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Is there an overlap between Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy/dysplasia?

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Abstract

The Brugada syndrome is a congenital syndrome displaying an autosomal dominant mode of transmission in patients with a structurally normal heart. The disease has been linked to mutations in *SCN5A*, a gene located on the short arm of chromosome 3 (p21-24) that encodes for the α subunit of the sodium channel. The syndrome is characterized by a dynamic ST-segment elevation (accentuated J wave) in leads V_1 to V_3 of the ECG followed by negative T wave. Right bundle-branch block of varying degrees is observed in some patients. The syndrome is associated with syncope and a relatively high incidence of sudden cardiac death secondary to the development of polymorphic ventricular tachycardia that may degenerate into ventricular fibrillation. An acquired form of the Brugada syndrome is also recognized, caused by a wide variety of drugs and conditions that alter the balance of currents active during the early phases of the action potential. Among patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia, there is a subpopulation with a clinical and electrocardiographic pattern similar to that of the Brugada syndrome. These cases of arrhythmogenic right ventricular cardiomyopathy/dysplasia are thought to represent an early or concealed form of the disease. This review examines the overlap between these 2 syndromes.

Keywords

Brugada syndrome; Concealed forms of arrhythmogenic right ventricular cardiomyopathy/dysplasia; "Acquired" forms of Brugada entity

In 1992, Pedro and Josep Brugada [1,2] presented the first description of the Brugada syndrome. The following year, Italian authors from a number of centers suggested that the alleged new entity was a form of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) [3,4].

In 1993, the Brugada brothers [5], in an Italian journal, replied to their colleagues from Padua and Bologna suggesting that these are 2 different syndromes because there is no underlying structural heart disease in the entity they had described. Martini et al [6], from Padua, claimed

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paternity to the discovery of what is now referred to as the Brugada syndrome, stating that his group had described the new entity 3 years earlier, in 1989. They suggested the eponym "Nava-Martini-Thiene syndrome" [7].

As pointed out by a number of investigators, this claim is unjustified because only 1 of the 6 cases linked to sudden cardiac death described by the Italian group presented with the typical electrocardiographic pattern reported by the Brugada brothers [8,9], and all were shown to have structural disease.

In 1996, Corrado et al [10] presented data in support of the hypothesis that a subpopulation of patients with ARVC/D, referred to as "concealed forms," present with the typical clinical and electrocardiographic features of the Brugada syndrome, including the presence of type 1 ST-segment elevation and polymorphic ventricular tachycardia (PVT).

In the same year, authors such as Ohe [11] and Fontaine [12] followed the hypothesis that these cases have a structural disease: the arrhythmogenic right ventricular cardiomyopathy/dysplasia. In 1998, Chen et al [13] linked mutations in *SCN5A*, the gene that encodes for the α subunit of the sodium channel, to the BrS, thus establishing it as a primary electrical disease.

The subpopulation of ARVC/D patients found to display ST-segment elevation and PVT characteristic of BrS have not been similarly linked to mutations in *SCN5A*. The vast majority of Brugada patients possess a structurally normal heart, consistent with the notion that this is a primary electrical heart disease. It is not unreasonable to speculate that fibrosis and myocarditis, however mild, may occur and may exacerbate or indeed trigger events in patients with the BrS, although definitive evidence in support of this hypothesis is lacking. It is noteworthy that recent studies suggest that some *SCN5A* defects may be capable of causing fibrosis on the His conduction system, sinus node dysfunction, arrhythmia, and right and occasionally left ventricular dilatation and dysfunction [14,15].

ARVC/D and BrS are distinct clinical entities both with respect to the clinical presentation and genetic predisposition. The only gene thus far linked to BrS is *SCN5A*, the gene that encodes the α subunit of the cardiac sodium channel [16], which is named today BrS1 or first BrS. The cardiac sodium channel isoform encodes hH1 and has been mapped to the short arm of chromosome 3 p21-24 loci [13].

A second more benign form, known as BrS2, was mapped to chromosome 3p22-25. This variant was reported by Weiss et al [17] in a single large family. A BrS locus distinct from *SCN5A* is associated with progressive conduction disease, a low sensitivity to procainamide testing, and a relatively good prognosis. Screening of several candidates in the region (including 2 sodium channels, SCN510A and SCN512A) failed to identify the causal gene.

ARVC/D has been linked to different chromosomal loci and 3 putative genes, different from those responsible for the BrS. Only the ARVC/D5 locus has been mapped to a region overlapping with the second locus for BrS, but the gene has not been identified as yet.

The risk of sudden cardiac death (SCD) appears to be sex-related in both syndromes. ARVC/D5 was reported to cause SCD in 44% of affected men, whereas women had a more benign course [18]. The greater risk associated with the male gender is similar to that observed in BrS [19,20].

Distinctions in arrhythmic manifestations and responses to neurohormonal and pharmacological agents are significant between the 2 syndromes. Catecholamines precipitate monomorphic ventricular tachycardia in ARVC/D patients but have an ameliorative effect in

BrS patients, causing the normalization of the ECG abnormality and suppression of PVT [21].

In BrS, some imaging techniques such as echocardiography, angiography, and radionuclide scintigraphy show no evidence of overt structural heart disease, whereas ARVC/D patients characteristically display right ventricular (RV) morphological and functional changes (such as global dilatation, bulgings/aneurysms, and wall motion abnormalities).

