Update on Brugada Syndrome 2019

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Abstract: Brugada syndrome (BrS) was first described in 1992 as an aberrant pattern of ST segment elevation in right precordial leads with a high incidence of sudden cardiac death (SCD) in patients with structurally normal heart. It represents 4% ~ 12% of all SCD and 20% of SCD in patients with structurally normal heart. The extremely wide genetic heterogeneity of BrS and other inherited cardiac disorders makes this new area of genetic arrhytmology a fascinating one. This review shows the state of art in diagnosis, management, and treatment of BrS focusing all the aspects regarding genetics and Preimplant Genetic Diagnosis (PGD) of embryos, overlapping syndromes, risk stratification, familial screening, and future perspectives. Moreover the review analyzes key points like electrocardiogram (ECG) criteria, the role of electrophysiological study (the role of ventricular programmed stimulation and the need of universal accepted protocol) and the importance of a correct risk stratification to clarify when implantable cardioverter defibrillator or a close follow−up is needed. In recent years, cardiovascular studies have been focused on personalized risk assessment and to determine the most optimal therapy for an individual. The BrS syndrome has also benefited of these advances although there remain several key points to be elucidated. We will review the present knowledge, progress made, and future research directions on BrS. (Curr Probl Cardiol 2021;46:100454.)

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Introduction

Brugada syndrome (BrS) was first described in 1992 as an aberrant pattern of ST segment elevation in right precordial leads with a high incidence of sudden cardiac death (SCD) in patients with structurally normal heart (Fig 1).[1]

It looked like a scientific curiosity, however, after all these years this syndrome is recognized as a major disease that integrated previous syndromes like idiopathic ventricular fibrillation, sudden unexplained death syndrome, and some forms of sudden infant death syndrome. BrS and other syndromes like long or short QT syndromes and catecholamine polymorphic ventricular tachycardia (CPVT) have as common denominator alterations of ionic currents leading to depolarization and/or repolarization abnormalities that result in ventricular arrhythmias (VAs) causing SCD.

BrS represents 4% ~ 12% of all SCD and 20% of SCD in patients with structurally normal heart. Where the syndrome is endemic, like in Asiatic south-east regions, it is a leading cause of death in men under 40 years old.[2,3] Prevalence of BrS is believed to range from 1 in 5000 to 1 in 2000. It is 8 -10 times more prevalent in men than women. ventricular fibrillation (VF) occurs at a mean age of 41 + 15 years but it may manifest at any age, usually during rest or sleep.[4]

At least 19 different genetic variants of BrS are known nowadays, with more than 300 mutations reported, most of them affecting the *SCN5A* gene that encodes for the cardiac sodium channel. The extremely wide genetic heterogeneity of BrS and other inherited cardiac disorders makes this new area of genetic arrhytmology a fascinating one.

We will review the present knowledge, progress made, and future research directions on BrS.

Electrocardiographic Features and Diagnosis

The diagnosis of BrS is a clinical-electrocardiographic one. The clinical presentation can be very variable, from completely asymptomatic to episodes of syncope and SCD, but also other manifestations like Atrial fibrillation (AF) and atrioventricular (AV) block.

Characteristically, patients with BrS have no apparent structural heart disease. The hallmark of BrS is the transient or persistent appearance of typical ECG changes in the right precordial leads.[5]

Three different ECG patterns (Fig 1), all featuring ST segment elevation in the right precordial leads, have been recognized: Type I is the only pattern that is diagnostic for BrS. It consists of a coved-type ST

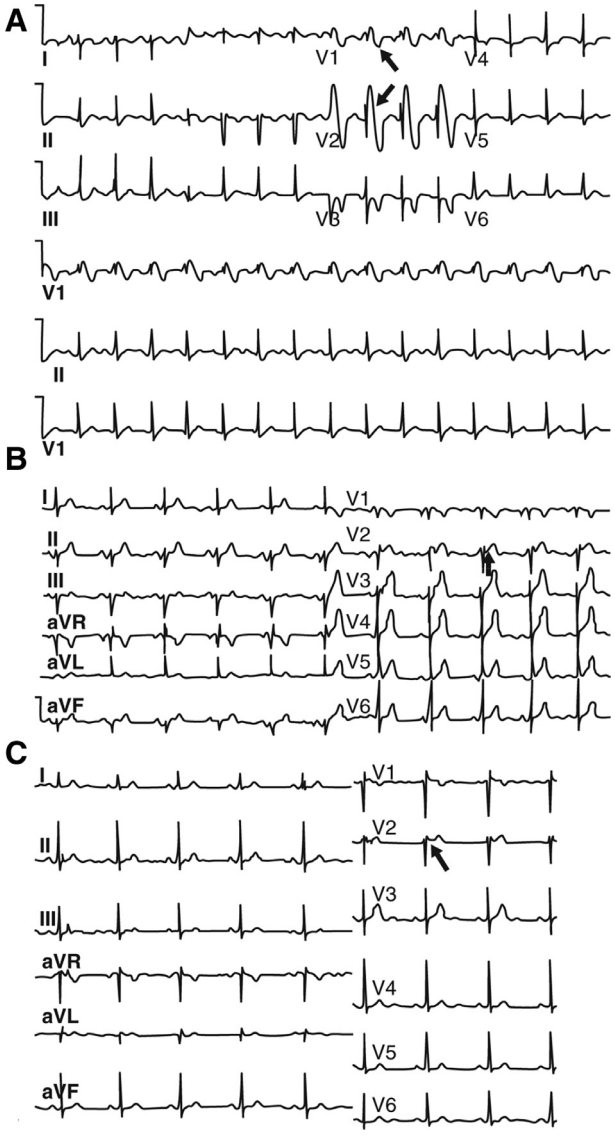

FIG 1. Brugada electrocardiogram (ECG) patterns. (A) A diagnostic coved-type (type I) Brugada ECG pattern documented in a 9-year-old girl who presented with syncope and positive family history of BrS. Note the pattern resembling a right bundle branch block (arrows) in leads V_1 and V_2, with typical ST elevation. (B) Baseline ECG of a 58-year-old asymptomatic man with positive family history of BrS. Example of a type II saddleback Brugada ECG pattern. Genetic analysis revealed a mutation in the *SCN5A* gene. Note the saddleback-shaped patterns, with a high initial augmentation followed by an ST elevation greater than 2 mm in lead V_2. (C) Example of a baseline type III saddleback Brugada ECG pattern (arrow) documented in a 61-year-old asymptomatic man who was diagnosed on the basis of a positive result on class IC antiarrhythmic drug testing.

segment elevation equal or greater than 2 mm, followed by a descending negative T wave in at least 1 right precordial lead (V1-V3). Type II and type III are saddleback patterns with a broad R' followed by a convex saddle-type ST configuration with elevation greater than 2 mm for type II and less than 2 mm for type III. Both patterns are suggestive of but they are not diagnostic for BrS. ECG appearance of "BrS" is not so uncommon in general population and identification of whom patient are really at risk is still challenging nowadays.

Consensus papers and guidelines were heterogenous and conflicting among years starting from BrS first description in 1992[1] through HRS, ESC consensus documents in 2002, 2006, and 2013 till Shangai criteria in 2016 and the last review made by Josep Brugada et al. in 2018.[6–8] Until 2013 we were able to diagnose BrS in a setting of Brugada ECG pattern plus symptoms which were needed to define the "syndrome." A patient had Brugada syndrome with a type 1 ECG pattern spontaneously or after provocative drug tests with intravenous administration of sodium-channel blockers plus 1 of the following:

- Documented VF or polymorphic VT.
- Inducibility of VAs with programmed electrical stimulation.
- Family history of SCD before age 45.
- History of nonvaso-vagal syncope
- Nocturnal agonal breathing.

