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REVIEW

Channelopathies That Lead to Sudden Cardiac Death: Clinical and Genetic Aspects

Jonathan R. Skinner, MBChB, DCH, MD [a,b,c*], Annika Winbo, MD, PhD [a,b,d], Dominic Abrams, MBChB, MD [e,f], Jitendra Vohra, MD [g,h], Arthur A. Wilde, MD, PhD [i,j]

[a]The Cardiac Inherited Disease Group, Auckland, New Zealand
[b]Greenlane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand
[c]Department of Paediatrics, Child and Youth Health, University of Auckland, New Zealand
[d]Department of Neurophysiology, University of Auckland, New Zealand
[e]Inherited Cardiac Arrhythmia Program, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA
[f]Harvard Medical School, Boston, MA, USA
[g]Cardiology Department and Department Of Genomics, The Royal Melbourne Hospital, Melbourne, Vic, Australia
[h]University Of Melbourne, Melbourne, Vic, Australia
[i]Heart Centre AMC, Department of Clinical and Experimental Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[j]Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA

Forty per cent (40%) of sudden unexpected natural deaths in people under 35 years of age are associated with a negative autopsy, and the cardiac ion channelopathies are the prime suspects in such cases. Long QT syndrome (LQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are the most commonly identified with genetic testing. The cellular action potential driving the heart cycle is shaped by a specific series of depolarising and repolarising ion currents mediated by ion channels. Alterations in any of these currents, and in the availability of intracellular free calcium, leaves the myocardium vulnerable to polymorphic ventricular tachycardia or ventricular fibrillation. Each channelopathy has its own electrocardiogram (ECG) signature, typical mode of presentation, and most commonly related gene. Long QT type 1 (gene, *KCNQ1*) and CPVT (gene, *RyR2*) typically present with cardiac events (ie syncope or cardiac arrest) during or immediately after exercise in young males; long QT type 2 (gene, *KCNH2*) after startle or during the night in adult females-particularly early post-partum, and long QT type 3 and Brugada syndrome (gene, *SCN5A*) during the night in young adult males. They are commonly misdiagnosed as seizure disorders. Fever-triggered cardiac events should also raise the suspicion of BrS. This review summarises genetics, cellular mechanisms, risk stratification and treatments. Beta blockers are the mainstay of treatment for long QT syndrome and CPVT, and flecainide is remarkably effective in CPVT. Brugada syndrome is genetically a more complex disease than the others, and risk stratification and management is more difficult.

Keywords Sudden death • Channelopathy • Long QT syndrome • Brugada syndrome • CPVT • Genetics

Introduction

Forty per cent (40%) of sudden unexpected natural deaths in people under 35 years of age are associated with a negative autopsy and the cardiac ion channelopathies are the prime suspects in such cases [1]. Often called ''SADS'' or sudden arrhythmic death syndrome, Long QT syndrome (LQTS), Brugada syndrome (BrS) and CPVT (catecholaminergic polymorphic ventricular tachycardia), are the most commonly found [2–7].

*Corresponding author at: Green Lane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Private Bag 92024, Auckland 1142, New Zealand. Tel.: +64 9 3074949 Fax: +64 9 6310785., Email: jskinner@adhb.govt.nz

More than two-thirds of all young sudden cardiac deaths occur at rest or sleep [8,9]; however, a positive genetic result for an ion channelopathy is more likely with a history of exercise or extreme emotion [7]. Among college athletes, SADS is up to three times more common than hypertrophic cardiomyopathy except in African-Americans [10].

Genetic mutations linked to cerebral ion channelopathies causing epilepsy occur in up to 6% of SADS cases [1] and whether these are cardiac or neurologic deaths is not clear, but ion channel dysfunction can present in the brain and heart in the same patient [11,12].

Presentation Other Than Sudden Death or Cardiac Arrest

Each ion channelopathy has its own electrocardiogram (ECG) signature, and typical mode of presentation (see Figures 1 and 2). They are commonly misdiagnosed as seizure disorders [13,14]. Their coincidental presence may make arrhythmic death more likely in the event of myocardial infarction or illnesses with metabolic disturbance or polypharmacy [15]. Fever-triggered cardiac events should raise the suspicion of BrS [16].

