T he congenital long QT syndrome (LQTS) is characterized by abnormally prolonged ventricular repolarization, leading to QT prolongation on the ECG, with frequent development of the polymorphic ventricular tachycardia known as torsades de pointes (Tdp), syncope or sudden cardiac death. Most cases of congenital LQTS are caused by gene mutations in several ion channels and their interacting proteins. Among these ion channel genes, *KCNQ1* (LQTS1), *HERG* or *KCNH2* (LQTS2) and *SCN5A* (LQTS3) are the most prevalent in the incidence. Gene mutations are identified in approximately 70% of patients with LQTS, which suggests the presence of unidentified genetic factors in the remaining 30%. On the other hand, all the gene carriers among LQTS family members do not necessarily show clinical signs of QT prolongation and ventricular tachyarrhythmias, including Tdp, suggesting the presence of factors modifying the clinical phenotypes. Acquired forms of LQTS are more frequently seen in clinical practice than the congenital forms, and comprise a leading cause of Tdp, indicating a need for careful attention to their genesis. Acquired forms of QT prolongation are supposed not to be caused by gene mutations as a major factor, but can be induced by multiple clinical conditions, including drugs, bradycardia, hypokalemia, congestive heart failure etc. Moreover, the QT interval and abnormal ST-T waves seen in LQTS are variously affected by changes in physiological factors, including serum electrolyte and catecholamine levels, which underlines both the different phenotypes and the time-dependent fluctuations in QT prolongation. Among the inciting conditions, bradycardia is a frequent cause not only of QT prolongation but also the development of Tdp. Kurita et al have demonstrated that patients with atrioventricular (AV) block-induced Tdp display abnormally prolonged QT intervals at slower heart rates (<60 beats/min), compared with those without Tdp.

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The genetic factors for patients with the combination of LQTS/AV block or acquired LQTS have been explored and several studies have indicated gene mutations encoding the cardiac ion channels as a causative factor. AV conduction disturbance associated with LQTS in infants and neonates is rare, but carries a high risk of arrhythmic events/sudden cardiac death, and these cases seem to be associated with homozygous gene mutation. Homozygous mutations of *HERG* or *SCN5A* have been presented mainly as case reports, but some have described accumulated cases in neonates or children with LQTS with 2:1 AV block.

Lapoglazof et al identified gene mutations in 17 of 23 neonates with LQTS with 2:1 AV block or sinus bradycardia. They found mutations in *KCNQ1* for all 8 patients with sinus bradycardia and in *HERG* for 9 of 15 patients with 2:1 AV block. Therefore, they concluded that neonate LQTS with 2:1 AV block may be associated preferentially with *HERG* mutations as opposed to persistent sinus bradycardia associated with *KCNQ1* mutations. Aziz et al also reported that gene mutations were identified in 6 of 12 neonates LQTS with 2:1 AV block: 4 patients had mutations in *HERG* and 2 had mutations in *SCN5A*. Three patients had Tdp, among whom 2 had mutations in *SCN5A* and 1 in *HERG*. These reports indicate that LQTS complicated with 2:1 AV block in neonates or children who demonstrate severe clinical symptoms, including Tdp, syncope and cardiac arrest, is closely associated with homozygous gene mutations in *HERG* or *SCN5A*, whereas their parents and family members with heterozygous mutations showed relatively mild phenotypes or nearly normal QT intervals.

In adult cases, QT prolongation and Tdp are frequently seen in patients with either complete or 2:1 AV block, but the conditions are preferentially caused by bradycardia and are supposed to be rarely caused by an association with congenital LQTS. Chevalier et al studied 420 patients with both AV block and pacemaker implantation over a 3-year period. They retrospectively identified 29 patients with complete AV block and QT interval >600 ms. A second study group included 22 randomly selected patients with complete AV block and QT interval <600 ms. A third group consisted of 100 normal individuals without medical history. Genetic screening of *HERG*, *KCNQ1*, *KCNJ1*, *KCNE2* and *SCN5A* was performed. In 5 of the 29 patients with AV block and “seemingly” acquired LQTS, 4 separate heterozygous mutations on genes encoding the K+ channel responsible for Ih and If were identified, in which 3 of 4 gene mutations were *HERG* (R528C, R696C and R1047L) and one was *KCNE2* (R77W). These mutations were not found among patients with AV block and QT interval <600 ms or in healthy individuals. Functional expression of 3 *HERG* mutations showed a dominant negative effect on the wild-type Ih and 1 *KCNE2* mutation did not alter the function of Ih. These findings indicated not only the existence of mutations in *HERG* but also their functional...
effects in congenital LQTS of adult patients with complete AV block complicated by QT prolongation >600 ms.

In this issue of the Journal, Oka et al. investigated the clinical and molecular background of patients with QT prolongation and AV block-induced Tdp. The study population comprised 14 AV block patients (57±21 years, 13 females) who developed QT prolongation (561±76 ms) in the presence of AV block, but shortened to 495±42 ms in the absence of AV block; 3 of the 14 patients had recurrence of Tdp during follow-up because of pacing failure. They underwent genetic screening for KCNQ1, KCNH2 (HERG), SCN5A, KCNE1 and KCNE2. The results revealed 4 heterozygous missense mutations on KCNQ1 and HERG in 4 patients (28.6%). Functional assays using heterologous expression system for 3 HERG (D111V, A490T and P846T) and 1 KCNQ1 (G272V) mutations showed loss of function and various gating dysfunction of Ik or Ik1, but of a relatively mild degree, which may explain why the patients with gene mutations showed delayed onset of their clinical symptoms and no family history of LQTS. Two other patients had a family history of sudden cardiac death and maternal LQTS, respectively. Altogether, 6 of the 14 patients (43%) with AV block and QT prolongation and Tdp might have a possible genetic background to their pathogenesis. Moreover, action potential simulation by a computer model demonstrated that most of the mutant channels induced bradycardia-related early afterdepolarization. The report by Oka et al. highlights the important point that a certain number of patients with “seemingly” acquired forms of LQTS has a genetic background similar to that of congenital LQTS and their functional abnormality could cause development of Tdp in bradycardia-related early afterdepolarization. Furthermore, the study indicated the importance of genetic screening for the clinical understanding of pathogenesis and possible management of such cases.

However, the study by Oka et al. contains several questions to be clarified before the clinical significance in similar clinical settings can be accepted. They did not examine genetic polymorphisms, which are sometimes present in such cases. The study population was relatively small and did not contain a control group for comparison. Moreover, 13 of the 14 cases (93%) were female, which suggests the presence of modifying factors other than genetic background to explain the clinical expression of LQTS, Tdp and AV block. Therefore, it is mandatory to perform a large-scale control study to further understand the pathogenesis of adult onset of LQTS, Tdp and AV block.

References