Brugada Syndrome

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KEYWORDS

• Brugada syndrome • Diagnosis • Implantable cardioverter defibrillator • Sudden cardiac death

KEY POINTS

- Brugada syndrome might stay undetected in patients until surviving cardiac arrest.
- Despite the prominent advances in exploring the disease in the past 2 decades, many questions remain unanswered and the controversies continue.
- Despite all mutations identified to be associated with the disease, two-thirds of cases have a negative genetic test.
- Future studies should be directed toward modulating factors to help physicians in risk stratification and optimally implementing an implantable cardioverter defibrillator to prevent sudden cardiac death.

CASE PRESENTATION

A 26-year-old man presented for evaluation after several episodes of palpitations over the last year. During these episodes that commonly happen at night, his lips turn purple and he has difficulty breathing. He had recurrent episodes of syncope. His electrocardiogram (ECG) showed interventricular conduction delay and underwent a procainamide challenge that did not show the Brugada pattern. However, his genetic test showed an SCN5A mutation c.5219 C>T (p. Ser1710Leu) and was diagnosed with Brugada syndrome. His daughter was diagnosed with Brugada syndrome owing to compound heterozygosity with 2 mutations in the SCN5A gene: Arg1512Trp and Ser1710Leu. His wife had the SCN5A Arg1512Trp mutation. He had another daughter that carries the SCN5A Ser1710Leu mutation. The patient was to have an electrophysiology study and an implantable cardioverter defibrillator (ICD) implantation.

DISCUSSION

The Brugada syndrome affects predominantly middle-aged men with mean age of diagnosis around 40 years old and is mostly diagnosed by incidental ECG findings. Although previous reports showed disease prevalence ranging from 1:2000 to 1:100,000 in different parts of the world, these remain rough estimates owing to its incidental finding, dynamic ECG pattern, and masked characteristic.[1] It is inherited in an autosomal-dominant manner with incomplete penetrance. It has been highly associated with high risk of

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sudden cardiac death. Patients are at high risk for sudden cardiac death with the cardiac event rate per year being 0.5% in asymptomatic patients, 1.9% in patients with syncope, and 7.7% in patients with aborted sudden cardiac death.[1–4] The syndrome is estimated to be responsible for 4% of all sudden cardiac deaths and 20% of sudden cardiac deaths among patients with structurally normal hearts.[1,3–5]

The Brugada syndrome is typically characterized by a right bundle branch block–like morphology along with 1 of 3 distinctive patterns of ST-segment elevation in the right precordial leads (V1–V3) on ECG in structurally normal hearts. Several Brugada syndrome cases with ST-segment elevation in inferior leads as well as the high lateral leads (I and avL) have been reported and showed a worse prognosis. According to these ST-segment patterns, the 2 Brugada consensus reports classified the disease into 3 types. Type 1 pattern has ST elevation of greater than 2 mm, giving rise to a coved-type ST segment, in electrical continuity with a negative T-wave and without a separating isoelectric (**Fig. 1**). Type 2 has a high take-off ST-segment elevation. In this variant, the J-point elevation (>2 mm) gives rise to a gradually descending elevated ST-segment (remaining >1 mm above the baseline) and a positive or biphasic T-wave. This ST-T segment morphology is referred to as the saddleback type. Type 3 is the coved- or saddleback-type with less than 1 mm ST-segment elevation. The Brugada pattern can be spontaneous or induced by procainamide, ajmaline, flecainide, or pilsicainide. Only type 1 pattern is pathognomonic of the Brugada syndrome; the other patterns are less significant. As for the definite diagnosis of Brugada syndrome, the ECG pattern should be combined with any of following clinical conditions: polymorphic ventricular tachycardia, ventricular fibrillation (VF), syncope, and early sudden cardiac death in the family (<45 years old). In addition to the ECG signs and clinical presentation, the diagnostic workup must exclude the following medical conditions that might mimic Brugada syndrome in ST segment elevation: acute pericarditis, Prinzmetal angina, acute pericarditis, and arrhythmogenic right ventricular cardiomyopathy.

Theories have emerged to explain the link between these ECG signs, possible underlying mechanisms and the increased susceptibility for ventricular arrhythmia.

Repolarization Versus Depolarization Theory

Although Brugada emerged as an exclusively cardiac channel dysfunction affecting the action potential (AP), other studies and even the first consensus report in 2002 included the possibility of underlying structural abnormality and recently investigators reported prevention of VF episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium.

