Review Article

Channelopathies - Emerging Trends in The Management of Inherited Arrhythmias

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Abstract

In spite of their relative rarity, inheritable arrhythmias have come to the forefront as a group of potentially fatal but preventable cause of sudden cardiac death in children and (young) adults. Comprehensive management of inherited arrhythmias includes diagnosing and treating the proband and identifying and protecting affected family members. This has been made possible by the vast advances in the field of molecular biology enabling better understanding of the genetic underpinnings of some of these disease groups, namely congenital long QT syndrome, catecholaminergic polymorphic ventricular tachycardia and Brugada syndrome. The ensuing knowledge of the genotype-phenotype correlations enables us to risk-stratify, prognosticate and treat based on the genetic test results. The various diagnostic modalities currently available to us, including clinical tools and genetic technologies, have to be applied judiciously in order to promptly identify those affected and to spare the emotional burden of a potentially lethal disease in the unaffected individuals. The therapeutic armamentarium of inherited arrhythmias includes pharmacological agents, device therapies and surgical interventions. A treatment strategy keeping in mind the risk profile of the patients, the local availability of drugs and the expertise of the treating personnel is proving effective. While opportunities for research are numerous in this expanding field of medicine, there is also tremendous scope for incorporating the emerging trends in managing patients and families with inherited arrhythmias in the Indian subcontinent.

Keywords: Channelopathies, Inherited Arrhythmias

Introduction

Inherited arrhythmias or cardiac channelopathies are primary electrical diseases of the heart characterized by dysfunctional ion channels which in turn lead to a spectrum of clinical manifestations ranging from complete lack of symptoms to life-threatening arrhythmias and sudden cardiac death (SCD) as the first symptom. In spite of their relative rarity they have come to the forefront as a group of potentially fatal but preventable cause of SCD in children

and (young) adults.

Congenital long QT syndrome (LQTS) is the inherited arrhythmia syndrome that has been studied in detail and whose genotype-phenotype correlations have largely been unraveled. Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are currently intensively studied and the rarer entities like short QT syndrome, early repolarization syndrome, familial atrial fibrillation, premature cardiac conduction disease and idiopathic ventricular fibrillation are still largely under the surface. [1] The latter is mainly due to the rarity of these diseases precluding sufficient patient numbers to draw meaningful conclusions.

The mode of inheritance is predominantly autosomal dominant; however, autosomal recessive and sporadic mutations, which subsequently transmit as an autosomal dominant trait, are not uncommon. Comprehensive management of inherited arrhythmias includes diagnosing and treating the proband and identifying and protecting affected family members. [2] It has been shown that this can be achieved effectively with 70-80% of presymptomatically tested family members, after a couple of years of follow-up on treatment. [3] This review aims to throw some light on the emerging trends and their clinical applicability in managing individuals and families with inherited arrhythmia syndromes, highlighting the focus areas for cardiogenetics in the Indian subcontinent.

Diagnostic evolution

Our understanding of genetic causation, of the correlation between dysfunctional mutant genes and clinical manifestations, and of the various factors that influence disease expression has grown in leaps and bounds in the last couple of decades.

Understanding the genetic underpinnings

The diagnosis of inherited arrhythmias has evolved mirroring the advances in the field of human genetics and genomics itself. [4] The hundreds of genetic aberrations that we now associate with this group of diseases is staggering; especially considering the fact that it was not long ago that the first causative genes for LQTS were discovered. [5] It is also interesting to note how the gap between basic and clinical science, or in other words between geneticists, primary care physicians and electrophysiologists, seems to close rapidly and an interdisciplinary team approach to patient care has emerged in this field of cardiology. [2]

Today, not only are medical professionals more aware and increasingly efficient in picking up the individual and familial manifestations of these diseases, but are also better equipped with the diagnostic and therapeutic armamentarium necessary to confirm clinical suspicion and deploy appropriate treatment. The timely and adequate management of affected patients consists of two arms; firstly, a high level of suspicion and clinical astuteness to recognize the phenotype in an individual who may initially present to the emergency care team or to any other medical specialty, and secondly, a well-coordinated cardiogenetic team to provide genetic counseling and testing, to interpret the genetic data and to carry out family screening, and to make individualized therapeutic and follow-up decisions. [6,7]

