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A SYSTEMATIC REVIEW ON SUDDEN CARDIAC DEATH WITH AN EMPHASIS ON PROLONGED QT INTERVAL SYNDROME AND THE ROLE OF MOLECULAR AUTOPSY IN THE DIAGNOSIS OF SUDDEN CARDIAC DEATH.

Forensic Medicine

V P Kumar Sriperumbuduru* Assistant Professor, Department of Forensic Medicine and Toxicology, Alluri Seetharama Raju Academy of Medical Sciences (ASRAM) Malkapuram, Eluru-534005, Andra Pradesh, India. *Corresponding Author

Sanjay Punuri Professor, Department of Forensic Medicine and Toxicology, Alluri Seetharama Raju Academy of Medical Sciences (ASRAM) Malkapuram, Eluru-534005, Andra Pradesh, India.

Srinivas Chebrolu Professor, Department of Forensic Medicine and Toxicology, Alluri Seetharama Raju Academy of Medical Sciences (ASRAM) Malkapuram, Eluru-534005, Andra Pradesh, India.

Mynedi Seetharamaiah Professor, Department of Forensic Medicine and Toxicology, Alluri Seetharama Raju Academy of Medical Sciences (ASRAM) Malkapuram, Eluru-534005, Andra Pradesh, India.

KEYWORDS

Sudden cardiac death, prolonged QT syndrome, cardiac structural abnormalities, cardiac functional abnormalities, epidemiology of sudden cardiac death, epidemiology prolong QT syndrome, risk factors of sudden cardiac death, risk factors of prolonged QT syndrome, aetiology of sudden cardiac death, aetiology of prolonged QT syndrome, the pathogenesis of sudden cardiac death, the pathogenesis of prolonged QT syndrome.

INTRODUCTION:

Sudden cardiac death is sudden and unexpected death from a cardiovascular ailment in a person with or without pre-existing cardiac disease, within 1 hour of the onset of a terminal illness The interaction between the triggers and underlying cardiac abnormalities leads to electrical instability (polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF)) which generates lethal ventricular arrhythmias. Sudden cardiac deaths are mostly due to coronary heart disease followed by cardiomyopathies or channelopathies (LQTS, BrS, SQTS, Catecholaminergic Polymorphic VT) which are caused by genetic alterations in ion channels or associated protein. Individuals with underlying structural heart disease, poor dietary intake or having inflammatory markers are more susceptible to sudden cardiac death. Diurnal/seasonal variation, physical activity, psychosocial determinants can act as triggers that increase sympathetic activity which can lead to arrhythmias and death eventually. It accounts for more than half of the deaths from coronary heart disease and 20% of all deaths.[1]

Etiopathogenesis of sudden cardiac deaths

Sudden cardiac death due to cardiac arrhythmias is one of the major causes of premature death. Hypertension, hyperlipidemia, diabetes mellitus, smoking and obesity contribute to coronary heart disease which in turn results in sudden cardiac death. The incidence of sudden cardiac death increases with age (around 35 years old) with male patients having a higher prevalence than premenopausal females and being black has a higher incidence [2]. Having a family history of cardiac arrest in a first-degree relative increases an individual's risk of cardiac arrest by half which is associated with genetic factors [2]. It is caused by mutations in 15 genes that have been linked to the LQTS phenotype [2]. Congenital Long QT syndrome is a genetic channelopathy, characterized by a prolonged QT interval due to delayed repolarization in the ventricular myocardium. This increases the vulnerability to develop ventricular tachyarrhythmia which impairs the cardiac output and blood pressure resulting in syncope and sudden cardiac death. A secondary event due to prolonged QT from acquired heart disease, side effects of the QT-prolonging drugs (quinidine, disopyramide, encainide, hydrochloride, procainamide, flecainide acetate, amiodarone, sotalol, and bepridil hydrochloride at therapeutic doses [2,6,8,15]), electrolyte imbalance (Diuretic-induced hypokalemia[6,15]), hypothermia, neurological events such as a stroke(CVA) and/or bradycardia is known as Acquired Long QT syndrome. Syncope is generally the most commonly encountered first episode in LQTS patients, and aborted cardiac arrest/sudden cardiac death (ACA/SCD) is rare (1–3%) [2].

Most of the cases of SCD over the age of 40 years is the result of coronary artery disease, while in the young-adult population (<35 years old) is often caused by arrhythmic syndromes [3]. Sudden unexplained death (SUD) is used in cases where a thorough postmortem examination including external, internal and ancillary investigation fails to determine the cause of death. Genetic testing can be used in making a diagnosis for identifying the cause of death in unsolved post-mortem cases. For the surviving family members, this test can be used for diagnosis of LQTS, gene and mutation-specific risk stratification and their management.

