Channelopathies – An update 2018

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Each passing year brings exciting new discoveries which enhance our understanding of the complex genetic-environmental interactions that define the clinical spectrum of channelopathies. The year 2018 was no different. Progress was made in personalization of treatment in channelopathies tailored to the genotype of the patient with discovery of agents with particular affinity to the affected ion channel (1,2,3). Increased availability of genetic testing and over-zealous cascade testing of relatives have opened a can of worms with relatives struggling to understand the need for testing or the clinician's interpretation of their test results. However, cardiac geneticists are attempting to bring a method to this madness by formulating an action plan for communication of genetic information and identifying areas of vulnerability (4). Two important papers in this year illustrated the importance of the clinical phenotype in the diagnosis of Long QT Syndrome (LQTS) and reminded us of the dangers of diagnosing a potentially life-threatening disorder without paying attention to our patients and their clinical presentations (5,6). In this article, we attempt to update the knowledge on channelopathies by briefly summarizing the literature, with specific emphasis on Brugada syndrome, CPVT and LQTS.

1. Personalized drug therapy in channelopathies

The Human genome project [7] has opened up the field of personalized medicine where the person's genotype will direct the ideal treatment of any illness. This is especially relevant in Cardiology where the genotype and epigenetic factors play a key role in the disease phenotype as well as the likely response to treatment.

Mexiletine has been shown to reduce the risk of arrhythmias in LQTS 3 [8]. However, it is not a very selective inhibitor of the late INa_v channel and concerns also exist about its off-target effects. It also has a short half-life which necessitates thrice daily dosing. Eleclazine is a novel sodium channel inhibitor which has been shown to reduce QTc interval in patients with LQTS 3 (9). El-Bizri and colleagues studied the effects of Eleclazine in the wild type and known mutant variants of the affected sodium channel by patch clamp technique and identified that Eleclazine binds rapidly and is a very potent inhibitor of the $Na_v1.5$ channel. It also exhibited an 84-fold specificity for the channel with almost no secondary off-field effects [1]. With clinical data already available documenting it's efficacy as well as safety [9,10], clinical implementation of Eleclazine should not be far off.

Inactivator mutations of the hERG channel have been implicated in LQTS2. Attenuation of the inactivation effect is hence one of the possible therapeutic targets in these patients. Ng and colleagues at the Cardiological Society of Australia and New Zealand (CSANZ) annual meeting presented their data on IC-105574, a hERG channel activator which was shown to attenuate inactivation of the potassium (K) channel in Chinese hamster ovarian cell lines with inactivator mutations [2]. However further bench testing to ensure drug safety would be necessary before clinical translation.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) unresponsive to beta blockers raises a serious therapeutic challenge given that insertion of an Implantable Cardioverter Defibrillator (ICD) is a double-edged sword with an increased risk of electrical storm. Recently, Flecainide has been shown to be effective in this difficult subgroup of patients [11]. Klipp and colleagues have shown that EL 20, a tetracaine derivative stabilizes the protein calmodulin and reduces diastolic calcium leak in myocytes in mice models of CPVT, reducing the risk of arrhythmias [3]. This drug would be a

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useful addition to the armamentarium in treatment of CPVT.

2. Brugada Syndrome

Fever has been shown to be a very important trigger for ventricular arrhythmias in Brugada Syndrome. However, the exact risk has never been established. Michowitz and colleagues reviewed the data from the Survey of Arrhythmic events in BRUgada Syndrome (SABRUS) Registry involving 678 patients with Brugada Syndrome, the largest registry of Brugada Syndrome. They identified that 6% of arrhythmic events were triggered by fever. The risk was highest in Caucasian children with 37% of arrhythmic events triggered by fever. The risk was even higher in the 0–5-year age group where more than 65% of arrhythmic events were directly related to fever. Children of both sexes were equally affected [12]. Interestingly, no fever triggered arrhythmias were detected in young Asians.

In the absence of simple treatment options in Brugada, the clinician's choice is limited to ICD implantation or close monitoring. Data on the efficacy of quinidine are conflicting and the drug is not available in our country. Hence it becomes important to stratify the risk clinically to identify patients who are likely to benefit from an ICD. Data from our own institute suggested a role for exercise stress testing in risk stratification [13]. Morita and colleagues reviewed 62 patients with Brugada syndrome including 14 who had at least 1 episode of Ventricular Fibrillation (VF). Patients who had VF were more likely to have spontaneous type I Brugada pattern, longer QRS duration and a longer T_{peak}-T_{end} interval (Tpe) [14].