Prevalence

Long QT syndrome occurs in 1 in 2,000 people with a slight predominance of females, [17] BrS occurs in about 1 in 10,000 people (higher in East Asia) [18], with over 70% being male [19], and CPVT in occurs in approximately 1 in 10,000. Short QT syndrome is very rare indeed and is not reviewed further here. Early repolarisation is an ECG feature of about 5% of the population, but it is suggested that 30% of cases of so-called idiopathic ventricular fibrillation (VF) are due to early repolarisation syndrome (ERS).

Mechanism of Arrhythmogenesis

The Cardiac Action Potential and Cellular Excitability

The cellular action potential driving the heart cycle is shaped by a specific series of depolarising and repolarising ion currents mediated by ion channels (Figure 1) [20–22]. Alterations in any of these currents distort the timing and shape of the action potential and leaves the myocardium vulnerable to dysrhythmia. The excitability of the cardiac cell also critically depends on availability of intracellular free calcium; if this is too high, the cell can spontaneously depolarise early (such as seen with digoxin toxicity and CPVT).

Dysfunctional Ion Channels

The ion channelopathies result from mutations in genes encoding channels or related proteins, altering their properties. A mutation may make a channel non-functional, underactive, overactive or leaky. An example is the cardiac sodium channel Nav1.5 and its encoding gene *SCN5A*; failure of the channel to close results in LQT type 3, and failure to open effectively, or to express functionally, causes Brugada syndrome. The same mutation may cause either within the same family [23].

Types of Arrhythmia

The cardiac ion channelopathies cause sudden death by causing rapid, usually polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF). At a tissue level the mechanisms can be *triggered* (due to an after depolarisation such as in LQTS and CPVT) with the arrhythmia sustaining through a circus movement-type re-entry [21], or re-entry *per se* typically due to adjacent areas of the myocardium having different electrophysiological characteristics, such as the right ventricular outflow tract in BrS [24].

Long QT Syndrome

The term ''long QT syndrome'' (LQTS) implies the inherited, or genetic, ion channelopathy, whereas ''acquired long QT syndrome'' is reserved for those where the QT interval is prolonged from acquired heart disease, biochemical or pathophysiological events, such as hypokalaemia, QT-prolonging drugs, hypothermia or neurological events such as a stroke.

The cardinal feature is prolonged repolarisation [14].

Diagnosis

The diagnosis of LQTS is made clinically, by combining clinical and family history and the 12-lead ECG [25,26], A clinical score (''Schwartz score'') [26] can be a useful guide. Manual measurement of the heart-rate corrected QT interval (QTc), focusses on leads 2 and V5, on two or more ECGs with no extraneous causes of QT prolongation. The ''tangent'' technique is preferred to determine the end of the T-wave (the steep slope of the T-wave is extended to the baseline) [27]. Use of the Bazett formula (QT length divided by the square root of the preceding R-R interval) is acceptable at all ages [28]. Qualitative assessment of T-wave morphology is as important as QT length (see Figures 1 and 2). Cardiomyopathies often have QT prolongation as part of the disease but the ST segments tend to be depressed inferolaterally and the T-waves biphasic or inverted.

An isolated QTc (in the absence of syncope or family history) >500 ms on more than one occasion is sufficient for the diagnosis of LQTS [25]. Many LQTS subjects have a QTc shorter than this, so a thorough clinical and family history must be taken—something which not all cardiologists do [29]. Following arrhythmic syncope, a diagnosis of LQTS can only be made if a QTc greater than 470 ms on repeated ECGs is found and vasovagal syncope is excluded.

A family history of sudden death can be pivotal to diagnosis [30].

Ancillary Diagnostic Tests

A QTc >445 ms at 4 minutes in recovery after exercise increases the probability of LQTS, with increased specificity using a cut-off of >480 ms [31,32]. Normative values are available for children [33].

