Texas Heart Institute Journal

Ali Massumi Cardiac Arrhythmia Symposium

Inherited Arrhythmia Syndromes

Jitae A. Kim, MD[1]; Mihail G. Chelu, MD, PhD[2]

[1]Department of Medicine, Baylor College of Medicine, Houston, Texas
[2]Section of Cardiology, Baylor College of Medicine, Houston, Texas

Inherited arrhythmias constitute a wide spectrum of disorders whose clinical manifestations range from no symptoms to sudden cardiac death (SCD). These disorders increase the risk of ventricular arrhythmias in the absence of structural heart disease and are a recognized cause of SCD in young, otherwise healthy individuals. The target of intense research for 3 decades, they are now known to be caused by underlying mutations to myocardial ion channels and handling proteins.[1,2] We review the recognized inherited arrhythmias: long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), early repolarization syndrome (ERS), and idiopathic ventricular fibrillation (IVF).

Long QT Syndrome

Long QT syndrome is one of the most common inherited arrhythmias, affecting approximately 1 in 2,000 individuals.[3] Mean age at symptom onset is approximately 14 years, and SCD is the initial presentation in up to 13% of cases.[4] Because there is no absolute cutoff value for a prolonged QTc, LQTS is often diagnosed by using the Schwartz scoring system, which combines clinical history and other electrocardiographic (ECG) findings.[5] Seventeen genetically unique subtypes of LQTS have been identified; three of them (LQT1, LQT2, and LQT3) account for >90% of cases.[6] Identification of the underlying genetic mutation in LQTS patients is clinically important because each subtype is associated with different triggering events, treatment responses, and survival rates.

The estimated 10-year mortality rate for untreated symptomatic LQTS is high, at nearly 50%.[7] Proper treatment, however, can reduce the mortality rate to approximately 1%, highlighting the importance of early intervention.[8] The primary treatment is with β-blockers (propranolol or nadolol).[9] The effectiveness of β-blockers appears to vary by LQTS subtype, with the most benefit for patients with LQT1, LQT2, and LQT3 subtypes.[10] Combining mexiletine with β-blockers has proven particularly beneficial for LQT2 and LQT3.[11,12] If β-blocker therapy fails, left cardiac sympathetic denervation is recommended; this is most effective against the LQT1 subtype.[9] Implantable cardioverter-defibrillator (ICD) therapy is indicated for secondary prevention, but should also be considered for primary prevention in patients with high-risk characteristics (including but not limited to QTc >500 ms, LQT2 or LQT3 genotype, and young age at presentation).[13]

Short QT Syndrome

Short QT syndrome is rare, having first been described in 2000 and reported in only about 220 cases since then.[14,15] The typical cutoff value for short QTc is 360 ms in the presence of an appropriate clinical history or 330 ms in the absence of symptoms.[16] Affected individuals are at increased risk of both ventricular and atrial arrhythmias, with slow atrial fibrillation resistant to cardioversion occasionally observed.[14] The most common presentation is SCD or aborted SCD, observed in up to 34% of affected families.[14] Several causative gene mutations have been implicated in affected families,

★ ***CME Credit***

Citation:
Kim JA, Chelu MG. Inherited arrhythmia syndromes. Tex Heart Inst J 2021;48(4):e207482. doi: 10.14503/THIJ-20-7482

Key words:
Arrhythmias, cardiac/genetics/physiopathology; Brugada syndrome; catecholaminergic polymorphic ventricular tachycardia; channelopathies; death, sudden, cardiac; electrophysiology; long QT syndrome; paroxysmal ventricular fibrillation; short QT syndrome

Corresponding author:
Mihail G. Chelu, MD, PhD, Section of Cardiology, Baylor College of Medicine, 7200 Cambridge St., BCM 621, Suite A6.137, Houston, TX 77030

E-mail:
mihail.chelu@bcm.edu

although in most cases no responsible mutation is found.[17] Treatment of symptomatic individuals includes ICD therapy for secondary prevention and quinidine for its QT-prolonging effects.[13,18] The role of treatment in asymptomatic patients is less clear, with further studies needed to accurately risk-stratify this population, given the overall low risk of SCD.[13,14]

Brugada Syndrome

First described in 1992, BrS is characterized by right bundle branch block with ST-segment elevation in leads V_1 through V_3 and a high incidence of SCD.[19] Symptoms typically occur at night or at rest. The estimated prevalence of BrS worldwide is 1 in 2,000 and even higher in Asian countries, where it is endemic.[20] The disorder occurs predominantly in males and, in endemic areas, is the leading cause of natural death in men younger than 40 years.[21]

The most prevalent BrS-associated genetic mutation (found in up to 25% of patients) occurs in *SCN5A*, a gene that encodes the I_{Na} sodium channel and is implicated in several other disorders, including LQT3.[17] Three distinct ECG patterns have been associated with BrS; however, only one, consisting of a coved ST-segment elevation followed by a negative T wave (type 1), is diagnostic. In cases where the diagnosis is uncertain, the type 1 pattern can be induced by challenge with a sodium channel blocker such as ajmaline or flecainide.