Pathological mutations in ion channels have been documented in nearly half of patients with Brugada syndrome and it is hence considered a channelopathy. However, structural abnormalities in the right ventricular outflow tract (RVOT) have been documented on pathological examination. Pieroni and colleagues performed three dimensional (3D) electro-anatomical mapping of the RVOT along with an endomyocardial biopsy in 30 patients with Brugada syndrome [15]. They identified low voltage areas in 93% of unipolar maps and half the bipolar maps. The biopsy also showed abnormality in 75% of cases with myocardial inflammation being the commonest abnormality noted. This data challenges our understanding of the pathogenesis of arrhythmias. It is possible that the genetic defect leads to inflammation and fibrosis which in turn provide an arrhythmogenic substrate, offering an alternative target to develop therapeutic options.

Sudden Arrhythmia Death Syndrome (SADS) especially in young adults could be related to an undiagnosed channelopathy. Molecular autopsy as well as testing of family members could improve the yield of diagnosis. Papadakis and colleagues screened 909 family members of 303 SADS victims. The relatives were screened by an electrocardiogram (including a high right precordial lead (hRPL)), Holter examination and exercise stress testing. An ajmaline challenge test was performed if initial evaluation was negative. A positive cardiac diagnosis was identified in 128 families with Brugada syndrome accounting for 85 families (28%). A vast majority of these families (97%) were diagnosed by ajmaline challenge testing with use of the hRPL leads increasing the diagnostic yield [16]. In limited follow up, 25% of identified families had clinical events.

However, Ajmaline challenge is also associated with risks. Data on its safety in children is not clear. Most protocols suggest stopping the infusion as soon as a 2 mm ST elevation occurs and using isoprenaline as well sodium bicarbonate infusions to treat arrhythmias. Despite following established protocols, malignant ventricular arrhythmias can occur which are quite difficult to treat. Poli and colleagues reported their experience and reviewed the literature where they identified 3 cases which required emergency initiation of extra-corporeal support [17]. On the other hand, Uocke

and colleagues attempted risk stratification by sodium channel blockade using Pilisicianide [18]. Their aggressive protocol was thought to be "audacious" in the accompanying editorial [19]. A vast majority of their patients had spontaneous type I pattern – a feature considered to be high risk and a relative contraindication to sodium channel blockade. The median ST elevation reported in their series was 6 mm and 10% of patients developed ventricular arrhythmias during testing. On follow up, 13% had at least 1 malignant ventricular arrhythmia. ST elevation greater than 3 mm (HR -2.8) and ventricular arrhythmias on testing (HR -3.6) were shown to be associated with an increased risk of arrhythmic events.

3. Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Idiopathic Ventricular Fibrillation (VF) was long considered a separate diagnostic entity. However wide spread use of genetic testing and identification of genetic substrate in other channelopathies have challenged the existence of this subset. Leinonen and colleagues subjected 76 patients diagnosed as idiopathic VF to genetic testing by next generation sequencing (NGS) or whole exome sequencing (WES) [20]. 7 patients were detected to have a pathogenic mutation in CPVT genes, and an additional 9 patients had a variant of unknown significance (VUS). As our understanding of the genetics and pathogenesis of channelopathies improves, it is possible that the entire diagnostic category may be reclassified, and appropriate treatment options can be offered to patients.

CPVT with poor response to beta blockers is a therapeutic challenge. Nadolol is not available in our country but recent data on the efficacy of Flecainide is encouraging [11]. ICD implantation in this subset is not without complications. An ICD discharge presents an intense adrenergic stimulus which in turn decreases the threshold for further ventricular arrhythmias and further shocks. This leads to an electrical storm which can be life threatening. Geraghty and colleagues reviewed the management of electrical storm including that occurring in patients with CPVT [21]. ICD reprogramming should be done emergently. In addition, sympathetic blockade by sedation, beta blockers as well as adjunctive therapies like neuraxial modulation, epidural analgesia and stellate ganglion block have been shown to be useful. Emergency intervention and catheter ablation are necessary in certain etiologies (21).

Till recently, only Ryanodine receptor (RyR) mutations were identified in CPVT. However, Calmodulin, calsequestrin and many other mutations are now being identified and our understanding of the genetic basis continues to expand. A subset of patients have been identified to have multiple variants in the Ryanodine Receptor gene which are believed to be pathogenic. Roston and colleagues looked at the clinical course of patients diagnosed to have multiple variants who were registered in the PACES registry. 15 of the 193 patients with a positive CPVT mutation were noted to have multiple variants (8%). The mean follow-up period was 4.3 years [22]. These patients were noted to have a higher risk of arrhythmias, but no deaths occurred during this period.

4. Long QT syndrome (LQTS)

Patients with LQTS are frequently misdiagnosed with seizure disorder. When the correct diagnosis is established, it is often thought that ventricular arrhythmias have been misinterpreted as seizures. Recently, the sodium and potassium channels implicated in LQTS have also been noted in neural tissue. A concept of "cardiocerebral channelopathy" is hence emerging. Gonzalez and colleagues looked at electroencephalographic (EEG) changes in mutation positive LQTS 1 and 2 patients and compared them with

controls. EEG abnormalities were detected in 34% of cases against just 5% of controls [23]. However, the study could not establish a genuine association with epilepsy in LQTS. Hence it is important not to ignore neurological symptoms in patients with LQTS.

