Atrial fibrillation associated with Wolff-Parkinson-White syndrome in a patient with concomitant Brugada syndrome

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Introduction

Atrial fibrillation (AF) is most prevalent in cardiac arrhythmic disease. It may be the first presenting manifestation in certain cases, such as Brugada syndrome (BrS) and Wolff-Parkinson-White (WPW) syndrome. BrS is an inherited cardiac arrhythmic disorder characterized electrocardiographically by coved-type ST-segment elevation in the right precordial leads (V_1–V_3).[1] Patients with BrS are susceptible to ventricular tachycardia (VT) and consequently to sudden cardiac death (SCD). It is reported to be more common in Asia than in Western countries, with the estimated prevalence ranging from 1:1000 to 1:10000.[1] There are 20 genes associated with BrS, and *SCN5A* is the major causative one.[2] Implantable cardioverter-defibrillator (ICD) is the most effective therapy to prevent SCD, and quinidine, isoproterenol, and catheter ablation are also recommended to reduce the incidence rate of arrhythmic events.[1] WPW syndrome is the most common cause of preexcitation, and usually it is presented with supraventricular tachycardia and AF. Even if the WPW syndrome case is asymptomatic, it may also lead to SCD.[3] Because both disease forms could have similar symptoms, coexistence of BrS and WPW syndrome raises question about exact pathogenesis, possible interaction, related risk stratification, and therapy. In this report, by analyzing a male case with BrS and WPW syndrome with *paroxysmal* AF (PAF), we aim to explore this phenomenon in a deeper level and summarize the current research status.

KEYWORDS Brugada syndrome; Wolff-Parkinson-White syndrome; Atrial fibrillation; Genetics; Sudden cardiac death
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Case report

In 2004, a 37-year-old man (II-5) admitted to the hospital because of an 8-year palpitation (once a year) and recurrent palpitation in the last 4 months (3 times). The palpitation was not associated with exercise and emotion, and the longest one lasted over 14 hours. A representative electrocardiogram (ECG) at rest revealed WPW syndrome with a short PR interval and positive delta waves in leads I, II, aVL, and V_1–V_6 and negative delta waves in leads III and aVF (Figure 1A). One episode of wide QRS tachycardia with irregular RR intervals was initiated at rest. Certain beats, which were conducted over the normal pathway, were compatible with type 1 Brugada ECG in leads V_1 and V_2 (Figure 1B). The proband did not experience any episode of syncope or SCD, but since he had a positive family history of SCD and typical Brugada pattern ECG, he was diagnosed with BrS.

Physical examination showed an irregular heart rhythm. The results of the laboratory tests, chest radiography and echocardiography, and biochemistry tests were within the normal range. The transesophageal electrophysiology study (EPS) revealed orderly (1) normal function of the sinoatrial node and atrioventricular node; (2) antegrade right accessory pathways (APs) and atrioventricular reentry tachycardia (AVRT); and (3) inducible AF, which was spontaneously terminated after a short duration.

Radiofrequency catheter ablation (RFCA) was performed under a drug-free and unsedated state. Three right posterior APs, located at 7:30, 8:00, and 8:30 positions, respectively, were ablated. After the procedure, both antegrade and retrograde conductions disappeared, and cardiac tachycardia could not be induced in the right ventricular apex and atria. However, stimulation was not performed in the right

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KEY TEACHING POINTS

- We first report a rare case with a family history of sudden cardiac death, who suffered from Brugada syndrome, Wolff-Parkinson-White syndrome with multiple accessory pathways, and atrial fibrillation, and who has undergone a comprehensive medical evaluation and systematic treatment with long-term follow-up.
- Although limited literature is available and standard treatment protocol is not provided, the management of Brugada syndrome and Wolff-Parkinson-White syndrome in the patient with atrial fibrillation should generally include implantable cardioverter-defibrillator and radiofrequency catheter ablation.
- Our genetic screening in the family first discloses that *SCN5A* could be, at least partially, the culprit gene in this kind of scenario, and further underlying mechanism study and clinical intervention are warranted.

ventricular outflow tract to induce VT/ventricular fibrillation (VT/VF). Two days after the procedure, the ECG showed disappearance of delta waves and appearance of coved-type ST-segment elevation followed by negative T waves in leads V_1 and V_2 (Figure 2A). One month later, the follow-up ECG confirmed that WPW syndrome and AF were diminished, but a typical type 2 Brugada pattern in the fourth intercostal space and a type 1 Brugada pattern in the second intercostal space were observed (Figure 2B). A similar Brugada pattern is discovered in the ECG after 9 and 12 years (Figures 2C and 2D).

