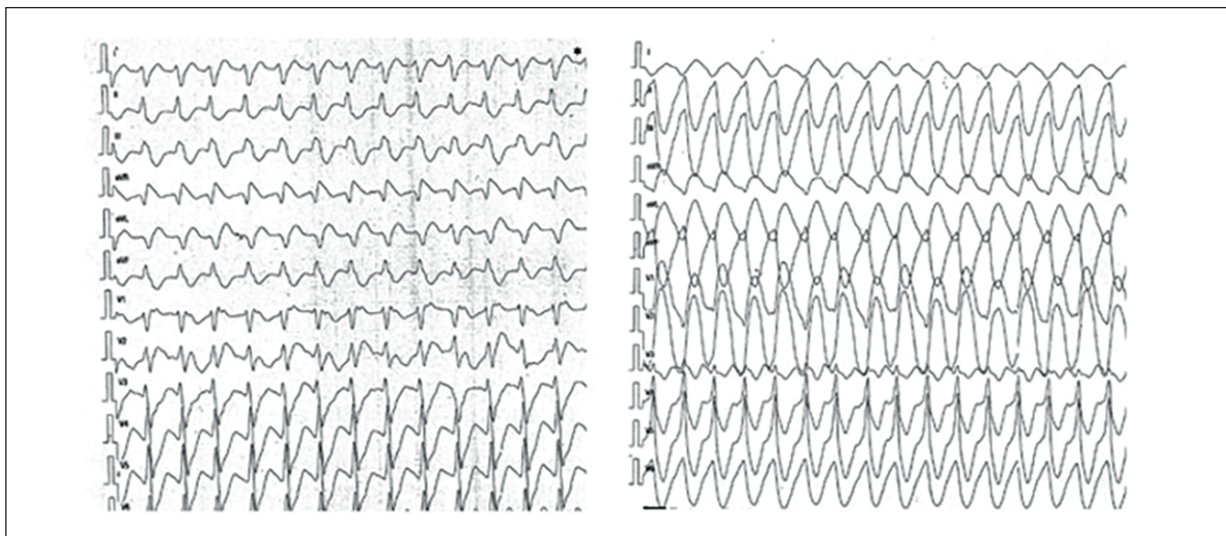

Figure 1. *Left:* ECG on admission. A wide QRS (160 ms) tachycardia (heart rate 120 bpm) is observed, with a right bundle branch block pattern and right axis deviation. *Right:* ECG recorded 2 hours after admission. A wide QRS tachycardia (QRS duration 200 ms; heart rate 135 bpm) with a right axis deviation, an undefined morphology in V1 and an almost sinusoidal aspect in some leads (e.g., DIII, aVL, V2, V6) is observed.
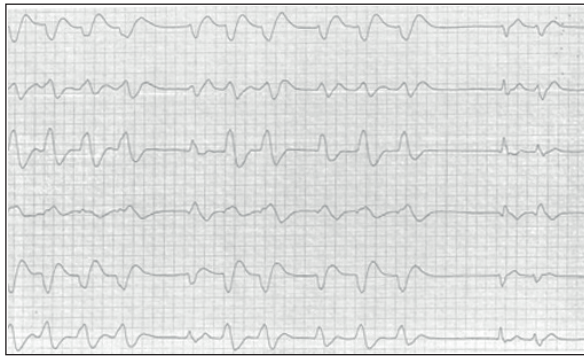
Figure 2. ECG recorded some hours after admission (peripheral leads). The ECG shows short phases of a wide QRS rhythm with right axis deviation (rate 75-85 bpm; QRS duration 200-240 ms), with small pauses (max 2.0 s) followed by tighter QRS complexes.

2 days later showed a normal sinus rhythm, with normal AV and intraventricular conduction, which remained stable throughout the remaining period of hospitalization (Figure 3, right).

Neurologic examination and a new brain CT scan were normal. Transthoracic echocardiogram and cardiac magnetic resonance confirmed normal anatomy and function of heart chambers. A maximal bicycle ECG exercise stress test (peak workload 150 W, HR 164 bpm) did not show any remarkable abnormality, although a corrected QT interval (cQT) of 506 was calculated at peak exercise. A 24-hour ECG Holter monitoring showed

no arrhythmias; mean HR was 60 bpm and the lowest, nocturnal HR 36 bpm.

