Clinical report of 8 families with atrioventricular nodal reentrant tachycardia from China

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Introduction Atrioventricular nodal reentrant tachycardia (AVNRT) is caused by a reentry circuit involving dual atrioventricular nodal (AVN) pathways. It had been regarded as a sporadic disease, until the first case of familial AVNRT was reported in 2004.[1] Subsequently, a series of familial AVNRT cases was published,[2-5] and we described 3 cases of familial AVNRT in China.[6] Michowitz et al[7] demonstrated that this disease is genetically determined to some extent. However, there has been no report on the pathogenic gene associated with AVNRT. It has been shown in 298 patients with AVNRT that the disease is associated with sodium and calcium handling detected using next-generation sequencing.[8] Most recently, we for the first time revealed potential candidate genes and pathways related to the neuronal system or ion channels in AVNRT using whole-exome sequencing.[9] Here, we describe 8 families with AVNRT in China and add to clinical evidence for further research.

Methods Our study patients were enrolled in the study in Sichuan Provincial People's Hospital between 2013 and 2020. Informed consent for an electrophysiological study (EPS) was obtained from all participants, and the study protocol was approved by the ethics committee of Sichuan Provincial People's Hospital.

The diagnostic criterion for nonsyndromic AVNRT was presented elsewhere.[10] Dual AVN physiology was defined as an increment ≥50 ms in the atrial-His bundle interval after a 10-ms decrement interval during single atrial extrastimulation or an increment ≥50 ms in the atrial-His bundle interval after shortening the pacing cycle duration by 10 ms. Familial AVNRT was diagnosed when at least 2 first--degree family members had AVNRT.

Statistical analysis Continuous variables were presented as mean (SD), and categorical variables, as number and percentage. All statistical analyses were performed using the IBM SPSS Statistics software for Windows, version 27.0 (IBM Corp., Armonk, New York, United States).

Results and discussion **Family 1** The proband (III-1) was admitted with intermittent palpitation with no clear trigger. Electrocardiography detected supraventricular tachycardia (SVT). The woman was diagnosed with AVNRT by EPS (FIGURE 1). In addition, the proband's mother (II-1) and her uncle (II-3) underwent radiofrequency catheter ablation (RFCA) for the treatment of palpitations. Patients II-1 and II-3 were diagnosed with AVNRT and atrioventricular reentrant tachycardia (AVRT; caused by the left lateral atrioventricular accessory pathway), respectively. The main complaints of the proband's brother (III-3), who was diagnosed with typical AVNRT through esophageal pacing (EP), also included palpitations.

Family 2 The proband (III-1) presented with sudden palpitations at rest. Electrocardiography was indicative of SVT. The man was diagnosed with AVNRT based on EPS findings. Tracing his family history, his uncle (II-3) had a definite diagnosis of AVNRT by EPS in 2015 because of severe palpitations after exertion.

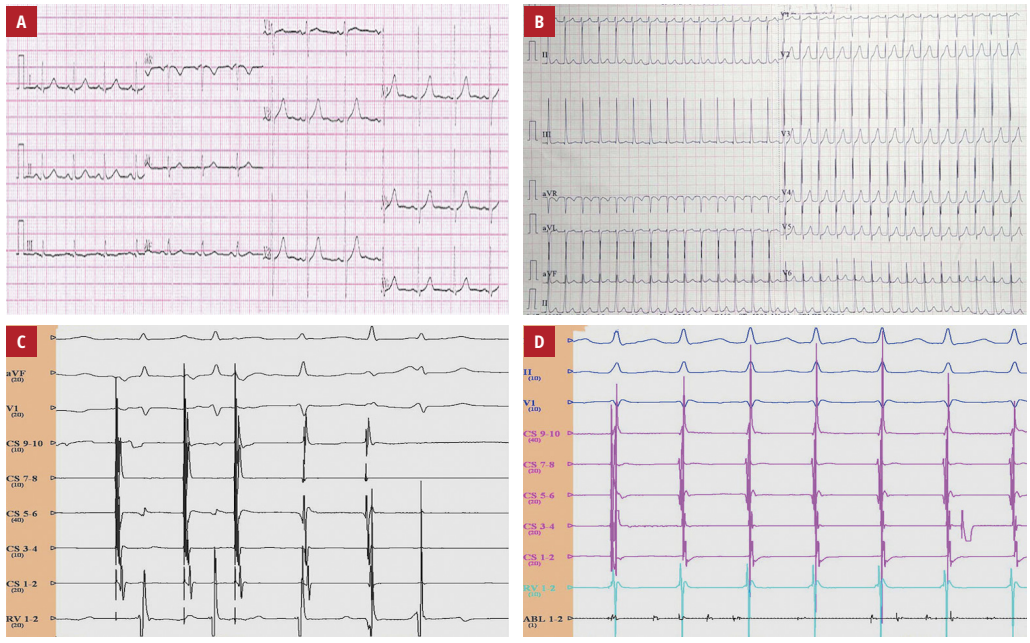

FIGURE 1 **A**, **B** – surface electrocardiograms at rest (**A**) and during attack (**B**); **C**, **D** – a typical induction of slow–fast atrioventricular nodal reentrant tachycardia after pacing (programmed stimulation S1S2) from the proximal coronary sinus of the proband in family 1

Family 3 The proband (III-1) presented to our hospital because of patent foramen ovale and palpitations. Electrocardiography revealed SVT. Then, AVNRT was confirmed by EPS and RFCA was performed. Another 4 individuals in his family suffered from palpitations. His mother (II-1) and aunt (II-5) were diagnosed with AVNRT by EP. His 2 aunts (II-3 and II-7) refused to undergo EP, although they had palpitations.