In a young patient presenting with the classical textbook features of an inherited arrhythmia syndrome, there is not much diagnostic ambiguity. For instance, aborted sudden cardiac arrest and prolonged heart rate corrected QT (QTc) interval in a previously healthy child with a family history of young sudden unexplained death is a clear indication of an underlying LQTS that can be confirmed by targeted genetic testing. However, knowing that incomplete penetrance is the rule rather than the exception in these diseases and that phenotypic and genetic variability are frequently encountered, next generation sequencing (NGS) techniques

now have a widespread role in detecting causative mutations when unsure of the underlying disease entity and in cases of SCD where corroborative clinical evidence is unavailable. The identification of a disease-causing gene in the proband then paves the way for cascade screening which is nothing but cardiovascular assessment, targeted genetic testing and presymptomatic treatment of at-risk family members. [8]

Reinforcing sound clinical knowledge

In the different disease entities the molecular analysis can be done in a targeted way, although current methods allow for a more unbiased approach. Yet, detailed knowledge of genotype-phenotype relationships is fundamental to the interpretation of the molecular genetic findings and the eventual therapeutic decisions to be taken. LQTS, as pointed out earlier, is the disease entity with the most clearly established genotype-phenotype relationship. Indeed, based on various aspects of the clinical history of the proband and his or her family members and based on the ECG features the underlying genotype can be predicted with significant certainty. [9] This holds in particular for the most prevalent LQTS, i.e. LQTS types 1, 2 and 3. Patients with LQT1 typically present with symptoms during exercise, whereas LQT2 patients have their symptoms triggered by emotion or startle (like an alarm clock). [10] In the other primary arrhythmia syndromes genotype-phenotype relationships are less clear, but this relates mainly to the fact that large cohorts with a diverse underlying genotype are generally not available.

In spite of the myriad diagnostic advantages of genetic testing, the ECG remains a classical but practical diagnostic and risk stratifying tool in the clinical setting. Two recent studies on exercise testing have implied that the QT interval during the recovery phase (3-4 minutes) may reveal a diagnostic QT prolongation in LQTS cases with borderline QTc interval at baseline, as depicted in **Figure 1**. [11,12]

Figure 1: ECGs of an exercise test in a 13-year old female with LQT1 (on beta-blocker therapy) are shown. QTc interval prolonged from 453ms (HR 85bpm) pre exercise (A) to 528ms (HR 95 bpm) 3 minutes post exercise (B). ECG=electrocardiogram; LQT1=long QT syndrome type1; QTc=corrected QT interval (Bazett's formula).

Further, postural changes from a supine position to standing may trigger a greater degree of QT prolongation in LQTS compared with controls and may eventually lead to the diagnosis of LQTS. [13] **Figure 2** portrays these changes in QTc with posture.
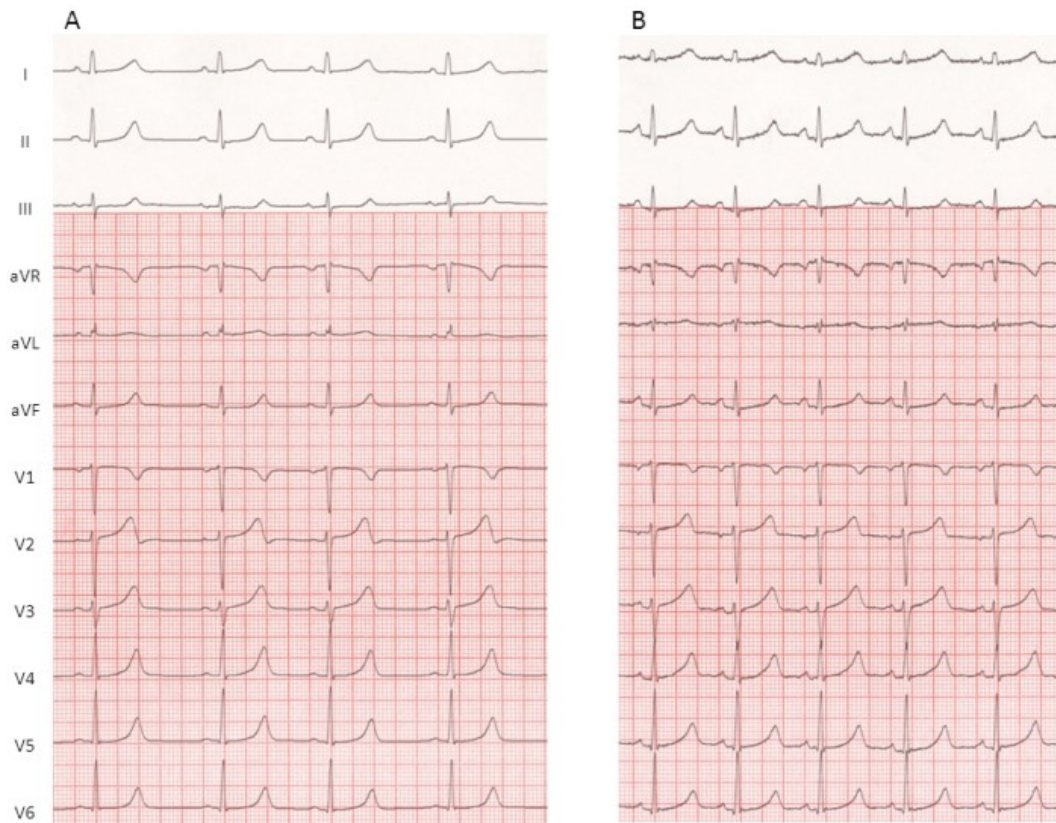