The myocardium is vulnerable to dysrhythmia when there are changes in cardiac action potential and cellular excitability causing alteration of the timing and shape of the action potential [4]. Each ion channelopathy has its electrocardiogram (ECG) signature, and typical mode of presentation [4]. Boys aged 5–15 years are at the highest risk [4]. Adult women, particularly up to 9 months post-partum are at the highest risk [4]. 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 [4].

LQTS with an autosomal dominant pattern (Romano-Ward syndrome) and a rare LQTS with autosomal recessive pattern (Jervell and Lange-Nielsen syndrome) are inherited by Mendelian fashion. In approximately 85% of genotype-positive cases of LQTS, the patient carries a mutation inherited from one of the parents while the remaining 15% is a de novo mutation [5]. Compound mutations (ie, ≥2 mutations) are found in 10% of genotype-positive patients and the clinical manifestation of disease in such patients is often more severe [5]. 24-h Holter recordings and an exercise or epinephrine test can be used to reveal subclinical QT prolongation in latent LQTS patients (1-3 diagnostic score) with normal QTc at rest. Of the patients who eventually become symptomatic, 50% experience their first cardiac event by the age of 12, and 90% by the age of 40 [5]. Adults between 18 and 40 years old are prone to experience any cardiac events with a history of ≥1 cardiac event before age 18 years, female sex, longer QTc interval (≥440ms) and LQT2. For patients older than 40 years, LQT3 patients have significantly more cumulative lethal arrhythmic events (35%) than LQT1 (14%), LQT2 (24%) and genotype-negative patients (10%) [5]. A history of epilepsy has been reported to be more common with LQT2, possibly because KCNH2 is expressed in the brain as well [5]. The risk for ACA/SCD is not significant in a first-degree relative with a family history of SCD. Family members with the same mutation could have different phenotypes (sudden death, syncope, asymptomatic) due to incomplete genetic penetrance and variable expressivity which may be influenced by multiple genetic and environmental factors in a more complex genetic model. Modifier genes are common genetic variants (>1% of affected individuals) that

influence the disease severity [5]. However, they have less significance compared to causal gene mutation. (Autosomal dominant & autosomal recessive). Beta-blocker therapy is the first choice for LQTS [5]. In patients with a history of aborted cardiac arrest (ACA) or who are non-compliant with β-blocker therapy, they tend to have recurrent events. To suppress recurrent cardiac events in LQT1 and LQT2, propranolol and nadolol are better than metoprolol. Cardiac sympathetic innervation can be denervated by ablation of the lower two-thirds of the left stellate ganglion together with the thoracic ganglia T2–T4 in Left cardiac sympathetic denervation (LCSD). Adjunctive therapy (Oral K+ supplements, mexiletine, ranolazine, Left cardiac sympathetic denervation) may benefit certain LQTS patients in conjunction with beta-blocker therapy. Only for patients who have frequent syncopal episodes despite being on maximal doses of β-blocker or at high risk of recurrent ACA/SCD, implantable cardioverter-defibrillator (ICD) is used.

Return of consciousness occurs in sudden termination of most tachyarrhythmia patients, however, it can also degenerate to VF which leads to death. Ventricular arrhythmia is the consequence of electrical instability, manifesting as dysmorphic T waves on ECG. This unusual QT and T-wave changes occur in approximately 8% of patients [6]. QT interval measurement should be made during rest because it is influenced by the autonomic tone and heart rate. Family history and electrocardiograms of all other family members should be taken once an individual is identified with QT prolongation or family history of early sudden death and unexplained syncope.

Repetitive triggered or sustained functional reentry can progress to EAD which is the trait of TdP. Mutation of LQTS genes may affect any stages of protein transcription, translation, trafficking to the cell membrane, and gating of the ion channels. Interference with IKr mainly in patients with a previously silent genetic mutation leads to action potential prolongation in most acquired LQTS. The normal range for the QT interval is 370 to 440 milliseconds for men, with the upper limit extended to 450 or 460 milliseconds in women [7].

LQTS diagnosing criteria;

(1) An LQTS risk score □of 3.5 without a secondary cause for QT prolongation [8].
(2) An unequivocally pathogenic mutation in one of the LQTS genes [8].
(3) In the presence of a corrected QT interval (QTc) □500 ms on repeated 12-lead ECGs using Bazett's formula in the absence of secondary cause for QT prolongation [8].