Within 10 seconds of brisk-standing, heart-rate increases [34]. In those affected by LQTS, the QT interval reduces much less than the RR interval. Ventricular ectopic beats or T-wave alternans and T-wave dysmorphology may be seen. This test can be problematic in ''fidgety'' young children; and

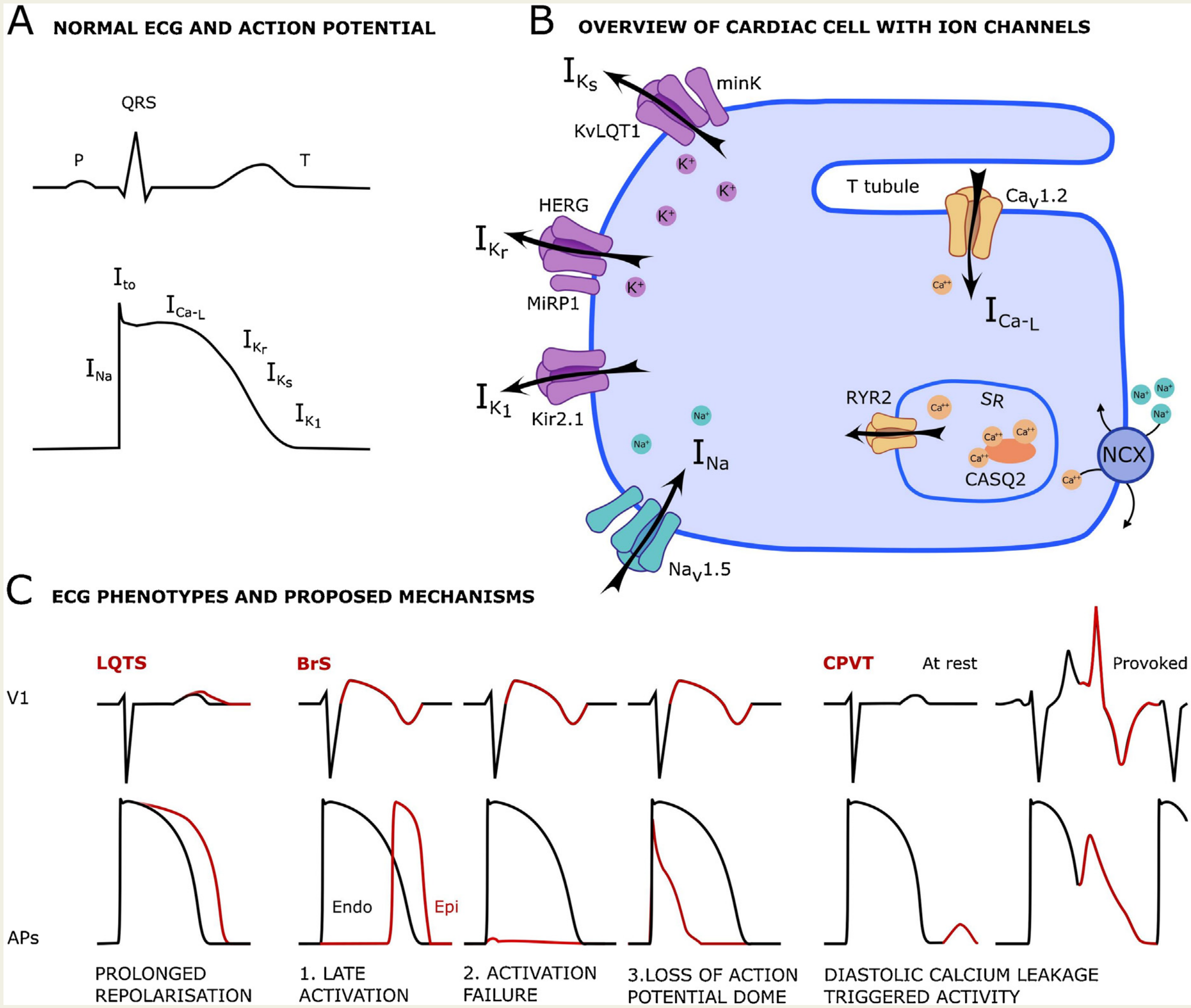

Figure 1 (A) The cellular action potential driving the heart cycle is shaped by a series of depolarising and repolarising ion currents (I). The major depolarising currents in ventricular cardiomyocytes are sodium (I_{Na}) and L-type calcium currents ($I_{Ca\text{-}L}$). The major repolarising currents are potassium currents (transient outward potassium current $I_{to,}$ rapid delayed rectifier current $I_{Kr,}$ and slow delayed rectifier current I_{Ks}). I_{K1} is an inward rectifier current maintaining resting membrane potential and controlling cellular excitability. (B) The ion channels and related proteins responsible for depolarising ($Na_V1.5$ and $Ca_V1.2$) and repolarising (KVLQT1/minK, HERG/MiRP1 and Kir2.1) currents are found in the cell membrane, either on the cell surface or in the transverse tubules (T tubules). The sodium/calcium exchanger (NCX1) contributes to the depolarising current via changing 3 sodium ions (Na^+) for 1 calcium ion (Ca^{2+}), resulting in a net positive inward current. Calcium handling and control during cardiomyocyte contraction and relaxation is mediated by the process of calcium-induced calcium release from the sarcoplasmatic reticulum (SR), where