LETTER TO THE EDITOR

WILEY

Rett syndrome with atrial tachycardia in a girl

To the editor:

A 26-month-old girl presented with atrial tachycardia as the main cardiac manifestation, which lasted for more than 1 year. The girl was born to healthy, non-consanguineous parents and had no family history of similar diseases. There was no asphyxia at birth and no abnormal feeding history. Her development was normal in the early stages. However, at the age of 17 months she did not respond to her name and hardly communicated with her parents. She was also unable to grasp things and repeatedly chewed on her hands. In the meantime, she frequently started grinding her teeth when awake.

On physical examination after admission, her body temperature was 36.2°C, pulse was 98 beats·min^{-1}, respiration rate was 26 times·min^{-1}, and blood pressure was 84/52 mmHg. She did not make eye contact and did not respond to the call. The range of the apex beat was normal when the heartbeat sounded strong. The rhythm of the heartbeat was irregular, and premature beats could be heard for 7 to 8 times·min^{-1}. There was no pathological murmur in any of the valve auscultation areas. The strength and tension of the muscle were reduced.

Her N-terminal pro b-type natriuretic peptide (NT-proBNP) level was 1083 pg·mL^{-1}, and an electrocardiogram (ECG) showed atrial flutter with no fixed conduction ratio after admission (Figure 1). Holter (24 h dynamic ECG) demonstrated a sinus rhythm accompanied by ectopic heart rhythm, frequent atrial premature beats (187 791/24 h), partial pairing, a short atrial tachycardia (5185/24 h), alternate multisource atrial tachycardia, and atrial flutter (2:1 conduction). Echocardiography was then performed, which revealed persistent left superior vena cava and dilated coronary sinus. The parents also underwent ECG and echocardiography with no abnormal findings. Whole exome sequencing identified a *de novo* heterozygous nonsense mutation, c.763C>T (R255X), in *MECP2* (NM_004992.3). After discussion with the neurologist, the child was finally diagnosed with Rett syndrome (RTT) with atrial arrhythmia, according to the RTT diagnostic criteria revised by the International Rett Search Consortium in 2010.[1]

Oral propafenone was administered for anti-arrhythmia treatment. One week after treatment, the ECG showed that atrial flutter and atrial tachycardia had disappeared, while atrial premature beats were significantly reduced. Holter monitoring showed sinus rhythm accompanied by ectopic heart rhythm, atrial premature beats (183/24 h), no partial pairing, and no short atrial tachycardia in the patient. Her NT-proBNP was 687 pg·mL^{-1}. Rehabilitation training and cardiology outpatient follow up are in progress.

We have reported, here, a girl with RTT with atrial arrhythmia as the major cardiac manifestation. Rett syndrome is a neurodevelopmental disorder that more commonly affects girls.[1] The main feature is progressive loss of cognitive and motor function followed by a period of normal development after birth. Rett syndrome is associated with mutations in the *MECP2* gene on the X chromosome. Atrial tachycardia has not been reported in patients with RTT before. Although without direct evidence, we speculated that atrial tachycardia might be another cardiac-related phenotype of RTT. Previous studies have shown that regulating the excitability of the cholinergic system may be a potential way to treat and prevent sudden cardiac death in patients with RTT, considering that arrhythmia results from loss of MECP2 function of cholinergic neurons.[2] This further indicates that the abnormal heart rhythm may be the result of the loss of MECP2 function. Moreover, immature brainstem autonomic control is associated with cardiopulmonary instability in children with RTT, which may be related to the loss of MECP2 in brainstem neuron.[3,4]

Most studies on abnormal cardiac rhythm in RTT have focused on autonomic nerve disorders. Animal studies showed a continuous increase in the Na^+ current in cardiomyocytes of a mice model of RTT. The Na^+ current

