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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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a standardized approach to syncope, an electrocardiogram (ECG) revealed ventricular tachyarrhythmia as the possible cause of a syncopal attack, and the patient was transferred to our tertiary center for ICD insertion after stabilization. His vital signs on admission were 105/70 mmHg blood pressure, 120 beats per minute (BPM) heart rate, 22 breaths per minute respiratory rate, and 36.7°C temperature. The physical examination was unremarkable. He has discharged with propranolol 10mg twice daily following the ICD insertion (Figure 1). After two weeks, he was readmitted to the hospital with a discharged ICD generator due to recurrent episodes of shock release. In 24 hours, an electrical storm was diagnosed regarding 16 appropriate ICD therapies for ventricular tachyarrhythmia. Transthoracic echocardiography (TTE) was performed to rule out structural heart disease and revealed normal biventricular size and function (ejection fraction of 55%). The primary cause was thought to be functional electrical abnormalities. After laboratory data ruled out electrolyte and endocrinology abnormalities (Table 1), ion channelopathies were investigated. Although the baseline ECG (Figure 2A) showed a 'J wave,' the patient experienced episodes of torsades de point (Figure 2B) during the cardiac care unit course; thus, pharmacological provocation tests with procainamide and epinephrine were performed to diagnose J wave syndrome, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. Provocative drug tests revealed no causes of the storm. The related channelopathies genes were examined through genetic analysis. Surprisingly, whole-exome sequencing (using Next Generation Illumina Sequencing) did not reveal any pathogenic mutations related to ion channelopathies; nevertheless, two known (bi-allelic) heterozygous mutations in USH2A (NM_206933:exon29:c.C5836T:p.R1946X) and GJB2 (NM_004004:exon2:c.G71A:p.W24X) genes were detected (Figure 3). After ICD reprogramming and medical treatment with amiodarone, beta-blockers, verapamil, and magnesium failed to control refractory VT/VF storm, the patient was taken to the catheterization laboratory for radiofrequency ablation. No arrhythmic focus was observed in epicardial and endocardial 3-dimensional mapping for ablation. We were forced to use deep sedation and general anesthesia to control the electrical storm. Empirical testing of the intracardiac pacing at a rate of 90 bpm was beneficial in ceasing the subsequent VT storm.

Follow-up visits to the outpatient clinic have revealed that the patient is in good health, with no previously experienced syncope and palpitation events and a normal ECG (Figure 2C).