calcium is bound by calsequestrin (CASQ2) and released into the cytosol by the ryanodine-receptor (RYR2) channel. (C) Suggested mechanisms of the LQTS, Brugada and CPVT ECG patterns. as seen in the first precordial lead (V1). APs: ventricular action potentials. LQTS: Reduced repolarising currents (I_{Ks} in LQT1 and I_{Kr} in LQT2) or increased depolarising currents (I_{Na} in LQT3) result in a prolonged repolarisation and a prolonged QT interval on the ECG. BrS: Three alternative pathophysiological mechanisms underlying the type 1 Brugada pattern have been proposed: (1) late activation of the right ventricle causes ST-segment elevation and repolarisation of the same myocardium causes the negative T-wave, (2) excitation failure at the right ventricular subepicardium causes ST-segment elevation and moderate activation delay at neighbouring sites causes the negative T-wave. (3), loss of the action potential dome at the right ventricular subepicardium but not the subendocardium, i.e. transmural dispersion in action potential duration. CPVT: Resting ECG features in CPVT are typically normal. Dysfunction of the sarcoplasmatic reticulum calcium release channel or calcium storage causes leakage of calcium in diastole, and increasing intracellular calcium concentrations causes delayed after-depolarisations and extrasystolic action potentials, that may trigger polymorphic VT. Abbreviations: CPVT, catecholaminergic polymorphic ventricular tachycardia; VT, ventricular tachycardia; ECG, electrocardiogram; LQTS, long QT syndrome.