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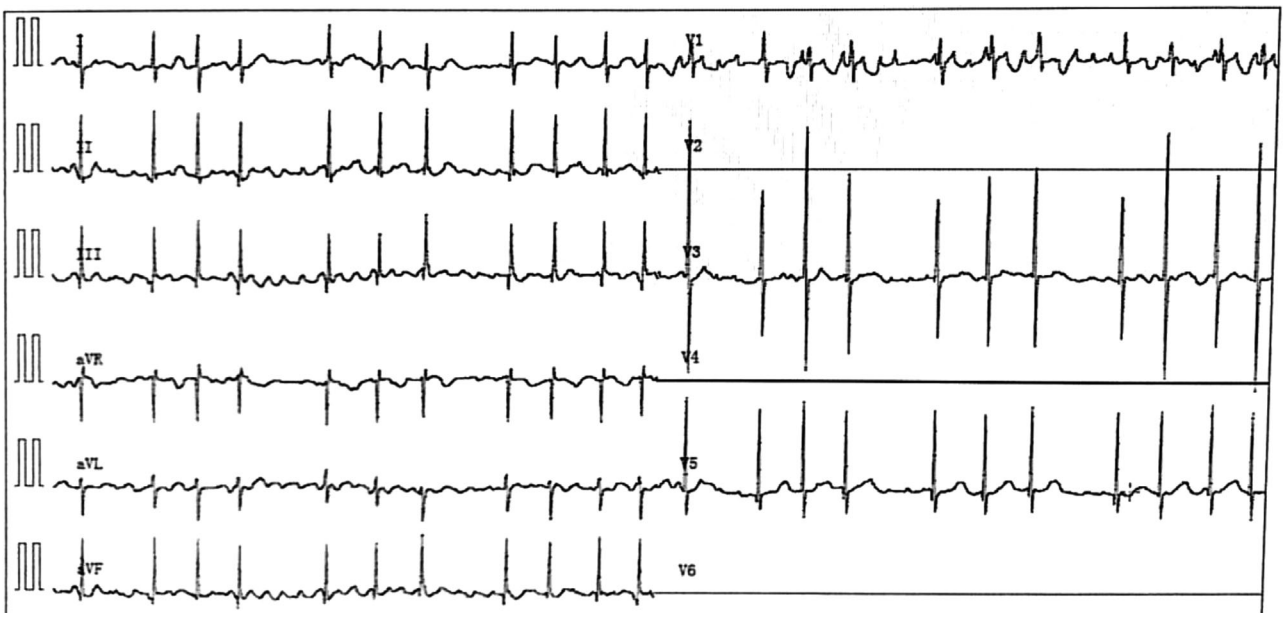

FIGURE 1 The electrocardiogram showed atrial flutter with no fixed conduction ratio of the patient with Rett syndrome.

returned to normal after treatment with Na^+ channel blockers.[5] Studies have shown that Na^+ current has an important role in atrial arrhythmia.[6] The potential mechanism may be that the increase of Na^+ current in the heart of these patients leads to abnormal expression of Na^+ channels of the atrium. The application of propafenone can eliminate atrial tachycardia further confirming the role of Na^+ channel in RTT arrhythmias. It was shown that altered function of hyperpolarization-activated cyclic nucleotide–gated (HCN) channels is also associated with sinus node dysfunction and other arrhythmias such as atrial fibrillation.[7] The transcription level of *Hcn* genes was changed in the hearts of *Mecp2*-null mice compared with that of normal mice.[8] We speculated that the *MECP2* gene may contribute to the development of atrial arrhythmia by affecting the function of the HCN channel. Some genes, including *T-box5*, connexin *Cx40*, and *Cx43* genes, may also affect the heart conduction.[8] Furthermore, MECP2 affects the development and differentiation of cardiovascular progenitor cells, myocardial cell structure, and the expression of some cardiac voltage-gated genes, which may also provide an explanation.[8]

In conclusion, we reported the case of a girl with RTT with atrial tachycardia. More clinical and basic studies are needed to further elucidate the mechanisms of RTT associated with atrial tachycardia.

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CONSENT FOR PUBLICATION

The patient's guardians provided informed consent for publication.

CONFLICT OF INTEREST

None.

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