Journal of Interventional Cardiac Electrophysiology (2019) 56:171–172
https://doi.org/10.1007/s10840-019-00606-y

CASE REPORTS

Novel AKAP9 mutation and long QT syndrome in a patient with torsades des pointes

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Received: 22 March 2019 / Accepted: 2 August 2019 / Published online: 15 August 2019

We report the case of an 84-year-old man with hypertension, diabetes, dyslipidemia, paroxysmal atrial fibrillation, CABG, previous right nephrectomy, and post-surgical hypothyroidism, who was admitted to neurosurgery for subdural hematoma after syncope. Admission electrocardiogram showed sinus bradycardia with prolonged QT duration. Echocardiography showed left ventricular hypertrophy with severe mitral regurgitation. During hospitalization, several episodes of torsade de pointes (8 s longest duration), treated with medical therapy (magnesium sulfate iv), occurred. ECG monitoring constantly showed long QT (QTC > 570–580 ms) while no evident cause of QT prolongation was found (e.g., drugs); a dual-chamber ICD was therefore implanted. Using next-generation sequencing (NGS) and subsequent mutation confirmation with traditional capillary Sanger sequencing analysis, a possible causative non-synonymous mutation was identified in the patient's DNA: heterozygosity for AKAP9 exon 9 (c.3673C>T G>A, p.Leu1150Phe) and mutation (Fig. 1). The variants have not been previously described in the literature and have not been previously reported in the Human Gene Mutation Database (HGMD); no other possible causative mutations were found.

The in silico analysis performed using SIFT and PolyPhen modeling programs suggests that this new variant may be harmful.

AKAP9 gene is a known modifier of LQTS clinical phenotype by altering QTc duration and influencing the risk of cardiac events and the severity of the disease. In particular, variants that impair the function or expression of AKAP9-encoded Yotiao are prone to influence channel properties, explaining the phenotypic differences described in literature [1, 2]. In this perspective, our case suggests possible association between the novel mutation found and potential life-threatening complications.

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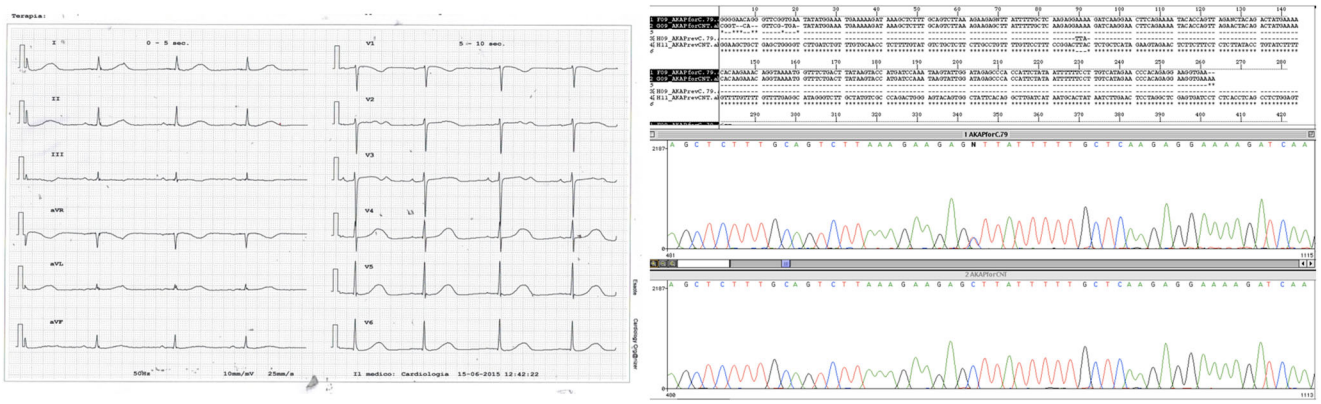

Fig. 1 Left: sinus bradycardia and prolonged QT (640 ms). Right: AKAP9 exon 9 (c.3673C>T G>A, p.Leu1150Phe) mutation

The patient was discharged 7 days after admission in therapy with metoprolol 100 mg; 2-year follow-up was uneventful and later electrocardiograms showed no significant differences.

AKAP9 (A-kinase-anchoring protein) is a protein-coding gene, located in the long (q) arm of chromosome 7 at position 21.2 (cytogenetic location: 7q21.2). The A-kinase-anchoring proteins (AKAPs) are a group of scaffolding proteins which have the common function of binding to the regulatory subunit of protein kinase A (PKA) determining the localization of protein kinase A and enzymes that regulate the PKA pathway, such as phosphatases or phosphodiesterases, and other kinases, such as PKC and PKD. In the heart, AKAP-mediated macromolecular complexes coordinate three critical ion channel proteins: the ryanodine receptor, or intracellular calcium-release channel, the L-type calcium channel, and the slowly activating delayed rectifier IK potassium channel.

References

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