Journal of Molecular and Genetic Medicine

Goit et al., J Mol Genet Med 2019, 13:1
DOI: 10.4172/1747-0862.1000413

Review Article Open Access

Atrial Fibrillation Associated with Wolf-Parkinson-White Syndrome in Patients with Brugada Syndrome: A Review

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Abstract

The Brugada syndrome is an autosomal dominant rare form of cardiac arrhythmia and has been associated with high risk of sudden cardiac death predominantly in younger male patients. It is associated with polymorphic ventricular arrhythmia/ventricular fibrillation, Supraventricular arrhythmia mainly atrial fibrillations and Wolf- Parkinson white syndrome. Patients can be presented with symptom like syncope, palpitation, sudden cardiac death and asymptomatically. Several pathogenic genes have been identified as associated with the disease but *SCN5A* is the most prevalent one. Several genetic mutations of different subunits of sodium, calcium and potassium channel have been involved. The management of Brugada syndrome and Wolf-Parkinson-White syndrome in patients with atrial fibrillation should be generally includes implantable cardioverter defibrillator and Radiofrequency catheter ablations. This brief review focuses on recent clinical diagnosis, genetic basis and advances in pharmacological treatment of Brugada syndromes with atrial fibrillation and wolf-Parkinson white syndrome.

Keywords: Brugada syndrome; Wolf-Parkinson white syndrome; Atrial fibrillation; Sudden cardiac death; Implantable cardioverter defibrillators

Abbreviations: ECG: Electrocardiogram; SCD: Sudden Cardiac Death; BS: Brugada syndrome; PVT: Polymorphic Ventricular Tachycardia; VF: Ventricular Fibrillations; WPW: Wolf-Parkinson-White Syndrome; ICD: Implantable Cardioverter Defibrillators; PAF: Paroxysmal Atrial Fibrillation; RFCA: Radiofrequency Catheter Ablations; AVNRT: Atrioventricular Nodal Re-entry Tachycardia; AF: Atrial Fibrillations

Introduction

Atrial fibrillation is most prevalent cardiac arrhythmia it may be first presenting manifestations in certain cases such as Brugada syndrome and wolf-Parkinson-white syndrome. Brugada syndrome is a rare cardiac arrhythmia characterized by electrocardiographic right bundle branch block and persistent ST-segment elevation in right precordial leads and associated with a high risk of sudden cardiac death [1,2]. Currently it is believed to be responsible for 12% of sudden cardiac death cases and 20% of sudden cardiac death in patients with structural normal hearts [3]. Patients may suffer from syncope or sudden cardiac death secondary to polymorphic ventricular tachycardia (PVT) or ventricular fibrillation [4,5]. However, majority of patients remains completely asymptomatic. Some of arrhythmia may occur after large meals, during rest or while sleeping, believed to be due to high vagal tones [6]. There are 20 genes associated with Brugada syndromes and *SCN5A* is the major causative one [7-9]. The symptom usually appears around 44 years of age and more common in male [10-12]. Wolf-Parkinson-white syndrome (WPW) is the most common causes of preexcitation and usually it is presented with Supraventricular tachycardia and atrial fibrillations [13]. Even if the WPW cases are asymptomatic, it may lead to sudden cardiac death [14]. Because both disease forms could have similar symptom, coexistence of Brugada syndrome and WPW syndromes arise question about exact pathogenesis, possible interaction, related risk stratification and therapy.

Implantable cardioverter defibrillator (ICD) is the most common effective therapy to prevent sudden cardiac death and Quinidine, Isoproterenol and Catheter ablations are also recommended to reduce the incidence rate of arrhythmia events [15-18].

Epidemiology

Brugada syndromes has been estimated to be account for 20% of sudden cardiac death in the absence of structural heart disease and may responsible for between 4-12% of all patients with sudden cardiac death [2,3]. The prevalence of Brugada syndrome varies according to location, being higher in east and south east and south East Asian population (Thailand, Japan, Philippines) than European descent [19]. The estimated prevalence ranges from 1:1000 to 1: 10000 [19].

Genetics

Brugada syndrome is a disease with an autosomal dominant pattern transmission [20]. Incomplete penetrance is frequent in families and disease can be sporadic in upto 60% of patients [20,21]. The several pathogenic genes have been identified as association with the disease but first pathogenic mutation in the *SCN5A* gene was identified in 1998 [22]. This gene encodes the alpha subunit of cardiac sodium channel [23]. More than 350 pathogenic mutations in several genes have been published (*SCN5A, GPD1L, SCN1B, SCN2B, KCNJ8, HCN4, KCNE5, KCND3, CACNA1C, CACNB2B, CACNA2D1, TRPM4*) [9,24]. These genes encode the subunit of cardiac sodium, potassium and calcium channel as well as genes involved in the trafficking or regulations of these channel. Despite the high number of gene mutations only about 35% of Brugada syndrome patients have been determined to have genetic causes. Of them, nearly about 30% carry a pathogenic mutation

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Received March 01, 2019; **Accepted** March 15, 2019; **Published** March 23, 2019

