Episodic long-lasting atrial standstill associated with an *SCN5A* variant resulting in atrial pacing failure: Is an atrial lead necessary for familial atrial standstill?

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Introduction

Atrial standstill (AS) is a rare arrhythmogenic condition characterized by the absence of electrical and mechanical atrial activity.[1] Electrocardiographically, AS manifests with transient or permanent absence of P waves and junctional escape rhythm (JER).[2] Familial AS has been associated with pathogenic variants of the *SCN5A* gene, which encodes the α-subunit of the Nav1.5 cardiac sodium channel protein. Pathogenic *SCN5A* variants have also been linked to other cardiac conditions, such as long QT syndrome, Brugada syndrome, atrial fibrillation, sick sinus syndrome (SSS), cardiac conduction defect, and rarely, dilated cardiomyopathy.[3] Some of these pathologic conditions may coexist, a condition referred to as cardiac sodium channelopathy overlap syndrome. Although pacemaker therapy is common for symptomatic SSS, distinguishing AS from sinoatrial node dysfunction is challenging.

We present a case of familial AS associated with a pathologic *SCN5A* variant in a young male patient whose implanted atrial lead was extracted because of atrial pacing failure.

KEY TEACHING POINTS

- Familial atrial standstill has been linked to the *SCN5A* gene.
- Familial atrial standstill should be considered in cases in which atrial pacing does not result in atrial capture anywhere in the right atrium during sinus arrest.
- An atrial lead may not be necessary in cases of atrial standstill in which atrial pacing is not possible.
- Familial atrial standstill may overlap with other genetic disorders associated with the *SCN5A* gene, such as Brugada syndrome.

Case report

The patient had been diagnosed with JER with sinus arrest at the age of 13, but he had no symptoms of bradycardia. His paternal aunt and great-aunt both had histories of pacemaker therapy, and his father was diagnosed with first-degree atrioventricular block in childhood (Figure 1A). At the age of 21, the patient experienced syncope after running. Holter monitoring showed several episodes of long-lasting JER at approximately 30 beats/min without discernable P waves, and he was admitted to a nearby hospital. During hospitalization, episodes of sinus arrest lasting up to 8.6 seconds and paroxysmal complete atrioventricular block (Figure 1B) were observed, which occurred only during sleep. Consequently, he was transferred to our hospital for pacemaker therapy.

At the time of admission, the resting electrocardiogram showed first-degree atrioventricular block in sinus rhythm (SR) (Figure 1C). Blood tests were normal, except for a mildly elevated serum brain natriuretic peptide level (54.9 pg/mL). Echocardiography during SR showed normal left ventricular systolic function, and contrast-enhanced cardiac magnetic resonance imaging showed no evidence of delayed enhancement in the ventricles. The patient was diagnosed with symptomatic SSS, and dual-chamber pacemaker implantation was scheduled; however, an electrophysiologic study was not performed.

At the time of entry into the catheterization room, the patient was in SR, which converted to JER with sinus arrest

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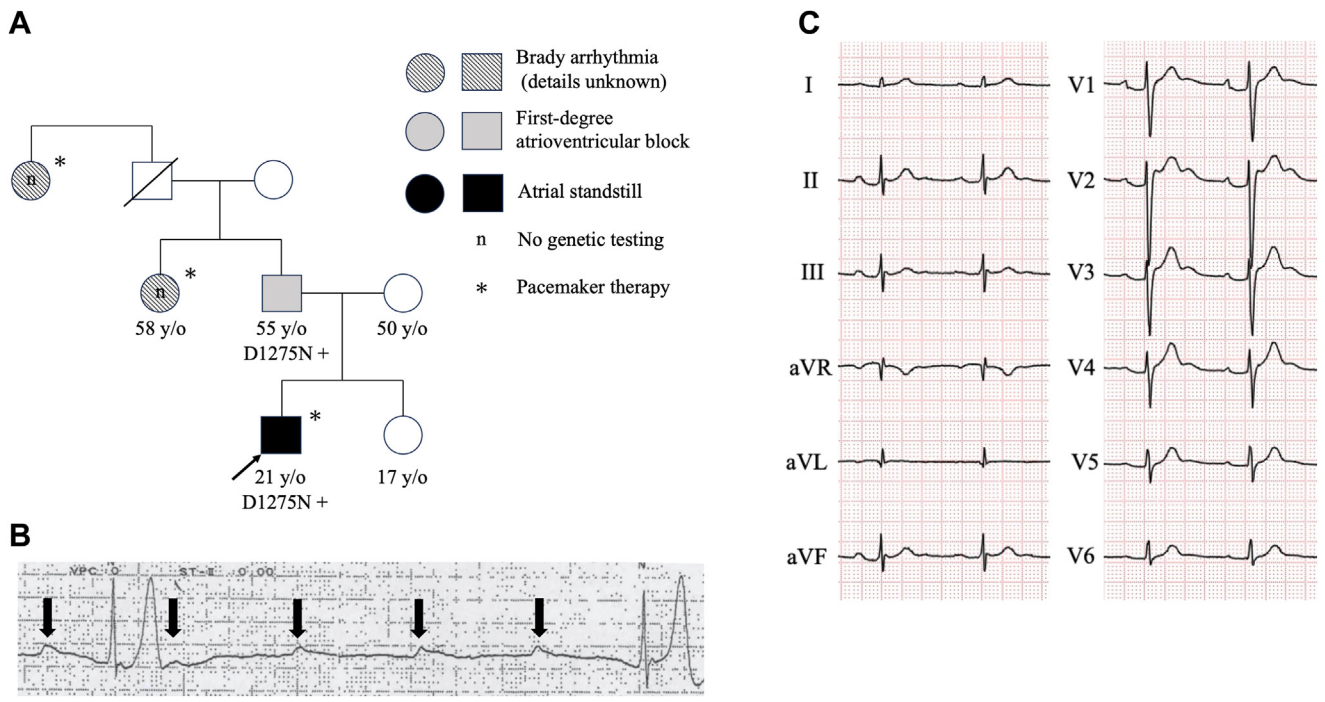