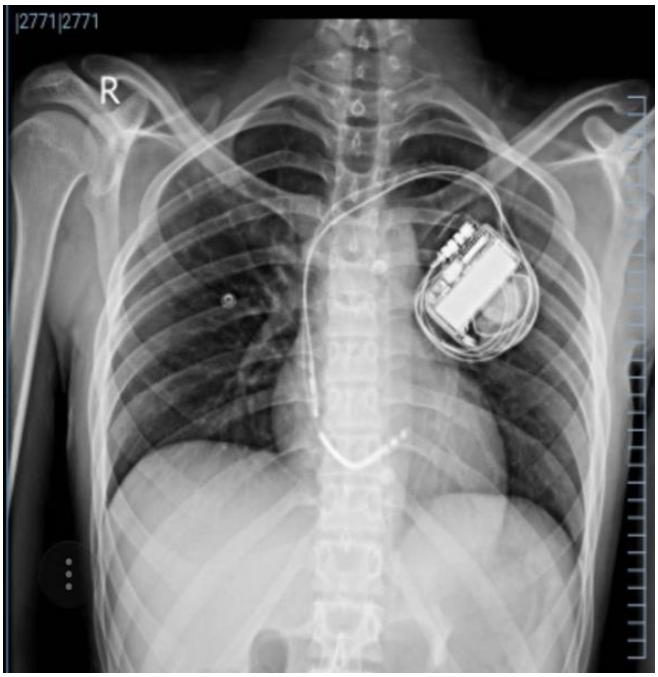

Figure 1. ICD has been inserted in the proper place

Table 1. Laboratory analysis

Laboratory parameters	Result	Normal range
Troponin I (ng/mL)	0.014	Less than 0.02
White cell blood count (10^3/µL)	4.5	4-10
Hemoglobin (g/dL)	12.1 **	13.5-18
Platelet count (10^3/µL)	165	150-450
Prothrombin time (sec)	13.6	12-14
Partial thrombin time (sec)	37	25-40
INR (Index)	1.01 *	0.9-1
C-reactive protein (mg/L)	2	Less than 6
ESR (mm/hr)	3	Less than 15
Fasting blood sugar (mg/dL)	86	Less than 99
Sodium (mEq/dL)	140	136-145
Potassium (mEq/dL)	3.8	3.5-5.5
Calcium (mg/dL)	8.7	8.6-10.3
Magnesium (mg/dL)	2	1.8-2.6
Phosphorus (mg/dL)	3.3	2.7-5.5
Blood urea nitrogen (mg/dL)	14	8-20
Creatinine (mg/dL)	0.8	0.7-1.4
SGOT (mg/dL)	24	0-40
SGPT (IU/L)	7	1-40
Alkaline phosphatase (mg/dL)	268	80-306
Albumin (mg/dL)	4.3	3.5-5.4
Total bilirubin (mg/dL)	0.93	0.1-1.2
Direct bilirubin (mg/dL)	0.14	0.1-0.3
T3 RIA (ng/dL)	138	up to 20 years : 90-260
T4 RIA (µg/dL)	8.42	adults : 4.50-13.00
TSH IRMA (mIU/L)	0.84	0.17-5.23
Triglyceride (mg/dL)	217 *	50-150
Cholesterol (mg/dL)	163	150-200
HDL-CH (mg/dL)	36	35-80
LDL-C (mg/dL)	88	30-155
Uric acid (mg/dL)	5.9	3.6-8.2

Discussion

We reported a young boy with no cardiac risk factors and a positive family history of SCD presented with an electrical storm. The stepwise diagnostic approach was ineffective in determining the causes of the electrical storm, whether it was structural heart disease, ion channelopathies, or other previously known causes. The GJB2 (Cx 26) gene mutation responsible for the current electrical storm was identified, and the storm was terminated using general anesthesia and intracardiac pacing.

Our case was extremely challenging and complicated. Initially, rapid screening was accomplished through 12-lead ECG, laboratory analysis, and TTE. Laboratory parameters revealed no evidence of electrolyte disturbances, infections, hyperthyroidism, intoxication, and substance abuse. TTE revealed no evidence of heart failure, valvular heart disease, or wall motion abnormalities. Due to a negative history of chest pain and dyspnea, no elevated cardiac biomarkers, and a lack of ischemic changes in the ECG, the patient had no indications to undergo coronary angiography and revascularization; additionally, atherosclerosis and coronary artery disease in a 17-year-old boy were uncommon.

There was no reason to perform cardiac magnetic resonance due to the lack of structural heart disease clues in TTE. Also, the lack of scar formation structure in epicardial and endocardial 3-dimensional mapping ruled out structural heart

