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Long QT Syndrome: How Effective Therapy in a Single Patient Favorably Influenced the Long-term Clinical Course and Genetic Understanding of this Hereditary Disorder

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When one thinks of medical research, the focus is usually on the basic science laboratory where new drug treatments and innovative devices for various medical conditions are developed. Of course, large clinical trials are required to substantiate the medical and scientific value of these new medical therapies. During the past 60 years, we have seen in cardiology the development and effective introduction of new diagnostic and therapeutic techniques in clinical medicine: the external heart defibrillator, artificial heart valves, pacemakers, antihypertensive therapy, drugs like beta-blockers and other medications to reduce heart damage after a heart attack and to treat heart failure, the echocardiogram, coronary bypass graft surgery, minimally invasive procedures to open blocked arteries and to keep them open with stents, and implantable defibrillators to reduce sudden cardiac death (SCD) in high-risk cardiac patients -- to name some of the major advances in the field. Each aspect of this progress required large financial investments and the involvement and collaboration of sizeable groups of basic scientists and clinical investigators, as well as the participation of large numbers of patients in the clinical trials to substantiate the diagnostic or therapeutic validity of the new approaches. We are all better off medically as a result of these developments and this progress.

It is not widely appreciated, however, that practicing clinicians are in a position to utilize their observational abilities, curiosity, and creative ingenuity to introduce logical and effective new therapy for individual patients who have a refractory medical condition for

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which no available treatment exists at the time. Dr. Arthur Moss, one of the authors of this commentary, is a clinical cardiologist who has provided new diagnostic and therapeutic approaches to many individual patients over the years that have improved the lives of these patients, and also the lives of others as a result of the publication of the relevant medical interventions.¹⁻⁴ The current report details how Dr. Moss came to initiate specific antiarrhythmic therapy in 1970 in a patient with the life-threatening form of long QT syndrome (LQTS)⁵ and how he then established an ongoing registry for LQTS patients to better evaluate the long-term follow-up of those affected and treated with the new therapy. The world-wide registry resulted in collaborations involving clinical, genetic, and basic-science investigators who have advanced the understanding and management of patients with this potentially fatal hereditary disorder.

The Clinical Situation

Syncope with brief loss of consciousness and quick recovery may be just a simple faint with no major consequences or implications. However, such spells, especially if they recur, can indicate a serious, underlying medical disorder. An adult white female experienced her first syncopal episode at age 39 in 1968, and she had four additional fainting episodes in the next eighteen months, with most episodes occurring in situations in which she was acutely excited or emotionally stressed. The first fainting spell was considered benign; but following the second syncopal episode, her physician became concerned about the possibility of a seizure disorder, such as epilepsy. The physician prescribed a common anti-epilepsy drug, diphenylhydantoin, but this medication was ineffective in preventing the recurrent spells. The five spells were all very similar in that they came on without any forewarning. She would collapse to the ground, and within a minute or so, would regain full consciousness with individuals hovering over her to see if she had hurt herself. The patient became increasingly concerned that she could be injured directly with a fall or indirectly should an unexpected faint occur while driving her car. Her internist became concerned that her recovery with return of full consciousness quickly after each faint was not consistent with epilepsy, that usually has a delayed recovery of full consciousness with a post-ictal state. After the first syncopal episode, the internist took an ECG looking for an underlying heart rhythm disorder. The ECG showed a regular heart rhythm but with ventricular repolarization of each heart beat having an unusual and abnormal appearance (Fig. 1A). The internist had not seen anything like this ECG pattern in all his years of clinical practice, and in 1970 he referred the patient, age 41, to Dr. Arthur Moss at the University of Rochester Medical Center.

Dr. Moss had never seen a patient with this type of abnormal ECG pattern. However, he did recall seeing a similar pattern in ECG tracings that were shown to him in 1957 by one of the leading cardiologists in Boston, Dr. Samuel Levine. During a social interaction, Dr. Levine shared with Dr. Moss a series of ECGs from a deaf boy who had recurrent fainting episodes that began at age 2 and continued intermittently until he died suddenly during a loss of consciousness spell at age 13. Most of the spells occurred during acute emotional stress. Post-mortem autopsy examination of the boy was unremarkable without evident heart disease. The parents and one older brother were healthy without deafness or fainting episodes. The several ECGs that were recorded on the young boy were most unusual with a

markedly prolonged QT interval. The configuration of this unusual ECG pattern would not be forgotten.