The patient underwent an electrophysiologic study. No ventricular tachyarrhythmias were induced, even during fast ventricular stimulation with triple extrastimuli, both in basal conditions and during isoproterenol infusion. Similarly, no atrial tachyarrhythmias were induced with atrial stimulation under the same conditions. An AV conduction time up to 480 ms at baseline and 260 ms under isoproterenol infusion was recorded. No changes in QRS morphology were noticed during atrial pacing. A prolongation of cQT to 510 during isoproterenol was observed. Genetic testing, however, was negative for the presence of gene variants responsible for known congenital long QT syndromes.

In the hypothesis that syncope was caused by a transient rapid ventricular tachyarrhythmia, a subcutaneous automatic implantable cardiac defibrillator (ICD) was implanted (Emblem MRI, Boston Scientific, Marlborough, MA), which was programmed to deliver shock therapy for HRs higher than 170 bpm. Furthermore, a subcutaneous internal loop recorder (ILR; Confirm RX, Abbott Italia, Roma, Italy) was also implanted for long-term ECG monitoring.

Forty-two days after discharge, the patient was readmitted because of recurrence of syncope, that, again, occurred while she was at school and was associated with an ICD discharge. On admission the patient was conscious, asymptom-

Figure 3. *Left:* ECG recorded the day after admission; a sinus rhythm 75 bpm, with a 1st degree atrio-ventricular block (PR interval 250 ms) and a QRS with a right bundle branch block is observed. *Right:* The ECG, recorded 3 days after admission, shows a normal sinus rhythm with normal atrio-ventricular and intra-ventricular conduction.
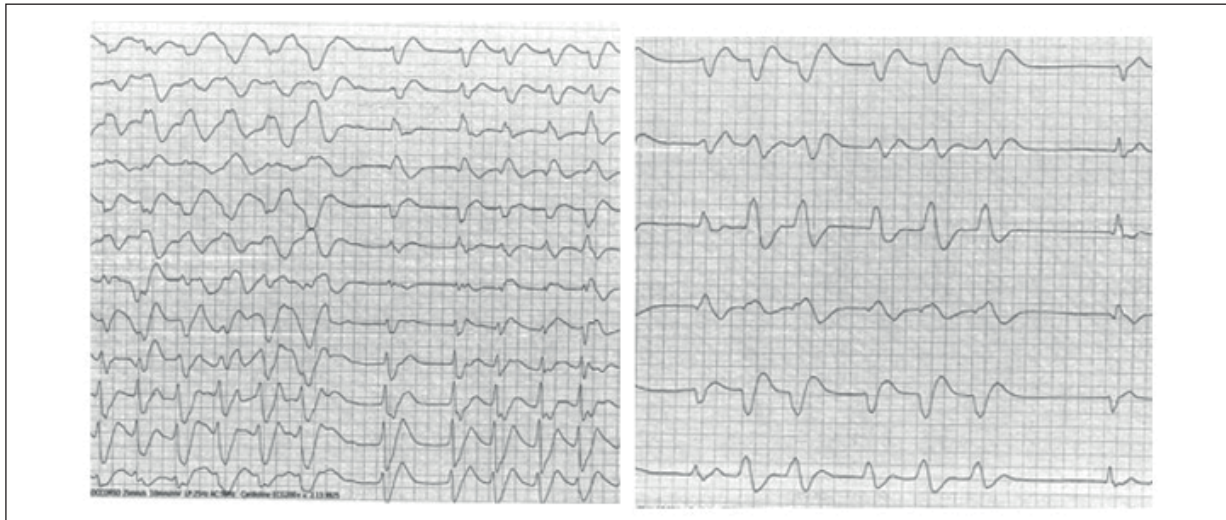
Figure 4. *Left:* The first ECG on the second admission shows a wide QRS (160 ms) rhythm similar to that of the first admission, but with a lower heart rate (84 bpm) and some short pauses (initial RR interval 1,320 ms). *Right:* Peripheral leads recorded some minutes later; a slowing down of the wide QRS rhythm, which appears irregular and with narrowing of QRS complexes after pauses, is observed.

atic and in stable hemodynamic conditions. BP was 120/80 mmHg and peripheral oxygen saturation 100%. Routine haemato-chemical exams, including electrolyte levels, were also normal. The admission ECG, however, showed the same type of wide QRS rhythm of the first episode, but with HR varying from 82 to 110 bpm and variable widening of QRS complexes (Figure 4, left). Subsequent ECGs showed increasing phases of bradycardia with irregular and polymorphic rhythms (Figure 4, right), with sporadic short phase of sinus P waves with an RBBB+RAD conduction.

