

CHAPTER 12

Long QT Syndrome

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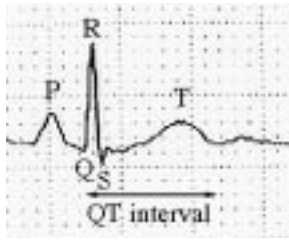
Long QT syndrome is one of the causes of sudden death in adolescents. By sudden death we mean death that occurs out of the blue in a teenager who is apparently healthy. It most frequently occurs during sporting events and is usually attributed to a sudden, unpredictable disturbance in the rhythm of the heart. Sudden death in adolescent athletes is uncommon but always such a shock to their communities that the death of these athletes is well-known and long remembered.

Long QT syndrome is thought to be the cause when sudden death occurs from ventricular fibrillation—a fatal abnormal heart rhythm, or arrhythmia—and no other explanation is found. The syndrome can also become apparent when a young person with fainting or secondary seizures has an ECG as part of their evaluation. It is especially important to look for the syndrome when the fainting or seizures are exercise-related. However, the symptoms can occur during less strenuous activities, upon awakening from sleep, and even when surprised, frightened or angry. Some people discover they have Long QT syndrome when they are being evaluated because a family member has Long QT syndrome. These individuals may have never had fainting or seizures. They are said to have the syndrome because their ECG shows a prolonged QT interval.

Prolongation of the QT interval on the ECG is the major marker for Long QT syndrome. The majority of the QT interval is the time during a single heartbeat when the heart muscle is becoming “recharged” for the next heartbeat. This is called repolarization and follows the phase of heart muscle contraction which actually pumps the blood and is called depolarization. The ECG records the electrical signals from the heart muscle and each wave is labeled as shown.

Measuring the distance from the beginning of the Q-wave to

the end of the T-wave is the QT interval. By knowing the speed the ECG paper is traveling (usually 25 mm/sec) this measurement can be converted to a time interval. If your heart rate is sixty beats per minute (or one beat per second) the normal QT interval should be less than 0.42 seconds—less than half the time between heart beats. Someone is said to have a long QT interval when this time interval is greater than 0.44 seconds.



There are many difficulties with making this measurement. For instance, the interval varies with the heart rate. In addition, the shape of the T-wave varies among individuals making it difficult to decide what to measure. By correcting the interval for the heart rate (the QTc, for QT corrected) a standardized criteria can be applied. However, what has been learned over time is that not all individuals with the Long QT syndrome have a long QT interval. Thus, it has been suggested that the condition should be called “congenital repolarization syndrome” as that seems to be the real mechanism of the arrhythmia leading to sudden death and would eliminate the contradiction in terms.

Since the syndrome was first described in the 1950s it has become obvious that it is congenital (present at birth) and genetic (inherited). The most common form of inheritance is the autosomal dominant form of Long QT syndrome (Romano-Ward form). Families with this form will have many members that have long QT intervals on ECG. This is because each person has a fifty-fifty chance of having the condition in an autosomal dominant inheritance pattern. Individuals in these families will have symptoms of different severity and some family members with long QT interval will have no symptoms. In addition, there will be family members who must have the syndrome based on the inheritance pattern and who have normal QT intervals! One reason genetic studies of these families was undertaken was to find a gene that marked the disease and to make the diagnosis more certain. This strategy would have great benefit if a gene could be found, given the dire

consequences of the condition.

In the past few years there have been important genetic discoveries in Long QT syndrome. These discoveries were made possible in large part by the efforts of Dr. G. Michael Vincent at LDS in Salt Lake City. In the 1970s he became interested in a very large family with a history of sudden death in many members stretching back over generations. This family was descended from two Danish brothers who immigrated to the United States in the nineteenth century. Several members of this family had long QT intervals on their ECGs and Dr. Vincent became convinced they had the autosomal dominant form of Long QT syndrome.

This disorder was first described in the European medical literature and was little known in the United States at the time. By meticulously searching out this and other large families with sudden death and long QT intervals, Dr. Vincent set the stage for the subsequent discovery of the molecular biology of this condition. By gathering these large family pedigrees enough individuals with a gene for Long QT syndrome were available for the difficult DNA mapping required to establish a genetic link with the condition.

Beginning in 1991 families with Long QT syndrome were discovered to have one of three specific genes that accounted for the syndrome. These genes were found on chromosomes 11 (named LQT1), chromosome 7 (LQT2) and chromosome 3 (LQT3) in different families. In 1995, Dr. Vincent's associate, Dr. Mark Keating and his molecular biology group at the Howard Hughes Medical Institute of the University of Utah, discovered that these genes produced proteins that were part of heart muscle ion channels. Ion channels are protein pores in the membranes of muscle and nerve cells that allow the cells to rapidly move ions from one side of the membrane to the other. This ion movement produces the electrical properties of depolarization and repolarization that are crucial for heart muscle cell contraction. The ion channels affected by the genes LQT1, LQT2 and LQT3 are all important in heart muscle cell repolarization. Since the length of the QT interval mostly represents repolarization of the heart as a unit, their discovery fit the theory that problems with heart muscle cell repolarization were the cause of Long QT syndrome.

Thus, the story of Long QT syndrome is becoming clearer as to what really happens to produce the long QT interval (the abnormal

ion channels) and who is at risk for sudden death (family members with the actual gene). The pieces of the puzzle still missing are why some people with the gene will and some will not have severe ventricular arrhythmias and what other genes are involved. Researchers know that there must be more than three genes that can produce Long QT syndrome since a French group has recently mapped another gene (LQT4 on chromosome 4). Some families with Long QT syndrome do not have any of these four genes.

Much of this information became known to our group of physicians while Kara was at Maine Medical Center and eventually she and her family were put in contact with Dr. Keating's lab. But that is getting ahead of the story. As it became apparent that Kara probably had Long QT syndrome it was important to protect her from another event. Her ECG showed normal QTc intervals most of the time, but some intervals were up to 0.50 seconds in length. Thus, she was kept on constant ECG monitoring until the cardiologists came up with an appropriate solution. In the first week we were not sure if Kara would make a meaningful recovery so monitoring alone seemed best. A bigger problem was to be sure the rest of the Anglim family was not at risk.

The Anglims are all athletes. Tom runs miles everyday at lunch. Maryann does aerobics three times a week. Guerin, as a high school senior, was voted "Swimmer of the Year" for 1995 in Maine's Class B and won the state 100-yard backstroke event. None of them had any recent problems, but because of the dominant inheritance pattern of Long QT syndrome they needed to have their ECGs checked. Tom's and Guerin's looked fine, but Maryann's had a 0.49 QTc and a U-wave (see below). These findings were enough to make our cardiologists monitor the three of them with ambulatory ECG recorders. This is a tape recorder-sized ECG machine with miniature chest leads that records heart beats constantly while worn. This test failed to show any arrhythmia in Tom, Guerin or Maryann, and Maryann's further evaluation was put off given all the other problems the Anglims were facing.