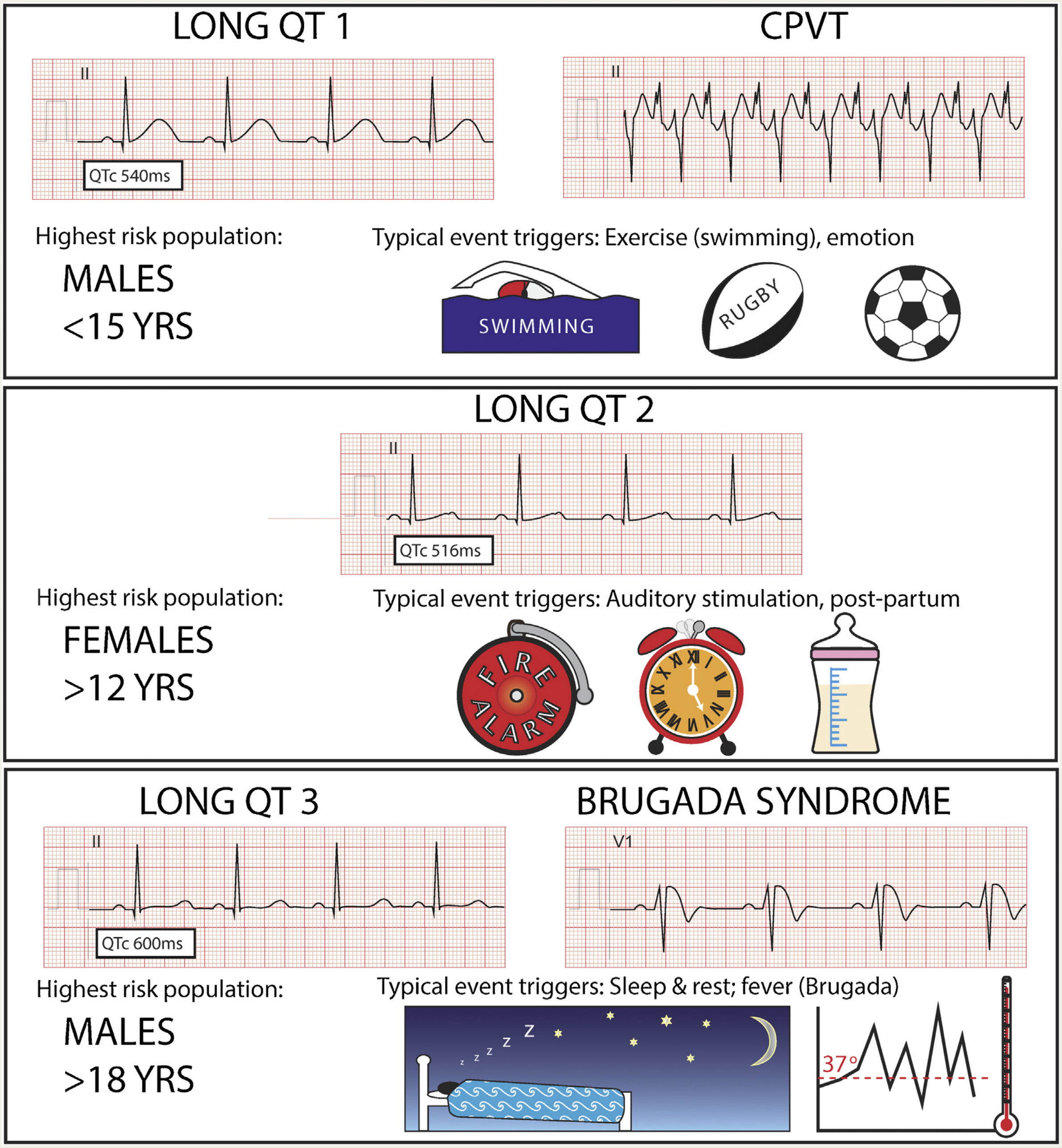

Figure 2 Diagram displaying typical phenotypic characteristics of the common cardiac ion channelopathies.

normative values are different from adults; at maximal tachycardia, mean QTc prolongation was 79 ms in children, vs 50 ms in adults [35].

Genetics

Long QT syndrome is caused by mutations in any of 17 LQTS genes (Table 1) [14,36]. Inheritance is usually autosomal dominant (previously called Romano-Ward syndrome).

The most common genotypes are LQT1, 2, 3 and 5 [37]. In each, a dysfunctional cardiac ion-channel results in prolongation and/or distortion of the cardiac action potential, and thus the QT interval and T-wave. Many of the hundreds of mutations are unique to a family or very rare. About a quarter of families with LQTS do not yet have a recognised genetic locus.

Two recently described syndromes are very severe and seem to affect only infants and young children: calmodulin related disease (genes, *CALM 1,2 and 3*) associated with seizures and developmental delay [12]; and the so-called triadin-knock out syndrome with recessive inheritance and inverted T-waves [38,39].

Determination of genotype can be useful to confirm diagnosis, allow genetic screening of potentially affected family members, assess degree of risk and hence tailor therapy.

Table 1 Long QT genes.

