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Genetic variants in post myocardial infarction patients presenting with electrical storm of unstable ventricular tachycardia

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ABSTRACT

Electrical storm (ES) is a life threatening clinical situation. Though a few clinical pointers exist, the occurrence of ES in a patient with remote myocardial infarction (MI) is generally unpredictable. Genetic markers for this entity have not been studied. In the present study, we carried out genetic screening in patients with remote myocardial infarction presenting with ES by next generation sequencing and identified 25 rare variants in 19 genes predominantly in RYR2, SCN5A, KCNJ11, KCNE1 and KCNH2, CACNA1B, CACNA1C, CACNA1D and desmosomal genes - DSP and DSG2 that could potentially be implicated in electrical storm. These genes have been previously reported to be associated with inherited syndromes of Sudden Cardiac Death. The present study suggests that the genetic architecture in patients with remote MI and ES of unstable ventricular tachycardia may be similar to that of Ion channelopathies. Identification of these variants may identify post MI patients who are predisposed to develop electrical storm and help in risk stratification.

1. Introduction

Sudden Cardiac Death (SCD) in patients with remote myocardial Infarction (MI) is due to the occurrence of malignant ventricular arrhythmias, the most common being 'Ventricular Tachycardia' (VT). Few patients in this subset during their natural history develop Electrical storm (ES) which is defined as "Three or more distinct episodes of ventricular tachycardia (VT)/ventricular fibrillation (VF) within 24 h, requiring the intervention of the defibrillator (anti-tachycardia pacing or shock)" [1]. The timing and occurrence of ES is unpredictable. It is a life threatening cardiac emergency with a reported incidence of 10–28% and an in-hospital mortality of 60–70% [2]. Current knowledge on genetic markers related to ventricular arrhythmias in post MI patients with LV dysfunction is very limited. This paper summarizes the genetic variations identified in patients with remote myocardial infarction presenting with ES of unstable VT by next generation sequencing.

2. Material and methods

2.1. Patient population

Consecutive patients with Left ventricular dysfunction (LVEF≤ 35%), underlying remote myocardial infarction (>1 year), presented to our institute with electrical storm and hemodynamically unstable monomorphic VT, were included in the study. Patients with ES and other underlying substrates and those with stable VT or VF were not included. Study patients were managed by standard institutional protocol involving mechanical ventilation, hemodynamic support, anti-arrhythmic medications, radiofrequency ablation and stellate ganglionectomy as indicated. The management protocol and clinical outcomes of these patients have been detailed in a separate manuscript [3].

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2.2. Genetic analysis by next generation sequencing

The saliva samples were collected for genetic analysis after taking informed written consent from the patients and genomic DNA (g DNA) was extracted using Q IA amp DNA mini kit (Quiagen, Hilden, Germany) according to the manufacturer's instructions. Patient's genomic DNA was sequenced using TruSight Clinical Exome panel (Illumina, San Diego, CA, USA) that contains genes associated with known inherited diseases by Strand Life sciences, Bengaluru, India. Of these, 145 genes associated with arrhythmias and coronary artery disease was assessed. The input DNA was first converted into adaptor tagged index using Nextera DNA library preparation protocol (Illumina, San Diego, CA, USA) followed by adapter ligation and enrichment. Target library was amplified using limited cycles PCR (ABI9700, Life Technologies) steps and sequenced using Miseq platform (Illumina, San Diego, CA, USA) according to the manufacturer's instructions.

The trimmed FASTQ files were generated using MiSeq Reporter from Illumina. The reads were aligned against the whole genome build hg19 using STRAND NGS v1.6 (http://www.strand-ngs.com/) which is an integrated platform that provides analysis, management and visualization tools for NGS data and interpreted using StrandOmics (a proprietary clinical genomics interpretation and reporting platform from Strand Life Sciences). The variants identified were classified according to the ACMG (American Society of Medical Genetics and Genomics) recommendation for standards for interpretation and reporting of sequence variations [4].