Recently Papavassiliu et al [22] prospectively evaluated cardiac magnetic resonance images in 20 consecutive patients diagnosed with BrS. Compared with normal controls, the right ventricular outflow tract (RVOT) area was significantly enlarged in patients with BrS. There was a trend toward larger RV end-diastolic and end-systolic volumes and lower RV ejection fraction in patients with BrS compared with controls. High intramyocardial T1 signals similar to fat signal were observed in 20% of the BrS patients, compared with none in controls.

Ultrafast computed tomography or electron-beam computed tomography has uncovered wall motion abnormalities in a series of Brugada patients tested [23–25]. Although such contractile abnormalities are commonly considered to be characteristic of structural disease, some studies suggest that such contractile dysfunction can result from loss of the action potential dome in regions of the RV epicardium and thus may be unrelated to any type of morphological defect. Loss of the dome leads to contractile dysfunction because Ca^{2+} entry into the cells is greatly diminished, and sarcoplasmic reticulum Ca^{+2} stores are depleted. Wall motion abnormalities were observed in 55% of patients with congenital long QT syndrome, another entity without structural heart disease. A peculiar double-peak pattern of late thickening was present on conventional echocardiography or transthoracic echocardiography in 11 patients and in no controls [27]. The mechanism underlying this phenomenon is Ca^{+2}-dependent [26] because it is completely abolished by verapamil.

Signal-averaged electrocardiography recordings have shown late potentials (LPs) in patients with BrS, especially from the epicardial surface of the anterior wall of the RVOT. Although these types of potentials are commonly considered to be representative of delayed activation of the myocardium secondary to structural defects, studies suggest that in the case of BrS, these LPs may represent the delayed second upstroke of the epicardial action potential or local phase 2 reentry [28]. LPs may also reflect interventricular conduction delays associated with *SCN5A* defects.

The question as to whether there is overlap or a link between BrS (a disease observed in most cases without structural heart disease [29]) and ARVC/D (a cardiomyopathy) is an issue of heated debate. From 1998 until year 2003, the prevalent position was that both entities were largely independent; however, new genetic-clinical-laboratory evidence is giving way to at least 3 distinct positions on the nature of BrS.

1. Predominance of a primary electrical defect giving rise to repolarization abnormalities with relatively minor structural changes and conduction defects as the principal substrate. This view of a largely functional defect is supported by Antzelevitch, and Brugada et al [5,30];
2. Organic or structural abnormalities theory supported by the Padua [7] and other [22] researchers;
3. A hybrid theory which maintains that a primary electrical defect leads to the development of prominent structural defect, giving rise to major conduction abnormalities, which contribute to the BrS phenotype, as proposed by Tukkie et al [31].

To examine a possible link between both entities, systematic ajmaline testing with 1 mg/kg body weight intravenously was performed by Peters et al [32] in 55 patients with ISFC/ European Society of Cardiology criteria [33] of ARVC/D. In 9 patients, ajmaline testing showed coved ST-segment elevation of at least 2 mm in at least 2 right precordial leads. The authors concluded that these observations with systematic ajmaline testing show a definite link between ARVC/D and BrS [34]. We disagree with these conclusions. We would argue that this result could also be interpreted to indicate that the ajmaline test is not specific for uncovering BrS. A positive test is observed with ajmaline in cases of Chagas disease, a parasitic cardiomyopathy, as well as with a wide variety of sodium-channel blockers in the acquired form of the syndrome [34].

A link or overlap between BrS and ARVC/D may exist when:

1. Documented PVT/ventricular fibrillation associated with a type 1 ST-segment elevation in V_1 to V_3 with a positive family history for SCD in a first-degree relative younger than 45 years;
2. Syncope or nocturnal agonal respiration;
3. Endomyocardial biopsy from RV free wall, RV inflow tract, RVOT, and apical region (dysplasia triangle) reveals microscopic lesions compatible with ARVC/D: fatty or fibrofatty substitution.

Antzelevitch [35] hypothesized that BrS could begin as a primary electrical or functional disease without structural heart disease and evolve over time to develop structural alterations, as observed with electrical remodeling during chronic atrial fibrillation [36] as well as in hibernating myocardium. In human hibernating myocardium, intracellular degeneration reduces cellular protein synthesis, and the replacement fibrosis contributes to structural abnormalities [37].

Ayerza et al [38] report the first case of a patient with BrS who required heart transplantation to control multiple “electrical storms.” The patient had ventricular normal imaging studies but was found to have fat and severe fibrosis on the right ventricle in subsequently reported (A Wilde, personal communication). Sudden unexplained nocturnal death syndrome (SUNDS, also known as SUDS) and BrS have been shown to be phenotypically, genetically, and functionally the same disorder [39]. In necropsies carried out in the United States in war refugees from the Southeast Asia, who had unexplained SCD, some structural abnormalities were found in the conduction system [40]. The same argument could be made in these cases. On the other hand, it has been recently proven that the affected *SCN5A* gene may be associated to dilated cardiomyopathy of the RV and occasionally of the LV with dysfunction, dromotropic disorders arrhythmias, and sinus node dysfunction. This is a heterozygous G-to-A mutation at position 3823 that changed an aspartic acid to asparagine (D1275N) in a highly conserved residue of exon 21 [15].

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