The ILR activated after syncope only showed a wide QRS rhythm with HR 105-110 bpm before syncope; ICD interrogation revealed that the ICD discharge was related to an inappropriate count of T waves in HR calculation (Figure 5).

After about half an hour from admission the patient suddenly collapsed with severe hypotension (BP 70/40 mmHg) and bradycardia (HR 55 bpm), with frequent changes in HR and QRS morphology. Treatment with magnesium sulphate and catecholamines was started and transcutaneous PM plates were positioned. While no hemodynamic improvement was observed, the patient developed seizures that required treatment with diazepam and oro-tracheal intubation. A PM was inserted, but no electrical response could be obtained by stimulation of the right as well as the left ventricle. The patient eventually developed asystole and passed away.

Autopsy Study

Autopsy was performed three days after death. Heart weight and dimensions were normal. Atria, valves, left and right ventricle presented no macroscopic anomaly. A diffuse subendocardial paleness and a slight hemorrhagic area in the sinus node region were observed. Coronary arteries did not show remarkable abnormalities. Histopathologic examination of the heart and of the other organs did not find any relevant anomaly. Toxicology testing was performed on blood and urine[5], which excluded any consumption of recreational drugs.
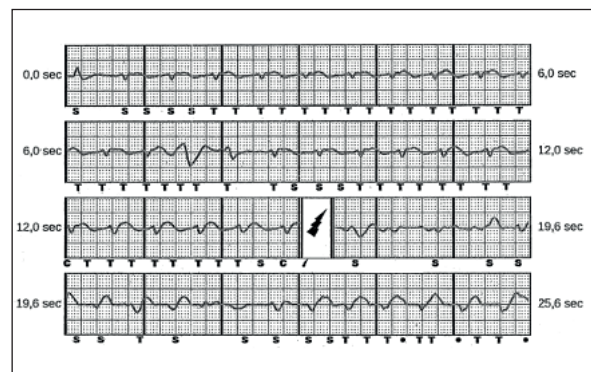

Figure 5. ECG tracing of the implanted cardioverter defibrillator (ICD). A wide QRS (160 ms) rhythm is appreciable, with a rate of 108-110 bpm; an inappropriate count of T waves by the device is appreciated (T), resulting in an inappropriate ICD discharge (arrow) with no effect on the patient's rhythm.

Table I. List of genes related with cardiac channelopathies and/or cardiomyopathies included in genetic tests.

ABCC9, ACTC1, ACTN2, AKAP9, ANK2, BAG3, CACNA1C, CACNA2D1, CACNB2, CASQ2, CAV3, CRYAB, CSRP3, DES, DMD, DMPK, DSC2, DSG2, DSP, EMD, FKTN, FLNC, GLA, GPD1L, HCN4, JPH2, JUP, KCND3, KCNE1, KCNE2, KCNE3, KCNE5, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, MYPN, NEBL, NEXN, NOS1AP, PDLIM3, PKP2, PLN, PRKAG2, RANGRF, RBM20, RYR2, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SCN10A, SGCD, SLMAP, SNTA1, TAZ, TCAP, TGFB3, TMEM43, TMPO, TNNC1, TNNI3, TNNT2, TP63, TPM1, TRDN, TRIM63, TRPM4, TTN, TTR, VCL.

Genetic Testing

After the autopsy, post-mortem genetic testing (molecular autopsy) was performed to assess for the presence of genic variants. The presence of variants was sought for genes reported associated with channelopathy and/or cardiomyopathy (Table I)[6,7], but also, due to the development of seizures during the two clinical manifestations, for genes potentially linked to epileptic syndromes (Table II)[8]. Next generation sequencing analysis on the DNA did not identify any variants of interest in the analyzed genes associated with arrhythmic or myocardial diseases, whereas detected two rare variants of genes associated with neurologic disease, both in two different subunits of voltage-dependent calcium channel complex. The first one, c.2264G>A [p.(Gly755Asp)], was detected in the CACNA1H gene, which encodes for Cav3.2 T-type calcium channel. This mutation was previously reported (CM046058) and associated with idiopathic generalized epilepsy (IGE)[9]. The second variant was found in the CACNA1I gene, c.4343G>A [p.(Arg1448Gln)], but, to the best of our knowledge, no clinical manifestations is known have hitherto been reported for this mutation. Of note, both these variants are rare (variant in the CACNA1H gene: Popmax Filtering AF: 0.0003496; variant in the CACNA1I gene: Popmax Filtering AF: 0.00006422, respectively)[10].

