Brugada Syndrome and Long QT-3 Syndrome: The Allelic Diseases

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Introduction

Both the Brugada syndrome and the long QT syndromes belong to a group of diseases termed as ion channel diseases or ion channelopathies of the heart. Other diseases in this group include familial polymorphic ventricular tachycardia, Lenegre-Lev disease, and possibly idiopathic ventricular fibrillation [1]. Ion channel diseases of the heart are caused by genetic defects in the ion channel proteins located on the cell membrane or the membrane of the sarcoplasmic reticulum. These abnormal ion channels result in abnormal conduction of the ions across membranes, therefore, causing disturbance in the electrical current flow in the heart, deriving the term primary electrical diseases of the heart. The ion channelopathies of the heart are inherited by an autosomal dominant pattern but with a variable penetrance. Patients with these diseases have otherwise structurally and functionally normal hearts, and sudden cardiac death might be the first manifestation of the disease. Death in these patients usually occurs in adolescence or early young age except in those with Lenegre-Lev disease, which primarily affects the cardiac conduction system and manifests with various degrees of atrioventricular block and intraventricular conduction delays usually at middle or old age, and may cause sudden death because of asystole or torsade de pointes (bradycardia or pause dependent) in spite of an otherwise normal QTc interval. The idiopathic ventricular fibrillation is a group of diseases that have not been well characterized. The Brugada syndrome has been branched off from the idiopathic ventricular fibrillation after Brugada and Brugada reported the first eight cases of this characteristic syndrome in 1992. It is estimated that up to 50% of patients of then described idiopathic ventricular fibrillation were of Brugada syndrome [2].

Demographics

The exact prevalence of Brugada syndrome and long QT-3 syndrome is not clearly known because Brugada syndrome was identified in the last decade, and, although the long QT syndrome was known before, various genetic and ion channel forms of the syndrome were characterized only in the last decade. The incidence of Brugada syndrome has been reported ranging from as low as 0.0006% to as high as 0.1%, depending upon the geographical region and the population studied, and could be even higher [3,4]. Both the Brugada syndrome and long QT syndrome have been reported worldwide. Probably the highest incidence of Brugada syndrome is present in the South Eastern regions of Asia [3,4,5]. About 10% of patients with long QT syndromes are of the long QT-3 syndrome. Brugada syndrome usually manifests during adulthood with male prevalence eight times more than females, and the mean age of sudden death in victims of Brugada syndrome is about 35 to 40 years. Conversely, long QT-3 syndrome manifests in pre-teenage or in teenage years, and is two to three times more prevalent in females [6]. It is estimated that Brugada syndrome is responsible for up to 50 % of all sudden cardiac deaths in patients with otherwise normal hearts.

Etiology

Both Brugada syndrome and long QT-3 syndrome share the same position on chromosome 3P21-24, and are inherited by an autosomal dominant pattern with a variable penetrance [7,8]. The Brugada syndrome is usually caused by mutations in a sodium channel gene, SCN5A, which encodes for a cardiac sodium channel located in cell membrane. However, there are reports of Brugada syndrome with normal SCN5A gene where loci distinct from SCN5A have been reported, but the candidate genes have not been identified [9]. On the other hand, of six forms of long QT syndrome (long QT-1 to long QT-6) caused by multiple genetic defects, five of those genes have been identified, and four (KCNQ1, HERG, KCNE1, KCNE2) of these are related to potassium ion channels and one (SCN5A) to the sodium ion channel [10]. As mutations in SCN5A gene cause long QT-3 syndrome, both the Brugada syndrome and

the long QT-3 syndrome are two allelic diseases caused by different mutations in SCN5A gene.

The sodium channels are voltage-gated membrane proteins responsible for the initial phase (phase 0) of the action potential in most excitable cells [11]. They open briefly upon depolarization and then rapidly inactivate (by a mechanism conferred fast inactivation) contributing to the initiation and conduction of action potential. On repetitive and prolonged depolarization, sodium channels enter most stable non-conducting states by a distinct mechanism called slow inactivation. Although it is the alpha sub-unit of the sodium channel that is involved in both Brugada and long QT-3 syndromes, the functional consequences of mutations in Brugada syndrome are different than those in long QT-3 syndrome. Mutations in Brugada syndrome are those of the loss in function of the sodium channel during early part of phase I of the action potential, whereas, the mutations in the long QT-3 syndrome are those of the gain in the function of sodium channel by their failure to close at the right time. The gain in function mutation in the long QT-3 syndrome results in a slow and constant entry of sodium during phase II of action potential.