It is interesting that a month or so after the meeting with Dr. Levine in 1957, Jervell and Lange-Nielsen, two physicians from Norway, published the first report of a family with four of ten children who were deaf, with the deaf children having recurrent fainting episodes.⁶ One of the four deaf siblings died suddenly before an ECG was taken, three of the remaining deaf children had ECG-documented QT prolongation, and two of these three deaf children subsequently died suddenly.

A year later in 1958, Drs. Samuel Levine and his colleague, Dr. Clyde Woodworth, reported their single patient with deafness, fainting episodes, QT prolongation, and SCD as a case report.⁷ This medical condition subsequently became known as the long QT syndrome. A few descriptive reports of individuals and of families with QT prolongation, syncope and SCD were published over the next decade in various medical journals. Most of the affected individuals in these reports did not have associated deafness. The pattern of QT prolongation, recurrent syncope, and unexpected SCD in several members of affected families suggested that this condition had a genetic underpinning with variable expression.

When Dr. Moss saw the ECG of the patient with recurrent syncope in 1970, he immediately recalled the ECG shown to him by Dr. Samuel Levine and recognized that the patient's ECG pattern showed QT prolongation diagnostic of the long QT syndrome and that the fainting episodes could be fatal. The patient was admitted to the University of Rochester Medical Center for evaluation and placed on an ECG monitor for observation. Physical exam was normal as were detailed blood tests, brain wave recordings, and an auditory evaluation. A medical history at that time revealed no evidence of passing out spells in her husband, her children, or in her extended family. On the third day of hospitalization, the patient had a syncopal spell when a blood sample was being withdrawn from a vein with localized pain and discomfort at the vein site. The ECG monitor showed two minutes of very rapid polymorphic ventricular tachycardia (VT) at a rate of over 200 beats per minute. This complex VT was responsible for the fainting episode. Such arrhythmias can either terminate spontaneously or deteriorate into fatal ventricular fibrillation with resultant SCD. Fortunately, the patient's VT stopped spontaneously and she quickly recovered from the faint. The patient had the long QT syndrome with recurrent syncope but without deafness, and she was at high risk for SCD. Subsequent ECG recordings on her asymptomatic children and her two grandsons also revealed QT prolongation consistent with the LQTS.

Therapeutic Intervention

The challenge in clinically managing the patient was that there were no drugs or devices available at that time to shorten the QT interval, to inhibit the development of the dangerous and potentially life-threatening VT episodes, or to terminate such heart rhythm disorders with an implantable defibrillator. It occurred to Dr. Moss that since her fainting episodes occurred with excitement or pain, activation of the intrinsic sympathetic nervous system to the heart might be playing a triggering role in initiating the dangerous, rapid heart rhythms. Such activation could stimulate the heart, increase the heart rate, and possibly further

lengthen the prolonged QT interval -- factors that could produce dangerous, rapid heart rhythms in a vulnerable heart.

Dr. Moss consulted a colleague, Dr. Joseph McDonald, Professor and Chief of Neurosurgery at the University of Rochester Medical Center, to determine if there was any way one could surgically remove the sympathetic nerves to the heart. At first, Dr. McDonald said no since the cardiac sympathetic nerves are distributed as a cob-web of fibers all over the heart, and it would not be possible to surgically remove most of sympathetic nerves without injury or trauma to the heart. On second thought, he mentioned that the sympathetic nerves course from the emotional centers of the brain to the heart through a group of ganglia that are located in the neck and upper chest adjacent to the spine. Dr. McDonald recommended local anesthesia block of the left- and right-sided stellate ganglia in the neck with an injection of lidocaine to determine if such temporary treatment would shorten the prolonged QT interval. An anesthesiologist performed the local anesthesia block of the stellate ganglia in the left (Fig. 1B) and right (Fig. 1C) neck, and only stellate block in the left neck shorted the QT interval.⁵ Dr. McDonald said he could surgically remove the ganglia in the neck and upper part of the chest on the left side of the spinal cord, thus removing most of the sympathetic innervation to the dominant left ventricle. He indicated that the surgery would require only a small neck incision, and the limited surgery would be a low-risk procedure.

