Progressive atrial myocardial fibrosis in a 4-year-old girl with atrial standstill associated with an SCN5A gene mutation

Yoshiaki Kato, MD, PhD,* † Yoshihiro Nozaki, MD, PhD,* Miho Takahashi-Igarı, MD,* Masato Sugano, MD, ‡ Naomasa Makita, MD, PhD, § Hitoshi Horigome, MD, PhD*

From the *Department of Child Health, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, †Division of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Suita, Japan, ‡Department of Diagnostic Pathology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, and §Research Institute and Omics Research Center, National Cerebral and Cardiovascular Center, Suita, Japan.

Introduction
Atrial standstill (AS) is a rare cardiac syndrome characterized by the absence of electrical and mechanical activity in the atria. Mutations in the sodium channel α-subunit SCN5A gene have been identified as the cause of arrhythmia syndromes, such as long QT syndrome, Brugada syndrome (BrS), progressive cardiac conduction disease, sinus node dysfunction, atrial fibrillation, and AS.1 Historically, these cardiac sodium channelopathies were considered to be purely electrical disorders. However, with the accumulation of cases, SCN5A mutations also came to be associated with structural disorders involving myocardial fibrosis.2–4 While studies have reported pathologic findings in the atria of patients with AS,5–7 none have associated these pathologic findings with SCN5A mutations in patients with AS. Herein, we report a pediatric case of AS with atrial fibrosis associated with an SCN5A mutation.

Case report
A 4-year-old girl presented to our hospital with severe bradycardia without syncope or dizziness. The patient’s 12-lead electrocardiogram (ECG) revealed irregular bradycardia with a junctional escape rhythm and supraventricular premature contractions without any ST-T wave changes (Figure 1A). Holter monitoring of the patient revealed severe bradycardia with an average heart rate of 40 beats per minute, a pause lasting 4.5 seconds, and paroxysmal atrial fibrillation (Figure 1B). Transthoracic echocardiography was also performed, which showed normal ventricular function (left ventricular ejection fraction of 70%), a slightly dilated left ventricular end-diastolic diameter of 38.6 mm (Z-score, +3.37),8 and mild mitral regurgitation. The brain natriuretic peptide level was 223.0 pg/mL (reference range 0–18.4 pg/mL). The patient had no fever, gastroenteritis, or other symptoms suggestive of myocarditis prior to admission. Furthermore, her history did not suggest Kawasaki disease. She had a negative family history for cardiac disease among her first- and second-degree relatives.

KEY TEACHING POINTS

- Although atrial standstill (AS) has historically been considered a transient syndrome, certain pathologic studies have revealed that atrial fibrosis occurs with AS. Histopathological examination in our case showed progressive atrial fibrosis.
- SCN5A mutations have been known to manifest as long QT syndrome, Brugada syndrome, sick sinus syndrome, atrial fibrillation, and progressive cardiac conduction disorders. The mutation is also associated with structural disorders such as dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy.
- Ours is the first case report of AS that developed in a child with histologically proven atrial fibrosis in association with an SCN5A mutation. An SCN5A gene mutation might be associated with myocardial fibrosis of the atrial myocardium as well as various arrhythmias, including AS.

KEYWORDS
Atrial standstill; SCN5A; Myocardial fibrosis; Sodium channelopathy; Pediatrics

Heart Rhythm Case Reports 2022;8:636–638

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Disclosure: None. Address reprint requests and correspondence: Dr Yoshiaki Kato, Division of Pediatric Cardiology, National Cerebral and Cardiovascular Center, 6-1 Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan. E-mail address: kato.yoshiaki@ncvc.go.jp.

2214-0271/© 2022 Heart Rhythm Society. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). https://doi.org/10.1016/j.hrcr.2022.06.010
After the informed consent was obtained from the parent, an electrophysiological study was performed under general anesthesia. During this study, no spontaneous atrial activation or atrial contractions were observed. Partial AS was confirmed by the absence of electrical activity on the atrial electrogram under the maximal pacing output at sites other than the interatrial septum or edge of the right atrial appendage (Figure 2). In the right atrial appendage pacing rhythm, the atrial–His bundle interval was 117 ms, and the His bundle–ventricular interval was 47 ms. During this procedure, paroxysmal atrial fibrillation was induced with an injection of isoproterenol (0.1 mcg/kg/min).

We performed a thoracotomy for epicardial pacemaker implantation. A histological specimen from the right atrial appendage was obtained surgically. The atrial capture could be obtained only at the epicardial site of the interatrial groove, which is an extension of the atrial septum on the epicardial side, using steroid-eluting lead with a pacing threshold of 1.75 V / 1.0 ms. At the time of implantation, the pacemaker sensitivity and output were set as 0.18 mV and 6.0 V / 1.0 ms, respectively. After pacemaker implantation, the patient spontaneously developed an atrial flutter, which necessitated treatment with a direct-current shock.