Because many patients with a type 1 ECG are asymptomatic, in 2013 an expert consensus statement proposed a definition only based on ECG appearance requiring any further evidence of malignant arrhythmias.[9]

Brugada ECG pattern can be intermittent and dynamic in the same patient and can be present only during physical activity or other conditions like fever or electrolyte imbalances.[10] Some drugs like calcium antagonists, nitrates, phenothiazines, selective serotonin reuptake inhibitors etc can also unmask BrS pattern. This has important implications for the diagnosis of BrS because the diagnosis can be completely missed if it is not suspected and a pharmacologic challenge is not performed to unmask the typical type I ECG.

A pharmacologic challenge test can be performed using sodium challenge blockers like ajmaline, procainamide, or flecainide (Fig 2). In Japan, pilsicainide is used for that purpose. Ajmaline in a dose of 1 mg/kg over 5 minutes seems to be the best drug.

The full stomach test was proposed as an alternative tool in diagnosing BrS.[11] Here, the ST segment changes appear to be provoked by an

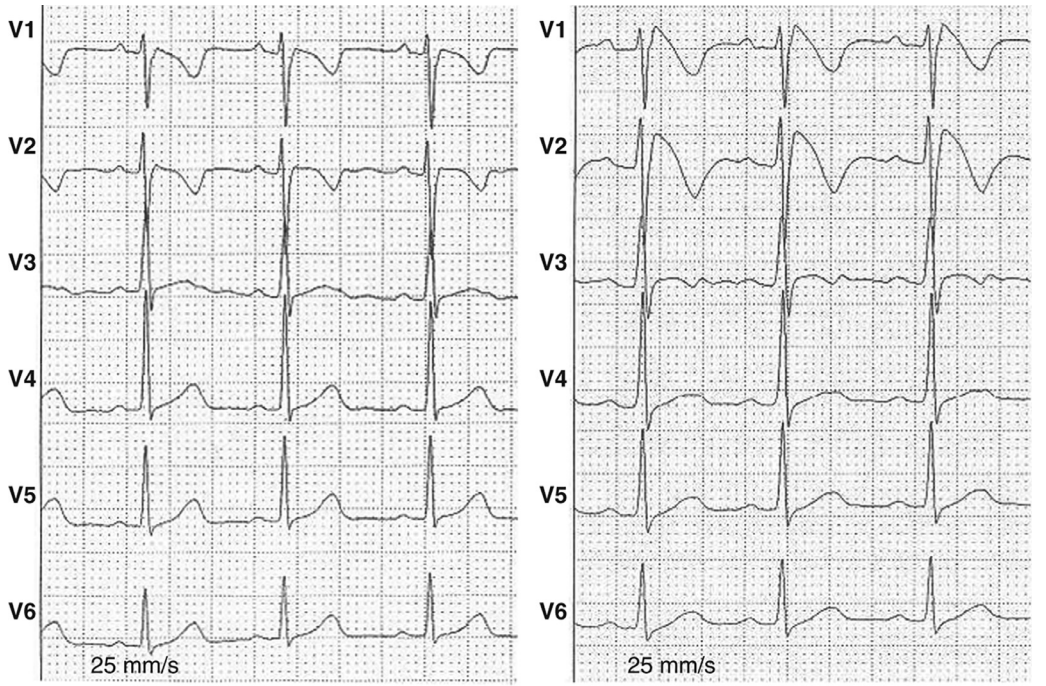

FIG 2. Induction of a diagnostic coved-type (type I) electrocardiogram (ECG) by administration of a sodium channel–blocking agent.

enhanced vagal tone. Adrenergic stimulation decreases the ST segment elevation, whereas vagal stimulation increases it.

It is important to rule out other causes of ST segment abnormalities in right precordial leads which mimic BrS before making the diagnosis. Those are known as BrS "*phenocopies*" (Table 1).[12]

A diagnosis of BrS requires a high degree of suspicion by physicians. Symptoms that suggest a possible BrS and promote its intensive research are: syncope of unknown origin, AF with a normal heart, peripheral or cerebral embolism (as a complication of AF), and cardiac arrest of unknown cause. These symptoms and signs can be the first and only manifestation of BrS.

TABLE 1. Acquired Brugada Syndrome (phenocopies): differential diagnosis of ST segment elevation in electrocardiogram leads V_1 and V_2.

Drugs	Antiarrhythmic drugs	• Class 1C sodium channel blockers (eg, flecainide, pilsicainide, propafenone) • Class 1A sodium channel blockers (eg, procainamide, disopyramide, cibenzoline) • Verapamil (L-type calcium channel blocker) • Beta-blockers (inhibit $I_{Ca,L}$)
	Antianginal drugs	• Nitrates • Calcium channel blockers (eg, nifedipine, diltiazem)
	Psychotropic agents	• Tricyclic antidepressants (eg, amitriptiline, desipramine, clomipramine, nortriptyline) • Tetracyclic antidepressants (eg, maprotiline) • Phenothiazines (eg, perphenazine, cyamemazine) • Selective serotonine uptake inhibitors (eg, fluoxetine) • Cocaine intoxication
	Antiallergic agents	• Histamine H1 antihistaminics. First-generation (dimenhydrinate)
Acute ischemia in RVOT		
Electrolyte disturbances	Hyperkalemia Hypercalcemia	
Hyperthermia and hypothermia		
Elevated insulin level		
Mechanical compression of RVOT		

RVOT, right ventricular outflow tract.

The presence of a type I BrS pattern in first-degree relatives with a family history positive for SCD can lead to a stronger suspicion of real BrS ECG pattern in our patient. We recommend an ajmaline test in these circumstances to prove or exclude the diagnosis.

Shangai criteria stated in 2016 rise up an important question, if a drug challenge test is really necessary when we find a type 2 BrS ECG pattern.[7]

In the absence of symptoms like syncope (non vaso-vagal) or a family history of SCD and type I BrS ECG the extensive use of drug challenge test seems to be unnecessary, given that the risk of SCD of those patients isn't higher and sometimes is lower than general population.[13] A "positive result" in those patients can have negative psychological consequences and unnecessary daily life restrictions like in agonist sports or "medical clearance" for some jobs.

We should also remember that sodium-channel blocker challenge test is not free from possible side effects.

Genetics

BrS is a familial disease. The most common type of inheritance is an autosomal dominant pattern. To date, more than 300 pathogenic variants in 19 different genes have been reported (Table 2). The first gene that was associated with BrS was the SCN5A gene which encodes for the alpha subunit of the cardiac sodium channel.[14] Mutations in the SCN5A gene result in loss of function of the sodium channel.

About 20%-25% of patients with BrS have a mutation in the SCN5A gene, classified as BrS type 1.[15]

Recently, an individual diagnosed with BrS and concomitant conduction system disease had a large-scale deletion of the SCN5A gene.[16] This copy number variation is the only rearrangement identified as a cause of the disease to date.

Despite these ongoing developments in understanding the genetic causes of BrS, only 30%-35% of clinically diagnosed cases are genetically diagnosed, and most of these (25%-30%) result from pathogenic alterations in SCN5A.[15]

Other mutations associated with BrS affect the SCN1B gene (codifying for the sodium channel beta-1 subunit), the SCN2B gene (sodium channel beta-2 subunit), and the SCN3B gene (sodium channel beta-3 subunit); all these mutations modify the channel's function (increasing or decreasing INa).[17–19]

Recently, SCN10A gene (neuronal sodium channel Nav1.8) has been shown to modulate SCN5A expression and the electrical function of the

TABLE 2. Brugada Syndrome (BrS) types.