Figure 1 Patient history and admission findings. **A:** Patient pedigree. He and his father had a heterozygous missense variant of the *SCN5A* gene (D1275N). His father was diagnosed with first-degree atrioventricular block in childhood and has not undergone pacemaker implantation. His paternal aunt and great-aunt had histories of pacemaker therapy, but genetic testing was not performed. **B:** Monitor electrocardiogram showing paroxysmal complete atrioventricular block during sleep. The *full arrows* show the P waves. **C:** Resting electrocardiogram in sinus rhythm of 62 beats/min with prolonged PQ interval (234 ms) on admission.

after sedation (Figure 2A). The ventricular lead (screw-in lead) was implanted in the right ventricular apex septum (pacing threshold, 0.7 V/0.4 ms; R wave amplitude, 8.9 mV; impedance, 685 Ω). During JER, atrial lead (screw-in lead) implantation was attempted at more than 15 locations, including the right atrial appendage, right atrial septum, lateral free wall, and the ostium of coronary sinus, but atrial pacing could not be achieved at any site despite high-power bipolar pacing (maximum output, 7.5 V/1.5 ms) (Figure 2B). After the patient was awakened from sedation and isoproterenol was administered at 1 μg/min, JER converted to SR (Figure 2C), and atrial pacing converted to capture a wide area of the right atrium at low-power bipolar pacing (Figure 2D). The atrial lead was implanted in the right atrium septum during SR, and atrial capture could be achieved (pacing threshold, 1.5 V/0.4 ms; P wave amplitude, 2.0 mV; impedance, 606 Ω); however, atrial pacing became impossible when SR converted to JER. Based on the findings during pacemaker implantation and family history, familial AS was suspected.

The following day, pilsicainide testing was performed to investigate the coexistence of Brugada syndrome as an overlapping pathologic condition with familial AS. After administering pilsicainide at 1 mg/kg intravenously, coved-type ST elevation appeared (Figure 3A, 3B).

To evaluate sinus function, an exercise stress test was performed after discharge. The patient's cardiac rhythm before the test was JER, but it converted to SR only during the test and shortly returned to JER at recovery time. No ventricular or supraventricular arrhythmias were recorded during the test. Pacemaker setting after implantation was a DDD mode (60–130 ppm), and during the first week after implantation, although 78% atrial pacing was seen on interrogation, there was atrial capture failure. The pacemaker settings were adjusted from DDD to VVI mode 1 week after pacemaker implantation. In VVI mode with a minimum ventricular rate of 40 ppm, the percentage of ventricular pacing remained between 20% and 25%.

