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Editorial

The compound mutation, a model for acquire long QT syndrome

Congenital long QT syndrome is a relatively rare disease and it has been reported that its incidence is 1:2000 [1]. Mutations that cause long QT syndrome usually alter cardiac repolarization currents and prolong action potential duration. Most of the patients have one mutation but some patients have two or more mutations simultaneously. From the general incidence of long QT syndrome, the theoretical frequency of patients with compound mutations will be 0.05% of the patients, but the real frequency is up to 9% of the probands [2–6]. Although the family members who have one of the mutations often have mild phenotype and relatively benign clinical course, probands who have compound mutations show more severe clinical phenotypes. Previous reports demonstrated that patients with compound mutations had longer QT interval [2,5,6], younger age at onset of the cardiac event [2,5], and were more likely to have cardiac arrest [2,4,6] than patients with a single mutation. Indeed, a patient reported by Ito et al. had markedly long QT interval with bizarre T wave morphology, and experienced aborted cardiac arrest [7].

Cardiac repolarization is regulated by periodical activation and inactivation of cardiac ion channels [8]. Inward currents by sodium (I_{Na}) and calcium ions (I_{Ca}) depolarize myocytes and outward currents by some potassium currents (I_{to}, I_{Kr}, I_{Ks}, and I_{K1}) repolarize myocytes to resting membrane potential. Disruption of the balance of the outward and inward currents prolongs action potential duration and then causes QT interval prolongation. Prolongation of the action potential duration results in calcium overload in the myocytes and inward depolarizing current by calcium ion initiates early after depolarization and triggered activity. Experimental studies have shown compound ion channel dysfunction promotes occurrence of torsades de pointes (TdP). Emori and Antzelevitch initially reported that the combination of the potassium current dysfunction by I_{Kr} (LQT2 model) and I_{Ks} blockers (LQT1 model) reproduced clinical phenotypes of acquired long QT syndrome and this can be applied to compound mutations [9]. After this report, others showed that a combination of blockers of the potassium currents and/or enhancers of the late sodium current in experimental models reproduced clinical phenotypes of compound mutations [10–12]. Although relatively low doses of a single drug alone had mild effects on cardiac repolarization and did not initiate TdP, a combination of these drugs prolonged action potential duration and QT interval, and frequently promoted TdP. Because several ion currents contribute to cardiac repolarization, mild to moderate dysfunction of an ion channel can be clinically latent. A combination of two or more dysfunctional ion channels results in the loss of repolarization reserve [13] and unmasks the prolongation of the repolarization phase.

Although the incidence of compound mutations is more frequent than that of expected theoretically, it is rare to diagnose patients with compound mutations in daily clinical practice. But two or more dysfunctioning ion channels frequently occur in elderly patients with long QT syndrome. Elderly patients have many chances to take drugs for various diseases. Mineral abnormalities, especially hypokalemia, can frequently occur from gastrointestinal, renal, or nutritional disorders. Drugs that prolong QT interval usually block I_{Kr} current and hypokalemia blocks both I_{Kr} and I_{K1}; the combination of these reduces the repolarization reserve. Existence of organic heart disease, heart failure, and bradycardia also alter the ion channel functions and prolong QT interval. In patients with congenital long QT syndrome, young patients often experience syncope or TdP by adrenergic stimulation (such as exercise and loud noise), but adrenergic stimulation as proarrhythmic triggers is less frequent in elderly patients. TdP often occurs by secondary triggers as hypokalemia, bradycardia, and drugs in elderly patients [14]. If patients have a single mutation, acquired triggers add the second ion channel dysfunction and eliminate repolarization reserve, then promote TdP. Compound ion channel dysfunctions can frequently occur in elderly patients with long QT syndrome.

In patients without mutations, compound ion channel dysfunctions can cause acquired long QT syndrome. Predisposing factors for acquired QT prolongation are female gender, age, drugs, mineral abnormalities, organic heart disease, arrhythmias, severe visceral dysfunction, and QT prolongation at baseline. Accumulation of predisposing factors markedly reduces repolarization reserve and increases the incidence of cardiac events [15]. Indeed, patients with syncope/TdP have more multiple predisposing factors at the time of QT prolongation than do asymptomatic patients. Patients with acquired long QT syndrome have complex T wave resembling electrocardiograms in animal models of compound ion channel dysfunction [9,10] and in patients with compound mutations. Compound mutations in patients result in a rare severe form of long QT syndrome, but it will be a clinical model of acquired long QT syndrome or elderly patients with a single mutation and secondary trigger.

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