Figure 2: QT prolongation provoked during a lying-standing test in a 30-year old female with LQT1 (without medication). QTc was 493ms (HR 55bpm) at baseline in supine position (A). QTc prolonged to 541ms (HR 77 bpm) upon standing (B).

These tests maybe particularly useful in borderline cases, but it has to be emphasized that prospective studies lack at this point in time. In both LQTS and BrS, drugs may give rise to a diagnostic ECG (and successive arrhythmic events), as is shown with the infusion of ajmaline in **Figure 3**.
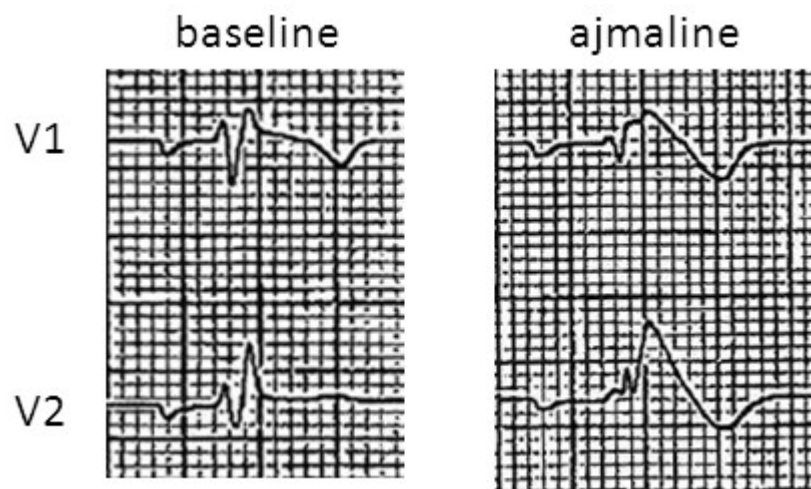

Figure 3: Typical type1 BrS ECG after intravenous ajmaline infusion. With ajmaline, coved-type ST elevation of >2mm and prolongation of PR interval is observed. The ECG was recorded from lead V1 and V2 from 2nd intercostal space.

Such drugs are not limited to antiarrhythmic agents alone but also include psychotropic drugs, anesthetics and some other substances. [14] Currently, healthcare providers can access websites which list an increasing number of drugs to be avoided in patients with LQTS and BrS (www.QTdrugs.org; www.brugadadrugs.org).

Because the underlying genetic substrate facilitates the diagnosis (in particular in family members) and impacts prognosis and therapeutic decisions, genetic testing in most of these syndromes is currently regarded a mandatory diagnostic procedure (i.e. a class 1 recommendation). [15] The yield of molecular genetic testing depends on the disease under scrutiny and varies from 50-60% in LQTS (≥90% in LQTS families) to 20-30% in Brugada syndrome. [6,15] Further, it is important to be aware that location and coding type of mutation affect the risk profile. For example, in LQT1, individuals with a missense mutation in the transmembrane portion (especially, a cytoplasmic loop) carry an increased risk of life-threatening cardiac events; [16] and in LQT2, males with a pore-loop (missense) mutation have a higher chance of life-threatening cardiac events whereas females have a high risk of life-threatening events regardless of the mutation location. [17]

Going beyond the causal mutation

As indicated, many of the diseases at stake are monogenic, i.e. one pathogenic variant in a gene is fully responsible for the phenotype. Yet, from the very first description of large families it was obvious that there are remarkable differences in disease expression even within the same family. Several factors play a role in explaining these differences, including gender, age, and drug use. However, in recent years it has become more and more clear that there are important modifying genetic factors. [18] In LQTS some of these factors have been identified, with NOS1AP as the most important example. [19,20] Also, genetic factors impacting on the expression of the protein (either via the normal allele or the abnormal allele) significantly impact on the severity of the phenotype, as has been shown in LQT1. [21] Occasionally, patients do harbor more than one pathogenic mutations and not surprisingly these patients are typically more severely affected. [22] We do expect that in the years to come the identification of these genetic modifiers will modify risk stratification schemes in LQTS as is already the case when there are two pathogenic mutations.