Chronotropic agents were given to maintain SR. Cilostazol at 200 mg/day was effective; but it was discontinued because of headaches. Oral isoproterenol at 60 mg/day was ineffective. Ultimately, no effective oral medications were found that could be used continuously. Two months after pacemaker implantation, genetic testing confirmed a heterozygous missense variant of the *SCN5A* gene (p.D1275N [c.3823 G>A]) (Figure 3C) in the patient and his father. This variant has already been reported as a causative variant for familial SSS.[4]

Six months after pacemaker implantation, we decided to extract the atrial lead because (1) the basic rhythm was JER with sinus arrest, and during sinus arrest, atrial pacing was not possible because of AS; (2) SR occurred only during exercise or for short periods throughout the day, and atrial pacing was only possible during SR, but it was not necessary because the patient had no sinus bradycardia; and (3) given the lead management and patient's age, the disadvantages should be considered. The atrial lead was easily removed with simple manual traction. After the atrial lead was

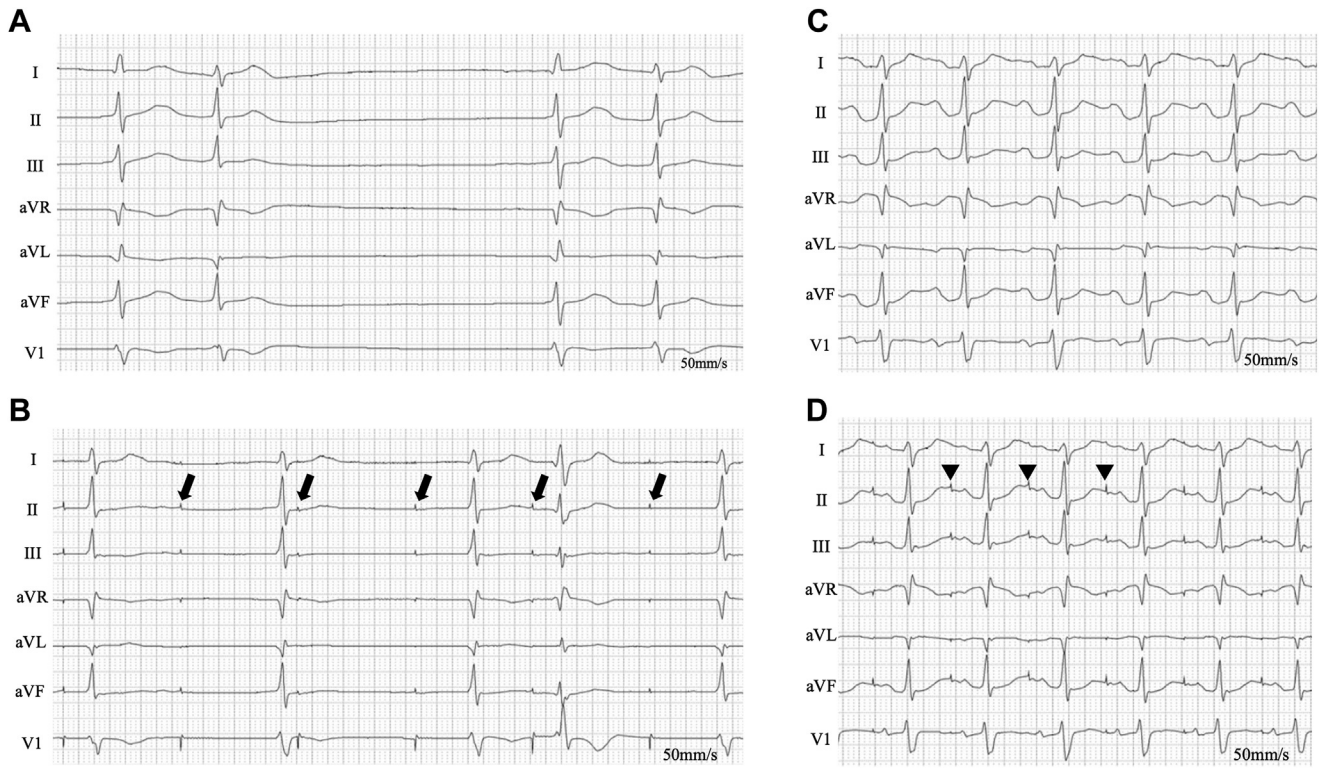

Figure 2 Electrocardiography findings during pacemaker implantation. **A:** When sedation was initiated, the patient's cardiac rhythm changed from sinus rhythm to ventricular escape rhythm. **B:** During ventricular escape rhythm, we could find no atrial capture site in the right atrium. The *full arrows* indicate failed atrial pacing. **C:** When the patient was awakened and isoproterenol was administered, his cardiac rhythm returned to sinus rhythm. **D:** Atrial pacing capture was achieved at low power over a wide area in right atrium. The *arrowheads* indicate atrial pacing capture.

extracted, the patient did not experience any episodes of shortness of breath or syncope.