Upon histological examination of the specimen obtained from the right atrial appendage, we observed that the loose connective tissue of the atrial wall was replaced diffusely by dense collagenous tissue with scattered intermingled myocardium. Under higher magnification, these fibrotic changes included different stages of fibrosis—that is, focal infiltration of active inflammatory neutrophils, loss of myocardiocytes, and scar formation with dense collagen deposition, suggesting that the process was active and progressive (Figure 3). Genetic testing using direct Sanger sequencing revealed a missense mutation, S910L (c.2729c>t), located in exon 16 of SCN5A; this is a pathogenic mutation characteristic of the BrS. The patient’s mother also underwent genetic testing, but she did not have the SCN5A mutation. ECGs of the patient’s older sister and mother showed no sinus bradycardia or ST-segment changes in the right precordial leads. The patient’s father did not consent for examination.

![Figure 1](image1.png)

**Figure 1**

A: Surface 12-lead electrocardiogram (ECG). Irregular bradycardia is observed with junctional escape beats and supraventricular premature contractions without ST-T wave changes

B: Holter ECG. Severe bradycardia with an average heart rate of 40 beats/min, with a pause lasting 4.5 seconds, along with paroxysmal atrial fibrillation.

![Figure 2](image2.png)

**Figure 2**

Electrophysiological study before a pacemaker implantation. A: Atrial capture was obtained at the edge of the right atrial appendage. B: Atrial capture was not obtained on the free wall of the right atrium even with pacing at maximum output. HIS = His bundle; RA = right atrium; RVA = right ventricular apex; Stim = stimulus.

Kato et al  SCN5A Mutation–Associated Atrial Fibrosis in AS 637
Although the underlying mechanism between atrial fibrosis and SCN5A mutation remains to be elucidated, we present a case of progressive atrial fibrosis and AS associated with an SCN5A mutation.

**Conclusion**

To the best of our knowledge, this is the first case report of AS that developed in a child with histologically proven atrial fibrosis in association with an SCN5A mutation. An SCN5A gene mutation might be associated with myocardial fibrosis of the atrial myocardium as well as various arrhythmias, including AS.

**References**

1. Wilde AAM, Amin AS. Clinical spectrum of SCN5A mutations: long QT syndrome, Brugada syndrome, and cardiomyopathy. JACC Clin Electrophysiol 2016;2:569–579.
2. McNair WP, Sinagra G, Taylor MR, et al. SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. J Am Coll Cardiol 2011;57:2160–2168.
3. Te Riele AS, Agullo-Pascual E, James CA, et al. Multilevel analyses of SCN5A mutations in arrhythmogenic right ventricular dysplasia/cardio-myopathy suggest non-canonical mechanisms for disease pathogenesis. Cardiovasc Res 2017;113:102–111.
4. Coronel R, Casini S, Koopmann TT, et al. Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: a combined electrophysiological, genetic, histopathological, and computational study. Circulation 2005;112:2769–2777.
5. Allensworth DC, Rice GJ, Lowe GW. Persistent atrial standstill in a family with myocardial disease. Am J Med Sci 1939;198:774–778.
6. Rosen KM, Rahimtoola SH, Gunnar RM, Lev M. Transient and persistent atrial standstill with His bundle lesions. Electrophysiologic and pathologic correlations. Circulation 1971;44:220–236.
7. Tanaka H, Atsuchi Y, Tanaka N, Nishi S, Kanehisa T. Persistent atrial standstill due to atrial inexcitability. An electrophysiologic and histologic study. Jpn Heart J 1975;16:639–653.
8. Lopez L, Colan S, Stylianou M, et al. Relationship of echocardiographic Z scores adjusted for body surface area to age, sex, race, and ethnicity: the Pediatric Heart Network Normal Echocardiogram Database. Circ Cardiovasc Imaging 2017;10:e006979.
9. Kaplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm 2010;7:33–46.
10. Rosenbaum FF, Levine SA. Auricular standstill: its occurrence and significance. Am J Med Sci 1939;198:774–778.
11. Grootte A, Kalman JM, Aguinaga L, et al. EHRA/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Heart Rhythm 2017;14:e3–e40.
12. Nademanee K, Raji H, de Noronha SV, et al. Fibrosis, connexin-43, and conduction abnormalities in the Brugada syndrome. J Am Coll Cardiol 2015;66:1976–1986.
13. Royer A, van Veem TA, Le Bouter S, et al. Mouse model of SCN5A-linked hereditary Lennègre’s disease: age-related conduction slowing and myocardial fibrosis. Circulation 2005;111:1738–1746.