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SCIENTIFIC EDITORIAL

Brugada syndrome and myocardial histology: Where may the truth lie?

Syndrome de Brugada et histologie myocardique : où est la vérité ?

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Background

Brugada syndrome was first identified in 1992, and was defined as a primary electrical disorder with no associated cardiomyopathy [1]. However, soon after this initial description, morphological and histological abnormalities were reported, indicating that Brugada syndrome may be more similar to arrhythmogenic cardiomyopathy [2,3]. Recent electroanatomical and electrophysiological studies of Brugada syndrome demonstrate frequent focal abnormalities of conduction, areas of low voltage and fractionated potentials at the epicardial right ventricle outflow tract (RVOT) [4]. In the literature, histological analyses of myocardial tissue from patients with Brugada syndrome have never yielded normal findings [5], but the relevance of the abnormalities found remains unclear. Are they truly causes of sudden cardiac death or just incidental findings?

Myocarditis and Brugada syndrome: An arrhythmogenic viral trigger?

In 2005, Frustaci et al. evaluated 18 patients with Brugada syndrome, and found 14 cases of histological myocarditis [6]. Histologically confirmed PVB19 myocarditis has been reported in four patients with Brugada syndrome with ventricular fibrillation [5,7]. Only one patient had magnetic resonance imaging findings compatible with myocarditis, while the other three patients exhibited no evidence of myocarditis until biopsy. The PVB19 virus can only infect

Abbreviations: RVOT, Right Ventricular Outflow Tract.
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hosts if the P antigen is present on the cell's surface. P antigen expression varies widely among individuals, and high P antigen expression on the surface of cardiomyocytes in some patients with Brugada syndrome may enhance their susceptibility to myocarditis. Similarly, the coxsackievirus and adenovirus receptor is a suspected modifier of cardiac conduction and arrhythmia vulnerability in the setting of acute myocardial ischaemia [8].

To be clinically significant, an inflammatory infiltrate must contain more than 14 cells, including more than seven T lymphocytes ($CD3^+$), per mm^2; the remaining cells are generally macrophages ($CD68^+$). Cardiotropic viruses are often identified in subjects who have died of causes other than myocarditis. Parvovirus B19 is often found, along with HHV6. To avoid overestimation, viral loads should be quantified. For parvovirus, a load of > 500 copies/μg of nuclear acid extracts indicates pathogenicity. The cut-off values are less clear for other viruses. It should be noted that without accurate quantification, the role of identified viruses may be overestimated.

Brugada syndrome and arrhythmogenic cardiomyopathy: The same disease?

It is intriguing that Brugada syndrome and arrhythmogenic cardiomyopathy share epicardial abnormalities and some electrocardiogram patterns. The literature includes only one report of a patient with Brugada syndrome with fibrofatty deposits that were possibly compatible with arrhythmogenic cardiomyopathy according to the 1994 Task Force (the 2010 criteria were not applicable because of a lack of precise data) [9]. This low incidence might be explained by patient selection, especially based on electrocardiogram criteria. Notably, only patients with spontaneous typical Brugada type 1 without epsilon waves were included, and patients with monomorphic ventricular tachycardia were excluded. Monomorphic ventricular tachycardia is not a specific manifestation of Brugada syndrome, except in cases with extensive fibrosis of the RVOT, or after catheter ablation.

A 1980 publication describes six patients who experienced ventricular fibrillation, one of whom had electrocardiogram criteria that now correspond to Brugada type 1, as well as echocardiographic findings that fit the major criteria for arrhythmogenic cardiomyopathy (RVOT dilatation and segmental kinetic abnormalities of the right ventricle) [10]. In 2001, the same team reported a series of patients presenting with a right bundle branch block and ST-segment elevation in the right precordial leads [2]. Histological findings suggested arrhythmogenic cardiomyopathy in 12 of 13 cases. However, there may have been biases in interpreting myocardial fatty infiltration. In an autopsy series of sudden unexplained death, Raju et al. found that fibrofatty replacement of the ventricular myocardium was insufficient to meet minor histological criteria for arrhythmogenic cardiomyopathy diagnosis in a proband from a family diagnosed with Brugada syndrome [11].