The repolarization theory is based on the transmural dispersion of repolarization and the unequal

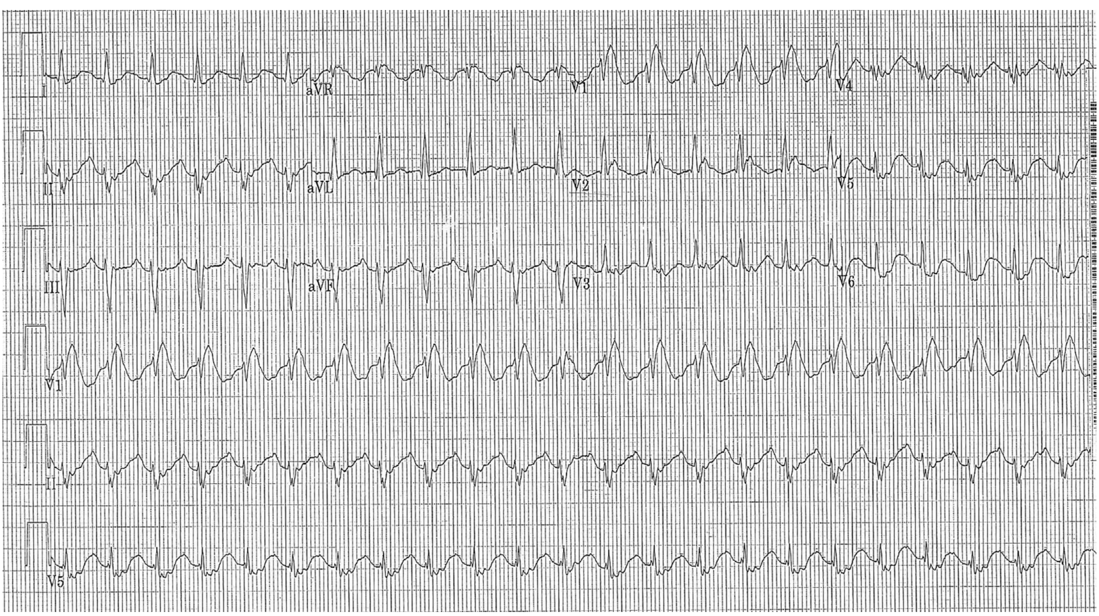

Fig. 1. Electrocardiogram of a patient with Brugada syndrome with a type 1 Brugada pattern.

expression of outward potassium current (I_{to}) between the epicardium and the rest transmural layers. Knowing that RV epicardium has abundant I_{to} channels, a more prominent transmembrane voltage gradient between the right ventricle (RV) epicardium and the endocardium results in early repolarization and responsible for the observed ECG patterns. Using sodium channel blockers to arterial perfused wedge preparations makes the opposing potassium currents more dominant and, thus, showed a notch and dome of epicardial AP. This loss of AP dome in epicardium but not in endocardium further accentuates the heterogeneity and dispersion of repolarization. Unequal shortening of the AP gives rise to development of a phase 2 reentry loop and premature beats that might trigger ventricular tachycardia/VF.

On the other side, depolarization theory explains Brugada syndrome based on a conduction delay in the RV outflow tract (RVOT). It was first shown by Nagase and colleagues[6] as the result of a late potential after the QRS in the free wall of the RVOT. This activation slowing and the delay in the AP of the RVOT causes the electrical gradient from the more positive RV to the RVOT, leading to ST-elevation in the right precordial leads and, as the RVOT depolarizes later (during repolarization of the RV), this gradient is reversed and the net current flows toward the RV, resulting in a negative T-wave in the same right precordial leads.[2,7] In support of this theory, focal fibrosis, myocarditis, apoptosis, and fibrofatty replacement of the RV free wall with RV enlargement, dilation, and RVOT enlargement were shown in Brugada patients.[2,7]