Citation: Goit LN, Shaning Y, Wang X (2019) Atrial Fibrillation Associated with Wolf-Parkinson-White Syndrome in Patients with Brugada Syndrome: A Review. J Mol Genet Med 13: 413 doi:10.4172/1747-0862.1000413

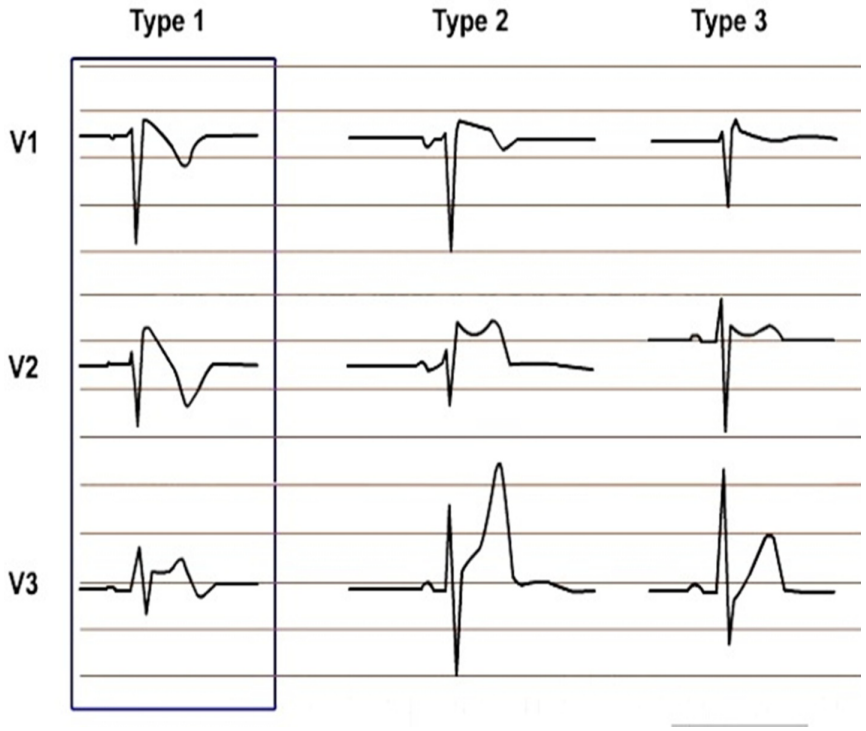

Figure 1: Figure showing pattern of ECG in Brugada Syndrome. Type-1 ECG pattern show Coved ST-Segment elevation >2 mm is followed by a negative T-Wave, with little or no isoelectric line separation that feature is present in from V1 to V2 in right precordial leads. Type -2 ECG patterns also characterized by ST-Segment Elevation followed by positive or biphasic T-wave that result in saddle back configuration. Type-3 ECG patterns show right precordial ST-Segment elevation <1 mm with saddle morphology [39,40].

in the *SCN5A* gene [25]. All other genes together are responsible for about 5% off all Brugada cases. Therefore 65% of cases do not have genetic origins. The atrial fibrillations are associated with mutations in both sodium and potassium channel [26]. The causative relationship between *SCN5A* and atrial fibrillations is confirmed by direct gene sequencing in small families [27].

WPW Syndrome has no clear familial involvement. WPW Syndrome is inherited as a simple or isolated trait of preexcitation. Syndromic presentation of WPW Syndrome account for a minority of inherited forms of preexcitation and include congenital Ebstein anomaly, familial hypertrophic cardiomyopathy (sarcomeric mutation), hypertrophic scar cardiomyopathy, WPW Syndrome and conduction system disease, metabolic myopathies. So, there is no linkage between *SCN5A* and WPW Syndrome has been reported by far.

Discussion

The patient with Brugada syndrome, WPW syndrome and atrial fibrillations is notice around the words and patients with the combination of all these and a comprehensive medical history with long term follow up is rare [28-33]. Atrial fibrillation is most usual atrial arrhythmia in Brugada syndrome, with an incidence of between 6-53%, because the substrate responsible for the development of ventricular arrhythmias may also contribute to atrial arrhythmogenesis [34]. The presence of atrial fibrillation is considered as a marker of more advanced stage in Brugada syndromes alone, since it has been related to more vicious prognosis with higher incidence of symptom and ventricular arrhythmia [26,35]. The syncope episode documented ventricular fibrillation and spontaneous type-1 ECG was observed in large percentage of patients with Brugada syndrome with spontaneous atrial fibrillation than in those without atrial fibrillation. However, family history, *SCN5A* mutation and ventricular fibrillation induction during the electrophysiological study were not related to spontaneous atrial fibrillation episodes [35].