Recent experimental data suggest some overlap between Brugada syndrome and arrhythmogenic cardiomyopathy. In intercalated discs, sodium channels and desmosome proteins are interdependent and form a connexon. Animal models reveal that PKP2 inactivation reduces the sodium current and increases the risk of ventricular fibrillation after flecainide administration. Thus, arrhythmogenic cardiomyopathy might lead to ''acquired Brugada syndrome'' via secondary inactivation of ion channels.

Ventricular myocardial fibrosis: An overestimated role?

RVOT abnormal fibrosis has been reported as a cause of the conductive disorders observed in Brugada syndrome; however, no patient with Brugada syndrome has exhibited fibrosis alone. Notably, biopsy results have only been reported as positive values, and some localized histological anomalies may have been underestimated. Additionally, epicardial abnormal structures have not been detected in endomyocardial biopsies. Autopsy studies of cardiac tissue from humans lacking pathological conditions have revealed that collagen content increases by almost 50% between the third and seventh decades of life [12]. Raju et al. [11] reported that myocardial fibrosis was among the most prevalent uncertain autopsy findings identified in unexplained sudden cardiac death, appearing in 12% of cases.

In 2007, Elizari et al. suggested that RVOT fibrosis may be related to abnormal migration of neural crest cells during embryogenesis [13]. Over the last 10 years, the use of specialized techniques — such as non-invasive electrocardiogram mapping and endocardial and epicardial electrophysiological investigations — has enabled the identification of slow conduction zones with fractional electrograms, as well as focal repolarization abnormalities within the RVOT epicardium. One study recently reported that patients with Brugada syndrome showed a high level (8%) of late gadolinium enhancement on magnetic resonance imaging [14]. It has been suggested that radiofrequency modulation of this arrhythmogenic substrate may suppress the Brugada type 1 electrocardiogram pattern.

Ventricular myocardial hypertrophy or pseudohypertrophy?

The literature includes autopsy data from four patients with Brugada syndrome, all of whom exhibited significant left ventricular wall hypertrophy. None of these patients had electrocardiogram criteria for left ventricular hypertrophy, and hypertrophy was not diagnosed in the three patients who underwent cardiac imaging. In 2006, Mango et al. described a mutation in the *TPM1* gene that resulted in overlap between familial hypertrophic cardiomyopathy and Brugada syndrome in a family [15]. In patients with pathogenic mutations in the *SCN5A* gene, the coexistence of left ventricular hypertrophy (e.g. secondary to high blood pressure) may significantly increase the risk of sudden cardiac death. It is possible that hypertension associated with myocardial remodelling acts synergistically with biophysical alterations secondary to *SCN5A* mutation. *SCN5A* mutation carriers may benefit from careful monitoring of hypertension

and hypertrophy, in addition to aggressive antihypertensive treatment.

Pseudohypertrophy exists, and pathological examination has several caveats. Parietal thickness measurements are unreliable and often overestimated. Measurements should not include the posterior pillars or epicardial adipose tissue. Moreover, a heart that weighs 350 g can be considered normal, and weight measurement is only reliable if the aorta and trunk of the pulmonary artery are not cut too high. Many examiners also encounter hypertrophic cardiomyopathy architectural pseudodisorganizations with fibrosis via poor sampling, particularly near the junction between the right ventricle and the left ventricle/septum. Cardiomyocyte entanglement may be a normal finding if the conjunctive tissue scaffold is normal. Investigators should also carefully search for intramyocardial artery wall dystrophies, which are a hallmark of hypertrophic cardiomyopathy.

Conclusions

In contrast to the classical definition of Brugada syndrome, no fully investigated patients with Brugada syndrome have had normal autopsy results or histological structure. Although the results of myocardial structural investigations must be interpreted cautiously, viral myocarditis and left ventricular hypertrophy seem to be recurrent findings among patients with Brugada syndrome who have experienced ventricular fibrillation/sudden cardiac death. The data presently available highlight the difficulty of sudden death risk stratification, and the weaknesses of current investigations in patients with a presumed channelopathy. It is likely that lethal ventricular arrhythmias may be triggered by a combination of non-specific structural findings together with functional electrical dysfunction. The current uncertainties underscore the importance of autopsy, with evaluation by an expert pathologist, omic studies and obtaining the medical history of first-degree relatives.

Disclosure of interest

The author declares that he has no competing interest.

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