



## Review

## Syncope in patients with inherited arrhythmias

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## ABSTRACT

Syncope, a common symptom of cerebral ischemia often shows a multifactorial etiopathogenesis. Although inherited arrhythmias causing syncope is uncommon, such an occurrence could be a warning sign preceding cardiac arrest. Long QT syndrome (LQTS) is a typical inherited arrhythmia causing syncope in children. Early diagnosis and treatment of LQTS using beta-blockers prevents recurrent syncope in LQTS. Brugada syndrome, another typical inherited arrhythmia causes syncope or sudden cardiac arrest in young individuals. Syncope as a symptom is useful for risk stratification of fatal arrhythmias and in selection of appropriate therapy. Catecholaminergic polymorphic ventricular tachycardia, another rare inherited arrhythmia causing recurrent syncope is associated with poor outcomes without medication. Early detection and therapeutic intervention improve prognosis; thus, correct diagnosis of syncope is imperative in cases of these inherited arrhythmias. We describe syncope associated with three typical inherited arrhythmias and discuss various diagnostic modalities.

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## 1. Introduction

Syncope, a very common complaint encountered in clinical practice is a transient loss of consciousness caused by global cerebral hypoperfusion, characterized by rapid onset, short duration, and spontaneous complete recovery. Although it can be triggered by multiple factors including orthostatic hypotension, a vasovagal response, seizures, cardiovascular factors, and cardiac arrhythmia [1], vasovagal syncope (benign reflex syncope) is the most common presentation. Although life-threatening causes of syncope are

rare, incorrect diagnosis can be dangerous, particularly when syncope could be a symptom of a likely fatal cardiac arrhythmia caused by hereditary arrhythmogenic syndromes [2]. We discuss hereditary arrhythmogenic diseases that cause syncope and additionally describe clues that should alert clinicians to the possibility of these malignant syndromes.

## 2. Diagnosis of syncope

A systematic approach is important for primary evaluation of a syncopal patient. The medical history interview is very important for the differential diagnosis of syncope. Information regarding circumstances at the time of the syncopal attack, such as during

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exercise or while in a supine position, the presence/absence of prodromal symptoms, recurrent or non-recurrent syncope, duration of syncope, syncope associated with or without convulsions or incontinence, and with or without external injury provides clues to arrive at an accurate diagnosis. Patients with arrhythmia-associated syncope usually have no or little prodrome, resulting in associated trauma due to sudden unconsciousness. Malignant arrhythmogenic syncope is often indistinguishable from epileptic seizures, and symptoms may be misdiagnosed [3]. Convulsions are known to occur commonly in patients with syncope; however, a syncopal patient who is found to be fully alert immediately following the convulsion is more likely to have had an episode of cardiogenic syncope [4]. Basic diagnostic evaluation of patients with syncope includes a medical history interview, physical examination, 12-lead electrocardiograms (ECGs), and echocardiography. Exercise tests and Holter ECGs could indicate angina pectoris, conduction blocks, and/or catecholaminergic polymorphic ventricular tachycardia, although this is less common. Such patients usually undergo coronary angiography, multi-detector computed tomography (MDCT), and cardiac magnetic resonance imaging (MRI), if needed. Results of these evaluations help determine presence or absence of structural heart disease. Once structural heart disease has been excluded, head-up tilt testing helps diagnose neurally mediated syncope (NMS). Patients requiring further evaluation are admitted and undergo specific evaluation, such as ambulatory electrocardiographic monitoring, electrophysiological study, and drug provocation tests to diagnose channelopathies. Implantation of implantable loop recorders (ILRs) is useful in patients with unexplained syncope. If patients who are diagnosed as having some inherited arrhythmic syndromes, their syncopal attacks may be caused by NMS or epilepsy, the ILR should be taken into consideration. Fig. 1 shows the process of differential diagnosis for syncope that we use at our hospital. In our report, we have particularly focused on the major hereditary arrhythmogenic syndromes causing syncope.