Genetic Component

Sodium channels

The syndrome has a genetic basis, and several mutations have been identified in genes encoding subunits of cardiac sodium, potassium, and calcium channels, as well as in genes involved in the trafficking or regulation of these channels (**Table 1**). Hundreds of variants in various genes have been associated with the Brugada syndrome; however, approximately 65% of Brugada syndrome cases could not be explained genetically. The first gene linked to Brugada syndrome is SCN5A, which encodes the α-subunit of the cardiac sodium channel and estimated to account for 30% of all Brugada cases and more than 75% of genotyped positive cases.[8] This channel is responsible for the inward current rapid initial phase of AP and mutations in SCN5A lead to its reduction. More than 300 mutations have been reported in this gene and linked to Brugada syndrome type I; one-third of these mutations consist of frameshift mutations, splice site, and insertions/deletions. Meregalli and colleagues[9] showed that carriers of such mutations are more likely to be symptomatic, having history of syncope owing to severe protein defect and the resulting reduction of inward sodium current. These patients, when evaluated, demonstrate a longer baseline PR interval and QRS prolongation.[9] Other SCN5A missense mutations carriers experience symptoms only when febrile, as shown in a study on T1620M mutation, which demonstrated current impairment only when incubated at temperatures representing febrile status.[10,11] In addition to SCN5A encoding the α-subunit of sodium channel, genes encoding the β-subunits and genes affecting trafficking of the channel have been reported. Glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L), linked to Brugada syndrome type II, was shown to affect expression of sodium channel on cell surface.[12] Mutations in GPD1L caused a 50% decrease in the inward current through abnormal trafficking.[12] SCN1B, encoding β1 and β1b subunits, is another gene involved in the sodium channel function and mutations reported have been linked to the disease and shown to decrease channel expression on cell membrane.[13] SCN3B, encoding β3 subunit, and MOG1 mutations also lead to inward current reduction through channel trafficking impairment.[14] Moreover, the voltage-gated sodium channel $Na_v1.8$, encoded by SCN10A, was recently shown to be also involved in Brugada syndrome. In a study done by Hu and colleagues,[15] 3 novel variants were identified in addition to other mutations, most of which were involving the transmembrane-spanning region. Interestingly, 16.7% of Brugada syndrome probands were positive for SCN10A mutations.[15] In addition, subjects carrying SCN10A mutations experienced more symptoms and ECG displayed longer PR and QRS intervals compared with other Brugada syndrome patients not exhibiting this specific gene mutation.[15] Functional studies using the most common SCN10A mutants, R14L and R1268Q, with wild types of SCN5A and SCN3B genes could demonstrate a tremendous reduction/loss of sodium channel function. These 2 mutants solely could reduce the peak density of the channel and caused a major shift of half-activation voltage.[15]

Calcium channels

Voltage-gated calcium channel, Cav1.2, is responsible for maintaining the plateau phase of AP (phase 2) through the influx of calcium ions. In 2007, Antzelevitch and colleagues[16] were the first

Table 1
Causative genes in Brugada syndrome

Channel	Brugada syndrome Subtype	Gene	Protein	Functional Effect
Sodium	BrS 1	*SCN5A*	α subunit of $Na_v1.5$	Loss of function
	BrS 2	*GPD1-L*	G3PD1L, interacts with $Na_v1.5$ α subunit	Loss of function
	BrS 5	*SCN1B/SCN1Bb1*	β1 subunit of $Na_v1.5$	Loss of function
	BrS 7	*SCN3B*	β3 subunit of $Na_v1.5$	Loss of function
	BrS 11	*RANGRF*	MOG1 protein: $Na_v1.5$ cofactor	Loss of function
	BrS 15	*SLMAP*	Sarcolemmal membrane-associated protein	Loss of function
	BrS 17	*SCN2B*	β2 subunit of $Na_v1.5$	Loss of function
	[a]	*SCN10A*	$Na_v1.8$ channel	Loss of function
Calcium	BrS 3	*CACNA1C*	α subunit of $Ca_v1.2$ (L-type voltage gated)	Loss of function
	BrS 4	*CACNB2b*	β2 of $Ca_v1.2$	Loss of function
	BrS 10	*CACNA2D1*	α2δ subunit of $Ca_v1.2$	Not Available
Potassium	BrS 6	*KCNE3*	MiRP2: β-subunit	Gain of function: I_{to}/I_{Ks}
	BrS 8	*KCNH2*	hERG1	Loss of function: I_{Kr} current
	BrS 9	*KCNJ8*	$Kir6.1/K_{ATP}$	Gain of function: I_{KATP} current
	BrS 12	*KCNE5*	MiRP4: β-subunit	Gain of function: I_{to}/I_{Ks}
	BrS 13	*KCND3*	α-Subunit of $K_v4.3$	Gain of function: I_{to} current
	[a]	*KCND2*	α-Subunit of $K_v4.3$	Gain of function: I_{to} current
	[a]	*ABCC9*	ATP binding cassette transporter of K_{ATP} channel	Gain of function: $I_{K\text{-}ATP}$ current
Miscellaneous	BrS14	*HCN4*	Hyperpolarization-activated cyclic nucleotide-gated channel 4	Not available
	BrS 16	*TRMP4*	Transient receptor potential melastatin protein 4 (TRMP4)	Loss or Gain of function OF NSC_{Ca}
	[a]	*FGF12*	Fibroblast growth factor homologous factor 12	Loss of function of voltage gated Na^+ and Ca^{2+} channels
	[a]	PKP-2	Plakophilin-2	Reduced I_{Na}
	[a]	PXDNL	Peroxidasin homolog (Drosophila)-like	Unknown
	[a]	IRX5	Iroquois homeobox 5	Upregulation of KCND3 channels
	[a]	DPPX	Dipeptidyl-peptidase-like protein 6	Unknown