Family Assessment

Family history was negative for sudden death and any possible genetically transmitted cardiac or neurologic disease. Both parents and the only 13-years old sister of the patient underwent clinical investigation and an ECG that did not reveal any significant abnormality in all of them.

Discussion

To the best of our knowledge, no previous report has hitherto described a clinical syndrome, such as that observed in our young patient. The electrical cardiac disorder that affected the patient, indeed, does not seem to be framed in any of the "arrhythmic diseases" known to be responsible for syncope and cardiac death in young people[1,4].

In both syncopal episodes that led to hospital admission, the ECG showed wide QRS rhythms (QRS duration up to 200 ms), initially presenting with a slightly elevated HR (up to 110-120 bpm) and an RBBB with RAD morphology. Subsequently, however, the QRS complexes showed frequent changes in morphology and duration and the rhythm tended to become bradycardic and irregular.

Of note, on both occasions, the hemodynamic conditions of the patient on admission appeared stable, with normal BP and left ventricle function (after the first episode). However, while the clinical course of the first episode was favorable, with a spontaneous restoration of sinus rhythm and a progressive, although slow, normalization of atrio-ventricular conduction and ventricular activation, the second was suddenly complicated by

Table II. List of further 115 genes related with epilepsy disorders included in genetic tests (alphabetical order).

ADGRV1, ADSL, ALDH7A1, ARHGEF9, ARX, ATP1A2, ATP6AP2, BRD2, CACNA1A, CACNA1C, CACNA1H, CACNA1I, CACNB4, CASK, CASR, CDKL5, CELSR1, CHD2, CHRNA2, CHRNA4, CHRNB2, CLCN2, CLN3, CLN5, CLN6, CLN8, CNTNAP2, CSTB, CTSD, DNM1, EFHC1, EPM2A, FOXG1, GABRA1, GABRB3, GABRD, GABRG2, GAD2, GAMT, GATM, GNAO1, GRIN2A, GRIN2B, HCN1, HCN2, HCN3, HCN4, HTR1A, HTR1B, HTR1E, HTR1F, HTR2A, HTR2B, HTR2C, HTR3A, HTR3B, HTR3C, HTR3D, HTR3E, HTR4, HTR5A, HTR6, HTR7, KCNA1, KCNA2, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ11, KCNMA1, KCNQ1, KCNQ2, KCNQ3, KCNT1, KCTD7, LGI1, MAPK10, MBD5, ME2, MECP2, MFSD8, NHLRC1, NRXN1, PCDH19, PHOX2B, PIGA, PLCB1, PNKP, PNPO, POLG, PPT1, PRICKLE1, PRICKLE2, PRRT2, RNASEH2A, RNASEH2B, RNASEH2C, RYR2, SAMHD1, SCARB2, SCN1A, SCN1B, SCN2A, SCN3B, SCN4B, SCN5A, SCN8A, SCN9A, SENP2, SLC25A22, SLC2A1, SLC9A6, SPTAN1, SRPX2, ST3GAL3, STXBP1, SUMO1, SYN1, TBC1D24, TCF4, TPP1, TREX1, TSC1, TSC2, UBE3A, ZEB2

a shock state, progressive HR reduction and lack of response to catecholamines and resuscitation maneuvers.

Several aspects of this case remain unresolved or questionable, including the origin of the abnormal rhythms, the pathophysiologic mechanism of the electrical disorders and the cause of syncope and death.

While a ventricular origin of the wide QRS rhythms of the patient is suggested by the frequent evidence of AV dissociation and the polymorphic aspect of QRS, the RBBB pattern with RAD observed during the short phases of sinus rhythm in the acute setting and after restoration of a stable sinus rhythm, may suggest a junctional origin with delayed intraventricular conduction at least for the presenting ECG rhythm (Figures 1 and 5). Independently of the origin of the multiform rhythms, however, it seems that the ECGs suggest the occurrence of a consistent delay in the electrical ventricular activation (excitation and/or conduction), together with abnormalities in the sinus origin and AV conduction. The ECG findings, in fact, often looked like those occurring in severe hyperkalemia or class 1C antiarrhythmic toxicity[11,12], conditions both excluded in our patient, together with other toxicologic causes.