Inheritance	Locus	Gene	Protein
(Sodium) Autosomic dominant	3p21-p24	*SCN5A*	Nav1.5
	3p22.3	*GPD1-L*	Glycerol-3-P-DH-1
	19q13.1	*SCN1B*	Navβ1
	11q24.1	*SCN3B*	Navβ3
	11q23.3	*SCN2B*	Navβ2
	3p22.2	*SCN10A*	Nav1.8
	17p13.1	*RANGRF*	RAN-G-release factor (MOG1)
	3p14.3	*SLMAP*	Sarcolemma associated protein
	12p11.21	*PKP2*	Plakofilin-2
(Potassium) Autosomic dominant	12p12.1	*ABCC9*	Adenosine triphosphate (ATP)- sensitive
	11q13-q14	*KCNE3*	
Chromosome X	12p12.1	*KCNJ8*	MiRP2
	15q24.1	*HCN4*	Kv6.1 Kir6.1
	1p13.2	*KCND3*	Hyperpolarization cyclic nucleotide-gated 4
	Xq22.3	*KCNE5*	Kv4.3 Kir4.3 potassium voltage-gated channel subfamily E member 1
(Calcium) Autosomic dominant	2p13.3	*CACNA1C*	Cav1.2
	10p12.33	*CACNB2B*	Voltage-dependent β-2
	7q21-q22	*CACNA2D1*	Voltage-dependent $\alpha 2/\delta 1$
	19q13.33	*TRPM4*	Transient receptor potential M4

heart.[20] Another gene reported as responsible for BrS is the GPD1-L. Mutations in GPD1-L reduce both the surface membrane expression and the inward sodium current.[21]

Kattygnarath et al. have published a study supporting that RANGRF can impair the trafficking of Nav1.5 to the membrane, leading to INa reduction and clinical manifestation of BrS.[22] Ishikawa et al. reported in 2012 pathogenic variations in the sarcolemmal membrane-associated protein's gene, a gene of unknown function that is found at T-tubules and the sarcoplasmic reticulum. Sarcolemmal membrane-associated protein's gene causes BrS by modulating the intracellular trafficking of the Nav1.5 channel.[23]

Pathogenic variations in the plakophilin-2 (PKP2) gene have been also reported to be associated with BrS.[24,25] PKP2 is the primary gene responsible for arrhythmogenic right ventricular cardiomyopathy, a desmosomal disease characterized by fibro-fatty replacement of myocardium leading to SCD in young men, mainly during exercise. Correlation between the loss of expression of PKP2 and reduced INa has been identified in BrS patients.

Apart from sodium channels, several potassium channels have been also related to BrS. The first one described was KCNE3 which codifies the MiRP2 protein which regulates the potassium channel Ito and

modulate some others potassium currents in the heart.[26] Another gene associated to BrS is the KCNJ8, previously related to early repolarization syndrome (ERS).[27] The KCNJ8 was described as a novel J-wave syndrome susceptibility gene and a marker of gain of function in the cardiac K(ATP) Kir6.1 channel.[28]

In 2011, Giudicessi et al. provided the first molecular and functional evidence implicating novel KCND3 gain-of-function mutations (Kir4.3 protein) in the pathogenesis and phenotypic expression of BrS with enhanced Ito current gradient within the right ventricle where KCND3 gene expression is the highest.[29]

Novel variants in KCNE5 were shown to cause gain-of-function effects on Ito. KCNE5 gene is located in the X chromosome and encodes an auxiliary β-subunit for K channels.[30]

A similar role is the one of sulfonylurea receptor subunit 2A (SUR2A), encoded by the ATP binding cassette subfamily C member 9 (ABCC9) gene.[31] Gain-of- function pathogenic variants in ABCC9 induce changes in ATP-sensitive potassium) channels and, when coupled with loss-of-function pathogenic variants in SCN5A, they may underlie a severe arrhythmic phenotype of BrS.

BrS was also associated gene HCN4 gene, which codifies for HCN4 channel or If channel (hyperpolarization-activated cyclic nucleotide-gated potassium channel 4). Its mutations predispose also to inherited sick sinus syndrome (SSS) and Long QT syndrome (LQTS) associated with bradycardia.[32]

Calcium channels have also been associated to BrS. Mutations in the CACNA1C gene are responsible for a defective a unit of the type-L calcium channel. Mutation of the CACNB2B gene leads to a defect in the L-type calcium channel. Both induce a loss of channel function.[33] It was reported that the CACNA2D1 gene was also responsible for BrS. The alpha-2/delta subunit of the voltage-dependent calcium channel regulates current density, and activation/inactivation kinetics of the calcium channel.[34]

Finally, pathogenic variations have also been reported in the transient receptor potential melastatin protein number 4 (TRPM4) gene, a calcium-activated nonselective cation channel that is a member of a large family of transient receptor potential genes.[35] This gene is involved in conduction blocks and the consequences of pathogenic mutations are different. Thus, reduction or increase in TRPM4 channel function may reduce the availability of the sodium channel and lead to BrS.

It is clear therefore, that BrS is an heterogenous genetic disease. It is not a surprise that many overlapping syndromes can exist due to this very variable and large spectrum of possible genetic causes. It also has to be clear that a

direct cause-to-effect relation between these mutations and BrS has not been completely established in the majority of genetic variations.

Genetic and Environmental Modulators

In recent years, several genetic and environmental modulators of the phenotype have been described. It is well known that environment may play a role in the predisposition to arrhythmias in patients with BrS. The identification of several triggering factors of the Brugada ECG pattern and of SCD as fever, cocaine, electrolyte disturbances, class I antiarrhythmic medications and a number of other noncardiac medications, some of them with a genetic predisposition, has important implications for the prevention of arrhythmias in patients with BrS.[36,37]

In addition, the incomplete penetrance of the disease, as well as the variable expressivity, has brought into question the role of additional genetic factors in the final phenotype. Single nucleotide polymorphisms became one of the first players to be studied in defining this variability. The SCN5A polymorphism p.H558R is present in 20% of the population. This polymorphism has been shown to partially restore the sodium current impaired by other simultaneous BrS causing mutations in SCN5A.[38] Thus, this common variant is a genetic modulator of BrS among carriers of an SCN5A mutation, in whom the presence of the less common allele makes BrS less severe.[39]

Genetics variants in the SCN5A promoter region may also play a pathophysiologic role in BrS. A haplotype of 6 polymorphisms in the SCN5A promoter has been identified and functionally linked to reduced expression of the sodium current in the Japanese population.[40] Other studies have shown the role of double or even triple mutants in causing a more severe phenotype.[41,42]

The role of the genetic mutation in risk stratification has yet to be clearly defined. Recent data proposed the type of genetic mutation as a tool for risk stratification in BrS. In this study patients and relatives with a truncated protein had a more severe phenotype and more severe conduction disorders. Despite that this is the proof of concept that some of the mutations appear to confer a worse prognosis, data are not yet sufficiently strong as to help in risk stratification.[43]

Overlapping Syndromes

Is it possible to find different BrS phenotypes within the same family even when they share the same mutation. Some individuals may present

with 2 different phenotypes at the same time, like BrS with a long or a short QT interval. These so-called "overlapping syndromes" represent a strong challenge to physicians for diagnosis and risk stratification.

ERS

ERS is a common electrocardiographic variant characterized by J-point elevation, ST-segment elevation with upper concavity and prominent T-waves in at least 2 contiguous leads.[44] ERS and BrS share cellular, ionic, and ECG common features, representing parts of a phenotypic spectrum called "J-wave syndromes," although the degree to which ERS and BrS may overlap remains undetermined.[7] Patients having both with BrS and ERS have been recently reported.[45] ERS has been linked to mutations in the *CACNA1C, CACNB2, CACNA2D1*, and *KCNJ8* genes.[46]

Lev-Lenegre Syndrome

Lev-Lenègre syndrome (also known as progressive cardiac conduction disease -PCCD) is a rare entity characterized by conduction disturbances at the atrioventricular level leading to complete AV block. The syndrome is a cause of syncope and even SCD. The presence of PCCD in the BrS families is not uncommon, as they both result from a reduction in the sodium current.