Abbreviations: ABCC9 (codes for the cardiac specific sulfonyl urea receptor 2A (SUR2A) subunit of the K_{ATP} potassium channel); *FGF12*, fibroblast growth factor homologous factor 12; *GPD1L*, glycerol-3-phosphate dehydrogenase 1-like; *HCN4*, hyperpolarization-activated cyclic nucleotide-gated channel 4 (responsible for I_f current); IRX5, Iroquois homeobox 5 (missense mutations were described in Hamamy syndrome with severe hypertelorism with midface prominence, myopia, mental retardation and bone fragility); NSC_{Ca}, calcium-activated nonselective cation channel (NSC_{Ca}) function (mediates monovalent cations across membrane and contributes to the transient inward current I_{ti} initiated by Ca^{2+} waves); *RANGRF*, RAN guanine nucleotide release factor; *SLMAP*, sarcolemmal membrane-associated protein; *TRMP4*, transient receptor potential melastatin protein 4.

[a] Novel genes identified and not linked to any Brugada syndrome subtype yet.

to establish the association between voltage-gated calcium channels and the Brugada syndrome by studying the *CACNA1C* and *CACNB2b* genes, which encode the α- and β-subunits of the L-type calcium channel, respectively. Mutations in *CACNA1C* have demonstrated major loss of channel activity and, because the β-subunit are involved in regulating gating process, mutations in *CACNB2b* showed channel trafficking impairment.[16] *CACNAD1* is another gene encoding $\alpha 2\delta$ subunit of this channel. In 2010, Burashnikov and colleagues[17] identified mutations that were associated with the Brugada syndrome, but the mechanism not well-understood and not investigated thoroughly to date.

Potassium channels

In addition to sodium and calcium channels, potassium channel defects have demonstrated a prominent role in the pathophysiology of Brugada syndrome phenotype in a significant number of cases. KCNE gene plays an important role in modulating various types of cardiac potassium channels. Delpon and colleagues[18] were the first to link KCNE gene mutations to Brugada syndrome.[18] KCNE3 encodes the MiRP2, one of the voltage-gated potassium channel subunits. Mutations in this gene led to increase in peak current and thus, early inactivation of I_{to}. As voltage-gated potassium channel consists of 5 homologous subunits, KCNE5 encodes another one of these β-subunits (MiRP4). Variants in this gene identified by Ohno and colleagues[19] also demonstrated a gain of function effect altering the peak current of I_{to}. More of gain-of-function gene mutations were identified in KCND3 gene, encoding the α-subunit of the channel, which resulted in I_{to} density increase and AP dome loss.[20] Moreover, the KCNH2 gene that encodes rapid delayed rectifier channel and is associated with the long QT syndrome, has been also linked to Brugada syndrome. Verkerk and colleagues[21] were the first to identify mutations of this gene in Brugada syndrome. Variants of this gene were shown to augment the initial upstroke of ventricular AP and Itoh and colleagues[22] confirmed later the gain-of-function effect of these mutations. K_{ATP} channel, encoded by KCNJ8, helps in stopping the inward rectifying potassium current and thus shortening the AP duration. KCNJ8 mutations led to augmented channel function with a reduced sensitivity to adenosine triphosphate. Likewise, the sulfonylurea receptor type 2A SUR2A or ABCC9 gene encodes the adenosine triphosphate binding cassette transporter of the channel and Hu and colleagues[23] could recently show its impact on channel sensitivity to adenosine triphosphate; they uncovered 8 mutations in Brugada syndrome patients.