Treatment for BrS includes ICD therapy (for patients with a history of ventricular arrhythmias), catheter ablation, and quinidine.[13] Fever and certain sodium channel–blocking drugs may unmask BrS, and avoiding them is recommended. In asymptomatic patients with only an inducible type 1 pattern, electrophysiologic studies may help identify high-risk patients who might benefit from intervention.[13]

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia is characterized by recurrent exercise-induced bidirectional or polymorphic VT[22] and is particularly malignant, causing SCD at initial presentation in up to 30% of patients and cardiac arrest by age 20 to 30 years in up to 50%.[23] The estimated prevalence of CPVT is 1 in 10,000.[24] In more than half of cases, a mutation in the gene encoding the ryanodine receptor is implicated; the consequent abnormal leakage of calcium from the sarcoplasmic reticulum leads to delayed afterdepolarizations and ventricular arrhythmias in response to known stressors.[17] Unlike other inherited arrhythmias, CPVT is often associated with a normal resting ECG, which can make diagnosis difficult.

Pharmacologic therapy for CPVT consists of β-blockers (nadolol or propranolol) with the addition of flecainide in refractory cases.[25] Left cardiac sympathetic denervation is also beneficial in refractory cases.[23] Implantable cardioverter-defibrillator therapy for CPVT is complicated, because the shocks delivered can precipitate further electrical storm through a vicious cycle of continued adrenergic stimulation. Therefore, ICD therapy is recommended only for survivors of cardiac arrest or patients who remain highly symptomatic despite maximal medical therapy.[13]

Early Repolarization Syndrome

Early repolarization (ER), characterized by J-point elevation and an upsloping ST segment, has long been considered a benign ECG finding and is seen in up to 13% of the general population.[26] However, recent evidence suggests that it increases the risk of SCD.[27-29] Early repolarization syndrome, defined as ER accompanied by unexplained ventricular arrhythmias, is now recognized as a distinct inherited arrhythmia. Although ER is common in the general population, ERS is rare, with an estimated prevalence of 0.5 per 100,000 in one study.[30] Only a handful of genetic mutations have been associated with ERS, and there is currently no role for routine genetic testing for them.[26] Early repolarization syndrome is associated with a high risk of recurrent ventricular arrhythmias (up to 40%),[28] and its treatment is limited to ICD therapy for secondary prevention and to quinidine in refractory cases.[13,16] Implantable cardioverter-defibrillator therapy can also be considered in asymptomatic patients with a strong family history of SCD and high-risk ECG features such as high J-wave amplitude and a horizontal/descending ST segment.[16]

Idiopathic Ventricular Fibrillation

Idiopathic ventricular fibrillation is defined as VF of unknown origin despite extensive diagnostic testing and exclusion of other primary arrhythmia syndromes. Historically, this definition has encompassed many other inherited arrhythmias that are now recognized as distinct, including BrS, LQTS, SQTS, and most recently ERS.[31] The true prevalence of IVF is therefore difficult to estimate. Its pathogenesis is unclear, although there is evidence that in some patients short-coupled premature ventricular contractions can elicit torsades de pointes and VF.[31] Microstructural cardiomyopathic areas acting as a substrate of VF re-entries may also play a role.[32] As with ERS, treatment consists of ICD therapy for secondary prevention and quinidine.[13,31] In addition, ablation can be an effective treatment for IVF initiated by premature ventricular contractions with a consistent QRS morphology.[13]

Conclusion

Inherited arrhythmias have wide clinical variability and are therefore challenging to diagnose and to manage. A better understanding of their underlying genetic causes has led to advances in their detection and treatment and to substantial reductions in associated morbidity and mortality. However, better means of identifying high-risk patients and reducing unnecessary treatment-related harm are still needed. Continued research into the genetic and cellular mechanisms underlying these disorders will help to achieve that goal and identify potential targets for improved disease-specific treatments.

Published: 15 October 2021

Section editor: Mohammad Saeed, MD, FACC

Meeting presentation: Presented at The Ali Massumi Cardiac Arrhythmia Symposium; Houston, 15 February 2020.

CME credit: To obtain CME credit, you must 1) carefully read the other CME-designated articles marked with a ★ in this issue of the *Journal*, and then 2) click this link for instructions on completing the assessment survey.