Figure 3A displayed the family pedigree of the index case. His elder brother (II-1) suffered from SCD during sleeping at the age of 39 years before the first admission of the proband. His asymptomatic younger brother (II-7) also had a spontaneous type 1 Brugada ECG pattern then (Figure 3B). However, both of them refused to receive an ICD. Nine years later, unfortunately, proband's youngest brother (II-7) also experienced SCD at night. Then, in 2013, the proband agreed to receive an ICD to prevent a lethal cardiac event. By screening all susceptible genes associated with BrS and WPW syndrome in this family, the *SCN5A*-R1193Q variant was found in the proband and his nephew (III-3, Figures 3A and 3C). After 12-year follow-up, the patient did not report any recurrence of palpitation, but still presents a type 1 Brugada ECG pattern. He has not received any antiarrhythmic drugs and has not experienced ICD discharge by far (Figure 3D). The lifestyle changes, as well as avoidance of inducible drug and fever, are recommended to the patient.

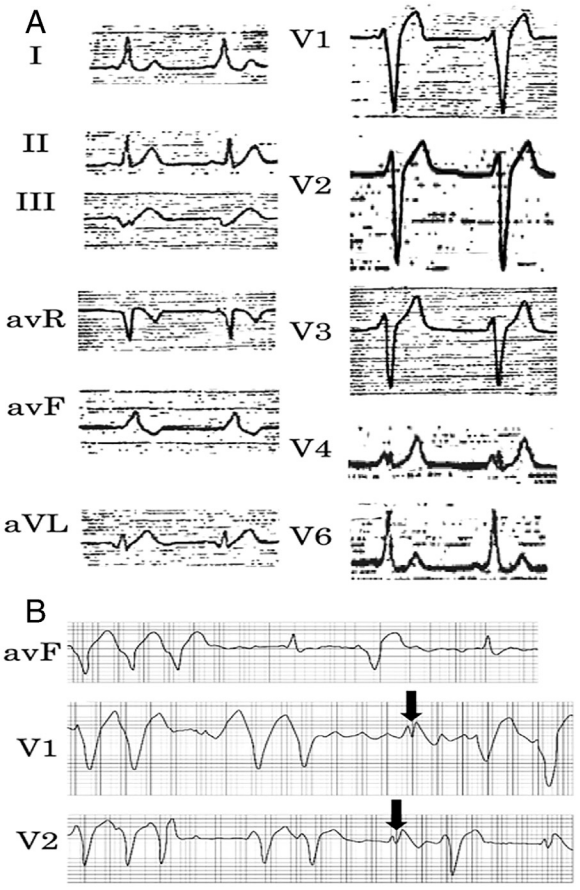

Figure 1 Proband's ECGs before ablation. **A:** Baseline ECG shows positive delta waves in leads I, II, aVL, and V_1–V_6 and negative delta waves in leads in leads III and aVF. **B:** One episode of atrial fibrillation in the presence of an accessory pathway recorded before ablation. Black arrows indicate concomitant type 1 Brugada ECG. ECG = electrocardiogram.

Discussion

Although the cases of BrS or WPW syndrome together with PAF have been reported in several medical literatures,[4,5] BrS with WPW syndrome has also been noticed around the world;[6–11] and a patient with the combination of all these and a comprehensive medical history with long-term follow-up is rare. AF is the most usual atrial arrhythmia in BrS, with an incidence between 6% and 53%,[12] because the substrate responsible for the development of ventricular arrhythmias may also contribute to atrial arrhythmogenesis. The presence of AF is considered as a marker of more advanced stage in BrS alone, since it has been related to a more vicious prognosis with a higher incidence of symptom and ventricular arrhythmias.[13,14] Kusano et al[13] demonstrated that syncopal episode, documented VF, and spontaneous type 1 ECG were observed in a larger percentage of patients with BrS with spontaneous AF than in those without AF. However, family history, *SCN5A* mutation, and VF induction during the EPS were not related to spontaneous AF episodes.[13] It is also well known that AVRT is the most