Clinical name	Chromosomal locus	Gene name	Current Affected	Non cardiac effects
LQT1	11p15.5	*KCNQ1 (KVLQT1)*	K^+ (I_{Ks})	Deafness with recessive form (JLNS)
LQT2	7q35-36	*HERG (KCNH2)*	K^+ (I_{Kr})	
LQT3	3p21-24	*SCN5A*	Na^+ (I_{NA})	
LQT4	4q25-27	Ankyrin B	Na^+ (I_{NA})	
LQT5	21q22.1-22.2	*KCNE1* (minK)	K^+ (I_{Ks})	Deafness with recessive form (JLNS)
LQT6	21q22.1-22.2	*KCNE2* (MiRP1)	K^+ (I_{Kr})	
LQT7 (Anderson)	17q23	*KCNJ2*	K^+ ($K_{ir2.1}$)	Anderson-Tahwil syndrome with some mutations
LQT8 (Timothy)	*12p13.3*	*CACNA1C*	*Ca + +*(I_{Ca-L})	*Timothy syndrome with some mutations*
LQT9	*3p25*	*CAV3 (Caveolin)*	Na^+ (I_{NA})	
LQT10	*11q23.3*	*SCN4B*	Na^+ (I_{NA})	
LQT11	*7q21-q22*	*AKAP9 (A −anchor protein 9)*	K^+ (I_{Ks})	
LQT12	*20q11.2*	*SNTA1 (alpha-1 syntrophin)*	Na^+ (I_{NA})	
LQT13	*11q24.3*	*KCNJ5*	K^+ (K_{ir})	
LQT14	14q24-q31	*Calmodulin1*	Many[#]	Seizures, developmental delay
LQT15	2p21.1-p21.3	*Calmodulin2*	Many[#]	Seizures, developmental delay
LQT16	*19q13.2-q13.3*	*Calmodulin3*	Many[#]	Seizures, developmental delay
LQT17		*Triadin*		

LQT7-Anderson syndrome is a rare neurological disorder characterized by periodic paralysis, skeletal developmental abnormalities, and QT prolongation.
[#]*Calmodulin*.

Genotype-Phenotype Correlation in LQTS and Indicators of High Risk

The three most common genotypes (LQT1, LQT2 and LQT3) tend to have genotype-specific syncope triggers for cardiac events, have characteristic T-wave morphologies [40], and age and gender correlated features of high risk (see Figure 2). Subjects with LQT1 and LQT2 tend to have several ''warning'' syncopal episodes before a sudden death, whereas in LQT3 the first presentation is commonly sudden death [41,42].

In LQT1, boys aged 5–15 years are at highest risk, especially during exercise and particularly swimming, and they have a broad T-wave. With LQT2, it is adult women, particularly up to 9 months post-partum who are at highest risk. Auditory or emotional stimulations feature, and nocturnal events are common, arrhythmias are usually pause-dependent, and the T-wave has a low amplitude notched, or ''double-bump'', appearance. With LQT3, gene carriers are often bradycardic with late onset T waves, and sudden death during sleep.

The strongest predictors for high risk are previous cardiac arrest or syncope and a QTc interval recorded at any time during follow-up of over 500 ms [43].

Multiple Mutations

Approximately 5% of families have two mutations, and family members with both mutations tend to be more severely affected [44]. Two mutations on opposite chromosomes in either the *LQT1* or *LQT5* gene causes a severe autosomal recessive form of LQTS usually with associated sensorineural deafness, low gastric acid secretion and iron deficiency anaemia (Jervell and Lange-Nielsen syndrome, JLNS) [45].

Not All Missense Mutations Are the Same

As increasing data are collated, some individual mutations seem to be rather benign and others more malignant [46]. In general, adult women with LQT2 are at greater risk of cardiac arrest than men. However if the missense mutation is in the pore loop regions, men are at greater risk [47].

Gene Modifiers

Modifiers of gene expression include untranslated regions which modify the RNA binding site in LQT1 [32] and minor changes (single nucleotide polymorphisms) in *NOS1AP*, a gene linked to QT prolongation in the general population [33].

LQT8-Timothy syndrome is a rare condition characterised by syndactyly, facial dysmorphism, autism and severe LQTS.

The polymorphisms S1103Y in *SCN5A* in Blacks, and D85N in *KCNE1* in Whites, increase the chance of medication or drug-induced QT prolongation and arrhythmia [48]. They do so by causing minor dysfunction, giving a reduced repolarisation reserve which is only unmasked by a drug which exacerbates the dysfunction [15].

Therapy

There are four levels of therapy in LQTS, applied according to severity.

1. All gene carriers must avoid QT prolonging drugs (see www.crediblemeds.org). Caution when swimming, especially for LQT1; remove loud alarm clocks for LQT2.

