

Brugada syndrome

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Abstract

In 1992 by Brugada et al. described a novel clinical entity characterized by ST segment elevation in right precordial leads (V1 to V3), incomplete or complete right bundle branch block and susceptibility to ventricular tachyarrhythmia and sudden cardiac death. This disease is now frequently called "Brugada syndrome" (BrS). Both sporadic and familial cases have been reported and pedigree analysis suggests an autosomal dominant pattern of inheritance. In approximately 20% of the cases BrS is caused by mutations in the SCN5A gene on chromosome 3p21-23, encoding the cardiac sodium channel, a protein involved in the control of myocardial excitability. Since the use of the implantable cardioverter defibrillator (ICD) is only therapeutic option of proven efficacy for primary and secondary prophylaxis of cardiac arrest, the identification of the high-risk subjects is one of the major goals in the clinical decision-making process.

Keywords

ventricular tachyarrhythmias, arrhythmogenic disease, SCN5A gene mutation, locus 3p21-23, sudden cardiac death

Disease name and synonyms

Brugada syndrome (BrS)

Idiopathic Ventricular Fibrillation

Definition

Brugada syndrome (BrS; OMIM 601144) (1), or "Idiopathic Ventricular Fibrillation" as defined by some author (2), is an autosomal dominant form of cardiac arrhythmia, presenting with a typical electrocardiographic (ECG) pattern of ST segment elevation in leads V1 to V3, and incomplete or complete right bundle branch block (1). Syncope, typically occurring at rest or during sleep is a common presentation of BrS

(3), and it is caused by fast polymorphic ventricular tachycardia. In some cases tachycardia does not terminate spontaneously and it may degenerate into ventricular fibrillation and lead to sudden death.

Genetic bases and pathophysiology

At the present time only one BrS-related gene is known. Mutations in the cardiac sodium channel gene, SCN5A, on chromosome 3p21-23, have been identified for the first time by Chen in 1998 (4). Interestingly, BrS is not the only phenotype linked to mutations in this gene. Known allelic disorders are: the LQT3 variant of Long QT syndrome (5) (MIM 603830), the progressive

cardiac conduction defect (PFHB, MIM: 113900) and the Sick sinus syndrome (SSS1; MIM: 608567) (6-8). *In vitro* expression of mutant SCN5A proteins showed that BrS, PFHB and SSS1 cause a loss of sodium channel function and, conversely, an excess of sodium inward current in the LQT3 defects (4). To add to the complexity of the SCN5A-related phenotypes, overlapping syndromes have been also described in association with some specific SCN5A mutations that may cause the coexistence of LQT3 and BrS (9-11) or LQT3, BrS and PFHB in the same individuals (7,12). Unfortunately, SCN5A mutations account only for approximately 20% of BrS cases (13). Few clues are currently available concerning the remaining still unknown BrS genes. Only an additional locus on chromosome 3p22-25 (14), has been identified by linkage analysis in a single large family, but, despite the screening of several candidates in the region, the corresponding gene has not been found.

Prevalence of BrS

The incomplete information concerning the genetic bases of BrS prevents a prevalence assessment among the general population. The current estimate is based upon electrocardiographic surveys among healthy subjects. These studies have been mostly done in the Japanese population and only one has been carried out among Caucasians. The suggested prevalence ranges from 5/1,000 (Caucasians) to 14/1,000 (Japanese) (15-17). It is important to stress the concept that this figure may be biased by the fact that it is currently not known whether a Brugada-like ECG always indicates the presence of the disease or it may be a non-specific finding in some cases. Therefore, the proposed figure may overestimate the actual cases of BrS among the general population.

The role of molecular diagnosis in BrS

SCN5A has a 6.048 Kb coding sequence spanning 28 exons. As of October 2004 approximately 105 SCN5A mutations have been reported (<http://pc4.fsm.it:81/cardmoc>), and approximately 65% of them are associated with a BrS phenotype but no specific clustering within the coding region is demonstrable. No hot spots have been also reported.

