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The association between GJB2 gene (producing Cx26 protein) and the ventricular storm: A case report

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OriginalArticle

Abstract

BACKGROUND: A structural heart disease or functional electrical abnormalities can cause an electrical storm.

CASE PRESENTATION: We present a young boy with an electrical storm who had no cardiac risk factors and a positive family history of sudden cardiac death. The stepwise diagnostic approach was ineffective in determining previously known causes as the origin of the electrical storm. However, whole-exome sequencing (with Next Generation Illumina Sequencing) revealed a mutation in the GJB2 (NM_004004:exon2:c.G71A:p.W24X) gene.

CONCLUSION: A mutation in the GJB2 gene, which forms the connexin 26 protein, a crucial component of the myocytes' intercalated disc of gap junction complex between the myocytes, results in an abnormal electrical cell-by-cell conductance, and, eventually, ventricular storm. General anesthesia was used to control the storm, and intracardiac pacing was fruitful in ceasing the subsequent VT storms.

Keywords: Electrical Storm; Sudden Cardiac Death; GJB2 Gene; Cx26 Protein; Case Report

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Introduction

Three or more sustained episodes of ventricular tachycardia (VT), ventricular fibrillation (VF), or appropriate shocks from an implantable cardioverter-defibrillator (ICD) within 24 hours are considered an electrical storm[1]. Despite the high proportion of structural heart diseases that cause the electrical storm, such as coronary artery disease, cardiomyopathies, congenital and valvular heart disease, it can also be induced due to inherited channelopathies, electrolyte disturbances, endocrinologic abnormalities, and other secondary causes[2]. In contrast to other studies that announced some previously known genes (e.g., SCN, KCNJ, KCNE) related to channelopathies[3], we report (1) GJB2 gene (constructing the connexin 26 protein as the crucial element in the myocytes intercalated disc[4]) as the new possible cause of the refractory ventricular storm in a boy, and (2) proper management to cease the storm.

Case presentation

On January 1st, 2020, a 17-year-old non-smoker Iranian boy with a previous history of migraine headaches as the only significant past medical history was referred to a local hospital with complaints of abrupt loss of consciousness before admission. He was born from a consanguineous marriage. The patient reported two cases of sudden cardiac death (SCD) with no known cause in his aunt and cousin (both on his father's side) at 25 and 30 years, respectively. After performing

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homeostasis of the cochlear fluids[10]; also, pathogenic variants in GJB2 are the most frequently identified causes of autosomal recessive sensorineural hearing loss[11]. However, Moscato et al. recently discovered Cx 26 expression in mammalian cardiomyocytes without explaining its function[4]. Mutations in Cx-related genes, which form the proteins of the gap junction complex, cause a decrease in the intercellular connection and, eventually, abnormal electrical cell-by-cell conductance. Some patients with Cx 43 (GJA1) mutations experienced tachycardia[10], and some studies illustrate that aging with a decrease in Cx43 leads to impaired electrical conduction and, ultimately, a predisposition for ventricular and atrial fibrillation[12,13]. Moscato et al. reported a similar modification in Cx 26 (GJB2 expression) in mammalian cardiomyocytes by aging last year[14]. However,no literature has reported the link between Cx 26 (expressed by the GJB2 gene) and cardiac ailment.

Our case had no hearing and visual impairment, which supported our hypothesis that the GJB2 expression is mostly related to myocytes and their intercalated disc rather than retinal photoreceptors and cochlear hair cells (cardiac tissue biopsy was not applicable due to patient dissatisfaction). The most likely mechanism to justify the phenotype (electrical storm) and its genotype is a defect in cell-by-cell electrical propagation. Intercellular connection disruption can be attributed to myocyte intercalated disc alteration (Cx26) due to GJB2 mutation.

After confirming the presence of a mutation in his parents, the association between the GJB2 gene and the electrical storm was confirmed. Although this report met its objectives, some limitations must be mentioned. First, some of the investigations were not feasible to perform.

There was no reason to perform angiography to rule out ischemic heart diseases (due to the patient's clinical condition, ECG, and troponin level), or normality of the heart structure was revealed via TTE and 3D-mapping (without operating the CMR). Additionally, a cardiac biopsy was not performed due to the patient's discontent. Nonetheless, appropriate alternative workups eliminated the possibility of error in the final result. Second, his relatives (except his parents and sibling) were unavailable for genetic testing. Third, it was impossible to examine the association of the GJB2 gene separately with the electrical storm (without the effect of USH2A); therefore, further research is recommended to be conducted in this regard.

Conclusion

This report found that an alteration in the intercalated disc (Cx 26) due to GJB2 gene mutation causes electrical conduction impairment and, eventually, ventricular storm. Thus, it can be a new probable reason for channelopathy that should be considered in a stepwise diagnostic approach and confirmed by genetic studies. After recognizing the GJB2 gene as the cause of the ventricular storm, intracardiac pacing should be applied to cease it.

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Conflict of interest

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Author's Contributions

Study concept and design: MH.N., Z.E., and H.B.; data collection and interpretation: AR.A, M.M, MR.H., and M.B.; drafting of the manuscript: MR.H and H.B.; critical revision of the manuscript for important intellectual content: MH.N., and Z.E.; All authors have read and approved the manuscript.

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