It is also known that AVRT is the most common arrhythmia in patients with WPW syndrome and PAF develop in up to one third of them [36]. The exact mechanism for the development of atrial fibrillation in patients with WPW Syndrome in not clearly understood but there is a several hypotheses, which including spontaneous degeneration of AVRT into atrial fibrillation, effects of APs on atrial architecture and intrinsic atrial muscle vulnerability are responsible for the genesis of PAF in patients with WPW Syndrome [36]. If an AP has a short anterograde refractory period, then rapid repetitive conduction to the ventricles during atrial fibrillation can result in a rapid ventricular response with subsequent degeneration to ventricular fibrillation. The majority of the PAF would be terminated after successful AP ablations procedures, which show an important role of the AP itself in the initiation of PAF. We performed the electrophysiological study to confirm the presences of three APs and inducible orthodromic tachycardia and ablation procedure was performed. After the Radiofrequency catheter ablation (RFCA) procedure, the patients present no symptom and AF during the 12 years follow up, which indicates that AF is associated with WPW syndrome but not directly with Brugada syndromes.

Clinical Manifestations

The clinical presentation can range from no symptom that is asymptomatic to sudden cardiac death [1]. Initial presenting symptom included palpitation, syncope, seizure, and nocturnal agonal respiration. About 25% of patients suffer from sudden cardiac death

have already experienced a syncope episode due to polymorphic ventricular tachycardia or ventricular fibrillation [1]. Upto 20% of cases, Supraventricular arrhythmia may exist, mainly atrial fibrillations. Although atrioventricular nodal re-entry tachycardia (AVNRT) and Wolf-Parkinson white Syndrome has also been reported [1]. Additionally, an association with sinus dysfunctions has also been reported. Symptom more frequently occurs during rest or during sleep time and after meals (especially between 12 am to 6 am and rarely in day time) under the influence of febrile episode or vagal activity [6]. The causes of death in Brugada syndrome are ventricular fibrillations.

Risk stratification

The risk stratification of Brugada syndrome is aimed to identify individuals most liable to sudden cardiac deaths, so that they can receive appropriate managements. It is accepted that etiology of Brugada syndromes is multifactorial involving genetics, environmental factors and hormonal that contribute to phenotypic manifestations. The Brugada syndrome typically manifest in adulthood with mean age of 41 ± 15 years [37]. However it may manifest in childhood and elderly person [38]. It is 8-10 time more common in men than women due to difference in hormone [38]. The family history present in about 20-30% of the patients.

Diagnosis

The diagnosis of PAF and WPW Syndrome was determined from clinical manifestation and ECG, the exact location of APs was confirmed by Electrophysiological study. The diagnosis of Brugada syndromes was determined from the family history, clinical manifestation and the ECG. There are three known ECG subtype pattern in Brugada Syndrome that can be dected in more than one right precordial leads (V1-V3), which have a diagnostic value in Brugada syndrome (Figure 1) [39,40].

Management

The management strategy should be decided according to the symptom and clinical judgment. However, treatment options included general lifestyle measures, Pharmacological therapies and Device management.

General lifestyle measures

The following are the lifestyle measures are recommended:

- Avoidance of excessive alcohol intake.
- Immediate treatment of Fevers with antipyretics drugs.
- Avoidance of drugs that aggravates ST-Segment elevations in right precordial leads.

If the patients have WPW Syndromes, eliminate the antetrade right accessory pathway with Radiofrequency catheter ablations (RFCA) [17,18,41,42]. If the patients have symptomatic Brugada syndrome, implant an implantable cardioverter defibrillators (ICD) [15,16,38,43,44]. for primary prevention and Quinidine and ablation of right ventricular outflow tract could also be a secondary choices and if atrial fibrillations is continued drugs or interventional therapy should be considered. By far Radiofrequency catheter ablations has reported success rate of 95% with recurrence rate < 5% [45].

Pharmacological therapies

Quinidine has anti arrhythmic property, and which reduces the incidences of arrhythmias in Brugada Syndromes and has been use successful in certain clinical conditions such as treatment of arrhythmia storm [6,46,47].

Conclusion

The Brugada syndrome is an inherited syndrome characterized by typically ST- segment elevation in right precordial lead that affects young individual, mostly male, predisposing to ventricular arrhythmia, Supraventricular arrhythmia mainly atrial fibrillations, Wolf-Parkinson white syndrome and sudden cardiac death. It is diagnosed by typically cove shaped ST-Segment elevation of > 2mm and negative T-wave with little or no isoelectric separation in more than one in right precordial leads. Several genetic mutations of the sodium, calcium and potassium channel has been involved. The majority of the patients with BS remain asymptomatic, however the most frequent symptom is syncope or SCD secondary to PVT or VF. Risk stratification is mainly based on symptom and surface electrocardiogram. Implantable cardioverter defibrillator is the only proven effective strategy for preventing SCD in BS patients. However, there are still dought and controversies regarding the underlying mechanism, the influences of different modulating factors and how to stratify the risk and treatment asymptomatic patients. The patient diagnosed with Brugada syndrome is counseled, such that they and their relatives are informed.

Conflict of Interest

There authors have no conflicts of interest to declare.

Acknowledgements

This review article is supported by the National Natural Science Foundation of China (31700736), Hubei Province Natural Science Foundation of China (2016CFB180), Hubei Province Health and Family Planning Scientific Research Project (WJ2016Y07), Hubei Province Scientific and Technological Research Project (Q20171306), Jingzhou Science and Technology Development Planning Project (JZKJ15063) and the Yangtze Fund for Youth Teams of Science and Technology Innovation (2016CQT04).

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