3. Results

There were 10 patients (9 males &1female) with a mean age of 59.92 ± 7.6 years. All patients had myocardial infarction, 101.4 ± 78.7 months prior to development of ES. The mean LVEF was $33.17 \pm 9.45\%$. The clinical and demographic profile of these patients is summarised in Table 1. Genetic analysis was performed in all the ten patients by next generation sequencing (NGS) of SCD panel, which screened for genes involved in arrhythmias and sudden cardiac death. (Table 2). Of the ten patients, two did not reveal any variation. In the remaining 8 patients, 25 rare variants were observed in 19 genes, predominantly in *RYR2, SCN5A, KCNJ11, KCNE1 and KCNH2, CACNA1B, CACNA1C, CACNA1D* and desmosomal genes - *DSP* and *DSG2*. These are essentially cardiac ion channel genes and previous studies have established their role in LQT and other arrhythmic disorders. The clinical significance of these rare variants as per *ClinVar* database ranged from being benign to uncertain clinical significance. However, In-silico tools predict some of these variants to be disease causing (Table 3).

Of the 25 rare variants, pVal125Leu of *SCN5A* was found to be pathogenic while p.Val30Met of DSP and p.Thr1107Met of RYR2 revealed mixed interpretations of pathogenicity.

In addition, variants of unknown significance were found in *JUP, JPH2, VCL, MYPN, NPPA, APOB* genes with possible, but not definite implications in the risk for life threatening arrhythmia events in coronary artery diseases, Brugada syndrome and atrial fibrillation respectively. Table 3 gives the list of all the variants identified.

4. Discussion

This report summarizes our findings of genetic analysis in ten patients with post myocardial infarction having LV dysfunction presenting with electrical storm of unstable VT. This critically ill cohort comprised of patients with an uncommon but clinically relevant entity and the genetics of such a patient cohort have not been studied earlier. To ensure homogeneity of the phenotype, we selected patients with a specific substrate presenting only with monomorphic unstable VT. We used next generation sequencing (NGS) which allows for large-scale and rapid assessment of genes, though it also carries the disadvantage of revealing several variants of unknown significance, a difficult task to decode clinically. 145 genes of the sudden cardiac death panel were screened by NGS which identified 25 variations in 19 genes.

4.1. Genetic variants of pathological significance

Of the 25 rare variants, a pathogenic missense variant p.Val125Leu in SCN5A was observed in a 69 year old male. This heterozygous missense substitution lies in the cytoplasmic topological domain (1–126 residues) and alters a conserved residue of the protein. It has been reported as a rare variant with an allele frequency of 0.2% in the South Asian population. *ClinVar* database reports the clinical significance of this variant as *'pathogenic'* (RCV000058596.2) with respect to congenital long QT syndrome. Three other variants viz *His558Arg, c.1141-3C>A, Asp819Asp* of SCN5A gene were observed in a male patient aged 60 years who showed recurrent VT. These were earlier reported as a haplotype in affected members of brugada family [5]. *His558Arg* alters a conserved residue in the sodium channel inter-domain cytoplasmic linker and has been reported to modulate the effect of arrhythmia-causing *SCN5A* variants. These polymorphisms may be used as genetic markers within a haplotype block in which they are linked to a functionally relevant gene variant [6].

SCN5A gene encodes the alpha subunit of the cardiac voltage-gated sodium channel which plays a crucial role in cardiac excitability and conduction velocity of the electrical impulse within the heart. *SCN5A* mutations so far described have been linked to sudden cardiac death associated with a number of inherited arrhythmic syndromes such as Brugada syndrome (BrS) and other cardiac arrhythmias like isolated cardiac conduction defects, atrial fibrillation, long QT syndrome (LQT3), left ventricular non-compaction (LVNC) and with a risk of pro-arrhythmia following usage of sodium channel blockers [7]. *SCN5A* mutations accounts for approximately 10% of LQTS cases with the triggering factors associated with

Table 1
Clinical profile of patients.

Patient no	Age	Gender	LVEF	Clinical presentation	No of VT morphologies
1	58	M	35	Recurrent VT	2
2	62	M	30	Recurrent ICD shocks	4
3	68	M	25	Recurrent ICD shocks	2
4	71	M	30	Recurrent VT	4
5	60	M	30	Recurrent ICD shocks	
6	64	M	30	Recurrent ICD shocks	6
7	63	F	18	Recurrent VT	5
8	60	M	25	Recurrent VT	2
9	71	M	32	Recurrent ICD shocks	4
10	69	M	38	Recurrent ICD shocks	3

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