In patients with Brugada syndrome, splice-donor, frame-shift, and missense types of mutations have been identified in SCN5A gene [12]. The SCN5A mutations in LQT-3 syndrome are missense and deletion. In addition, an overlap syndrome has been reported to exist [13,14,15]. Veldkamp et al [13] reported a single SCN5A insertion mutation that may present with features of both the Brugada syndrome and the long QT-3 syndrome by influencing diverse components of sodium channel gating function. This mutation produces an early sodium channel closure, but augments the late sodium channel current due to a slower recovery of the sodium channel from inactivation as well as due to a defect in the inactivation of the channel, which is common for both Brugada syndrome and long QT-3 syndrome phenotypes. Bezzina et al [14] described a family of a large 8-generation kindred characterized by a high incidence of nocturnal sudden death, with QTc interval prolongation and Brugada-type ECG pattern occurring in the

same subjects. In affected individuals, the QRS complex and QT intervals were prolonged and there was an ST segment elevation in the right precordial leads. Twenty-five family members had died suddenly, 16 of them during the night. An insertion mutation was linked to the phenotype and was identified in all the electrocardiographically affected family members.

Priori et al [15] reported that, upon flecainide challenge, certain long QT-3 patients demonstrate not only the prolonged QT interval but also an elevation of the ST-segment on the electrocardiogram. During flecainide administration to 13 patients from 7 long QT-3 families, the QT, QTc, JT and JTc interval shortening was observed in 12 out of 13 patients, and surprisingly, concomitant ST segment elevation of more than 2 mm in leads V1 to V3 was observed in 6 out of these 13 patients. This study demonstrated the existence of an association between long QT-3 and Brugada syndrome and implied that both syndromes may share a common genotype.

Pathophysiology

Although Brugada syndrome and long QT-3 syndrome are similar genotypically, both syndromes encompass different phenotypic characteristics because of the difference in the functional consequences of the mutations causing these syndromes. The gain in function in sodium channel causes continued entry of sodium ions into the cell during phase II of repolarization, thereby, lengthening the repolarization, which is manifested on surface electrocardiogram as a prolonged QT interval. In Brugada syndrome the sodium channel I_{Na} loses the function and is closed before time; therefore, there is no prolongation in the repolarization and the QT interval remains essentially unchanged [12].

The ST segment elevation in right precordial leads in Brugada syndrome represents the early repolarization of the right ventricular subepicardial myocardium [16,17]. In humans, the transient outward currant I_{to} is most prominent at

the subepicardial layer compared to the other layers of myocardium. The Ito is an initial repolarization current underlying inscription of the phase 1 of the action potential. In Brugada syndrome where the depolarizing inward directed rapid sodium current is terminated earlier, the Ito is left relatively unopposed, and can easily overwhelm the inward calcium current I_{Ca} resulting in an earlier repolarization, which is more pronounced in subepicardial myocardium of the right ventricle because this area being rich in Ito current. With an earlier repolarization in the subepicardial regions of right ventricle, an early loss of action-potential dome occurs while the other layers of myocardium maintain the normal duration of action potential resulting in a wider transmural dispersion of the repolarization and refractoriness. As a result, the subepicardial myocardium with a shorter duration of action-potential and a shorter refractory period could be excited by the adjacent cells with the normal duration action-potential and refractory period resulting in a phase II re-entry based polymorphic ventricular tachycardia characteristic of the Brugada syndrome.

In long QT syndrome, prolonged repolarization results in formation of early afterdepolarizations in phase III of the action potential. These early afterdepolarizations trigger ventricular ectopics, which initiate a short-long-short cycle, starting torsade de pointes in an underlying myocardial substrate of increased dispersion of repolarization with partial recovery of action potential, especially in the middle layers (M cell) of myocardium [18,19,20]. In long QT-3 syndrome, there is a marked trans-myocardial dispersion due to a slower repolarization in M-cells because M-cells possess the lowest concentration of slow activating delayed rectifying I_{Ks} current [18,19,20].