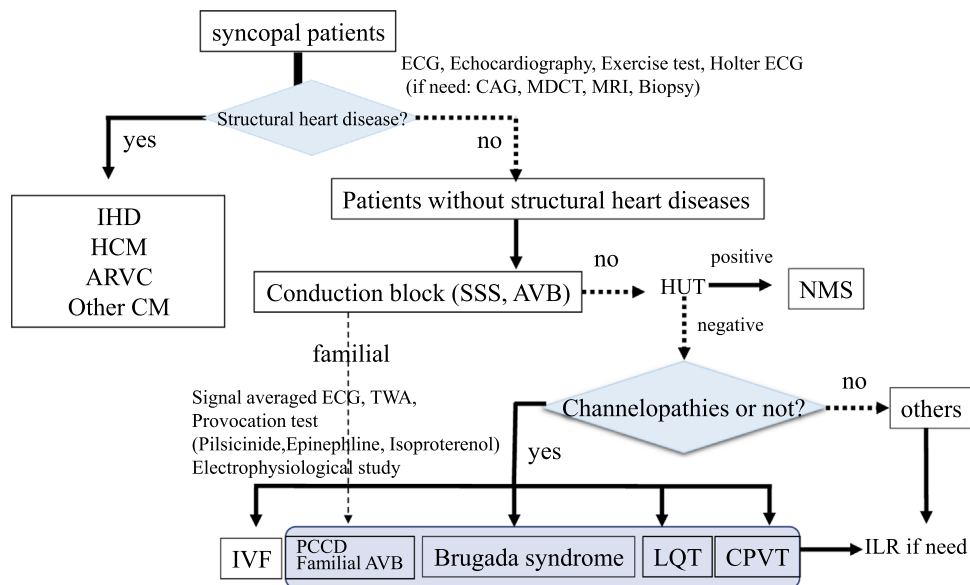
### 3. Long QT syndrome

Long QT syndrome (LQTS) is characterized by a 12-lead ECG pattern showing a prolonged QT interval that can progress to a polymorphic ventricular tachycardia (VT) known as torsades de pointes (TdP). Fig. 2 shows the ECG obtained in a 26-year-old resuscitated woman with LQTS (genotype-undetermined). Ventricular premature beats (VPBs) appeared on prolonged T-wave and triggered TdP. Clinically, TdP can produce syncope, ventricular fibrillation (VF), or even sudden cardiac death (SCD). Prevalence of congenital LQTS is reportedly 1:2000 [5], and the condition is diagnosed based on the Schwartz score (Table 1). Patients with a Schwartz score  $\geq 3.5$  points in the absence of a secondary cause to explain the QT prolongation are diagnosed with LQTS [6]. In 2013, an expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes was published by the Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society (APHRS) [7].

This statement recommended a diagnosis of congenital LQTS in patients fulfilling the following criteria:

- (1) An LQTS risk score  $\geq 3.5$  without a secondary cause for QT prolongation.
- (2) An unequivocal pathogenic mutation in one of the LQTS genes.
- (3) The presence of a corrected QT interval (QTc)  $\geq 500$  ms on repeated 12-lead ECGs using Bazett's formula in the absence of a secondary cause to explain the QT prolongation.