Discussion

This patient had long-lasting AS with atrial pacing failure and paroxysmal complete atrioventricular block and Brugada syndrome associated with an *SCN5A* variant. This case highlights 2 important considerations: (1) atrial pacing failure attributable to AS, and (2) the need for genetic analysis to investigate overlapping pathologic conditions.

When familial SSS is suspected based on the family history and electrocardiogram, the risk for atrial pacing failure because of AS should be considered at the time of pacemaker implantation. In a prior study of familial AS, 65% of pediatric patients had *SCN5A* variants, 40% had intermittent AS, and atrial pacing capture was achieved in only 27% of cases when atrial lead implantation was attempted.[5] In the current case, we were unable to achieve effective atrial pacing; atrial pacing failed when it was required and succeeded only when it was not required. Therefore, although familial AS generally requires pacemaker therapy, given that atrial pacing failure is common, atrial lead implantation may not be necessary in all cases. It is important to identify such cases of familial AS that do not require atrial leads. We believe there is little benefit from atrial leads in AS cases in which atrial pacing is not possible during bradycardia. Furthermore, an atrial lead may not be necessary in cases of (1) persistent AS with constant atrial pacing failure and (2) intermittent AS, where atrial pacing is not possible during sinus arrest and unnecessary during SR because of the absence of sinus bradycardia, as in this case. This patient's basic heart rhythm had become mostly JER with sinus arrest, and AS had progressed. In addition, in cases in which effective atrial pacing is initially achieved but later becomes impossible, atrial lead extraction may be considered.

However, the decision of atrial lead implantation in patients with familial AS should be carefully weighed. Most of these patients are young, and familial AS is associated with a high incidence of juvenile stroke because of lack of atrial activity and supraventricular arrhythmia.[5,6] In this case, at pacemaker implantation, atrial flutter was induced by atrial pacing only once during isoproterenol administration but terminated spontaneously. We used medications to prevent stroke and increase atrial activity. We prescribed edoxaban 30 mg, an oral direct factor Xa inhibitor, for stroke prevention. Isoproterenol has been shown to convert the cardiac rhythm from AS to SR.[5] In our patient, administration of isoproterenol, awakening from sedation, and exercise resulted in conversion of JER to SR, and atrial pacing became possible. Thus, considering that increased heart rate and activation of the sympathetic nervous system would convert JER to SR, we initially prescribed cilostazol and achieved SR, but the therapy was discontinued because of persistent