Because of this genetic heterogeneity the screening for known mutations is not feasible. Therefore, most of the Labs usually screen the SCN5A coding region by performed by SSCP (Single Strand Conformational Polymorphism) or DHPLC (Denaturing High Performance Liquid Chromatography), and DNA sequencing.

Establishing a diagnosis of BrS in an asymptomatic individual based on the ECG phenotype is a big responsibility for the clinician

as it implies informing a young "healthy" subject of being at risk of sudden death and to have a risk of generating offspring at risk.

Molecular genetics may free the cardiologist from the burden of defining diagnosis in difficult cases. This may be particularly important in conditions such as BrS that may present incomplete penetrance (18,19). In this case the detection of a genetic defect within a family may represent the only tool for the identification of all the subjects that may be at risk of cardiac events and may transmit the disease to the offspring. This information has a direct relevant impact for clinical management. Unfortunately, the yield of genetic testing in BrS is currently limited by the low rate of SCN5A mutations among affected patients and therefore a negative result does not exclude diagnosis. Furthermore, the clinical manifestations are not different between genotyped and not-genotypes patients, thus making poorly applicable the genotyping for risk stratification (13).

Diagnosis and clinical features

BrS is characterized by a typical ECG pattern of incomplete or complete right bundle branch block and ST segment elevation ($\geq 2\text{mm}$) in leads V1 through V3 with a "coved morphology". This pattern may be spontaneously evident or induced by provocative pharmacological test with sodium channel blockers (Ajmaline or Flecainide). The diagnostic criteria for BrS have been recently updated and summarized in a consensus article (20).

In their initial report on 8 patients, Brugada et al. also emphasized the lack of structural cardiac abnormalities and the high recurrence rate of life threatening cardiac events (1). On the other hand, other authors described the typical V1-V3 ST segment elevation and right bundle branch block also in patients affected by the Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC; MIM: 107970) and others (21,22). Interestingly, recent data have suggested that a specific SCN5A mutation (D1275N) causes dilated cardiomyopathy with preferential right ventricular involvement in a family (23), and other authors reported histological abnormalities compatible with dilated cardiomyopathy in a single patient who was compound heterozygous carrier of two severe SCN5A mutations (W156X and R225W) (24). Taken together these findings suggest that some SCN5A mutations may induce degenerative changes of the myocardium through a yet unknown mechanism. It is not clear at the moment whether these mutations may also be associated with the typical ECG features of BrS. Nonetheless, it is probably worth to carefully evaluate the possibility of structural myocardial involvement in all patients presenting with BrS pattern.

BrS manifests with syncope and cardiac arrest, typically occurring in the third and fourth decade of life, and usually at rest or during sleep. In 1998 Brugada et al. presented data on 63 patients, in whom, after a mean follow up of 34 ± 32 months, 34% of previously symptomatic (syncope and/or cardiac arrest) patients had recurrence, while a first cardiac event occurred in 27% of the asymptomatic individuals. These results called for an aggressive therapeutic strategy in all patients with BS and, since no pharmacological treatment of proven efficacy was (and still is) available, it led to ICD (Implantable Cardioverter Defibrillator) implant in several young asymptomatic individuals. However, a different picture is emerging from more recent epidemiological surveys. In 2000 Priori et al showed a 16% incidence of recurrence of a cardiac arrest in symptomatic patients while none of the asymptomatic individuals at enrolment had a cardiac event after three years of follow up (25). The low incidence of events at follow up in the subgroup of patients who are asymptomatic at diagnosis has been subsequently confirmed by Atarashi et al. (26) 1.5%, Takenaka et al. (27) 0%, and Brugada et al. (28,29) 8%.