The pathophysiologic mechanism responsible for the cardiac electrical disorder of our patient remains also unknown. In young people, about 60% of sudden deaths are caused by cardiac issues, mainly inherited arrhythmogenic syndromes, i.e., channelopathies and cardiomyopathies[1-4]. In our case, congenital long QT syndromes had been excluded by genetic testing during life and the autopsy excluded any possible structural cause of death.

Albeit post-mortem genetic testing is not mandatory in these cases[6], we also performed a molecular autopsy, which failed to find any gene variants possibly responsible for cardiomyocyte ion channel dysfunction or cardiomyopathy.

Furthermore, tests of genes encoding for neuronal ion channels, potentially involved in epileptic syndromes, which might have some effects on the regulation of ion channel function also in myocardial cells, were also seemingly unremarkable. We, indeed, identified 2 rare variants of genes encoding for protein members of a subfamily of calcium channels that are present in the membrane of most excitable cells[13]. However, one of these variants, the c.2264G>A [p.(Gly755Asp)] variant of the CACNA1H gene, was previously associated with IGE[9], but our patient did not present findings of IGE and no apparent associa-

tion with cardiac disorders have previously been reported for the mutation. The second variant, found in the CACNA1I gene (c.4343G>A [p.(Arg-1448Gln)]), was not previously reported and its role in determining clinical manifestations, therefore, remains unknown.

Yet, despite the inconclusive results of genetic tests, we cannot exclude that the electrical cardiac disorder of our patient still had a genetic origin. The involved genetic abnormality, indeed, might have been missed as it might have concerned a gene, or even regulatory gene variants, not covered by our panel[7,10].

The role of genetic factors in our patient is, in fact, strongly suggested by the presence of congenital deep neurosensorial deafness. Congenital deafness, indeed, may be related to a dysfunction of ion channels of neuron membranes also involved in the regulation of cardiomyocyte electrical activity and has, in fact, been associated with gene variants responsible for both severe tachyarrhythmias (as in the Jervell-Lange Nielsen long QT syndrome)[14] and bradyarrhythmias[15,16].

Finally, what caused the syncopal episodes and the fatal event in our patient also remains debatable. Based on the ILR-recorded ECG of the last episode, indeed, it does not seem that syncope could be attributed to some severe tachy- or bradyarrhythmia able by itself to explain the loss of consciousness. While a sudden loss of atrial activity and passage to a dyssynchronous activation of the ventricles might contribute to explain the syncope through a transient fall of BP, we are tempting to speculate that the trigger mechanism of the clinical picture might have consisted in an unidentified severe neurologic dysfunction able to be simultaneously responsible for the loss of consciousness and the global electrical dysfunction of the heart[17]. The loss of consciousness might have, in fact, be related to the neurologic dysfunction itself, but, possibly, also to the induction of severe hypotension. This, indeed, occurred on both occasions, being transient and resolved by norepinephrine administration during the first admission, but persistent and possibly contributing, together with the progressive bradyarrhtyhmias, to the negative outcome of the patient during the second one. The neurologic-mediated severe disorder of the electrical activity of the heart might, on the other hand, have eventually resulted in a dramatic impairment of myocardial contractile function as an effect of a severe impairment of excitability, as also suggested by the lack of any electrical response to ventricular pacing in the final episode.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 2015; 36: 2793-2867.

2) Wallace E, Howard L, Liu M, O'Brien T, Ward D, Shen S, Prendiville T. Long QT syndrome: genetics and future perspective. Pediatr Cardiol 2019; 40: 1419-1430.

3) Pieroni M, Notarstefano P, Oliva A, Campuzano O, Santangeli P, Coll M, Nesti M, Carnevali A, Fraticelli A, Iglesias A, Grassi S, Brugada R, Bolognese L. Electroanatomic and pathologic right ventricular outflow tract abnormalities in patients with Brugada syndrome. J Am Coll Cardiol 2018; 72: 2747-2757.