Criteria for the patient who is eligible for diagnostic testing.

(1) strong suspicion for LQTS based on clinical examination [8,10,11].
(2) patient has asymptomatic QT prolongation in the absence of other clinical conditions that may prolong QT interval [8,10].
(3) A patient is asymptomatic, with QTc values 446 ms (prepuberty) or 448ms (adults) on serial 12-lead ECG [8].
(4) LQTS-causative mutation is identified in an index case, mutation-specific genetic testing is recommended for the family members [8]

Diagnostic scoring system table[9]

Table 1. Diagnostic Criteria for LQTS

Finding	Score
Electrocardiographic Corrected QT interval, ms	
>480	3
460-470	2
450 (in males)	1
Torsades de pointes	2
T-wave alternans	1
Notched T-wave in 3 leads	1
Low heart rate for ages	0.5
Clinical history Syncope	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history	
Family members with definite LQTS Unexplained	1
SCD in immediate family members <30 yrs old	0.5

Scoring:

< 1 point, low probability of long QT syndrome(LQTS): 2 to 3 points, intermediate probability of LQTS: and >4points, high probability of LQTS. ↑Findings in the absence of medication or disorders known to affect these electrocardiographic findings. The corrected QT interval is calculated by Bazzet's formula: QT/RR. ↕Torsades de pointes and syncope are mutually exclusive. Resting heart rate below the second percentile for age. The same family member cannot be counted in both categories. Reprinted, with permission, from Schwartz et al.[9]

Triggers, risk, biophysical function, location of mutations and lethality of developing cardiac events in LQTS patients depend on the LQTS genotypes. Coassembly or trafficking defects and formation of defective channels involving mutant subunits are the two distinct biophysical mechanisms that moderate the reduced repolarizing current in patients with potassium channel mutations. Delayed repolarization due to mutations in the alpha-subunit of ion channels involving either the slowly (IKs, KCNQ1, LQT1) or rapidly (IKr, KCNH2, LQT2) acting repolarizing cardiac potassium currents can induce QT prolongation. Different LQTS genotypes have their characteristic T wave. Failure of channels to properly close after initial depolarization and continued leakage of sodium into the channel due to SCN5A sodium-channel mutations leads to prolonged action potential.

Three major causative genes recognized for LQTS and associated with LQTS types 1-3 are KCNQ1, KCNH2, SCN5A (90%) [3,5,8]. Loss-of-function mutations in KCNQ1 cause about 35% of LQTS type 1 (LQT1), while loss-of-function KCNH2 mutations contribute approximately 30% of LQTS (LQT2) [10]. Gain-of-function SCN5A mutations underlie roughly 10% of LQTS (LQT3) [10]. Additional ion channel α subunits(CACNA1C, KCNJ5), key cardiac potassium-(AKAP9, KCNE1, KCNE2) and sodium-channel (CAV3, SCN4B SNTA1) interacting proteins, or calcium-binding messenger proteins (CALM1, CALM2) are encoded by minor LQTS-susceptibility genes which only limited to genotype-phenotype correlations.

CACNA1C encoded cardiac L-type calcium channel (LTCC) α subunit that is important for excitation-contraction coupling in the heart and mediates an inward depolarizing current in cardiomyocytes. (we stopped here)Mutation of this gene leads to a gain-of-function with increased ICaL, and increased cell surface expression of the mutant ion channel consistent with the clinical phenotype of QT interval prolongation and prolong cardiac action potential [10]. Mutation in the KCNJ5-encoded G protein-coupled, inwardly rectifying potassium channel subunit Kir3.4 leading to a loss-of-function electrophysiological phenotype associated with reduced plasma membrane expression. Their symptoms are recurrent palpitations with usually recurrent syncope, and with either persistent or permanent atrial fibrillation (AF) or atrial tachycardia (AT) [10]. Ion channels do not operate in isolation but instead function as macromolecular complexes consisting of the ion channel pore-containing α subunits as well as auxiliary β subunits and other regulatory proteins that interact with and influence ion channel activation and deactivation/inactivation. Mutation in the gene encoding them will lead to persistent late sodium current thus leading to action potential prolongation [10]. Mutations (D130G-CALM1 and D96V-CALM2) in genes (CALM1 and CALM2) that encode for calmodulin, an essential calcium-signalling protein that is involved as a Ca2+ sensor for Ca2+- dependent inactivation of the LTCC (Cav1.2), inactivation of the cardiac sodium channel (Nav1.5), and activation of the voltage-gated potassium channel (Kv7.1). These missense mutations localize to critical EF-hand calcium-binding motifs and reduce calmodulin's calcium-binding affinity by seven-fold. Usually, they have common cardiac features of life-threatening ventricular arrhythmias occurring very early in life (three of four during infancy), including frequent T-wave alternans (all cases), markedly prolonged QT intervals (QTc > 600 ms, all cases), and intermittent 2:1 AV block (3 of 4 patients), Ventricular fibrillation and had some degree of neurodevelopmental delay ranging from mild delay in language development to severe cognitive or motor development and seizures [10]. Genetic tests must be understood as probabilistic rather than unconditionally deterministic, and the genetic test results must be interpreted cautiously and incorporated into the overall diagnostic evaluation for these disorders [10].

