

## Multifocal Ectopic Purkinje-Related Premature Contractions: Sorting the Wheat From the Chaff

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### **Conflict of Interest Statement**

The author reports no relationships that could be construed as a conflict of interest

Even in the modern age, new diseases continue to be reported. Some—for example, infectious disorders—are caused by previously undetected or unknown noxious agents or pathogens, but others are discovered by careful clinical observation and pattern recognition; the new entity of multifocal ectopic Purkinje-related premature contractions (MEPPC) caused by mutations in the gene SCN5A is one such condition.

Voltage-gated sodium channels are responsible for the inward sodium current ( $I_{Na}$ ) in excitable cells and initiate an action potential by inducing a fast depolarization of the cell membrane [1,2]. Sodium channels consist of two different subunits: the  $\alpha$ -subunit that constitutes the voltage-gated sodium-selective aqueous pore, and the  $\beta$ -subunits that participate in channel regulation and localization. Nav1.5 is the voltage-gated sodium channel protein isoform expressed specifically in atrial and ventricular myocytes and Purkinje fibres. Once a cell is electrically stimulated by a current from adjacent cells, the Nav1.5 channels open, causing a rapid influx of sodium ions into the cell and depolarization of the cell membrane. Nav1.5 is inactivated by two physically distinct inactivation processes—fast and slow—with only the fast coupled directly to activation.

Nav1.5 is encoded by the SCN5A gene located on chromosome 3p21. Mutations in SCN5A cause Long QT syndrome, Brugada Syndrome, sick sinus syndrome (SSS), progressive cardiac conduction disease (PCCD) and atrial fibrillation. They are also reported in association with dilated cardiomyopathy (DCM) [3]. Pathogenic SCN5A mutations are usually inherited as an autosomal dominant trait with incomplete penetrance, but recessive homozygous or compound heterozygous mutations are described. The phenotypic diversity associated with SCN5A mutations is partly explained by the various biophysical consequences of individual mutations on channel function that can lead to loss- or gain-of-function as well as other environmental and genetic factors.

Over the past decade, a small number of SCN5A mutation carriers that have frequent premature ventricular complexes arising from the Purkinje system (4,5,6,7,8) has been reported (MEPCC). Studies of the first mutation to be characterised—R222Q—have shown that it causes a negative shift in both voltage dependence of activation and

inactivation—that is, both a gain- and loss-of-function but with a net increase and shift in window current (a range of potentials where inactivation is not complete and overlaps with activation thereby creating a current). The mutation causes delayed repolarisation in Purkinje cells that is often worse at rest, a phenomenon also observed in mutation carriers.

Age at diagnosis for MEPPC varies but is often before the age of 30 years. DCM is a frequent association and affected individuals often have conduction abnormalities, atrial fibrillation and atrial ectopic beats. Some reports suggest that ectopic activity can be controlled with quinidine, amiodarone and flecainide.

In this edition of *the Journal*, Calloe and colleagues [9] describe a typical MEPPC phenotype associated with another SCN5A mutation, G213D which has been previously reported in DCM [10]. Electrophysiological studies of wild type and mutant channels expressed in CHO-K cells revealed a gain-of-function phenotype in which sodium channels are activated at lower voltages compared to wild type, thereby leading to hyper-excitability of the cardiac cells. There are several lessons that can be learnt from this paper, but for clinicians perhaps the most important is that diagnosis of what might seem to be a somewhat esoteric condition is in fact based on the recognition of a remarkably small number of characteristics: a family history, frequent ectopy (of Purkinje origin) and DCM. By establishing the clinical phenotype, the value of subsequent molecular testing is enhanced as it not only aids interpretation of identified sequence variants, but also informs family counselling, cascade genetic testing of relatives and the formulation of a treatment plan.

Of course, unanswered questions remain. Some reports have suggested MEPPC can be associated with sudden cardiac death, and more work needs to be done on stratifying risk and understanding the role (if any) of prophylactic implantable cardioverter defibrillators. The mechanism of DCM is also unresolved. Several pathophysiological mechanisms have been proposed to explain the association between SCN5A mutations and left ventricular dysfunction, including frequent arrhythmia, alterations in intracellular  $\text{Ca}^{2+}$  concentration and cellular acidification. It has also been suggested that disruption of protein-protein interactions at locations such as the intercalated disc might trigger downstream cascades that induce structural changes. Further work to understand

the association will hopefully guide approaches to therapy in the future.

Time to muse on rare diagnoses is a luxury that few doctors can afford in busy everyday clinical practice, as the need for management of an immediate problem causing symptoms or endangerment takes precedent. When the clinical problem is an arrhythmia, diagnostic pathways focus on its anatomical origin, frequency and potential adverse complications. For most individuals, this pragmatic approach leads to effective therapy and probably does little harm. However, failure to suspect and diagnose rare aetiologies such as MEPPC could result in inappropriate management and a failure to diagnose a genetic disease with all the potential ramifications for relatives. As genetic testing becomes a mainstream activity, it is likely that diseases currently thought to be rare will in fact be more commonplace. The universal hope is that their recognition will lead to a more bespoke approach to management with improved long term outcomes.

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