Electrocardiogram

Both the Brugada syndrome and the long QT-3 syndrome have electrocardiographic patterns that can facilitate the diagnosis. The electrocardiogram in Brugada syndrome is characterized by a right bundle branch block-type of appearance with ST segment elevation in precordial leads V_1, V_2 and V_3. The ST segment elevation could be of coving

type or the saddle type. A coving type ST segment elevation is a more specific diagnostic sign than the saddle type elevation because saddle type ST segment elevation has been reported in other conditions, including incomplete right bundle branch block, pectus excavatum, Chagas' disease, Steinert's disease, and mediastinal tumors [21]. The right bundle branch block-type appearance in Brugada syndrome is not typical of the classic right bundle branch block, and could be differentiated from it by distinct characteristics. First, in Brugada syndrome, there is no deep, wide S wave in the anterolateral limb and chest leads (lead I, AVL, V_5 and $V_{6.}$) Second, in right bundle branch block, the ST segment is usually either isoelectric or depressed in leads $V_{1,}$ V_2 and V_3 as a result of repolarization change secondary to the conduction block. Third, in right bundle branch block, the QRS complex is wide, the magnitude of width depends upon the severity of block, but in Brugada syndrome although the QRS appearance in the right precordial leads resembles right bundle branch block, the QRS complex duration remains well within normal limits.

The QT interval is not prolonged in Brugada syndrome. However, the PR and HV intervals could be prolonged. It is possible that Brugada syndrome patients who have prolonged PR or HV interval may share genetic resemblance with the Lenegre-Lev disease, a disease caused by loss of function type mutations in the sodium channel. The long-term follow up of these patients will clarify this issue because Lenegre-Lev disease results in progressive degeneration of the conduction tissue that manifests at later ages. The possibility of a subclinical overlap between both diseases has been further strengthened by a recent observation by Shirai et al [22] where a sodium channel disease with overlapping characteristics of Brugada syndrome and Lenegre-Lev disease has been reported.

Patients with Brugada syndrome may not manifest the typical electrocardiographic pattern or may have a normal electrocardiogram. In addition, the Brugada syndrome electrocardiographic pattern is not persistent, and patients may only intermittently display characteristic electrocardiograms with normal electrocardiograms in between. Administration

of Class IA and Class IC sodium channel blocking drugs increases the ST segment elevation in the right precordial leads in Brugada syndrome and predisposes the patient to polymorphic ventricular tachycardia or ventricular fibrillation [23,24]. On the other hand, these agents shorten the repolarization phase and QT interval in patients with long QT-3 syndrome, and, therefore, encompass beneficial effects in such patients. In Brugada syndrome, fever, vagal stimulation, bradycardia, and adrenergic blockade with beta-blockers increases the ST segment elevation; whereas, adrenergic stimulation, tachycardia, and isoproterenol administration decreases or may even normalize ST segment elevation [25]. The heart rate acceleration decreases the ST segment elevation by restoring the action potential dome and reducing the notch. This happens because the Ito current is slow to recover from inactivation and, therefore, is less available at faster heart rates. Similarly, in long QT-3 syndrome tachycardia shortens the QTc interval and decreases the chance of development of torsade de pointes and sudden cardiac death. In fact, cardiac pacing is a highly acclaimed treatment for patients with long QT-3 syndrome. Exercise decreases the ST segment elevation in Brugada syndrome or it may even become isoelectric, and in long QT-3 syndrome exercise decreases the QT interval that may become even super-short.

Mexiletine, a class 1B sodium channel blocker, decreases the QT interval and dispersion of repolarization in long QT-3 syndrome as well as in long QT-1 and long QT-2 syndromes by shortening the repolarization of M-cells in a larger extent than the subendocardial and subepicardial layers. Although mexiletine is a sodium channel blocker it does not have effect in Brugada syndrome because it inhibits the inactive state of the sodium channel and have rapid kinetics. The I_{to} channel blocker 4-aminopyridine decreases or abolishes the ST segment elevation in Brugada syndrome but potassium channel openers increase the ST segment elevation.