The asymmetry of the T wave is an important clue to the diagnosis of LQTS. However, it appears that the degree of asymmetry could provide prognostic information as well. Tse and colleagues performed a metanalysis on the utility of the Tpeak-Tend interval in LQTS [24]. They identified 5 studies which included 388 patients. The Tpeak-Tend interval was significantly increased in patients with clinical events (Mean difference-13 ms and standard error-4ms). However, the Tpeak-Tend/QT interval was not different between the two groups.

Anti-histamines are the cornerstone of management of allergies. Many anti-histamines are contraindicated in LQTS. A review article in Annals of Allergy Asthma and Immunology provided recommendations for the management of allergies and anaphylaxis in LQTS [25]. Local manifestations can be safely managed with Cetrizine, Levocetrizine or Desloratidine. Pulmonary manifestations should initially be managed with nebulized ipratropium with salbutamol reserved for uncontrolled wheeze. Anaphylactic shock would still require intra-muscular or intra-venous epinephrine with early addition of Glucagon. Continuous cardiac monitoring is mandatory if epinephrine or salbutamol are used.

The efficacy of Mexiletine in LQTS 3 is well documented. But a role for Mexiletine is emerging in other types of LQTS as well. Li and colleagues reviewed the literature on Mexiletine in the Journal of Electrocardiology [26]. The efficacy of Mexiletine in LQTS 3 has been shown to be the inversely proportional to the baseline QTc interval. While beta-blockers are the cornerstone of clinical management in patients with LQTS 1 and 2, a subset of patients exhibit prolongation of QTc at low heart rates. The sodium current has been shown to contribute to the bradycardia related QTc prolongation in these patients. Mexiletine which inhibits the sodium current has a clinical role in such patients irrespective of the genotype.

The mechanical effects of the repolarization abnormalities in LQTS have been hypothesized. However very few studies exist on this electro-mechanical correlation. Zuya and colleagues performed magnetic resonance imaging (MRI) on rabbit models of LQTS 1 and noticed that an increased QTc interval was associated with increased systolic contraction and decreased diastolic relaxation [27]. In the accompanying editorial, Haugaa and Stokke lamented the lack of focus on electro-mechanics in electrophysiology [28]. They dwelled on the negative electro-mechanical window in LQTS. The aortic valve closure at end systole coincides with the end of the T wave. However due to prolongation of the QTc, aortic valve closure may occur before the end of the QT interval in LQTS. The period between aortic valve closure and end of the T wave is a vulnerable period for ventricular arrhythmias. This can be easily demonstrated on routine trans-thoracic echocardiogram and could emerge as a risk stratification tool in LQTS.

Mazzanti and colleagues reviewed 1710 patients with LQTS with a mean follow up of 7 years. This large study in an uncommon disorder revealed interesting phenotype-genotype correlations [5]. Asymptomatic patients with a positive genotype and a QTc interval of less than 450 ms have a very low risk of lethal arrhythmic events (LAE). The risk increases by 15% with every 10 ms increase in QTc with an even higher risk in LQTS 2 and 3. Nadolol was shown to be the most significant beta blocker in reducing the risk of LAE. The study adds to the growing evidence favoring non-selective beta blockade in general, and Propranolol as well as Nadolol in particular in channelopathies. The long half-life as well as decreased central nervous system (CNS) penetration of Nadolol is an important factor in ensuring compliance and reducing beta blocker withdrawal periods [29]. Nadolol should hopefully be available in our country in the near future and benefit patients with channelopathies.

Clemens and colleagues examined all reported pathogenic variations in the KCNQ1 gene and compared them with genetic data from the genome aggregation database. They also used state of the art laboratory data to validate the pathogenic claims of doubtful mutations [6]. The results were startling. 13% of mutations previously classified as pathogenic were most likely benign. On trying to trace how these mutations were thought to be pathogenic, it was discovered that the compendia which reported the mutations did not rigorously examine the phenotype of the patients and accepted a referral diagnosis of possible LQTS in interpreting the genetic results. This study reiterates the importance of a thorough clinical evaluation of the proband and confirmation of clinical diagnosis of LQTS before proceeding with genetic testing and offering cascade testing to the extended family.

This brings us to an interesting contemporary review on genetic counselling in channelopathies by Burns and Ingles [4]. They identified uncertainty about the diagnosis, poor understanding of the results and fractured family relationships as the key challenges in maximizing the impact of genetic testing. They stressed on the importance of pretest genetic counselling and provided a checklist which identifies vulnerable points in the genetic testing pathway where interventions could assist the vulnerable families.

In summary, the year 2018 has further advanced our knowledge on management of patients with channelopathies and has set the bar high for the years ahead.

Competing interests

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