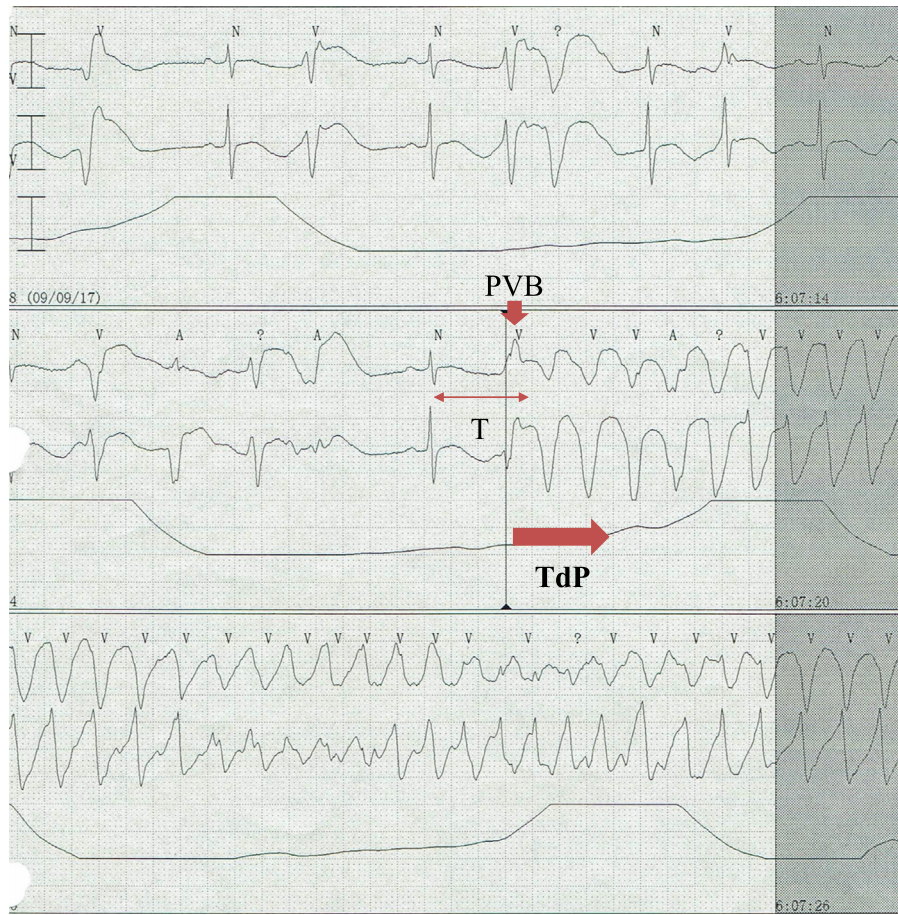
This statement indicated that LQTS can be diagnosed when the QTc is between 480 and 499 ms on repeated 12-lead ECGs in patients with unexplained syncope, without a secondary cause for QT prolongation, in the absence of a pathogenic mutation. Typical ECGs for LQT1-3, shown in Fig. 3, present with a broad-based T in LQT1, a notched T in LQT2, and a late-appearing T in LQT3.



#### Hereditary arrhythmogenic syndromes

VF:ventricular fibrillation, IHD: ischemic heart disease, HCM:hypertrophic cardiomyopathy, ARVC:Arrhythmogenic right ventricular cardiomyopathy,LQT:long QT syndrome, CPVT:cathcolamine sensitive VT/VF, IVF:idiopathic VF, MDCT:multidetector computed tomography,MRI:magnetic resonance imaging, TWA:T wave alternans,HUT: head up tilt test, NMS: neurally mediated syncope, ILR: implantable loop recorder SSS: sick sinus syndrome, AVB: atrioventricular block, PCCD: progressive cardiac conduction defect

**Fig. 1.** Process used for the differential diagnosis of syncope at our hospital. First, we rule out structural heart disease. In patients without structural heart disease, we perform assessment to diagnose whether or not channelopathy is a cause of syncope.



**Fig. 2.** Prolonged QT-wave and torsades de pointes (TdP). **Fig. 2** shows the electrocardiogram (ECG) in a 26-year-old woman with LQTS (genotype-undetermined) who underwent resuscitation. Ventricular premature beats (VPBs) appear on prolonged QT-wave and triggered TdP.

**Table 1**  
Diagnosis of long QT syndrome.

Parameters		Points
Electrocardiographic findings <sup>a</sup>	A QTc time <sup>b</sup>	≥480 ms 3 460–479 ms 2 450–459 ms (male) 1
	B 4-min recovery QTc after exercise test	≥ 480 ms 1
	C torsade de pointes <sup>c</sup>	2
	D T-wave alternance	1
	E notched T wave	1
	F Low heart rate for age <sup>d</sup>	0.5
Clinical manifestations	A Syncope <sup>e</sup>	with stress 2 without stress 1
	B Congenital deafness	0.5
Family history	A Family members with definite LQTS <sup>e</sup>	1
	B Unexpected sudden cardiac death age < 30 years in family members	0.5

LQTS: Long QT syndrome.  
 ≥3.5 points: Diagnosed as LQTS; 1.5-3 points: Suspect of LQTS; ≤1point: unlikely LQTS.