Among long QT-3 syndromes, the patients with long QT-3 syndrome have the longest QTc interval. The ST segment remains essentially isoelectric in long QT-3 syndrome, and the T wave is late appearing but of high amplitude.

The ST-T wave changes of long QT-3 syndrome resemble that of a combined electrolyte disorder of hypocalcemia with moderate hyperkalemia. There is no conduction disturbance in long QT-3 syndrome, although a repolarization dependent atrioventricular block may develop if QTc interval is markedly prolonged. A feature unique to long QT-3 syndrome is the presence of sinus bradycardia and pauses, described in half of the patients with long QT-3 syndrome.

Ventricular Tachycardia

Symptoms in patients with Brugada syndrome are caused by a fast polymorphic ventricular tachycardia or ventricular fibrillation. The polymorphic ventricular tachycardia in Brugada syndrome has a short coupling interval, whereas, in long QT-3 syndrome it has a long coupling interval. The ventricular tachycardia in Brugada syndrome is one of non-torsade type and is faster than the torsade de pointes with a higher tendency to degenerate into ventricular fibrillation. Patients with Brugada syndrome may develop ventricular fibrillation without developing antecedent ventricular tachycardia. The arrhythmias in Brugada syndrome usually appear without warning, and are more prevalent during sleep. Fever has been shown to worsen the electrocardiographic pattern in Brugada syndrome and precipitate ventricular arrhythmias.

In long QT syndrome the polymorphic ventricular tachycardia is of torsade type characterized by a markedly prolonged QT interval in the last sinus beat preceding the onset of the arrhythmia, progressive twisting of the QRS complex polarity around an imaginary baseline, complete 180 degree twist of the QRS complexes in 10 to 15 beats, changing amplitude of the QRS complexes in each cycle in a sinusoidal fashion, a heart rate between 150 to 300 beats/min, and irregular RR intervals [26]. The episodes of torsade de pointes in long QT-3 syndrome, being bradycardia or pause dependent, are most prevalent during sleep and rest. Most of the torsade episodes are self-eliminating, but it could degenerate into ventricular fibrillation. Unlike the Brugada syndrome, initiation of ventricular

fibrillation without preceding polymorphic ventricular tachycardia has not been reported in patients with long QT-3 syndrome. In familial polymorphic ventricular tachycardia, another electrical disease of the heart, there is a preceding acceleration in the heart rate before initiation of the ventricular tachycardia because the polymorphic ventricular tachycardia in this condition is catecholamine dependent, which is not the case with Brugada syndrome or with the long QT-3 syndrome.

In Brugada syndrome the tendency to develop ventricular tachycardia depends on the shortening of the action potential in the right ventricular subepicardial myocardial layers, whereas, in long QT syndrome, the relatively more prolonged repolarization of M-cells in middle myocardial layers results in lengthening of the QT interval and abnormalities in T- and U-waves providing a substrate for torsade de pointes.

Symptoms

Clinically both the Brugada and long QT-3 syndromes present with syncope, seizures, or sudden death. Patients with Brugada syndrome have a higher incidence of sudden death during sleep due to pause and bradycardia dependency, because the Ito current becomes more prominent at slow heart rate increasing the heterogeneity of refractiveness further between the subepicardial and subendocardial layers of the right ventricle. In Brugada syndrome about 85 % of the sudden death events occur during sleep or at rest, and in the long QT-3 syndrome 60 % of the sudden cardiac death events occur during sleep and at rest. Other triggers for symptoms in Brugada syndrome include fever, hyperglycemia, and the use of class IA and IC antiarrhythmic drugs, antimalarials, neuroleptics, antihistamines, antidepressants and cocaine [27,28,29,30,31,32]. About 60 % of patients with symptomatic Brugada syndrome have a family history of sudden death or have family members with electrocardiographic pattern of Brugada syndrome. Other 40% of patients have sporadic de novo mutations. About 10% of patients with Brugada syndrome suffer from

paroxysmal atrial fibrillation [33]. Therefore, palpitations in patients with Brugada syndrome could be due to polymorphic ventricular tachycardia or atrial fibrillation.