The majority of events occur during exercise and the inability of the QT interval to shorten with the increase in heart rate is thought to be the mechanism [11]. In LQT1, cardiac events frequently occur during exertion or emotional stress (I.e: swimming) [5,11]. LQT1 the T-waves were tall and broad [5,11]. LQT2, the T waves were frequently notched, bifid and of low amplitude [4,11]. In LQT2 events are frequently precipitated by emotion, alarm clocks, doorbells or a telephone ring

can precipitate an event [4,11]. It is reported that about 5% of sudden infant death syndrome (SIDS) is due to LQTS, mostly due to LQT3 [11]. In LQT3 events mostly occur during sleep, rest or at night [5,11]. LQT3 there was a long isoelectric segment with narrow and peaked T waves and appears at the very end of the QT interval [11]. Not all LQTS patients will have an identifiable mutation [11]. Genetic testing involves DNA sequencing of at least the three common genes associated with LQTS: KCNQ1, KCNH2 and SCN5A [11]. The presence of prolonged QT on the ECG (positive phenotype) strongly increased the likelihood of finding a positive mutation on genetic testing [11]. A negative test does not exclude it as the patient may have as yet unidentified mutation [11]. Risk stratification of LQTS patients, genotyping is very useful in excluding the diagnosis in family members once the mutation has been identified in the proband and will save unnecessary treatment with beta-blockers and restriction of sporting activities [11].

LQT1 is caused by a loss-of-function mutation in IKs, which lead to decreased potassium efflux during repolarization and therefore prolongation of the action potential [3,7,12]. LQT2 is due to a loss-of-function mutation in IKr, which leads to decreased potassium efflux during repolarization and therefore prolongation of the action potential [3,12]. LQT3 involves a gain-of-function mutation in the SCN5A gene leading to an increase in INa; this sustained inward sodium current during the plateau phase of the action potential opposes normal repolarization and prolongs the action potential [3,7,12].

Andersen-Tawil syndrome (ATS)-LQT7 is a skeletal muscle and cardiac muscle disease characterized by periodic paralysis, developmental dysmorphisms, and prolonged QT intervals. Mutations in KCNJ2 were found to underlie this multisystem disorder. KCNJ2 encodes the inward rectifier K+channel alpha subunit Kir2.1, which is expressed in skeletal and cardiac muscle cause trafficking defects, and hence loss of functional channel activity, of inwardly rectifying potassium channels [13]. Timothy syndrome(TS)- LQT8 is a wide variety of organ dysfunction, including lethal arrhythmias, webbing of fingers and toes (syndactyly), autism, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and markedly prolonged QT intervals on the ECG. Mutations in a splice variant of the gene (CACNA1I) coding for the alpha-subunit (Cav1.2) of the L-type calcium channel. Cav1.2 channel is a principal pathway for calcium entry in cells in which it is expressed in the heart, its activation and inactivation are critical regulators of action potential waveforms and activation of contraction [13].

Adaptor protein (Ankyrin B) mutation-LQT4.Ankyrin-B is not an ion channel protein, but an adaptor protein that is associated with cytoskeletal interactions. Ankyrins bind to multiple proteins that can contribute (directly or indirectly) to the cardiac electrical activity which include the anion exchanger (Cl–/HCO3– exchanger), the Na+, K+–ATPase, voltage-sensitive sodium channels, the Na+/Ca2+ exchanger (NCX, or INa-Ca), and calcium release channels including those mediated by ryanodine or inositol trisphosphate (IP3) receptors where disruption of these channels' cellular organization could lead to arrhythmia [13,14]. Mutation of this protein leads to LQT-4 [13,14].