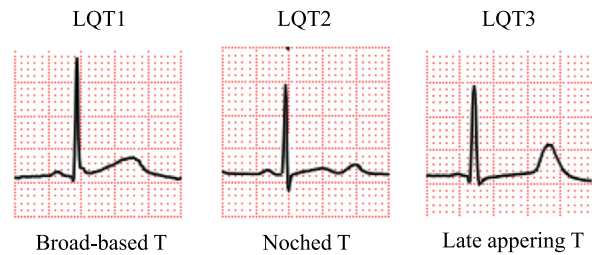
<sup>a</sup> In the absence of medications or disorders known to affect these electrocardiographic features.

<sup>b</sup> QTc calculated by Bazett's formula where  $QTc = QT / \sqrt{RR}$ .

<sup>c</sup> Mutually exclusive.

<sup>d</sup> Resting heart rate below the 2nd percentile for age.

<sup>e</sup> The same family member cannot be counted in A and B.



**Fig. 3.** Typical ECG pattern in a case of LQT1-3. A broad-based T wave is present in LQT1, a notched T wave in LQT2, and a late-appearing T wave in LQT3.

Mean age for occurrence of the first cardiac event is 8 years in male patients and 14 years in female patients. The first cardiac event manifests in 90% of patients younger than 40 years of age. Among LQTS patients, the risk of cardiac events is higher in male patients until puberty and higher in women during adulthood [8].

A study examining different arrhythmogenic triggers in 670 LQTS patients with known LQTS genotypes (LQTS 1–3), found that 62% of symptomatic patients with LQT1 experienced cardiac events during exercise, whereas only 3% experienced such events during rest or sleep. However, in LQT3 patients, 39% of events occurred during sleep or rest and only 13% occurred during exercise. LQT2 patients have an intermediate pattern, with only 13% of events occurring during exercise and 43% occurring in association with emotional stress [9].



T-wave alternans (TWA), which is included in the diagnostic criteria for LQTS, indicates repolarization instability, and an unstable intracardial and transmural dispersion of action potentials may induce fatal arrhythmias. Microvolt TWA in precordial leads was recently reported to be a useful predictor of fatal arrhythmias in those diagnosed with LQTS [10].

Prolonged QTc interval ( $\geq 500$  ms) and history of cardiac events (including syncope) were reported as factors that can greatly affect and predict a poor prognosis in patients with LQTS [2,11]. Therefore, distinguishing between patients with LQTS and those with syncope is very important. Reportedly, male gender ( $< 13$  years) and female gender ( $\geq 13$  years) in cases with LQT1 and female gender in those with LQT2 increases the risk of cardiac events [12].

When LQTS is suspected in a patient with syncope, the following procedures are performed at our hospital (Fig. 4): (1) Repeat 12-lead ECG in borderline cases. (2) Attempts to obtain 12-lead ECGs of family members of the patient. (3) Exercise testing. (4) Holter recordings to check ambulatory QTc. (5) T-wave alternans testing. (6) Epinephrine provocation tests. (7) Genetic tests [13]. It has been shown that 15 genes including three major LQTS-causative genes—*KCNQ1*-encoded Kv7.1 channel subunit (LQT1), *KCNH2*-encoded Kv11.1 (LQT2), and *SCN5A*-encoded Nav1.5 (LQT3) are instrumental in the pathogenesis of this condition [14–

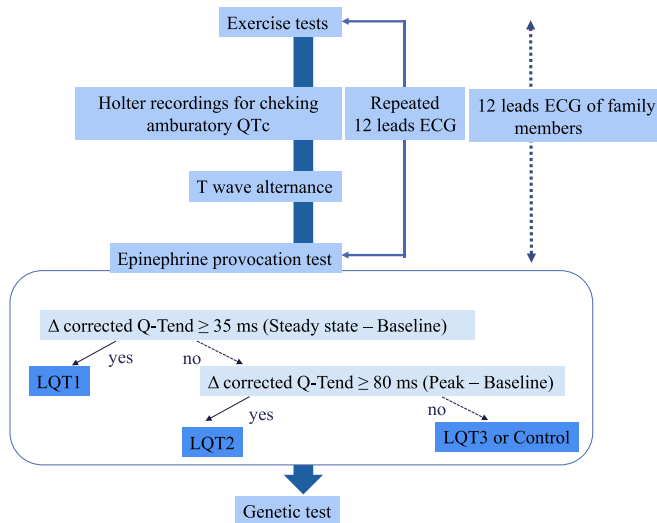
16]. Genetic testing for LQTS contributes to not only the diagnosis but also helps with mutation-specific risk stratification and gene-specific patient management.