Approximately 40% of the Brugada syndrome patients with syncope or resuscitated sudden cardiac death develop a new episode of polymorphic ventricular tachycardia within two years. Among patients who are asymptomatic but with electrocardiographic pattern of Brugada syndrome, one-third present for the first time with polymorphic ventricular tachycardia or ventricular fibrillation within two years of the follow up.

Diagnosis

The diagnosis of both Brugada and long QT-3 syndrome is made on the basis of the clinical characteristics, the electrocardiographic findings, and the family history [34]. Unexplained syncope or sudden cardiac death in a family member, especially in a child or a young adult should raise a strong suspicion of the possibility of presence of a primary electrical disease of the heart in kindred. Genetic testing could be of help in borderline cases or in the cases where a new mutation is suspected, although it has not become a routine part of the diagnostic work up in Brugada or long-QT syndromes. The pharmacological test for suspected Brugada syndrome patients could be done by administering a sodium channel blocker and test is considered positive if an additional 1 mm ST segment elevation appears in precordial leads V1, V2, and V3 of the electrocardiogram [35]. Drugs that could be used for provocative testing include procainamide 10-mg/kg body weight intravenously in 10 minutes, flecainide 2-mg/kg body weight intravenously in 10 minutes, or ajmaline 1 mg/kg body weight intravenously in 5 minutes. Ajmaline is a better option for provocative testing because of its short half-life that makes it safer, and its stronger sodium channel blocker effect that increases the sensitivity of the test. The magnitude of ST elevation with sodium channel blockers is inversely proportional to the rate of dissociation of the drug from the sodium channel.

The electrocardiographic criteria of Brugada syndrome include incomplete right bundle branch block pattern and ST elevation of equal to or more than 2 mm in precordial leads V1, V2, and V3 at baseline or after administration of intravenous sodium channel blockers. The most powerful marker of cardiac arrest is presence of spontaneous ST elevation in these leads combined with a history of syncope. It has been recently demonstrated that an electrocardiogram taken with precordial leads placed in higher intercostal spaces, with or without the provocative testing, increases the detection rate in sudden unexplained death syndrome survivors and their relatives [36]. This is because the accentuation of action potential notch and loss of dome in subepicardium creating a voltage gradient between subepicardium and subendocardium may not be uniform throughout the right ventricle. Thus the ST segment elevation depends on the position of the precordial electrodes relative to the specific site affected which explains a high detection rate of higher placed precordial leads and right ventricular leads as compared to normal placed precordial leads because higher precordial lead and right ventricular leads will record electrical activity from right ventricular outflow tract and right ventricular free wall, respectively [36,37,38].

In symptomatic patients with Brugada syndrome, ventricular tachycardia is inducible in about 80 % of cases by giving 1 or 2 ventricular premature beats during programmed stimulation. The HV interval is prolonged in about half of the patients but rarely exceeds 70 milliseconds. Prolongation of HV interval explains the slight prolongation of the PR interval on surface electrocardiogram. Studies are conflicting regarding the association between inducibility of ventricular tachycardia and precipitation of life threatening events. In one study, the electrophysiological evaluation failed to demonstrate an association between inducibility by programmed electrical stimulation and spontaneous occurrence of ventricular fibrillation, with a specificity of only 34%, which was not different when two versus three premature stimuli were used [39]. On the other hand, in other studies inducibility of sustained ventricular tachycardia was a powerful

predictor of arrhythmic events both in symptomatic and asymptomatic individuals of Brugada syndrome [40,41]. Among the noninvasive markers (late potentials, microvolt T-wave alternans, QT dispersion), presence of late potentials has the most significant correlation to the occurrence of life-threatening events [42].