Sudden death in infancy can be attributed to infection, cardiovascular anomalies, child abuse/ negligence, accidents, homicide or metabolic/genetic disorders and for the unknown causes even after following a death scene and medico-legal investigation including autopsy is known as sudden infant death syndrome (SIDS) [15]. SIDS' pathophysiological mechanisms remain poorly understood but it may be caused by cardiac arrhythmias (prolonged QT interval) [15]. There are no apparent warning signs and sudden death often occurs as the sentinel event in nearly half of young victims (1 - 35 years old), so the medico-legal investigation and autopsy are needed to determine the cause and manner of death [15]. A post-mortem examination may detect a non-cardiac origin for the sudden death (asthma, epilepsy or pulmonary embolism) [15]. SCD is the prevailing cause of sudden death in young people, with structural cardiovascular abnormalities often evident at autopsy (hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), congenital coronary artery anomalies and myocarditis) [15]. Autopsy-negative sudden unexplained death (SUD) is an absence of identifiable morphologic abnormalities at autopsy which occurs up to 30% of sudden deaths involving previously healthy children, adolescents and young adults [15]. Higher occurrence of ARVC over HCM in SCD may be related to a distinct genetic predisposition or perhaps there has been a noticeable reduction in HCM-associated sudden deaths due to their uncompromising pre-participation screening programme [15]. A significant number of sudden deaths remain unexplained following a comprehensive post-mortem investigation including full autopsy may be associated with heritable cardiac channelopathies with having a family history of sudden premature death, suggesting a heritable predisposition for a malignant dysrhythmia [15]. Some of the cases were preceded by triggers such as physical exertion or strong emotion [15]. Congenital LQTS comprises a distinct group of cardiac channelopathies characterized by delayed repolarization of the myocardium, QT prolongation and increased risk for syncope, seizures and SCD in a structurally normal heart and otherwise healthy individual [15]. Individuals with LQTS may or may not manifest QT prolongation on a resting 12-lead surface electrocardiogram (ECG) [15].

This repolarization abnormality is usually not followed by a consequence, however (rarely), when triggered by exertion, swimming, emotion, auditory stimuli such as an alarm clock or during the period following childbirth, the tachyarrhythmia can occur leading to a potentially life-threatening event [15]. It is a genetically heterogeneous disorder most often inherited in an autosomal dominant mode that encodes for critical cardiac ion-channel subunits involved in cardiac action potential [15]. CPVT is heritable arrhythmia syndrome that classically manifests with exertion-induced syncope or sudden death, commonly in young males and closely mimics that of LQTS [15]. It has a completely normal resting ECG and is electro cardiographically suspected following either exercise or catecholamine stress testing that demonstrates significant ventricular ectopy in a structurally normal heart [15]. Mutations in the RyR2-encoded cardiac ryanodine receptor/calcium release channel represents the most common genetic subtype of CPVT [15]. Incomplete penetrance and variable expressivity are hallmarks in arrhythmia syndromes such as LQTS and CPVT and consequently lead to 'concealed' forms of these disorders which not be enough to detect LQTS or CPVT in unsuspecting individuals [15]. A molecular autopsy is genetic testing of autopsy material which can help investigators to determine the spectrum and prevalence of pathogenic cardiac ion channel mutations in unique series of SUD cases and subsequently benefit those left behind [15]. Considering that autopsy-negative SUD accounts for a significant number of sudden deaths in young people and that epidemiological, clinical and now post-mortem genetic analyses all suggest that approximately one-third of SUD after the first year of life may stem from a lethal cardiac channelopathy, the cardiac channel molecular autopsy should be viewed as the standard of care for the post-mortem evaluation of SUD [15].

CONCLUSION:

Sudden cardiac death is the most common lethal manifestation of a cardiac condition. Sudden cardiac death is most commonly due to ventricular tachyarrhythmia. The arrhythmic events are inclined in patients associated with coronary heart disease or other forms of structural heart disease. Most genetic abnormalities identified appear to prolong the duration of action potentials by decreasing potassium current (loss of function mutation) or increasing sodium/calcium current (gain of function mutation). This will then result in prolonging QT on ECG. It is influenced by age, genotype, gender, environmental factors, therapy, and possibly other modifier genes. LQTS can be classified into acquired and congenital. The acquired type is mostly due to drugs or electrolyte imbalance whereas the congenital type is due to the dysfunction of the potassium and the sodium channel. To determine the spectrum and prevalence of pathogenic cardiac ion channel mutations in unique series of SUD cases and subsequently benefit those left behind, molecular autopsy which is a genetic test of autopsy material helps the investigators.

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