Clinical Presentation

Clinical manifestations of the Brugada syndrome are heterogeneous and range from being asymptomatic throughout the lifetime to sudden cardiac death. Although most patients remain asymptomatic, palpitations, syncope, seizures, and even aborted sudden cardiac death can occur at all ages and the peak has been reported to be around the fourth decade of life.[2,24] Ventricular arrhythmias/VF represent the main underlying cause of sudden cardiac death and other symptoms. Symptoms might be triggered or augmented in the predominance of vagal activity such as during sleep. Around 40% of Brugada syndrome patients experience syncope; 23% of patients presenting with sudden cardiac death are reported to have history of syncopal episodes. Spontaneous atrial fibrillation has been shown to be high in Brugada patients, with up to 39% of cases in 1 study.[11]

Risk Stratification

Most Brugada syndrome patients are identified incidentally or when they survive aborted sudden cardiac death. It is important to establish guidelines for risk stratifying Brugada patients to receive the appropriate primary management. Many clinical markers and modulating factors have been studied as potential risk parameters, such as a family history of sudden cardiac death, syncope, history of supraventricular tachycardia, a history of atrial fibrillation, and genetic markers. To date, there is no well-established combination of these markers that would help the physician in identifying patients at high, moderate, or mild risk of sudden cardiac death. Although it is clear for patients experiencing recurrent serious symptoms as syncope, seizures, or agonal respiration, it is debatable with respect to the majority of subjects.[25] The preponderance of evidence suggests that inducibility of VF during electrophysiology study alone as a risk factor is not an important predictor for sudden cardiac death. The Japanese guidelines, in 2011, emerged and focused on 3 main “risk” factors: syncope, a family history of sudden cardiac death, and a positive electrophysiology study.[26] The Heart Rhythm Society (HRS), the European Heart Rhythm Association (EHRA), and the Asia Pacific Heart Rhythm Society (APHRS) consensus document focused on spontaneous type 1 Brugada ECG (coved), syncope and electrophysiology study to recommend for primary preventive ICD therapy.[27] Recently, Okamura and colleagues[26] studied these risk factors and provided the significance of combining these factors in risk stratifying patients. These 3 risk factors included spontaneous type 1 Brugada ECG, a positive electrophysiology study (defined as VF or polymorphic ventricular tachycardia lasting >30 s or requiring direct current shock induced at a coupling interval of $\geq$200 ms) and syncope (judged as likely caused by ventricular arrhythmia and excluding likely neurocardiogenic). Patients with 2 or more of these 3 risk factors were found to be at a higher risk of fatal arrhythmia and sudden cardiac death. A family history of sudden cardiac death was not an independent risk factor for fatal arrhythmia and sudden cardiac death.[26] Priori and colleagues[28] showed from the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry that the presence of a spontaneous type I ECG, history of syncope, ventricular effective refractory period less than 200 ms and QRS fragmentation favor primary prevention ICD implantation candidacy.

MANAGEMENT

Brugada syndrome patients should avoid medications that might induce a Brugada pattern on ECG (www.brugadadrugs.org), avoid alcohol consumption, and be advised to treat fever aggressively. The ICD is the only effective therapeutic strategy to prevent sudden cardiac death in Brugada syndrome. The eligibility of young patients needs to be assessed for the subcutaneous ICD with screening test designed to identify susceptibility to T-wave oversensing during rest and stress. Isoproterenol (which increases I_{ca} current) is useful for management of electrical storm in Brugada syndrome. Quinidine (which blocks I_{to}) prevents VF induction, and suppresses ventricular arrhythmias in Brugada syndrome patients. Radiofrequency ablation of the PVCs triggering VF as well as a low-voltage substrate over the anterior right ventricular outflow tract epicardium prevented VF episodes in Brugada syndrome patients who were refractory to pharmacologic treatment. Family screening for the Brugada syndrome is recommended in first-degree relatives.

CASE PRESENTATION: FOLLOW-UP

The patient's SCN5A mutation c.5219 C>T (p. Ser1710Leu) is predicted to be deleterious by SIFT and probably damaging by Polyphen-2. His daughter had compound heterozygosity mutations in the SCN5A gene: Arg1512Trp and Ser1710Leu (trans mode). Previous studies showed worse phenotype for compound heterozygosity compared with single allele heterozygosity for the Brugada syndrome.[29]

SUMMARY

The Brugada syndrome might stay undetected in patients until surviving cardiac arrest. Despite the prominent advances in exploring the disease in the past 2 decades, many questions remain unanswered and the controversies continue. Moreover, despite all mutations identified to be associated with the disease, two-thirds of cases have a negative genetic test. Future studies should be directed toward modulating factors and their impact on patients' risk for sudden death to help physicians in risk stratifying their patients and optimally implementing ICD to prevent sudden cardiac death.

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