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【 EDITORIAL 】

Acquired Long-QT Syndrome: Mild but Abnormal?

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Long-QT syndrome (LQTS) is characterized by QT interval prolongation and subsequent polymorphic ventricular tachycardia, torsades de pointes (TdP), and leads to sudden cardiac death. In most cases, congenital LQTS is caused by gene mutations that affect the ion channels, such as mutations of the *KCNQ1*, *KCNH2* and *SCN5A* genes, whereas patients with acquired LQTS (aLQTS) exhibit marked QT interval prolongation that is provoked by drugs (*i.e.*, antiarrhythmic drugs, certain antihistamines, antibiotics, or antipsychotics) and non-drug triggers (*i.e.*, hypokalemia, or bradycardia). However, not all LQTS-gene mutation carriers show a prolonged QT interval, and some show a normal QT interval. This brief case report by Nakajima et al. (1), highlighted a case of complete atrio-ventricular block (AVB)-induced acquired TdP in a subject who had a considerable genetic background.

Moss and Schwartz proposed that some cases of drug-induced TdP, also known as aLQTS, show the instances of a "forme fruste" (*i.e.*, a normal or borderline QT interval) of congenital LQTS (2). Recently, a number of studies suggested that some patients with aLQTS have genomic backgrounds similar to those of patients with congenital LQTS. Itoh et al. reported the comprehensive genetic screening results of 188 patients with aLQTS, 28% of whom were found to share underlying mutations with patients with congenital LQTS (3). They showed that most prevalent mutations in aLQTS were of the *KCNH2* gene, followed by the *KCNQ1* gene. The baseline QTc interval of aLQTS patients who carry mutations is shorter than in that of patients with congenital LQTS but still longer in comparison to non-carriers. Thus, genetic carriers with mild QT prolongation could be at risk of developing aLQTS.

Female gender has been also identified as an independent predisposing factor for TdP during AVB, as well as congenital LQTS (4). Oka et al. reported the clinical and genetic background of 14 patients (13 female) with AVB-induced QT prolongation and TdP. Genetic screening for AVB-induced aLQTS revealed four (29%) heterozygous mutations; 1 *KCNQ1* mutation (G272V) and 3 *KCNH2* mutations (D111V, A490T, P846T) (5). The functional analyses revealed that G269S exerted moderate dominant-negative suppression of the I_{Ks} channel, and that it blunted the response to phosphorylation by protein kinase A; thus it was sensitive to sympathetic stimulation and caused adrenergic-induced LQTS (6). Moreover, G269S, which is located in the S5 domain of the KCNQ1 channels, is a well-observed LQT1 mutation. This is the so-called "hot-spot" site, to which - according to our multi-center LQTS registry - more than half of the *KCNQ1* mutations in Japan (including G269S) belong. Among these hot-spots mutations, G269S carriers were found to have an intermediate cardiac event rate (30%) and many of the subjects were asymptomatic carriers, which might be due to a moderate functional change in the I_{Ks} channel.

In chronic complete AVB and acquired TdP, a significant downregulation of delayed rectifier K^+ currents was identified in a canine experimental model (7). The normal function of the I_{Kr} and I_{Ks} currents contributes to preserving a stable repolarization process and a sufficiently large repolarization reserve. The concept of a "reduced repolarization reserve" implies that whenever repolarizing currents are genetically reduced - as occurred in this G269S mutation that affected the affecting I_{Ks} channel - the superimposition of even common environmental factors, such as hypokalemia, I_{Kr} blocking drugs, or AVB may unmask this latent vulnerability and precipitate TdP. This is especially apparent in subjects who only present with a long QT interval and when a trigger is present but it shows a normal QT interval at baseline.

The development of TdP remains unpredictable in individual subjects without a preceding history of syncope or ventricular arrhythmia; however, in general, older-aged women with a borderline or prolonged QT interval (QTc > 440 ms) are considered to be at risk of aLQTS. Although the QT interval returns to normal after the removal of the causative trigger in most aLQTS cases, it remains prolonged

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in some. In the present case, the baseline QTc (449 ms) during sinus rhythm recorded 4 months before AVB was slightly longer than the normal range, suggesting that the patient was a genetic carrier; however, in general, such cases are difficult to be identified before the event.

Finally, genetic screening is valuable for the assessment of genetic risk and for the diagnosis of both congenital LQTS and aLQTS, which may prevent lethal arrhythmic events. However, in clinical practice, it remains controversial whether the genetic background in aLQTS subjects should always be clarified.

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References

1. Nakajima T, Sugawara T, Kaneko Y, Kurabayashi M. Atrioventricular block-induced torsades de pointes associated with *KCNQ1*-G269S. Intern Med **57**: 905-906, 2018.

2. Moss A, Schwartz PJ. Delayed repolarization (QT or QTU prolongation) and malignant ventricular arrhythmias. Mod Concepts Cardiovasc Dis **51**: 85-90, 1982.

3. Itoh H, Crotti L, Aiba T, et al. The genetics underlying acquired long QT syndrome: impact for genetic screening. Eur Heart J **37**: 1456-1464, 2016.

4. Chorin E, Hochstadt A, Viskin S, et al. Female gender as independent risk factor of torsades de pointes during acquired atrioventricular block. Heart Rhythm **14**: 90-95, 2017.

5. Oka Y, Itoh H, Ding WG, et al. Atrioventricular block-induced Torsades de Pointes with clinical and molecular backgrounds similar to congenital long QT syndrome. Circ J **74**: 2562-2571, 2010.

6. Wu J, Naiki N, Ding WG, et al. A molecular mechanism for adrenergic-induced long QT syndrome. J Am Coll Cardiol **63**: 819-827, 2014.

7. Volders PG, Sipido KR, Vos MA, et al. Downregulation of delayed rectifier K(+) currents in dogs with chronic complete atrioventricular block and acquired torsades de pointes. Circulation **100**: 2455-2461, 1999.