Beta blockers (preferably long-acting ones such as nadolol or sustained-release propranolol) are clinically indicated for prevention of recurrent syncope in LQTS [17,18]. Based on the 2013 expert consensus statement, patients who present with syncope or cardiac arrest before age 7 demonstrate a higher probability of recurrent arrhythmic events even with administration of beta-blockers [7].

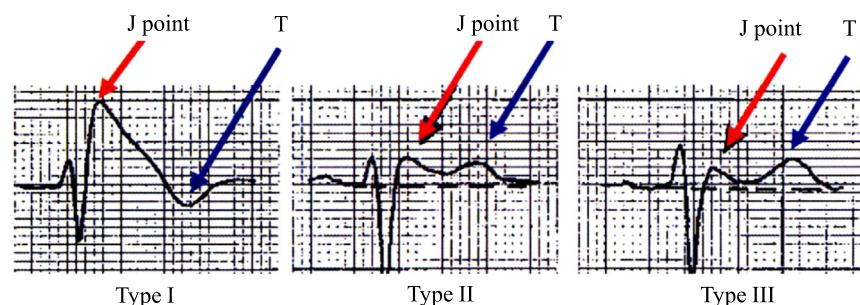
#### 4. Brugada syndrome

Brugada syndrome (BrS), an inherited arrhythmogenic disorder characterized by a typical Brugada-type ECG pattern of ST-segment elevation in the right precordial leads and a high risk of VF or even SCD [19], shows high prevalence in Asian and Southeast Asian countries, especially in Thailand, the Philippines, and Japan, at approximately 0.5–1/1000 individuals. BrS is 8–10 times more prevalent in men than in women and typically manifests in adulthood, with a mean age of  $41 \pm 15$  years [20]. Diagnosis of BrS is based on the HRS/EHRA/APHS consensus statement released in 2013 [21]. BrS can be conclusively diagnosed based on typical electrocardiographic evidence of a type 1 ST-segment elevation either spontaneously or after intravenous administration of a sodium channel blocking agent in at least one right precordial lead (V1 or V2), which is placed in a standard or a superior position (up to the 2nd intercostal space) [21]. ECGs demonstrating the typical type 1–3 BrS are shown in Fig. 5. Syncope is one of the main clinical manifestations of BrS, and symptoms often occur during rest or sleep, as well as during vagotonic dominant conditions [20]. Risk stratification of SCD associated with BrS has not been completely elucidated. Kamakura et al. reported that a family history of SCD at age  $< 45$  years and coexistence of inferolateral early repolarization noted on BrS ECGs were independent predictors of fatal arrhythmic events [22].

Several previous studies including two large European BrS registries (FINGER and PRELUDE) report that a history of syncope was significantly associated with VF events [23,24]. A large Japanese BrS cohort has demonstrated that syncope, QRS duration  $> 90$  ms in lead V<sub>2</sub>, an inferolateral J wave, and/or horizontal ST-segment morphology after J wave were important indicators to predict cardiac events [25]. In Japan, the indication for the use of an implantable cardioverter-defibrillator (ICD) for primary prevention of SCD in BrS patients is based on a combination of three risk factors (syncope, family history, and induction of VF in an electrophysiological study), based on guidelines of the Japanese



**Fig. 4.** Flow chart showing diagnosis in cases when LQTS is suspected. We performed the following investigations in cases with syncope with a high index of suspicion for LQTS. (1) Repeat 12-lead ECG in borderline cases. (2) 12-lead ECG of family members of the patient. (3) Exercise testing. (4) Holter recordings to check ambulatory QTc. (5) T-wave alternans testing. (6) Epinephrine provocation tests. (7) Genetic tests.