4) Gray B, Ackerman MJ, Semsarian C, Behr ER. Evaluation after sudden death in the young: a global approach. Circ Arrhythm Electrophysiol 2019; 12: e007453.

5) Ripoll T, García AB, Gomila I, Heine D, Poncela JL, Sánchez N, Pérez C, García E, Hernández E, Barceló A, Busardo FP, Barceló B, Musib Research Group. Post-mortem toxicology in the diagnosis of sudden death in young and middle-aged victims. Eur Rev Med Pharmacol Sci 2019; 23: 9135-9149.

6) Campuzano O, Sarquella-Brugada G, Fernandez-Falgueras A, Coll M, Iglesias A, Ferrer-Costa C, Cesar S, Arbelo E, García-Álvarez A, Jordà P, Toro R, Tiron de Llano C, Grassi S, Oliva A, Brugada J, Brugada R. Reanalysis and reclassification of rare genetic variants associated with inherited arrhythmogenic syndromes. EBioMedicine 2020; 54: 102732.

7) Mates J, Mademont-Soler I, Fernandez-Falgueras A, Sarquella-Brugada G, Cesar S, Arbelo E, García-Álvarez A, Jordà P, Toro R, Coll M, Fiol V, Iglesias A, Perez-Serra A, Olmo BD, Alcalde M, Puigmulé M, Pico F, Lopez L, Ferrer C, Tiron C,

Grassi S, Oliva A, Brugada J, Brugada R, Campuzano O. Sudden cardiac death and copy number variants: what do we know after 10 years of genetic analysis? Forensic Sci Int Genet 2020; 47: 102281.

8) Partemi S, Vidal MC, Striano P, Campuzano O, Allegue C, Pezzella M, Elia M, Parisi P, Belcastro V, Casellato S, Giordano L, Mastrangelo M, Pietrafusa N, Striano S, Zara F, Bianchi A, Buti D, La Neve A, Tassinari CA, Oliva A, Brugada R. Genetic and forensic implications in epilepsy and cardiac arrhythmias: a case series. Int J Legal Med 2015; 129: 495-504.

9) Heron SE, Phillips HA, Mulley JC, Mazarib A, Neufeld MY, Berkovic SF, Scheffer IE. Genetic variation of CACNA1H in idiopathic generalized epilepsy. Ann Neurol 2004; 55: 595-596.

10) Grassi S, Campuzano O, Coll M, Brión M, Arena V, Iglesias A, Carracedo A, Brugada R, Oliva A. Genetic variants of uncertain significance: How to match scientific rigour and standard of proof in sudden cardiac death? Leg Med (Tokyo) 2020; 45: 101712.

11) Littmann L, Gibbs MA. Electrocardiographic manifestations of severe hyperkalemia. J Electrocardiol 2018; 51: 814-817.

12) Bhardwaj B, Lazzara R, Stavrakis S. Wide complex tachycardia in the presence of class I antiarrhythmic agents: a diagnostic challenge. Ann Noninvasive Electrocardiol 2014; 19: 289-292.

13) Durmus N, Kaya T, Gültürk S, Demir T, Parlak M, Altun A. The effects of L type calcium channels on the electroencephalogram recordings in WAG/RIJ rat model of absence epilepsy. Eur Rev Med Pharmacol Sci 2013; 17: 1149-1154.

14) Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT interval, and sudden death. Am Heart J 1957; 54: 59-68.

15) Platzer J, Engel J, Schrott-Fischer A, Stephan K, Bova S, Chen H, Zheng H, Striessnig J. Congenital deafness and sinoatrial node dysfunction in mice lacking class D L-type Ca2+ channels. Cell 2000; 102: 89-97.

16) Baig SM, Koschak A, Lieb A, Gebhart M, Dafinger C, Nürnberg G, Ali A, Ahmad I, Sinnegger-Brauns MJ, Brandt N, Engel J, Mangoni ME, Farooq M, Khan HU, Nürnberg P, Striessnig J, Bolz HJ. Loss of Cav1.3 (CACNA1D) function in a human channelopathy with bradycardia and congenital deafness. Nature Neuroscience 2011; 14: 77-84.

17) Bates MGD, Bourke JP, Giordano C, D'Amati C, Turnbull DM, Taylor RW. Cardiac involvement in mitochondrial DNA disease: clinical spectrum, diagnosis, and management. Eur Heart J 2012; 33: 3023-3033.