Treatment

The antiarrhythmic drugs and beta-receptor blockers do not protect against sudden cardiac death in Brugada syndrome. The only effective treatment available at this time for these patients is implantable cardioverter defibrillator. Beta-blocker use, actually, increases the ST segment elevation in right precordial leads signaling worsening in the repolarization abnormality. Symptomatic patients with Brugada syndrome should receive implantable cardioverter defibrillator to prevent sudden cardiac death [42]. Asymptomatic patients with an abnormal electrocardiogram and inducible polymorphic ventricular tachycardia or ventricular fibrillation on programmed electrical stimulation should also receive implantable cardioverter defibrillator. Asymptomatic patients with an electrocardiogram abnormal only after drug challenge and no inducible ventricular tachycardia could be followed up carefully without implantable cardioverter defibrillator placement. Similarly, asymptomatic patients with spontaneous abnormal electrocardiogram, but non-inducible polymorphic ventricular tachycardia and no family history of sudden cardiac death could also be followed carefully without implantable cardioverter defibrillator. The asymptomatic patients with spontaneously abnormal electrocardiogram, non-inducible ventricular tachycardia, but with family history of sudden cardiac death could be offered implantable cardioverter defibrillator, although there is not sufficient data to support this approach conclusively. The repeated episodes of polymorphic ventricular tachycardia (electrical storm) in Brugada syndrome could be treated temporarily with isoproterenol.

The preferred treatment for symptomatic patients with long QT-3 syndrome is cardiac pacing to avoid

bradycardia and pauses because the episodes of torsade de pointes in long QT-3 syndrome are bradycardia or pause-dependent. Regarding the asymptomatic patients with long QT-3 syndrome, the treatment modality is uncertain although may benefit from pacemaker if they have persistent bradycardia, especially those with family history of sudden cardiac death. It could be argued to implant permanent pacemaker in all patients (symptomatic and asymptomatic) with long QT-3 because the chances of having first event that could be lethal are up to 35 %, and because pacing is most effective in patients with long QT-3, which is consistent with the observation that with increasing heart rates, long QT-3 patients have a shorter QTc interval compared to long QT-1 and long QT-2 patients [43]. Pacemaker rates should be sufficient to normalize the QTc interval below 440 milliseconds. Beta-adrenergic blockers, which are preferred drugs for other long QT syndromes, should be used in patients with long QT-3 syndrome only after permanent pacemaker is placed, because these patients may develop beta blockade induced inappropriate bradycardia, which may even precipitate torsade de pointes [44].

Left high cervical-thoracic sympathectomy is another anti-adrenergic therapy for long QT syndrome, but is not frequently used because it requires trained personnel, and its possibility of producing Horner's syndrome [45]. Automatic implantable cardioverter defibrillator is used in those patients with long QT-3 syndrome who have survived aborted sudden death and who are symptomatic in spite of having permanent pacemaker placed and being on maximum tolerated beta-blockers. Considering the high lethality of a single episode of torsade de pointes in patients with long QT-3 syndrome, and the availability of a combined device of pacemaker with cardioverter defibrillator, it would be appropriate to use this device initially.

Mexiletine is effective in long QT-3 patients and could be used along with pacemaker and beta-adrenergic blockers in patients who remain symptomatic [46,47]. Although experimental studies have demonstrated beneficial effects of both mexiletine and flecainide in patients with long QT-3 syndrome, caution should be used while using

flecainide in these patients, as flecainide may precipitate ventricular tachycardia in cases they have SCN5A mutations of both long QT-3 syndrome and Brugada syndrome [15].

Prognosis

Up to 40% of the individuals with electrocardiograms suggestive of Brugada syndrome develop an episode of polymorphic ventricular tachycardia or sudden death during the next two years of follow up. Recurrence of malignant arrhythmia is higher after the occurrence of symptoms. Asymptomatic patients and carriers with normal electrocardiogram in whom the electrocardiographic pattern becomes manifest only by sodium channel blocking drugs or who are noninducible on programmed electrical stimulation have a relatively benign course [41]. Among asymptomatic individuals, those with a spontaneously abnormal electrocardiogram and inducible ventricular arrhythmias have poor prognosis [48]. Aborted sudden death, syncope, a family history of sudden death, spontaneously abnormal electrocardiogram, inducibility of ventricular arrhythmias, and presence of late potentials are the markers of life-threatening events [40,41,42]. The annual mortality in Brugada syndrome ranges from 1 to 15 % and that in long QT-3 syndrome from 5 to 10 %. Approximately, 20% of all cardiac events in long QT-3 syndrome are fatal. Although patients with long QT-3 syndrome has less number of episodes of torsade de pointes compared to the patients with other long QT syndromes, the lethality of an individual episode of torsade de pointes is higher in long QT-3 syndrome.

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