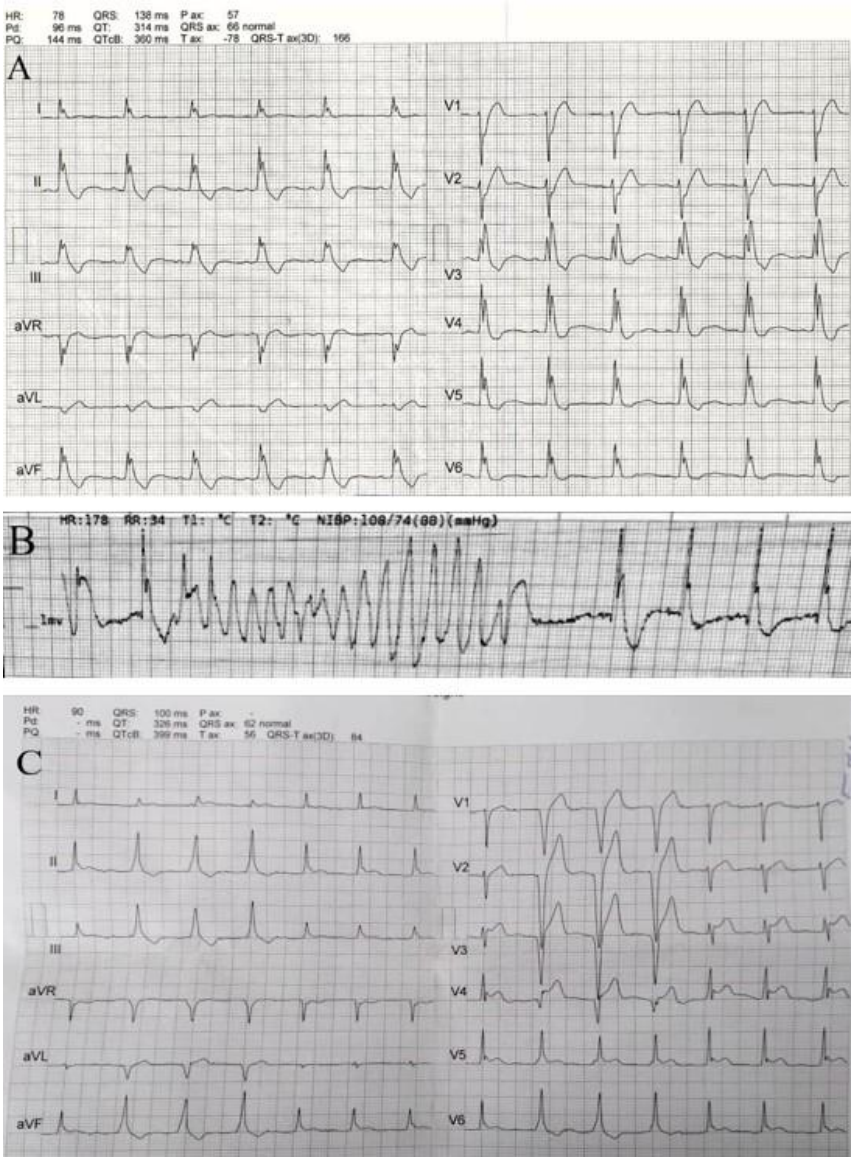

Figure 2. Electrocardiogram on admission with J wave and normal QTc (A), episodes of torsades de point at another time (B), and final ECG after management via intracardiac pacing (C).

diseases like ARVC. The primary cause remained inherited genetic abnormalities. The most perplexing aspect of this case was that the ECG, containing the normal QTc interval and J wave, favored J wave syndrome, such as Brugada syndrome. Termination of the electrical storm via intracardiac pacing was consistent with long QT syndromes, according to the guideline[5]. Contrary to all these interpretations, the pharmacological provocation test yielded no results, and whole-exome sequencing revealed mutations in the USH2A and GJB2 genes. *Usher syndrome* is a genetic syndrome characterized by visual impairment due to retinitis pigmentosa and varying degrees of deafness with or without vestibular involvement[6]. The basement membrane protein Usherin, encoded by the USH2A gene, has been identified in retinal photoreceptors and cochlear hair cells[7].

Although, in Usher syndrome, Usherin is not affected, Bhattacharya et al.[8] suggested that Usherin could be present in other organ tissues such as the spleen or testis. However, they firmly declined the possibility of USH2A presentation in the cardiac, smooth muscle. Since no study has shown that the USH2A gene is expressed in heart tissue, it is impossible to assume this gene is the cause of the ventricular storm.