*Priori et al. HRS/EHRA/APHS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes. Heart Rhythm, 10 (12)1932-1951, 2013*

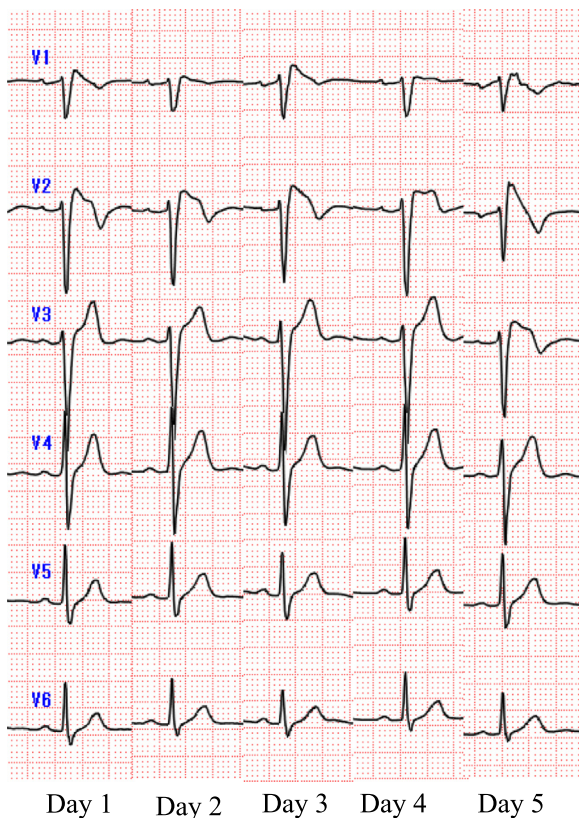
**Fig. 5.** Typical ECG patterns seen in patients diagnosed with type 1–3 Brugada syndrome (BrS). Type 1 and type 2 ECGs showing a coved-type ST-segment elevation (J point ST elevation  $\geq 2$  mm or not) and type 3 ECG displaying a saddleback-type ST-segment elevation.

Circulation Society 2011 (2012 focused update). The indication for an ICD is categorized as class IIa for patients with two or three risk factors. Clinicians should be mindful of the fact that syncope in patients with BrS could sometimes include NMS. An ILR is useful to differentiate between NMS and syncope precipitated by ventricular arrhythmias in BrS. Vasospastic angina sometimes complicates the picture observed in BrS patients. BrS patients with history of syncope should preferably undergo coronary angiography (CAG) and acetylcholine or ergonovine maleate provocation tests.

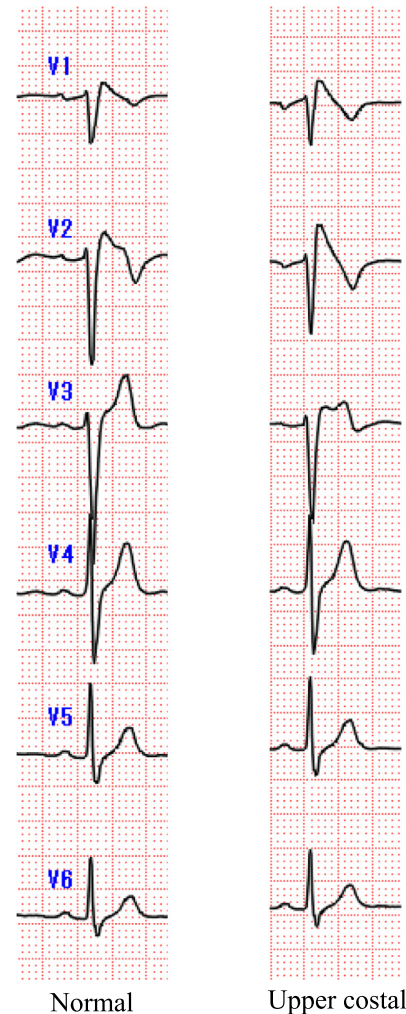
Use of programmed electrical stimulation for risk stratification of patients with BrS is controversial. The prospective PRELUDE registry did not show that sustained VF induction identifies high-risk patients [24]. The number of extrastimuli that induce ventricular arrhythmia was recently reported to be a prognostic indicator for patients with BrS, and BrS was found to be the greatest risk factor observed among patients induced using single or double extrastimuli [26–28].