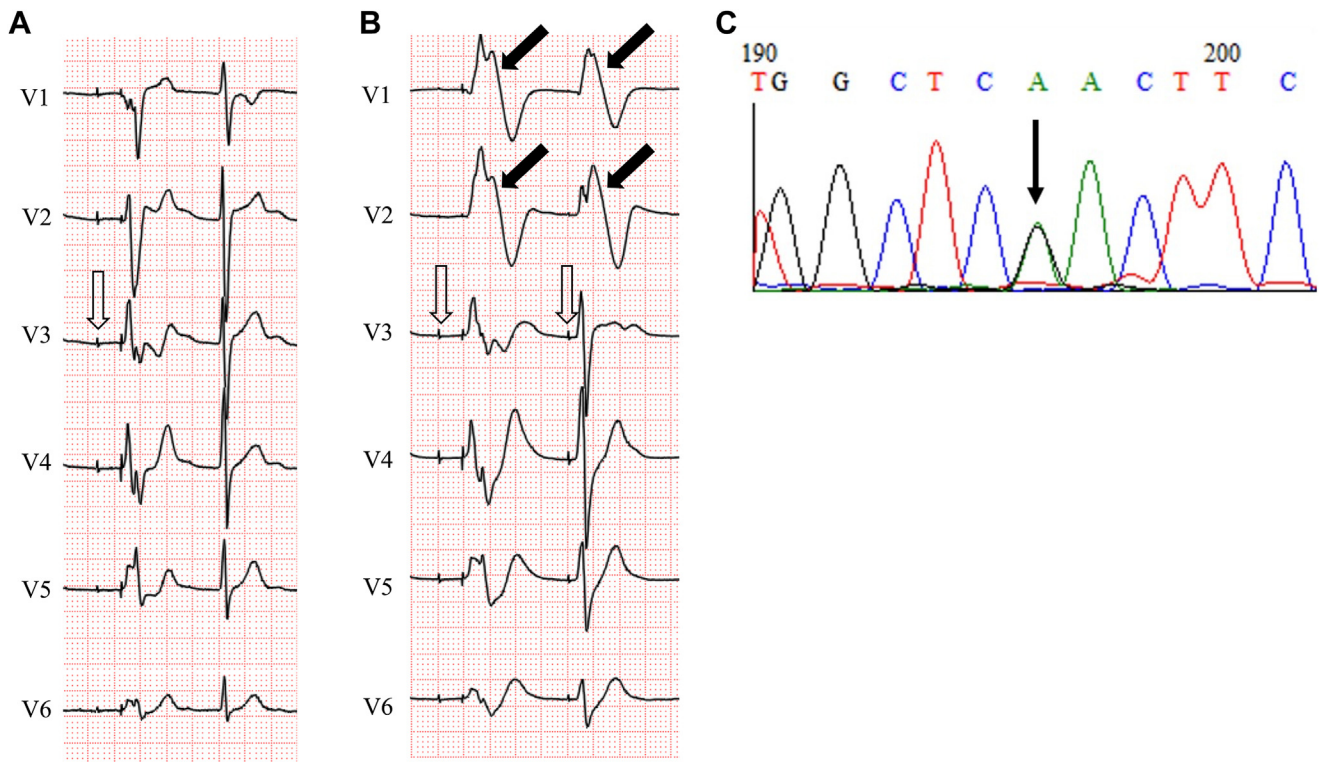

Figure 3 Postprocedural testing results. **A:** Electrocardiography findings before administering pilsicainide during ventricular pacing and junctional escape rhythm. The first beat is ventricular pacing, and the second beat is junctional escape rhythm. The *hollow arrow* shows atrial pacing failure. **B:** Electrocardiography findings after administering pilsicainide at 1 mg/kg intraveneously during ventricular pacing and junctional escape rhythm. The *hollow arrows* show atrial pacing failure, and the *full arrows* show coved-type ST elevation in leads V1 and V2. The first beat is ventricular pacing, and the second beat is junctional escape rhythm. **C:** Sequence of the proband's genomic DNA. The *arrow* indicates the heterozygous G to A variant at site 3823 in the *SCN5A* gene (c.3823G>A, p.D1275N).

headaches. We tried oral isoproterenol; although intravenous isoproterenol was effective, oral isoproterenol was not. Currently, few studies are available on medication for familial AS. Continuation of tolerable medication therapy may have had some effect. In particular, there has been a case of recovery of atrial pacing after implantation of an atrial lead in a patient with AS and no atrial conduction at the time of implantation.[5] Given the possibility of atrial recovery and that management in AS remains unclear with limited reports of AS, it would be important to be aware of both scenarios of atrial noncapture and recovery of atrial pacing. It may be worth considering whether implantation of atrial leads is successful in certain AS patients, because the ability to pace the atrium and avoid long-term anticoagulation in a young child is not insignificant.

Whether the atrial lead should have been extracted in this case may be controversial. Leaving a lead in which atrial pacing is not possible in a young patient increases the risk of lead-related complications such as lead fracture and venous obstruction. Extraction of the atrial lead prevented monitoring of atrial arrhythmias, but given the age of this patient, the lack of recovery of atrial pacing for 6 months after implantation, and the possibility of needing an implantable cardioverter defibrillator (ICD) lead for Brugada syndrome in the future, we considered that fewer leads were better in this patient and the atrial lead should be extracted before the adhesion become severe. Because only 6 months had passed since pacemaker implantation, the adhesion of the lead was considered to be mild and the extraction technique probably not difficult. We performed the atrial lead extraction, with great care regarding infection. There was little adhesion of the atrial lead, and it was easily extracted with simple manual traction only.

Another important takeaway from the current case is that genetic testing should be considered in cases of suspected inherited arrhythmias, particularly in young patients. Young patients with pathogenic *SCN5A* variants often exhibit overlap phyenotypes.[7] In the current case, AS, cardiac conduction defect (Figure 1B), and Brugada syndrome (Figure 3B) were present simultaneously. An apparent bradycardia was documented, and because this was thought to be the cause of the syncope and the patient did not have ventricular fibrillation, a pacemaker was implanted rather than an ICD. Given that sudden death has been reported in cases of AS with pathogenic *SCN5A* variants,[8] consideration of an ICD might be warranted. Although the role of electrophysiology study is not well established, particularly in patients with drug-induced Brugada pattern with no history of ventricular arrhythmia, ventricular extra-stimulation could have been considered for risk stratification at the time of atrial lead extraction. This patient should be closely monitored for the potential development of fatal ventricular arrhythmias, and he may require an upgrade to an ICD in the future.

Conclusions

This case highlights the importance of considering atrial pacing failure caused by AS in patients with suspected familial SSS and emphasizes the need for genetic analysis to investigate other possible overlapping pathologic conditions. An atrial lead may not be necessary in cases of familial AS in which atrial pacing is not possible.

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