It has been described as a different expression of the same genetic phenotype. The first mutation associated with PCCD was described in the *SCN5A* gene 39, 40, and on its B61 subunit.[17,47,48] Patients with clear BrS can die suddenly because of AV block and asystole, not only because of ventricular fibrillation (Fig 3).

Sick Sinus Syndrome

SSS is characterized by persistent inappropriate sinus bradycardia, sinus arrest, atrial standstill, and tachycardia-bradycardia syndrome, associated with sinoatrial node dysfunction. Patients may exhibit varied symptoms including syncope, and even SCD. The course of SSS can be intermittent and unpredictable, related to the severity of the underlying heart disease.[49] Both autosomal recessive and dominant forms have been described.

In 2003 an association between *SCN5A* mutations and congenital SSS was reported.[50] In 2005 a novel *SCN5A* mutation was identified in patients presenting both SSS and BrS, showing that in the same family both diseases may be related to the expression of a loss-of-function mutation in *I*na.[51]

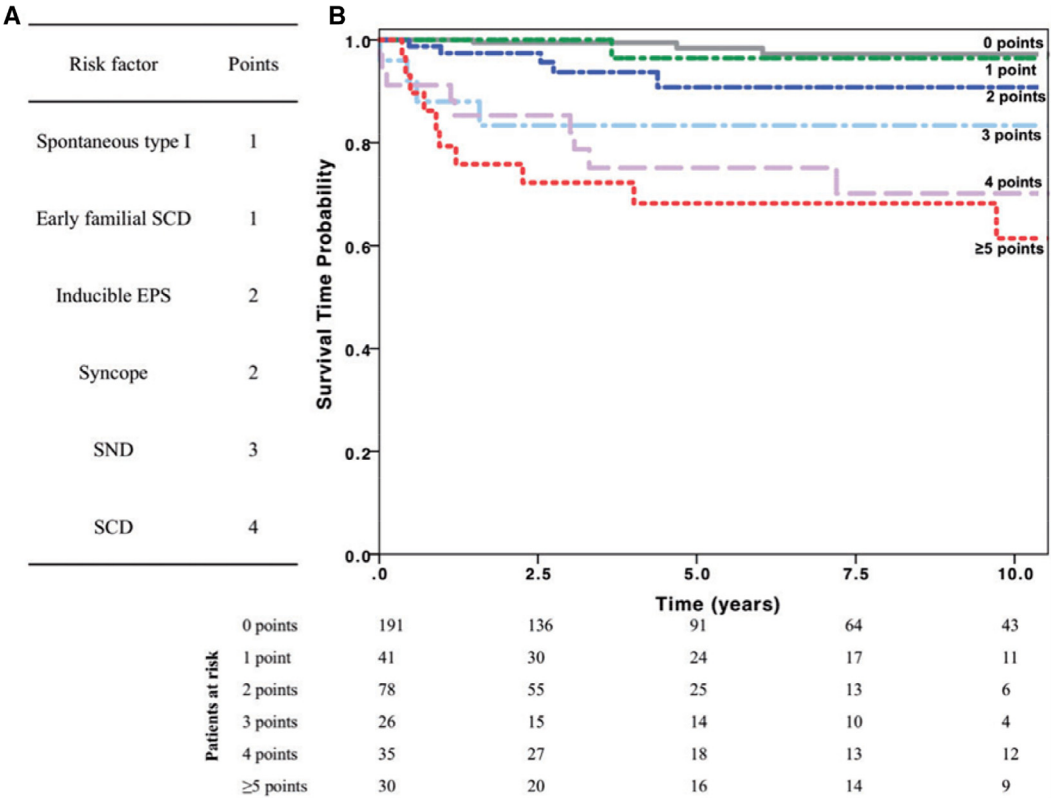

FIG 3. Survival curves in BrS depending on score.[56]

The presence of SSS has important prognostic implications in BrS because it increases SCD risk, particularly in children.

AF

AF is the most common atrial arrhythmia found in BrS.[52] AF can be the first manifestation of BrS, and, sometimes, its complications like peripheral or cerebral embolization could be the first symptom.

BrS should be excluded by drug challenge in all individuals with atrial flutter or AF and a normal heart if we have a suspicion of diagnosis.

Approximately 15%-20% of patients with BrS will develop supra VAs.[53] Some studies reported prolongation of atria-His and His-ventricular intervals; these changes occur principally in patients with *SCN5A* mutations and are consistent with a decreased excitability in the conduction system secondary to loss of function of sodium channel.[54,55]

Long QT Syndrome Type 3

LQTS is an inherited arrhythmogenic disease characterized by prolongation of the QT interval and susceptibility to VA. Among all described subtypes of LQTS, type 3 (LQT3) has a prevalence of 7%-10%.[56]

LQT3 is caused by mutations in the *SCN5A* gene. A most intriguing report showed that some individuals may display the electrocardiographic pattern of LQT3, while others the pattern of BrS in the same family and with the same mutation.[57] The overlap between the LQT3 and BrS phenotypes was also reported in other *SCN5A* mutations.[58] However, it is still unclear whether development of the BrS phenotype in a patient with LQT3 is solely determined by the biophysical properties of the mutant channel or by coinherited genetic variations, gender, ethnicity, or other environmental factors.[59]

Epilepsy and Schizophrenia

Some arrhythmias are related to abnormal ion channel function due to gene mutations. Epilepsy neuronal function disorder involving abnormal channel function. It's demonstrated that etiologies of both BrS and epilepsy may sometimes overlap.

It has been reported that *SCN5A* mutations may confer susceptibility for recurrent seizure activity, supporting the emerging concept of a genetically determined cardio-cerebral channelopathy.[60,61]

A high percentage of patients with schizophrenia (around 12%) shows a BrS ECG pattern and this is not related to sodium channel blocker drugs. The reasons of these findings are unclear.

Myotonic Phenotypes

To date, except for nonspecific cardiac arrhythmias described in 2 *SCN4A*-associated case reports, no overlapping phenotypes between muscular and cardiac sodium channelopathies have been reported.[62]

In a recent study, Bissay et al. reported a high number of patients with coexisting BrS and sodium channel myotonia, suggesting a possible impact of *SCN4A* variants on the pathophysiological mechanism underlying the development of a type 1 ECG pattern and malignant arrhythmias in some patients with myopathies.[63]

Risk Stratification

After BrS diagnosis the first questions are mainly related to the patient's outcome and prognosis.

To date, some markers of high risk in BrS patients have been clearly identified and accepted by all groups, but the issue of risk stratification in asymptomatic BrS patients remained controversial until the recent report by our group.[64]

The reported annual rate of events decreased from the first case reports to the most recent published series. This probably reflects the inherent bias during the first years following the description of a novel disease due to the fact that particularly severe forms of the disease are most likely to be diagnosed.[65]

A recent study by Sieira et al. shows that arrhythmic events in asymptomatic BrS patients are not insignificant (0.5% annual incidence rate). In this cohort, inducibility of VAs, spontaneous type I ECG and presence of sinus node dysfunction might be considered as risk factors and used to drive long-term management.[66]

A recently published meta-analysis showed that asymptomatic subjects with either spontaneous diagnostic ECG pattern or inducible VAs at electrophysiological study (EPS) are at increased risk.[67] The risk of lethal or near-lethal arrhythmic episodes among previously asymptomatic patients with BrS varies according to the series: 8% recurrence rate at 33 ± 39 months of follow-up reported by Brugada et al., 6% recurrence rate at 34 ± 44 months by Priori et al., 1% recurrence rate after 40 ± 50 months and 30 ± 21 months of follow-up, respectively by Eckardt et al. and Giustetto et al. and finally, Probst et al. reported a 1.5% recurrence rate at 31 months of follow-up.[68–71]

Several clinical variables have been demonstrated to predict a worse outcome in patients with BrS.