Recently, we reported that a novel logistical model using previously described noninvasive risk factors of VF in BrS patients [a combination of history of syncope, r–J interval in V1, QRS duration in V6, and Tpeak–Tend interval (Tp–e) dispersion] is useful for risk stratification in routine clinical practice [29].

Syncope is a very important determinant of BrS, being the first manifestation of cardiac events, and it additionally plays a critical role in risk stratification of patients. Distinguishing “arrhythmic syncope” from “nonarrhythmic syncope” is important to avoid missing a diagnosis of BrS [30]. It is important to note that ST-segment elevation observed in BrS shows day-to-day variation and multiple ECG recordings need to be repeated in a standard or superior position. Fig. 6 shows day-to-day variations in the ECG



**Fig. 6.** Day-to-day variations in ECGs observed in patients diagnosed with Brugada syndrome. Five 12-lead ECGs are shown in a 32-year-old man with a history of syncope. Brugada-type ECGs show a day-to-day variation, fluctuating between a saddle back and coved type.

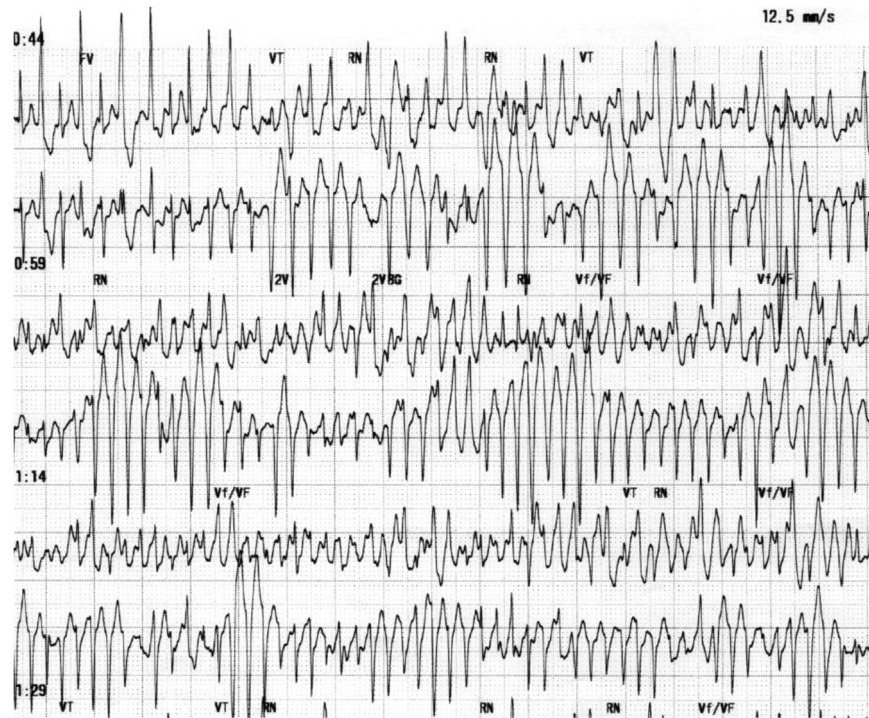


**Fig. 7.** Precordial ECG in a patient with BrS in the normal and upper costal leads. The upper costal leads showed Brugada-type ECG patterns, the ECG in the normal costal leads shows a type 2 ECG in the V2 lead, but the ECG in the 3rd intercostal space shows a typical type 1 ECG in the V2 lead.

patterns of BrS in a 32-year-old man with a history of syncope. VF was induced by an electrophysiologic study (EPS), and he underwent ICD implantation following which he developed VF. Fig. 7 shows a precordial ECG in a BrS patient demonstrating a type 2 ECG in the normal costal V2 lead, but a typical type 1 ECG in the 3rd intercostal V2 lead.