References

1. Cirino AL, Harris S, Lakdawala NK, Michels M, Olivotto I, Day SM, et al. Role of genetic testing in inherited cardiovascular disease: a review. JAMA Cardiol 2017;2(10):1153-60.
2. Wilcox JE, Hershberger RE. Genetic cardiomyopathies. Curr Opin Cardiol 2018;33(3):354-62.
3. Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, et al. Prevalence of the congenital long-QT syndrome. Circulation 2009;120(18):1761-7.
4. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348(19):1866-74.
5. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: an update. Circulation 1993;88(2):782-4.
6. Wallace E, Howard L, Liu M, O'Brien T, Ward D, Shen S, Prendiville T. Long QT syndrome: genetics and future perspective. Pediatr Cardiol 2019;40(7):1419-30.
7. Ackerman MJ. The long QT syndrome: ion channel diseases of the heart. Mayo Clin Proc 1998;73(3):250-69.
8. Rohatgi RK, Sugrue A, Bos JM, Cannon BC, Asirvatham SJ, Moir C, et al. Contemporary outcomes in patients with long QT syndrome. J Am Coll Cardiol 2017;70(4):453-62.
9. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management [published erratum appears in Circ Arrhythm Electrophysiol 2012;5(6):e119-20]. Circ Arrhythm Electrophysiol 2012;5(4):868-77.
10. Priori SG, Napolitano C, Schwartz PJ, Grillo M, Bloise R, Ronchetti E, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA 2004;292(11):1341-4.
11. Bos JM, Crotti L, Rohatgi RK, Castelletti S, Dagradi F, Schwartz PJ, Ackerman MJ. Mexiletine shortens the QT interval in patients with potassium channel-mediated type 2 long QT syndrome. Circ Arrhythm Electrophysiol 2019;12(5):e007280.
12. Mazzanti A, Maragna R, Faragli A, Monteforte N, Bloise R, Memmi M, et al. Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3. J Am Coll Cardiol 2016;67(9):1053-8.
13. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [published erratum appears in Circulation 2018;138(13):e419-20]. Circulation 2018;138(13):e272-e391.
14. Bjerregaard P. Diagnosis and management of short QT syndrome. Heart Rhythm 2018;15(8):1261-7.
15. Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman BR, Bjerregaard P. Idiopathic short QT interval: a new clinical syndrome? Cardiology 2000;94(2):99-102.
16. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10(12):1932-63.
17. Garcia-Elias A, Benito B. Ion channel disorders and sudden cardiac death. Int J Mol Sci 2018;19(3):692.
18. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, et al. Long-term follow-up of patients with short QT syndrome. J Am Coll Cardiol 2011;58(6):587-95.
19. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20(6):1391-6.
20. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association [published erratum appears in Circulation 2005;112(4):e74]. Circulation 2005;111(5):659-70.
21. Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation 1997;96(8):2595-600.
22. Pflaumer A, Wilde AAM, Charafeddine F, Davis AM. 50 Years of catecholaminergic polymorphic ventricular tachycardia (CPVT) – time to explore the dark side of the moon. Heart Lung Circ 2020;29(4):520-8.
23. Roston TM, Vinocur JM, Maginot KR, Mohammed S, Salerno JC, Etheridge SP, et al. Catecholaminergic polymorphic ventricular tachycardia in children: analysis of therapeutic strategies and outcomes from an international multicenter registry. Circ Arrhythm Electrophysiol 2015;8(3):633-42.
24. Napolitano C, Priori SG, Bloise R. Catecholaminergic polymorphic ventricular tachycardia. 14 Oct 2004 [updated 13 Oct 2016]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews [Internet]. Seattle: University of Washington, Seattle; 1993-2021.
25. Sumitomo N. Current topics in catecholaminergic polymorphic ventricular tachycardia. J Arrhythm 2016;32(5):344-51.
26. Adler A, Gollob MH. A practical guide to early repolarization. Curr Opin Cardiol 2015;30(1):8-16.
27. Gussak I, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. J Electrocardiol 2000;33(4):299-309.

28. Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358(19):2016-23.
29. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009;361(26):2529-37.
30. Dalos D, Fiedler L, Radojevic J, Sponder M, Dichtl W, Schukro C. Prevalence of early repolarization syndrome and long-term clinical outcome in patients with the diagnosis of idiopathic ventricular fibrillation. Heart Vessels 2019;34(4):625-31.
31. Visser M, van der Heijden JF, Doevendans PA, Loh P, Wilde AA, Hassink RJ. Idiopathic ventricular fibrillation: the struggle for definition, diagnosis, and follow-up. Circ Arrhythm Electrophysiol 2016;9(5):e003817.
32. Haissaguerre M, Duchateau J, Dubois R, Hocini M, Cheniti G, Sacher F, et al. Idiopathic ventricular fibrillation: role of Purkinje system and microstructural myocardial abnormalities. JACC Clin Electrophysiol 2020;6(6):591-608.