Family 4 The proband (II-1) presented with palpitations after vigorous exercise, such as swimming and running. Electrocardiography showed SVT, and EPS revealed typical features of AVNRT. His daughter (III-1) was closely monitored, as she experienced palpitations while playing badminton. Considering her age, she underwent EP and was diagnosed with AVNRT.

Family 5 The proband (II-1) presented with recurrent palpitations. The man was diagnosed with AVNRT and underwent RFCA. Two years later, he again underwent RFCA of the left lateral atrioventricular accessory pathway. His family history revealed that his mother (I-2) was diagnosed with AVNRT by EPS in 2007.

Family 6 The proband (II-1) displayed palpitations without evident cause. Electrocardiography was remarkable for SVT. Then, the man was diagnosed with AVNRT and treated with RFCA. Following family screening, his brother (II-6) was diagnosed with AVNRT and also underwent RFCA.

Family 7 The proband (II-1) suffered from irregular palpitations. Electrocardiography demonstrated SVT. The man underwent EPS and was diagnosed with AVNRT. His sister (II-3) was treated with RFCA for tachycardia and it turned out that she had AVNRT. In addition, the proband's daughter (III-1) was diagnosed with AVNRT by EP.

Family 8 The proband (II-1) complained of palpitations and dizziness when urinating and was admitted to hospital because of syncope. Electrocardiography demonstrated SVT, and RFCA revealed typical features of AVNRT. The man's son (III-1) had syncope while swimming. His electrocardiogram showed early repolarization syndrome. As a result of AVRT, his sister (II-3) also experienced syncope. There were 2 patients with syncope (II-3 and II-7) suspected of having AVNRT, but they refused to undergo further examination.

Family trees and clinical characteristics are shown in Supplementary material, *Figure S1* and *Table S1*. The mean (SD) age of the study patients was 40.2 (11.8) years, and the proportion of men was 55% (11 of 20 individuals). All patients were male in families 2 and 5. Only 2 patients had cardiovascular complications in families 1 and 3.

Atrioventricular nodal reentrant tachycardia has been considered a sporadic disease with a prevalence of 22.5 cases per 10 000 persons in the general population.[11] However, a larger familial AVNRT prevalence of 127 cases per 10 000 persons was reported in 2017.[7] In the present study, a total of 600 patients with AVNRT were admitted to our hospital between 2013 and 2020, among whom there were 8 families with AVNRT. Therefore, the prevalence of familial AVNRT can be estimated at around 1.3%.

A recent study has shown that the sex ratio (female to male) was approximately 1.5 (926/630) in patients with sporadic AVNRT,[7] and another study reported a ratio of 2.28 (57/25) in 600 patients with sporadic AVNRT.[9] Increasing evidence suggests that the sex ratio (female to male) in familial AVNRT reaches 3.6 (11/3).[1] This may be explained by the effect of sex hormones on AVN in women, the imbalance of estrogen and progesterone; for example, higher plasma levels of 17β-estradiol would reduce the electrical conduction of the right atrium and prolong the intranodal conduction time.[12] However, in our study, the proportion of men was 55% (11/20). Therefore, we hypothesize that the different sex ratio noted in familial AVNRT may be caused by the small number of families with AVNRT or some families may have potential X-linked genetic patterns.

Hayes et al[1] demonstrated that autosomal dominant inheritance with partial penetrance is the most likely mode of inheritance in patients with AVNRT,[1] and Stec et al[5] indicated that AVNRT may be inherited through the maternal line.[5] The inheritance mode appeared to be autosomal dominant or X-linked in our study.

Exercise or urination led to the appearance of AVNRT symptoms and even syncope in families 4 and 8. Therefore, we infer that increased sympathetic activity causes AVNRT, and excess vagal activation results in syncope.[13] Moreover, AVNRT was triggered by increasing vagal tone, since it prolongs the refractory period of the fast pathway, whereas anterograde slow and retrograde fast pathway refractoriness were not significantly longer.[14] Furthermore, we also identified potential AVNRT--related genes in the sympathetic nerve and vagus nerve pathways.[9]

Distinct factors were noted in family 8, in which the patients experienced syncope accompanied by the classic prodromal symptoms prior to reflex vasovagal syncope, including palpitations and dyspnea. Persistent nausea and pallor present when the episode occurred also suggested a reflex event. Moreover, both the proband and his daughter in family 4 also suffered from AVNRT during exercise. These phenomena indicate that the sympathetic nerve and vagus nerve may contribute to AVNRT and even syncope.

Notably, both AVNRT and AVRT were found in 3 families in the present study, and it was further demonstrated in identical twins.[15] These findings suggested that the diseases may have different phenotypes with the same pathogenic gene or even the same pathogenic point mutation. Therefore, future research is needed to identify the genetic background of AVNRT.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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