Brugada syndrome has always been regarded a monogenic disease but recent data point to the fact that it might actually be an oligogenetic disease, i.e. based on a variety of gene variants, each of them with a smaller effect size compared to a pathogenic variant, but in combination sufficient to cause the full-blown phenotype. [23] Whether the presence of more variants also impact on prognosis remains to be determined. It is interesting to note that genome wide association study (GWAS), an approach that involves rapidly scanning markers across genomes of many individuals to find genetic variations associated with a particular disease, is throwing light on the new candidate genes that play a part in disease expression and severity. A very recent GWAS study involving 100,000 individuals from over 150 centers worldwide has identified 35 common variant loci associated with QT interval that collectively explain ~ 8-10% of QT interval variation and highlight the importance of calcium regulation in myocardial repolarization. [24]

Broadening the application of genetic tests

Several studies in the last decade have helped reveal the genetic abnormalities underlying SCD and sudden infant deaths following which molecular autopsy or the genetic testing of deceased individuals has become integral in the diagnostic evaluation of families bereaving the sudden death of a close relative. [25]

The use of NGS strategies (extended panels or even whole exome sequencing) has increased

the yield of pathogenic mutations but at the same time has also dramatically increased the yield of variants of uncertain significance. While significant research is underway in the area of familial cardiomyopathies in South Asians in India, [26] there are but a handful of publications describing inherited arrhythmias in this ethnically diverse population. 27,28] A concerted effort across the nation to gather existing data, plug the gaps in clinical evaluation and proceed with genetic counseling and testing is the way forward in this era where research-based as well as commercial genotyping opportunities with sound bioinformatics backing are currently more readily available. [29]

Therapeutic advances

Treatment options for inherited arrhythmias include lifestyle modifications, pharmacological agents, device therapy and surgical interventions. The recent consensus statement by Priori et al provides a lucid approach to risk-stratification and choice of treatment modality in the different arrhythmia syndromes. [2] However, a case-based rather than a disease-based strategy is emerging as the key factor in the successful management of affected patients and families.

Managing patients with drugs as first line therapy

Beta-blockers, sodium channel blockers and a few other antiarrhythmic agents have proven to be of value in preventing arrhythmias of channelopathic origin. The role of beta-blockers, a globally available and cost-effective group of drugs, cannot be underestimated when dealing with adrenergic mediated primary arrhythmias such as LQT1, LQT2 and CPVT. The choice of beta-blocker should be based on history of cardiac events, type of LQTS, age of the patient, comorbidities and local availability of drugs. [30,31] While nadolol, a non-selective beta-blocker with unique pharmacodynamic and pharmacokinetic properties, has better arrhythmia suppressing ability compared to the other beta-blockers, it's use is often limited by its lack of availability. [32] On the same note, quinidine, the singular antiarrhythmic agent useful in BrS and idiopathic ventricular fibrillation, is unavailable in most parts of the world which warrants the immediate attention of policymakers. [33] For LQTS, new drugs targeting the late sodium inward current are on the way. [34] Acute administration of ranolazine has been tested already in small LQT3 patient cohorts. [35] However, long-term studies with these drugs are awaited. In CPVT, flecainide has recently shown to be quite effective in suppressing arrhythmia burden both experimentally and clinically (**Figure 4**). [36] In clinical studies, flecainide was used in addition to beta-blocker therapy (plus verapamil in some cases).

Choosing appropriate adjuvant therapies

Implantable cardioverter defibrillator (ICD) is an arrhythmia-aborter for ventricular arrhythmias that may spiral to lethal proportions and is therefore an integral part of managing high-risk channelopathic patients. The high complication rate and the excessive cost associated with this choice of therapy are major disadvantages, thus once again precluding its uniform utilization globally. Having said so, weighing the pros and cons of the device versus the risk of SCD is the only way out of the therapeutic dilemma of whether or not to implant one in young patients and their family members. [37,38] It has to be highlighted that while technological advances have lead to procedure-light options such as wearable ICDs, the healthcare inequalities are still so prevalent in low and middle income countries that reuse of ICDs has been tested and even shown to be successful. [39,40] In BrS with (multiple) ICD shocks due to recurrent ventricular fibrillation (VF), catheter ablation of epicardial arrhythmic substrates in the right ventricular outflow tract is a powerful adjunctive therapy to suppress arrhythmic events. [41] Currently, this complex procedure is reserved only for severely affected patients with recurrent VF events and only centers with extensive experience in epicardial ablation with surgical backup should perform the procedure. [42]