2. Long acting beta blockers are recommended in all types, including LQT3 [46]; and, are given to most except those at the lowest risk, such as asymptomatic pre-pubertal females and adults over 20 years with LQT1 and a consistently normal QT interval [49].

3. Left cardiac sympathetic denervation is especially effective in (high risk) LQT1, or in those who need but are unable to take beta blockers. Side-effects are common but usually well tolerated [50].

4. Implanted defibrillators are reserved for those who have had a cardiac arrest, those with syncope whilst taking beta blockers and others still at high risk despite the above therapies [51,52], such as adult women with LQT2 and a QTc over 550 ms especially if there is a history of syncope [14,53].

J-Wave Syndromes: Brugada Syndrome and Early Repolarisation Syndrome

The J-wave syndromes include BrS and early repolarisation syndrome (ERPS) [60]. They are distinct entities but have some clinical similarities, namely they share a similar predisposition for sudden cardiac death in the third decade of life, male predominance and response to medical therapy [60]. The pathophysiological mechanism of these disorders is disputed (see Figure 1) [60]. The mechanism of arrhythmogenis may be quite distinct as well [54,55].

Brugada Syndrome

Brugada syndrome is diagnosed when the typical ECG signature is observed in an apparent structurally normal heart and is more prevalent in South Asian countries. This ECG signature associates with a risk of potentially lethal arrhythmias that typically occur under vagal triggers (e.g., after meals and during the night) or during fever [18]. Risk of arrhythmias is highest is in the fourth and fifth decades, and males are more affected than females.

The pathophysiology of the ECG features and the arrhythmogenic substrate are disputed but increasing evidence is emerging that minor structural abnormalities in the right ventricular outflow tract (RVOT) area underlie the disease. As such, BrS may have to be regarded as part of the ARVC spectrum (arrhythmogenic right ventricular cardiomyopathy) [56].

Diagnosis

To diagnose BrS, the typical 'type 1' ECG is required (Figures 1 and 2) [57], where right precordial concave ST segment elevation (J-point elevation of at least 2 mm), followed by ST-depression, occurs in the same leads. The ECG sign may not be consistently present and could be unmasked by a class Ic drug challenge (i.e. ajmaline, flecainide). *However, when the ECG is unmasked by drugs, additional clinical criteria are required for the diagnosis BrS* [57]. Associated arrhythmias have their origin in the RVOT; usually, a short coupled extra systole is followed by a rapid polymorphic VT/VF.

Genetics

The genetics of BrS is more complex than the other primary arrhythmia syndromes. The first gene identified, i.e *SCN5A*, still stands as a potential causal gene but all other 20+ genes, encoding for different ion channel (subunits) are now all disputed as causal, monogenetic, causes for BrS [58]. In fact, there is increasing evidence that BrS is an oligogenetic disease, with involvement of more than one genetic factor with different effect sizes [59]. The more of these genetic factors one has, the higher the likelihood of having a type 1 Brugada pattern.

Currently, molecular genetic testing should be limited to *SCN5A* and in *SCN5A* families (presymptomatic) and counselling should include an ECG, because phenotype positive–genotype negative cases have been described within these families [60]. There might be some role for genetic testing in risk stratification [61].

Therapy

All patients are advised to manage fevers and avoid large meals late before going to bed. An implantable cardiac defibrillator (ICD) is indicated for resuscitated patients, and those with documented ventricular arrhythmias or typical arrhythmic syncope. The risk for asymptomatic patients with a spontaneous type 1 ECG is not well defined and methods to define their risk more accurately are disputed. Different studies provide controversial results [62]. Probably the most reliable risk markers are spontaneous variation in the ECG pattern and marked fractionation of the QRS complex.

An emerging therapy is ablation of fractionated signals picked up from the epicardial layer of the RVOT. Extinction of all fractionated activity in this area normalises the ECG and abolishes arrhythmias during initially reported follow-up [63]. Pharmacological therapies exist in the form of oral quinidine or, in acute situations with an arrhythmic storm, isoprenaline given intravenously.