In almost all analysis the presence of symptoms before diagnosis like an history of syncope, a spontaneous type-1 ECG at baseline and male gender have consistently shown to be related to the occurrence of cardiac events in follow-up.[72,73]

Spontaneous type 1 ECG has been identified as an independent predictor of VAs in multivariate analysis of the largest cohort of BS patients published to date (HR = 1.8; 95% CI 1.03-3.33; P = 0.04) and in the majority of series by other authors.[71]

Male sex has consistently shown more arrhythmic events in all the studies and has been defined as an independent predictor for a worse outcome in a meta-analysis.[74]

Spontaneous AF, which can be present in 10%-53% of cases, has been shown to have a prognostic value and spontaneous AF was associated with higher incidence of syncopal episodes (60.0% vs 22.2%, $P< 0.03$) and documented VF (40.0% vs 14.3%, $P< 0.05$).[75]

Little controversy exists on the value of a previous cardiac arrest as a risk marker for future events (between 17% and 62% of patients will have a new arrhythmic event within 48 and 84 months of follow-up).

Syncope

Syncope is an indisputable risk factor, well-recognized in literature which identifies patients carrying a high risk of events.

Between 17% and 62% of BrS patients with syncope will have a new arrhythmic event 48-84 months after diagnosis, which might lead to SCD.[76]

Syncope in combination with a spontaneous type 1 ECG pattern has a poor prognosis during follow-up (arrhythmic event in 6%-19% within 24-39 months of follow- up).[77]

Appropriate clinical evaluation to rule out vasovagal/neuromediated syncope is recommended as these patients do not appear to have an increased risk of VAs during follow-up.[78]

It is not always easy to understand the real nature of syncope in some patients, including those with BrS. Both BrS and neurally-mediated syncope share a susceptibility to vagal tone. High incidence of positive Head-up Tilt test has been demonstrated in asymptomatic subjects with Brugada pattern.[79]

There is general agreement that these patients should be protected with an implantable cardioverter-defibrillator (ICD) irrespective to the presence of other risk factors, accepting the risk to overprotect a patient with vaso-vagal syncope and Brugada ECG pattern with an ICD.

Electrophysiological Study

Although large registries agree that VAs inducibility by ventricular programmed stimulation (VPS) is greatest among BrS patients with previous cardiac arrest or syncope there is no consensus on the value of the EPS in predicting outcome.[68]

Results of our previous data indicated that VAs inducibility was an independent predictor for SCD and Giustetto et al. stressed on its good negative predictive value (none of the patients with a negative EPS developed arrhythmic events vs 15% of patients with a positive EPS during a 30 ± 21 months of follow-up); other registries failed to demonstrate that.[68–71]

The largest series of BrS patients published so far, found that inducibility of sustained Vas was significantly associated with a shorter time to first arrhythmic event in the univariate analysis but, when performing the multivariable analysis, inducibility did not predict arrhythmic events.[72]

In 2015 a single center study has been published, showing results in a cohort of 96 BrS patients with various clinical presentations and inducible VF with an aggressive VPS protocol.

The authors reported an excellent protective effect of class 1 antiarrhythmic drug (mainly quinidine) during EPS and an excellent clinical outcome in drug-treated patients.[80] Sieira et al. published a series of 403 BrS patients. Authors conclude that VPS is a good predictor of outcome in individuals with BrS.[81]

If symptomatic patients have more easily induced arrhythmias during EPS is still controversial. The absence of induction with VPS alone is not sufficient to identify low-risk individuals, especially in symptomatic patients.[82]

So far, EPS could have a role in asymptomatic patients who still carries a 0.5%-1.2% annual incidence of arrhythmic events and might be of special value to guide further management. VPS may identify patients with BrS at increased risk for cardiac arrest but the association appears most relevant in patients induced with single or double extra-stimuli rather than more aggressive stimulation protocols.[77] Aggressive stimulation protocol may lead to an excess of false positive results.

A recent study by Pappone et al. demonstrated how the extent of arrhythmic substrate in EPS is a predictor of inducibility of VT or VF and may serve as marker for risk stratification and therapy by substrate ablation.[83]

Current European guidelines for SCD prevention don't give guidance about use of EPS for BrS risk stratification but simply state that an ICD may be considered in cases of inducible VAs.[9]

We still do not have a clear answer if VAs inducibility is a risk factor strong enough for clinical decision-making and patient's management.

Looking at present evidence EPS can be a part of BrS patient evaluation but it isn't enough to classify patient's risk.

EPS with VPS in asymptomatic patients with BrS is reasonable but that the decision to proceed should be individualized after clinical risk stratification and detailed counseling with patients about the implications of a positive or negative result.

Genetics

A family history of SCD or the presence of an *SCN5A* mutation have not been proven to be risk markers in any of the large studies conducted thus far.[74] However, recent data suggest that other genetic findings like mutations leading to a truncated protein or the presence of common polymorphisms located in *SCN5A* might have some prognostic implications.

A recent publication by Meregalli of 147 BrS patients with *SCN5A* identified mutations showed a significantly higher rate of syncope among patients carrying *SCN5A* truncation mutations (caused by a premature stop codon) and those with *SCN5A* missense mutations resulting in a decrease of more than 90% of the INa (nonfunctional Na+ channels), compared to patients with *SCN5A* missense mutations that produce a decrease of Na current ($\leq$90%). They could not demonstrate a higher rate of more serious arrhythmic events (SCD or VF) in those patients with mutations encoding nonfunctional Na+ channels. The first 2 groups of patients also presented longer PR interval in the basal ECG and showed a greater increase of PR and QRS intervals after the class I antiarrhythmic drugs (AAD) test. This is the first study that proposed the use of genetics in risk stratification for BrS.[43]

The recent finding that common polymorphisms located in *SCN5A* may modulate the effect of mutations resulting in a counterbalance of its deleterious consequences with improvement of the BrS phenotype opens the possibility of identification of polymorphisms as risk stratification tools. These data also suggest that polymorphisms may be possible targets for therapeutical interventions.

Results of genetic screening do not currently influence prognosis or treatment and no conclusive studies published focus on prognostic value with regard to the genetic analysis.

Other Risk Factors

In an effort to solve the complex issue of risk stratification in BrS, several other risk factors were postulated like QRS fragmentation, ST-segment elevation during recovery from exercise, conduction abnormalities.[84,85]

An early repolarization pattern in the inferior and/or lateral leads is associated with an increased risk of arrhythmic events and may be present in 10%-15% of patients.[86]

Other risk factors evaluated are: a decreased nocturnal standard deviation of the "5 minutes averaged NN intervals " (SDANN) measured in Holter-ECG recordings, an S wave width in V1 $\geq$ 80 milliseconds and ST-segment elevation $\geq$ 0.18 mV in V2, spontaneous changes in ST-segment, a corrected QT interval (QTc) higher than 460 milliseconds in V2; prolonged T peak-T end (Tpe) interval and T p-e dispersion, the "aVR sign" (R wave $\geq$ 0.3 mV or R/q $\geq$ 0.75 in lead aVR), prolonged QRS duration in precordial leads (r-J interval in V2 $\geq$ 90 milliseconds and QRS $\geq$ 90 milliseconds in V6; QRS $\geq$ 120 milliseconds in V2).

Even an indicator of interventricular mechanical dyssynchrony has been recently found to be associated with high risk of fatal or near-fatal arrhythmias in BrS.

The usefulness of late potentials (LP) assessed by signal-averaged ECG as a marker of high risk has been extensively studied by various groups and a recent prospective study showed that positive LP was an independent marker of high risk in BS patients with a hazard ratio of 10.9 (95% confidence interval 1.1-104.3, P = 0.038), sensitivity of 95.7%, specificity of 65%, positive predictive value of 75.9%, negative predictive value of 92.9%, and predictive accuracy 81.4%. Before including LP as a marker for risk, there is the need of more prospective studies, including more patients and with a longer follow-up, evaluating the value of different noninvasive markers of risk in BrS.

