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VT storm in remote myocardial infarction: Is it all in the genes?

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In this issue, Rangaraju et al. presents a study in which rare genetic variants were detected in patients with remote myocardial infarction (MI) presenting with electrical storm [1]. The authors need to be congratulated on conceiving this novel study and studying a subset of patients who are difficult to treat and have a high mortality rate. The authors carried out genetic screening in 10 patients with remote MI who presented with electrical VT storm. These patients underwent next generation sequencing of a part of their exomes. Exomes constitute coding regions in the DNA which are responsible for production of proteins [2]. The patients were tested for 145 genes associated with arrhythmia which were studied by direct genotyping.

The results revealed 25 rare genetic variants in 8 patients. 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. Variants of unknown significance were found in other genes. Coding sequence variants if synonymous would cause no phenotypic consequences. They have to be non-synchronous in order to cause alteration in the protein it codes [2,3]. Most of these polymorphisms were rare ones with an allelic frequency of <0.5%.

Does this imply that these patients with genetic variants have susceptibility to develop VT storm in particular clinical conditions? The answer lies some where in between a complete yes and no.

Ventricular arrhythmias in the setting of remote MI are complex phenomenon [4]. These are initiated by multiple reentrant circuits in the border zone of the scar formed due to MI. Most of these scars mature and turn quiescent in a 5–6 week period following an MI [5]. The scar though persistent and quiescent would still undergo dynamic changes due to remodeling which would result in changes in scar pattern and anatomy. The border zone around the scar can be influenced by modifiers like ischemia burden, variations in hemodynamics like blood pressure, heart rate and autonomic activity, change in electrolytes, drug interactions and lastly genetic profile [3,6].

For purposes of genetic interpretation, MI and scarring tends to be discrete phenotypes while electrolyte levels, blood pressure levels, autonomic activity, ischemia etc. tend to be quantitive phenotypes [3,4]. Unlike Mendelian disorders where the phenotype is a manifestation of a single gene mutation, presence of VT storm in patients of remote MI would be tend to be a polygenic disorder influenced by polygenic variants and non-genetic factors [2,4].

However, the study by Rangaraju et al. still throws up interesting results. The authors detected a pathogenic missense variant P.Val12Leu in SCN5A in a 69 year old male. Its association with congenital long QT syndrome type 3 is well known [7,8]. A missense variant tends to be less deleterious than nonsense and frameshift variants, thereby causing sub-clinical phenotype [2,3]. This patient would have had a sub-clinical form of long QT, which would have some role to play in genesis of the VT storm. Other reasons for sub-clinical form of the disease are incomplete penetrance and effect of modifier genes and environment [3]. This would be similar to detecting sub-clinical forms of congenital long QT syndrome in patients with acquired torsades de pointes. Itoh et al. found that 28% of acquired long QT subjects have mutations in congenital long QT genes [9]. Hu et al. also found genetic predisposition to post-MI prolongation of QT interval and torsades (in days 2–11 following the event) [10]. They found that 6 of the 8 patients had same polymorphism in the KCNH2 genes as seen in patients with congenital long QT interval. In the current article by Rangaraju et al., the clinical condition was remote MI unlike an acute MI. However, subclinical ischemia and borderline prolonged QT intervals (with dynamic changes in repolarization reserve) may still contribute in some of the patients making them susceptible to arrhythmias.

In patients with remote MI, the substrate tends to play a larger role in arrhythmias compared to the role of the ischemia. Ion channel and gap junction remodeling with reduced Connexin43 (Cx43) expression in border zones of the scar would reduce intercellular coupling and can cause slow conduction conducive for re-entry [4]. This is definitely determined to a certain extent by genes which are responsible for expression of Cx43. In an animal study carried out in pigs, Cx43 gene therapy delivered by an adenovirus vector in pigs with healed/remote MI resulted in overexpression of Cx43 and completely eliminated inducible VT [5]. This would suggest that genetic contribution in formation of the arrhythmic substrate and also a role for future genetic therapy.

The other gene variants detected in the study were reported as mixed interpretation of pathogenicity and variants of unknown significance. A variety of in-silico tools aid in the interpretation of sequence variants detected by these tests. These are useful and advised to be applied for interpretation in Mendelian (single gene) disorders. The ACMG cautions against interpretation of variant which are observed in multigenic non-Mendelian complex disorders [11]. Variants of low frequency as seen in this study need to further studied by family-based, extreme-phenotype and

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population-based studies to establish a relationship between the genotype and the phenotype [3].

The authors need to be congratulated on carrying out this study. However there are a few caveats that remain with regards to this study as mentioned by the authors. The number of patients tested was only 10 (the subset of such patients is not very common) and there is no case-control group to compare these genetic variations. Association of these gene variants with disease phenotype would need further research. The disease is a complicated one to be explained by simplistic mechanisms and we need to acknowledge this complexity. We need to carry out further studies to understand the mechanisms and genes responsible for these arrhythmias.

Disclosures

Nil.

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