ERPS (Early Repolarisation Syndrome)

Elevation of the J point, at the end of the QRS complex is a common, benign phenomenon, occurring in the inferolateral ECG leads. It is diagnosed when a J point notch or ST segment is elevated greater than 1 mm in two or more contiguous inferior and or anterior leads excluding V_1-V_3 [25].

However, early repolarisation is more prevalent among those with idiopathic VF, and rare rhythm strips have shown a rising J point prior to VF onset [64]. However, the ECG appearance of ERPS is so common (over 5% of the normal population, and 25% of athletes), that it cannot be used as a screening tool for risk of sudden death on a population basis. When identified after a cardiac arrest or an autopsy negative sudden death, and other causes are excluded, it may be diagnosed as a cause of the event if ECG criteria are met [57].

Like in BrS, arrhythmia prevention may be achieved with quinidine along with defibrillator back-up, and arrhythmia storms can be managed with isoprenaline [57].

Genetic testing has no value in these patients to date.

CPVT (Catecholaminergic Polymorphic Ventricular Tachycardia)

Typical Presentation and Diagnosis

The typical presentation is a child between the age of 4 and 12 years presenting with sudden exercise-related syncope or cardiac arrest, often related to swimming, and tending to be worse in males [65,66]. Sudden Arrhythmia Death

Syndrome autopsy series find CPVT almost as commonly as long QT syndrome [7,67], so, given it is much rarer than LQTS, it is clearly much more severe. Cases in infancy (sudden infant death) are rare, and milder or later presenting forms in mid-adult life are being recognised increasingly. Many syncopal episodes in fact occur during ''wakeful rest'' [66]. The resting 12-lead ECG is normal. The diagnosis is made by exercise testing, after the exclusion of structural heart disease, by documenting premature ventricular contractions usually at heart rates over 100 beats per minute on exercise testing, which progress to polymorphic VT, and sometimes to the classic ''bidirectional VT'' which is pathognomonic (see Figure 1).

Cellular Basis and Genetics

Catecholaminergic polymorphic VT mutations lead to increased calcium release from the sarcoplasmic reticulum during diastole, and adrenaline stimulates further calcium release, resulting in delayed after depolarisations and triggered activity (see Figure 1). Approximately 60% of patients with CPVT have a mutation in the cardiac ryanodine receptor gene *RyR2* (CPVT1) [66,68]. Although this is autosomal dominant, cases presenting in young childhood are commonly *de novo*, reflecting the severity of this condition. The mutations are highly penetrant. CPVT2 is autosomal recessive and very uncommon, caused by calsequestrin mutations (*CASQ2*) [69]. Other rare cases have been linked to other calcium handling genes *CALM1* (encoding calmodulin) [70] and *TRDN* (encoding Triadin) [38]. *KCNJ2* mutations and *TECRL* have also been implicated [71,72].

Therapies and Risk Stratification

The mainstay of therapy is beta blockade. However breakthrough events are common [65]. There have been three significant lessons relating to management over the last decade:

1. Left cardiac sympathectomy was shown to be effective [73].
2. Flecainide prevents VT by inhibiting RyR2-mediated calcium release [74,75]. If beta blockers cannot be tolerated, flecainide has been used alone [76]. It also works in RyR2-negative cases [77].
3. It was recognised that ICDs can be counter-productive in polymorphic VT due to CPVT; a shock may be ineffective, and the ensuing adrenergic output can worsen the VT storm [78]. Guidelines currently suggest ICDs should be implanted after cardiac arrest for CPVT [79]; although, this is being questioned due to the remarkable efficacy of flecainide, beta blockade and cardiac sympathectomy [80]. Implantable cardiac defibrillators should be programmed to shock after a long delay, to cardiovert VF rather than worsen the VT [78].

On the Horizon for Cardiac Ion Channelopathies

Being largely monogenetic conditions, there is the possibility of gene therapy. A mouse *CASQ2* model has been created and then cured by viral transfection [81]. We might hope that pluripotential cells lines might lead to new therapies in cardiac ion channelopathies, such as flecainide has become for CPVT [82]. In the meantime, clinicians have a responsibility to screen families of individuals with a channelopathy, or an unexplained sudden death, and encourage families to participate in clinical registries to further the goal of individualised therapy.

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