All those risk factors arise from observational studies and require validation in larger series. Their limit is that although they increase statistically the probability of VAs during follow-up only few of those patients have arrhythmic events. For this reason they're not useful for ICD implant evaluation right now.

In summary, few things are clear from the risk stratification data:

- Symptomatic patients are at higher risk than asymptomatic ones.
- Sudden death survivors are at higher risk than patients with syncope; males are at higher risk than females.
- Patients with type I ECG at baseline have a higher risk than those who require drug challenge test.

We should not forget that asymptomatic patients may also die suddenly. This latter statement is based on the fact that all symptomatic patients with BrS have remained asymptomatic for decades.

Thus, at present the biggest challenge is the detection of these few asymptomatic who will develop symptoms.

Scoring Systems for Risk Quantification

An analysis of several prospective studies on clinical outcome in BrS patients showed that incidence of SCD in asymptomatic patient was 0.38% for spontaneous type 1 ECG pattern and 0.06% after sodium-channel blockers challenge test. Patients who died for VAs (24/1568) had more risk factors (spontaneous type 1, syncope, SCD in relatives, induction of VA after VPS) compared to other patients and probably they should have been implanted with an ICD.[13]

Sieira et al. analyzed long-term follow-up in 400 patients with BrS and concluded that 6 variables were related to a poor outcome and contributed with a certain value to a scoring system developed by careful statistical analysis (Table 3 and Fig 3). Multivariate analysis showed that the presence of a spontaneous type I ECG, a family history of sudden death (<35 years or several cases), a history of syncope, inducibility during VPS, SSS, and a previous cardiac arrest were the 6 variables that could be assigned a certain value in points (Table 3). The survival curves without sudden death or appropriate ICD discharge are shown for the different score categories in Fig 3. While the incidence of events increases clearly depending on the number of points, it has to be stressed that the first 2 categories (0 and 1 point) have still a high incidence of sudden death as compared to the general population without BrS. Thus, a possible risk of sudden death of 0.3% per year in the first category (0 points) represents at least a 30 times increase of the risk as compared with an individual of the same age without BrS (who has a general risk of sudden death of 1:10.000 per year at age 40).[62]

BrS patients remain at risk for many years after diagnosis. A simple risk score might help in risk stratification and management of BrS patients.

TABLE 3. Risk factors for sudden death in BrS.

Risk factor	Points
Spontaneus type I ECG	1
Family history of sudden death	1
Inducibility during PES	2
History of syncope	2
Sick sinus syndrome	3
Resuscitated SCD	4

Therapeutic Options and Management of BrS Patients

ICD

Actually the only proven effective therapeutic strategy for the prevention of SCD in BrS patients is the ICD as in other primary arrhythmogenic hearth diseases and cardiomyopathies with high arrhythmic risk.[87]

Outcome of ICD implantation in BrS was outlines by Sacher in 2013[88] with a multi-center study (378 patients) and a long follow-up. Appropriate shock rate at 10 years was 48% for sudden cardiac arrest, 19% for syncope, and 12% for asymptomatic patients. Total 37% of patients received an inappropriate shock at 10 years. Lead failure was found in 29% of patients.

Conte et al. recently supported ICD implantation in preventing SCD, treating potentially lethal arrhythmias in 17% of patients during a follow-up period of nearly 85 months. Appropriate shocks were significantly associated with the presence of aborted SCD.[89]

It is important to remark that ICDs are not free from several disadvantages, especially young individuals, facing a long-lasting coexistence with the device and multiple device replacements.

Some series have reported low rates of appropriate shocks (8%-15%, median follow-up 45 months) and high rate of complications, mainly inappropriate shocks (20%-36% at 21-47 months follow-up).[90–92]

In a recent study, Rodriguez-Mañero et al. published that T-wave oversensing is a potential cause of inappropriate shocks by ICD in patients with BrS. In the vast majority it can be solved by reprogramming. However, in some patients it still requires invasive intervention.

Incidence is significantly lower using an integrated bipolar lead system when compared with a dedicated bipolar lead system and hence the latter should be routinely used in BrS cases.[93]

So, ICD implantation, especially in young patients, is not without a significant price, with concern in risk of inappropriate therapy (due to sinus tachycardia, supraventricular tachicardia, T-wave oversensing, lead failure).[94]

Subcutaneous ICD is an alternative device to reduce some risks, like ICD related infections.[95]

ICD implantation is recommended (class I) in case of aborted cardiac arrest or sustained VT. It can be useful in patients with spontaneous type 1 ECG and a history of syncope judged to be caused by VAs. It may be considered when sustained VAs/VF are induced by VPS during EPS even if current guidelines don't give clear indication when to use of EPS for BrS risk stratification; ICD implantation is not indicated in asymptomatic

BrS patients with spontaneous or drug-induced type I ECG and on the basis of a family history of SCD alone as their risk for life-threatening events is very low.[9]

Pharmacological Treatment

With the aim to normalize ionic currents altered in BrS during drugs that inhibit the Ito current or increase the Na+ and Ca+2 currents have been tested.

Isoproterenol (which increases the Ica L current) has proved to be useful for management of electrical storms in BrS.[96]

Quinidine, a class Ia AAD with Ito and I-Kr blocker effects, has shown to prevent induction of VF and suppress spontaneous VAs in a clinical setting and it's currently used in patients with ICD and multiple shocks, in patient in which ICD implantation is contraindicated or for the treatment of supra VAs. It has been suggested that it could be also useful in children with BrS as a bridge to ICD or as an alternative to it.

However, recent data from the international SABRUS registry have shown that quinidine is of no value to prevent sudden death in BrS.[97]

Transcatheter Ablation

Morita et al. demonstrated in their animal model of BrS that right ventricular outflow tract (RVOT) was the main substrate site, especially at the epicardial site.[98]

There is a general consensus that arrhythmic substrates responsible for the abnormalities seen in the typical BrS ECG pattern are located on the anterior RVOT especially in the pericardium. This substrate is well-identified during electrophysiological mapping by abnormal electrograms characterized by low voltage, prolonged duration, and fractionated late potentials clustering in the RVOT epicardium and/or RV anterior free wall. Some patients have also inferior wall arrhythmic substrates. Wider abnormal areas were found in patients with the worst clinical presentation and/or type 1 BrS ECG pattern.

Extensive electrophysiologically well-defined abnormal areas are unmasked by sodium channel blockers, with the best results obtained by ajmaline.[99,100]

After the demonstration that VAs events could be triggered by ventricular ectopy of similar morphology, radio-frequency (RF) ablation of ventricular ectopy has been postulated as a therapeutic approach in BrS patients.

Haïssaguerre et al. were the first to attempt catheter ablation from the endocardial site to treat patients with BrS with recurrent VF.[101] Patients with BrS rarely have PVCs making this approach impractical.

Case reports in high-risk BrS implanted with an ICD have shown no short-term recurrence of VF, syncope, or SCD.[98,102–104]

Nademanee et al. have presented the first series showing that electrical epicardial substrate ablation in the RVOT can prevent VF inducibility in a high-risk population.[104] At a mean follow-up of 20 ± 6 months, only 1 of 9 patients had any recurrences of VF episodes, and there were no shocks from the ICD. Postprocedure, predischarge, and follow-up 12-lead ECG confirmed the absence of BrS ECG pattern before and after flecainide test in all patients and after a median follow-up of 5 months ECG remained normal despite flecainide testing. ICD did not show arrhythmic events.