Figure 4: ECGs during exercise testing before and after drug treatments in a 31-year old female with CVPT. At baseline before medication (A), NSVT and bouts of VES were observed. After metoprolol (100mg/day), frequent VES still appeared during the test. With metoprolol (100mg/day) and flecainide (150mg/day), ventricular arrhythmias were suppressed and only a few VES were recorded throughout the test. Notably, there is no QRS prolongation during exercise on flecainide therapy. ECG=electrocardiogram; NSVT=non-sustained ventricular tachycardia; CPVT=catecholaminergic polymorphic ventricular tachycardia; VES=ventricular extrasystoles.

Left cardiac sympathetic denervation (LCSD), which refers to surgical resection and removal of the lower part of the stellate ganglion and the upper fibers of the thoracic ganglia, has become established as a neuromodulator in the management of therapy-resistant arrhythmias and recurrent ICD shocks. [43] A significant reduction in arrhythmia episodes was observed in Dutch LQTS and CPVT patients after LCSD, and LQT1 was more responsive than LQT2. [44] There appears to be a potential role for bilateral cardiac sympathetic denervation in the abolition of ventricular tachycardia storm and in treating refractory ventricular tachycardia but its value in long-term care warrants exploration. [45]

Applying the emerging trends in our patients

In the Indian context, there are both positives and negatives. While clinically diagnosed cases are being treated as per the international guidelines with some modifications based on local conditions, there is a need to educate healthcare professionals on identifying the red flag signs of underlying channelopathic diseases. Genetic counseling and genotyping are yet to become routine practice for even the well-established diseases like LQTS, and postmortem molecular diagnostics is non-existent. It is surprising to note that a detailed family history and pedigree chart, as critical as they are in proband evaluation, are not adequately documented in cases provisionally managed as inherited arrhythmias. With only a few tertiary referral hospitals using electronic health records, data retrieval of suspected cases is proving tedious.

Nevertheless, systematic, coordinated steps are underway to address these issues at a nationwide level, keeping in mind the success stories of international registries and collaborative teamwork in understanding and addressing the complex inherited arrhythmia disorders.

Research avenues

Research opportunities abound in this rapidly expanding field of medicine. As diagnostic challenges still continue to daunt experts, newer avenues in stem cell biology and genetic technologies, such as induced pluripotent stem cells and genome wide association studies, are potential answers to the various unsolved mysteries of ion channel diseases. [46,47] Research into fetal diagnosis and management of LQTS utilizing newer imaging modalities is proving promising. [48] While randomized trials are almost impossible in these rare and lethal disease entities, observational studies and retrospective analyses of large databases are filling the knowledge gap.

Strong headways are also being made to expand the treatment options with the relentless support of translational research groups and clinical research projects. Expanding the realms of existing therapeutic modalities, such as with highly evolved ICDs and increasingly precise denervation techniques, is the focus of experts at the present time. Recently, renal denervation and other neuromodulators have gained attention in the alteration of heart failure progression and atrial arrhythmogenesis, and might have potential application in the management of channelopathies as well. [49] On another note, experimental evidence is accumulating for microRNA-mediated regulation of atrial fibrillation, and they appear to be promising therapeutic targets for this common arrhythmia. [50] The fact that developing nations are investing resources in medical and basic science research is a very positive sign and young clinicians and scientists should make every attempt to develop their research skills with the broader aim of advancing patient care.

Concluding remarks

The diagnostic and therapeutic tools available with us today are to be applied judiciously to reduce the mortality and morbidity due to undiagnosed and uncontrolled inherited arrhythmias. While we are fortunate to be part of the ongoing genetic revolution, the sheer volumes of genetic data churned out on a case per case basis also challenge us. There is probably a need for interdependency, now more than ever before, amongst the various specialists in a cardiogenetic team to fully understand the complex situation at hand, to gain the confidence of patients, to help them make informed decisions and to provide lifelong care and support for affected families. With information technology coming in pocket sizes and microchip shapes, being up-to-date with global trends in this field is not only crucial for our own personal sakes but also for the appropriate counseling of young individuals seeking evidence-based answers to questions and dilemmas relating to their potentially lethal but treatable medical conditions.

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