Clinical management and risk stratification

Being affected by a genetically determined disease, BrS patients are exposed to a life-long risk of events, but very long (years) intervals of complete well-being between the cardiac events usually characterize the disease. Therefore, the implant of an ICD may remarkably impair quality of life and it is of utmost importance to precisely identify the subgroup of individuals in whom this aggressive therapeutic approach is mandatory because of their high risk of events.

Programmed electrical stimulation (PES) has been initially considered a rational approach to risk stratification in BrS (30), but these data have not been subsequently confirmed (13,25,31). Low reproducibility of PES in these patients (32) and lack of uniformity of stimulation protocols may be confounding factors to this regard. Furthermore, PES inducibility could also vary depending on the same "transitory" factors, like autonomic tone (33-35), thus being intrinsically poorly related with the life-long risk of cardiac events. In a recent observational study (13) the natural history of BrS in a large cohort of patients has been analyzed by means of multivariate survivorship analyses. Interestingly, BrS patients presenting with history of syncope and a spontaneously abnormal ECG (i.e. independently from the provocative test with intravenous sodium channel blockers) showed a significantly increased risk of cardiac arrest (HR 6.1). In these patients the implant of an ICD may be indicated. The presence of only spontaneous ST segment elevation was associated with a

moderate risk of life-threatening events (HR 2.1), while the history of syncope alone was not an independent predictor of outcome. These patients, as well as the silent gene carriers, belong to a low risk group. Although rare instances of life-threatening events may occur among this latter category, the most effective strategies for their identification remain to be established and the wide-spread use of ICD is not indicated since device-related complications outweigh the benefits.

Some experimental evidences suggested that quinidine should be considered as an effective pharmacological treatment in BrS patients (36). Subsequently, preliminary clinical evidences (37-39), showed that that quinidine administration is able to normalize the ECG pattern and prevent the inducibility of arrhythmias in BrS patients. It is currently too early to include this drug in the routine management of BrS patients since its effectiveness on clinical arrhythmias and long term survival is not established, nonetheless quinidine could become a therapeutic option for BrS patients.

Differential diagnosis

ST segment elevation in leads V1-V3 may be found during acute anterior myocardial infarction. In such instances angina pectoris and myocardial necrosis markers (CK, CPK-MB, Troponin I, LDH) are common findings and the differential diagnosis is easily established. Furthermore there are several other disorders in which, although not constantly observed, ECG abnormalities resembling BrS may develop: arrhythmogenic right ventricular dysplasia/cardiomyopathy (21), Prinzmetal's variant angina (40), Acute pericarditis/myocarditis (41-43), Friedreich's ataxia (44), Duchenne muscular dystrophy (45), Hypercalcemia / Vitamin D intoxication (46), Hyperkalemia (47), Acute pulmonary thromboembolism (48), Acute cholecystitis (49), Transthoracic cardioversion (50), Myotonic dystrophy type 1 (51), Chagas disease (52), Hypothermia (53), Vomiting (54). Obviously, all of the above mentioned disorders should be considered when approaching to a suspect Brugada syndrome patient.

Besides specific diseases, before BrS diagnosis can be definitely established, it is important to exclude the assumption of few drugs potentially inducing a BrS-like ECG:

- Class I A antiarrhythmic drugs: ajmaline (20,33), procainamide (20), dysopiramide (55);
- Class I C antiarrhythmic drugs: flecainide (20,55), propafenone (56), pilsicainide (57-59);
- Local anesthetics (non antiarrhythmic): bupivacaine (60);
- Cocaine (61);
- Alpha adrenergic agonists: methoxamine, noradrenaline (33);
- Beta-blockers: propranolol (33);

- Potassium channel activators: pinacidil (62);
- Parasympathetic agonists: acetylcholine (63);
- Ergot alkaloids: ergonovine (63);
- Tricyclic antidepressants (64);
- Opioid analgesics: propoxyphene (65);
- First-generation antihistamines: dimenhydrinate (66).

Referral centers

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