Forkmann et al. reported a BrS case in which epicardial ventricular tachycardia ablation was performed and noninducibility of any VT during PVS was identified. During a 9 months follow-up, device interrogation showed no recurrence of any VAs.[105]

Recently, a study focused on epicardial ablation has been published showing an apparent elimination of the BrS ECG phenotype. Epicardial ablation was performed during subcostal implantation of the ICD where the ICD leads are implanted around the heart epicardially (Fig 4).[105]

Pappone found well-defined abnormal epicardial areas identified as BrS substrate, responsible for type 1 BrS-ECG pattern and VT/VF inducibility on a series of 135 patients. Persistent ECG pattern normalization without VF inducibility, even after repeated ajmaline challenge, suggested that substrate

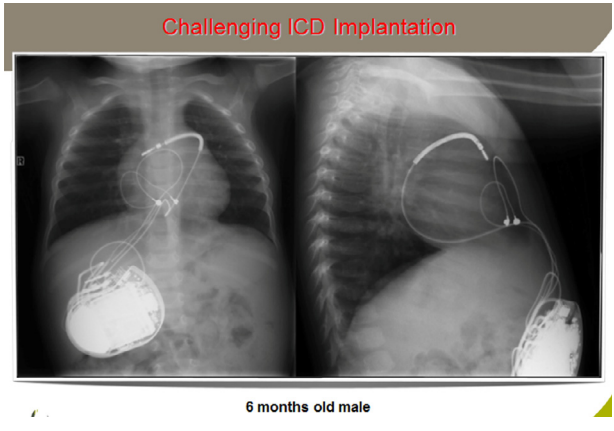

FIG 4. X-ray after ICD implantation in a 6 months old child: Epicardial electrode on epicardial right ventricle free wall, defibrillation electrode around the heart in the sinus tranversus. Generator in abdominal position.

ablation can be considered as a potential therapy for preventing recurrent VT/VF.[106]

As seen by those authors, adequately identify any potential substrate represents the only way to successfully perform RF ablation in order to ensure that the entire arrhythmic electrical substrate area is ablated and to minimize the amount of healthy tissue ablated.

These findings clearly suggest that regardless of clinical presentation and/or spontaneous ECG pattern, the BrS population has a well-defined arrhythmic substrate which in many patients may be difficult to activate in the absence of modulating factors or triggers.

Nowadays the only case when transcatheter ablation could be the first choice is a patient refusing ICD implantation as suggested by a case report of RF ablation without ICD implantation with a 18 months of follow-up without arrhythmic events.[107]

We have to remember that the target of ablation is the elimination of the phenotypic characteristic that is traditionally used to decide whether an ICD should be implanted in a genetic disease such a BrS. So EPS followed by ablation of substrate may be a future direction to prevent VAs and need for ICD implantation, preventing also all the complications associated with device therapy in those young patients; this promising approach still need long-term follow-up data before it could be considered an alternative to ICD.

A randomized multi-center trial which is ongoing (Ablation in Brugada Syndrome for the Prevention of VF - BRAVE) probably will help us understanding better the results of trascatheter ablation.

PGD of Embryos

A therapeutic option that can be considered to stop further genetic transmission of the disease is PGD. The use of this technique is only possible when the genetic cause of the disease is well-known. Embryos are prepared via an in vitro fertilization. When the embryos are large enough (about 16 cells) they are biopsied and tested genetically. Only embryos not affected by the mutation are implanted in the mother. In this way one can be sure that the offspring will not suffer from the mutation.

Use of this technique has been criticized from the ethical and philosophic point of view, however, this is only a moral and nonscientific issue. There have been also retractors to this technique that state that BrS may be a polygenic and not a monogenic disease, so that eliminating a single mutation may be not sufficient to eliminate the disease.

On the other side, the theory of multiple genetic hits favors to this PGD approach. According to the multiple genetic hits theory a single mutation is not sufficient to cause a disease but multiple abnormalities (hits), from mutations to polymorphisms, may be necessary to really suffer from the disease. According to this theory, eliminating 1 genetic hit (1 mutation) may thus also be sufficient to prevent all manifestations of the disease. Patients managed this way at our centre have not suffered from any unwanted consequences so far, however, the offspring is still too young to make any conclusions about manifestations of the BrS.

A first follow-up after puberty will be essential to make the first conclusions.

Brugada Syndrome, the Environment, and External Factors

The ECG in BrS can be intermittent and dynamic; it typically changes over time among different types or even become completely normal. Thus, it is imperative to record serial ECGs when the syndrome is suspected.[108]

Modulating factors play a major role in the dynamic nature of the ECG and also may be responsible for the ST-segment elevation in genetically predisposed patients.

Sympatho-vagal balance, hormones, metabolic factors, and pharmacologic agents, by means of specific effects on transmembrane ionic currents, are thought to modulate not only the ECG morphology, but also to explain the development of VAs under certain conditions. Indeed, bradycardia and vagal tone may increase ST-segment elevation and arrhythmia initiation by decreasing calcium currents.[109] This explains the greater ST-segment elevation recorded in vagal settings and the notorious incidence of cardiac arrhythmias and SCD during night-time in patients with BrS.[110,111]

The role of sex hormones has been established. Published data suggest that they might also play a role in the phenotypic manifestations of BrS.[112] For example, regression of the typical ECG features has been reported in castrated men and levels of testosterone seem to be higher in Brugada male patients as compared with controls.[113,114]

According to hormonal hypothesis, the few available data existing thus far on BrS in children have not shown a difference in phenotypic presentation between boys and girls.[115]

The gender-related differences in the phenotypic expression of BrS have been widely reported but the basis for gender distinction is not yet fully understood.[116]

Body temperature may be an important modulator in some patients with BrS. Premature inactivation of the sodium channel has been shown to be accentuated at higher temperatures in some *SCN5A* mutations, suggesting that febrile states may unmask certain BrS patients or temporarily increase the risk of arrhythmias.[117] It seems that fever would be a particularly important trigger factor among the pediatric population.[10,115]

Brugada Syndrome and Pregnancy

During pregnancy autonomic and hemodynamic alterations occur and estrogen and progesterone blood levels are reduced at peripartum. The largest study of pregnant women with BrS has been reported from our institution. This study showed a relatively benign course of pregnancy and peripartum period among women with BrS.[118] In addition, only a few cases exhibiting syncope were found and the presence of syncope during pregnancy did not seem to be related to a worse outcome of the disease, neither in postpartum nor peripartum periods. Nevertheless, the management of pregnant women affected by BrS should be very strict and multidisciplinary in cooperation with a cardiologist and an anaesthesiologist.[119]

Further clinical assessment and follow-up during the pregnant, postpartum, and peripartum periods should be performed, taking into account the favourable maternal and fetal outcome of the disease.

Brugada Syndrome in Children

SCD accounts for approximately 20% of sudden deaths on pediatric population. Inherited arrhythmias are increasingly known as responsible for these deaths. The prevalence of BrS in children is variable among different studies, accounting up to 0.0098% in Japanese series.[120]

Despite progresses in characterizing BrS, little is known about this disease in the pediatrics.

In the initial description of the disease, 3 out of 8 patients were children.[1] Since then, several authors have reported isolated cases.[121]

In 2007 Probst et al. published a study with 30 affected individuals less than 16 years of age from 13 European institutions, the largest series in pediatric BrS patients by that time, but nowadays most of our understanding of the BrS in children has come from the SABRUS registry.[97,115] This study has confirmed the very poor prognosis of children with BrS and particularly the inability of quinidine to prevent SCD.

The largest series of children with BrS and with the largest follow-up has been reported from our Institution.[122] Data on a total of 95 children with age <19 years and BrS were used to create a risk stratification

system. Results were similar as in adults showing that a spontaneous type I ECG, syncope, SSS, conduction disturbances, and VAs inducibility during VPS could be used to create a scoring system.

Diagnostic and Clinical Presentation

Brugada ECG pattern in children remains the same as in adults, taking into account its transiency.

Moreover, there are no standardized data for optimal positioning of the right precordial leads in children and the shape of the chest in a growing body can lead into confusion. With all these characteristics, symptoms of syncope associated with typical ECG pattern should alert to the possibility of BrS.