Reportedly, the *SCN5A* gene, which codes for cardiac voltage-gated sodium channels is found to be a causative gene for BrS [31], and many other susceptibility genes have been identified [32]. However, despite its major role in causation of this condition, the *SCN5A* gene accounts for only 11–28% of cases [33]. A recent Japanese cohort comprising BrS probands in the presence and absence of *SCN5A* mutation demonstrated that BrS probands with *SCN5A* mutations exhibit a greater number of conduction abnormalities in an ECG and carry a higher risk of cardiac events [34]. Despite a better understanding of the role of genes in the causation of the disorder, this condition cannot be completely explained on genetic grounds in many patients with BrS, and genetic testing is not routinely performed for a diagnosis of BrS [35]. Mutation-specific genetic testing is categorized as Class I (recommended testing) for family members and appropriate relatives following identification of the BrS causative mutation in index cases [7]. Recently, we reported that ECGs obtained from BrS patients with *SCN5A* mutations exhibit a greater number of





**Fig. 8.** Polymorphic ventricular tachycardia (VT) during an exercise test in a 12-year-old adolescent female patient diagnosed with catecholaminergic polymorphic ventricular tachycardia (CPVT). Biphasic premature ventricular contractions (PVCs) were noted shortly after starting an exercise test and these were seen to develop into polymorphic VT.

conduction abnormalities, and that these mutations are associated with a higher risk for cardiac events [36]. BrS patients with a history of syncope have a particularly high risk of fatal arrhythmia, and genetic testing may be useful in such cases.

In a recent genome-wide association study, three single-nucleotide polymorphisms, *SCN10A*, *SCN5A*, and *HEY 2*, were reported to be associated with BrS [37]. We confirmed the results through a separate study and could demonstrate that the *HEY2* single-nucleotide polymorphism (SNP) could be a useful prognostic marker for BrS [38].

### 5. Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disorder characterized by adrenergic-induced bidirectional and polymorphic VT [39]. Prevalence of this disease is estimated to be 0.1 in 1000 individuals [7]. However, because a resting ECG is usually normal in CPVT patients and cardiac imaging results are unremarkable, precise evaluation of its prevalence in the population is difficult, and an accurate prevalence rate is unknown [40]. CPVT causes repetitive syncope and may often be indistinguishable from epilepsy. Biphasic VT and premature ventricular contractions are clinical characteristics common to both—the LQT7 form of congenital LQTS and CPVT, making differential diagnosis difficult. Several ECG characteristics can assist in the differential diagnosis such as presence of TU wave patterns, an enlarged U-wave, relatively slow polymorphic or biphasic VT, and frequent VPBs at rest, and these may be useful in distinguishing LQT7 from CPVT [41].

The circumstances of syncopal events are especially important in patients with CPVT, because syncopal attacks in most CPVT patients occur during exercise or in association with emotional stress. Therefore, exercise stress testing is useful in cases with a high index of suspicion for CPVT. A resting ECG in CPVT patients

sometimes shows sinus bradycardia with subsequent development of VPBs followed by polymorphic VPBs and bidirectional or polymorphic VT [42].

Fig. 8 shows polymorphic VT during an exercise test in a 12-year-old adolescent female patient with CPVT. Exercise-induced atrial arrhythmias including atrial fibrillation are a clinical phenotype noted in CPVT patients. An epinephrine challenge test is also a useful predictor of this condition [43]. Marjamaa et al. report in a recent review that a detailed clinical history could increase clinical suspicion. Additionally, 12-lead Holter monitoring and 12-lead exercise stress testing could help establish the diagnosis followed by confirmatory genetic testing. Despite administration of beta-blockers, one-third of patients are known to develop recurrent symptoms necessitating the need to explore newer therapies [44].

Our approach to a patient presenting with syncope is that a life-threatening arrhythmia, although rare, must be considered in the differential diagnosis because it must be borne in mind that missing the diagnosis may be fatal in such patients. Therefore, obtaining a detailed history, especially regarding the circumstances of the syncopal attacks is most important. Repeat 12-lead ECG recordings, ambulatory ECG monitoring, exercise testing, and/or drug challenge testing may provide useful clues to help diagnose a hereditary arrhythmogenic syndrome. Genetic testing is a useful aid in establishing a definitive diagnosis. Evaluation of the cause and assessment of short- and long-term morbidity and mortality risk for syncope are recommended for risk assessment of syncope [45].

### Disclosures

None.

## Conflict of interest

All authors declare no conflict of interest related to this study.

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