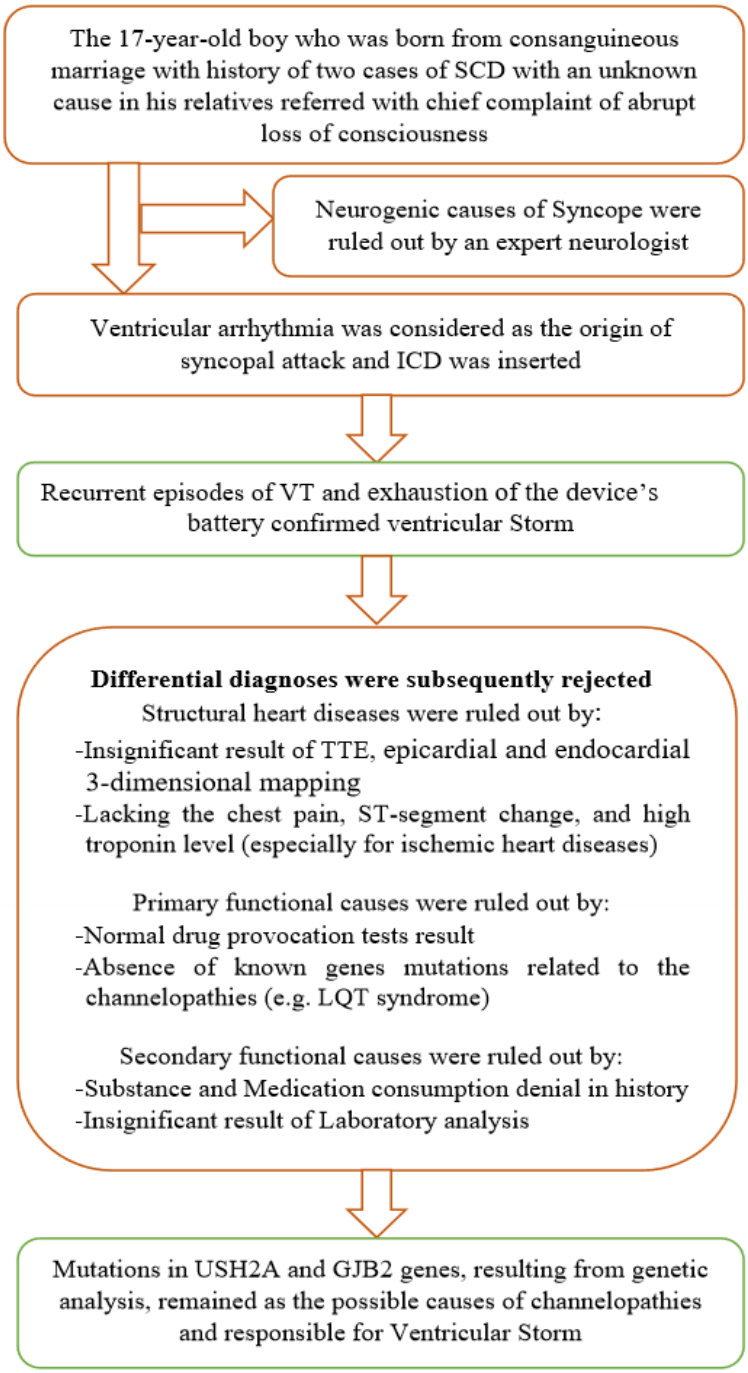

Figure 3. Stepwise diagnostic approach flow chart

Gap junctions mediate direct communication between two cells, such as transmembrane signaling via ion exchange between adjacent cells. A gap junction is formed as a channel constructed by two docked connexons of opposing cells, each containing six connexins (integral membrane protein) subunits. Connexin (Cx) proteins, essential elements for communication, are expressed in various tissues. In the heart, these channels primarily attune depolarization of the cardiac myocytes, allowing these cells to function as syncytium[9]. Cx43 (expressed by GJA1), Cx40 (GJA5), and Cx37 (GJA4) participate in forming intercalated disks (gap junctions) in the ventricle, atrium, and vascular tree, respectively, whereas Cx 26 (GJB2) used to be known to be expressed in the inner ear and is responsible for

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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