From asymptomatic patients (mainly discovered in routine ECG screening or familial screening) to sudden death, in children as in adults the whole spectrum of clinical presentations is possible. In contrast to adults, no male predominance in symptomatic patients is found. This could be related to lower levels of testosterone in prepuberal children.[115] Several case reports have demonstrated the importance of fever as a precipitating factor for VAs in children, probably not because of special predisposition of children. Interestingly, as febrile state can unmask BrS pattern, a 12-lead ECG should be recorded during fever. Also, as febrile convulsions are a relatively common occurrence in childhood, we wonder if ECG should be part of the diagnostic routine when a febrile seizure occurs to exclude BrS and VAs as the cause of the convulsions.[115]

Drug Challenge Test

Sodium channel blockers test (ajmaline 1 mg/kg over 5 minutes or flecainide 2 mg/kg over 10 minutes) should be restricted to children with normal baseline ECG and typical symptoms with a positive family history.[123]

The existence of an age-dependent response to ajmaline challenge is an intriguing recent finding and might have relevant clinical implications.[124] Thus, in a recent study, Conte et al. showed that repeating ajmaline challenge after puberty unmasked BrS in 23% of patients with a previously negative drug test performed before puberty. The ECG phenotype does not appear during childhood in most cases, but may develop later in response to hormonal, autonomic, or genetic factors.[125]

As in adults, spontaneous type I ECG pattern is enough to establish the diagnosis.

EPS in Children

If controversy exists whether performing EPS testing or not in adult population, even more if children should undergo VPS to test malignant arrhythmias inducibility.[4] When indicated, the stimulation protocol remains the same as in the adult population.

Therapeutic Implication and ICD Implantation

BrS can overlap with other syndromes as long QT syndrome type 3 or Lev-Lenègre syndrome. Brady-arrhythmias can be a cause of death in these patients, thus pacemaker implantation is mandatory in certain cases.[115]

Hydroquinidine has not been a good alternative to ICD implantation.[97]

Patients presenting with aborted SCD and syncope with spontaneous type I ECG are clearly at high risk of malignant arrhythmias should receive an ICD, irrespective of age.

Special approaches for ICD implantation have been described for small children when needed (Fig 4).

Brugada Syndrome in Elderly

The fourth decade of life is the mean age of clinical manifestations of BrS, mainly in men. Thus, the clinical course and prognosis of BrS in older individuals is unknown.

Recently, Conte at al. published a systematic analysis of BrS in the aging population, reporting a benign prognosis and lower risk category of BrS patients in comparison to younger patients. Consequently, older patients presented less VAs and less family history of SCD.

However, 2 main challenges remain controversial: use of drug-induced tests and device guided management. Thus, despite Conte et al. reporting in the same above mentioned study that "*BrS was diagnosed after ajmaline challenge in 86% of elderly patients,*" the value of unmasking a type I ECG as well as its safety has not been methodically assessed.[125] Regarding the use of an ICD, a consensus conference reported that older BrS patients with syncope should undergo ICD implantation if life expectancy is at least 6 months.[5]

Recently, Kamakura et al. reported that long-term follow-up of high-risk BrS patients with ICD showed a low incidence of VF in those aged >70 years. Considering the increasing risk of inappropriate shocks because of the relatively late onset of supraventricular tachycardia and lead failures, avoidance of ICD implantation or replacement may be considered in elderly BrS patients who remain free from VF until 70 years of age.[126]

However, clinical decisions regarding both controversies should be analyzed on a case-by-case basis.

Familial Screening

Since BrS follows an autosomal dominant genetic pattern with variable penetrance, first-degree relatives should be screened by clinical history and 12-lead ECG (basal and upper intercostal space recording). Genetic test should be performed in index cases and, when a positive result is obtained, mutation analysis can be done in children, whatever age they are, in order to follow recommendation on fever control and avoidance of listed drugs. Mutation carriers should be annually screened for ECG when asymptomatic, taking into account that whatever symptom of dizziness should carry out a 12-lead ECG.

In the era of personalized medicine using high-throughput tools (Next Generation Sequencing -NGS), is the best cost-effective approach to identify the cause of the disease. The main problems in using NGS technologies are the large amount of data provided and the insufficient experience to translate this information into clinical practice. One of the crucial elements for the correct interpretation of pathogenicity is the genotype−phenotype correlation in families.[127,128] This leads to the need for each family to be studied separately, analyzing the variations in each relative, and correlating clinical-genetic information.

Final decisions should be made by a group consensus based on the experience of each of the members of the working group in each institution dedicated to this purpose.

Is Brugada Syndrome a Rare Disease?

After all these years of scientific research much has been learned about BrS in terms of pathophysiologic mechanisms, prognosis, and the value of the ICD to prevent SCD.

However, all the considerations have been made accepting that BrS was a rare disease. Clear data to really assess the true prevalence and incidence of the disease have not been available.

It is only recently that a study by Papadakis et al. has brought a completely different picture about BrS and its prevalence.[129] In their study they analyzed data from 303 individuals who died suddenly and where no diagnosis could be done even after autopsy. In the 911 relatives studied by ECG, echocardiogram, exercise test, adrenaline, and ajmaline test, a diagnosis of inherited cardiac disorder could be made in 42% of the families. Of them, 85 suffered from BrS (28% of the total) followed by 22 individuals (7%) in whom a diagnosis of long QT syndrome was made.

Thus, the general idea that long QT syndrome is the most common cause of SCD in individuals with a structurally normal heart has to be abandoned. The most common cause is BrS, but the diagnosis can only be done with the systematic use of ajmaline test.

Thus, BrS is not a rare disease, on the contrary it is the first diagnosis that has to be considered after SCD of an individual with a structurally normal heart considering, in particular, all the information deriving from an accurate analysis of ECG to avoid misinterpretation.[130]

The Future

In recent years, cardiovascular studies have been focused on personalized risk assessment and to determine the most optimal therapy for an individual. The BrS syndrome has also benefited of these advances although there remain several key points to be elucidated. Future genetics, epigenetics, transcriptomics, proteomics, metabolomics, and animal model approaches can help us to understand the complexity of BrS-like diseases through the establishment and use of more reliable models at in silico, in vitro, and in vivo levels.

The genetic revolution in cardiac diseases was initiated with the knowledge of the human genome and has advanced exponentially linked to the development of new genomic technologies (Next Generation Sequencing NGS). These new genetic technologies will allow to perform comprehensive genetic analysis in BrS patients, improving the identification of pathogenic variations.

Research in stem cells is one of the last fields that it has been incorporated into the cardiac arrhythmia scenario. It has improved the identification, derivation, and characterization of human stem or progenitor cells, comprising embryonic stem cells ESC, and the recently described induced pluripotent stem cells iPS. The human iPS cells from patients diagnosed with long QT syndrome can differentiate into cardiomyocytes, allowing electrophysiological and molecular understanding of arrhythmic mechanisms.[131–134] However, BrS has not yet fully benefited from all these advances.

Another interesting point is the use of animal models. They constitute useful tools for addressing the role of genetic and environmental modifiers on cardiac electrical activity. The only genetic model of the BrS to date is the *SCN5A* knockout mouse. The heterozygous *SCN5A* null allele results in impaired AV conduction, delayed intramyocardial conduction, increased ventricular refractoriness, and ventricular tachycardia.[134]

Computational power allows molecular modeling and molecular dynamics simulations of complex proteins. A full in silico model of potassium channel has been developed based on the available structures of channels which includes all transmembrane segments.[135]

Altogether, there is still a long way to be made towards the future of cardiac diseases associated to SCD, supporting the need to use the new emerging tools in the field of biomedicine.

In spite of these limitations, it has to be recognized that the progress in the understanding of BrS has been steady and that the future of patients with BrS looks very promising. It should not take too long before we will be able to genetically manipulate and cure the disease.

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