Since the proposed surgery had never been done for LQTS, the surgical procedure was explained to the patient in detail including the potential risks and benefits. The patient approved of the planned surgery. In the present era, hospital-based Human Investigation Committees exist and they have to approve and monitor such experimental therapies. However, such safety committees did not exist in 1970 when surgical removal of her left-sided cardiac sympathetic ganglia was planned – a procedure that Dr. McDonald estimated would take only one hour to complete under general anesthesia and should not cause any systemic adverse effects.

The surgical procedure, a left-sided cervicothoracic sympathetic ganglionectomy, was successfully carried out without complications, and the prolonged QT interval did indeed shorten (Fig. 1 D). Drs. Moss and McDonald decided to observe the patient for a year during normal activity in her home setting to determine if she would remain free from recurrent fainting episodes. She did not have any recurrent syncopal spells, and it appeared that the surgical ganglionectomy was successful during this follow-up period. Drs. Moss and McDonald realized that if their new beneficial therapy was to be of value to others, it should be published. The details of this therapy, the associated ECGs (Fig. 1) and the favorable one-year result were published in October 1971.⁵

Effective therapy for a life-threatening condition produces a special positive doctor-patient relationship, and this certainly occurred between the patient and her treating physicians. The patient has continued to be followed clinically by Dr. Moss since the beneficial surgery was performed in 1970, and presently she is alive and well at age 85 without recurrent syncope.

LQTS Registry

The results of the medical publication of this individual patient initiated a spectrum of responses that were unexpected. Since no therapy for long QT syndrome had previously existed, a number of patients with this disorder were referred by U.S. physicians to Dr. Moss for management. Of course, there were skeptics who felt a single case report with clinical follow-up of just one year had little or no meaning. On the other hand, the case report stimulated a host of clinicians and investigators from around the world to become more involved in the care of patients with the LQTS once there was available treatment for this condition. There were still many unanswered questions. What was the fundamental cellular mechanism responsible for the LQTS? What was the genetic underpinning of this disorder since most but not all of the affected patients had some first-degree relatives with this condition? Would insight into the LQTS provide mechanistic clues for similar heart rhythm disorders in common conditions such as coronary disease, hypertension, and heart failure?

Currently, the prevalence of the LQTS is estimated at 1 in 2,000 live births, with approximately 4,000 new patients with this disorder in the United States (US) each year. The frequency of this condition is estimated to affect about 50,000 people in the general population of the US. In the early 1970s, there were less than a few hundred subjects identified with this disorder in the US, with only a few physician-cardiologists having one or two families in their practice with this condition.

With publication of the first effective therapy for this disorder reported in 1971, Dr. Moss received an increasing number of consultation requests involving patients with LQTS. The number of referred patients with this cardiac disorder was more than he could manage. To maintain contact with these patients, Dr. Moss established a LQTS Registry in 1974 at the University of Rochester Medical Center with detailed baseline medical information on each referred patient plus affected and unaffected family members with scheduled regular 1-year follow-up contacts, mostly by phone interviews. The main objective of the Registry was to better understand the natural history, clinical course, and efficacy of various therapies over time in patients with QT prolongation as well as having a comparison control group of unaffected family members with normal QT duration.

The oral medication, propranolol, with beta-adrenergic blocking activity was introduced in 1974 for the treatment of patients with myocardial infarction, and this medication had anti-sympathetic effects on the heart similar to the sympathetic ganglionectomy surgery. Dr. Moss and other physicians then utilized oral propranolol therapy in patients with the LQTS, and the preliminary results appeared beneficial. The surgical ganglionectomy was then reserved for patients who were refractory to or intolerant of propranolol or similar beta-blocking medication.

Collaboration

The patient referrals to the Rochester Registry initially came from physicians in the US, but also from a few physicians in Israel and Italy. Over time, the source of the referrals expanded and involved more physicians from around the world. As a result, the Rochester Registry was upgraded to the International LQTS Registry in 1979,⁸ with active

collaboration among the physicians enrolling patients into the Registry. This International Registry initiated a series of clinically relevant investigative LQTS studies while continuing to enhance enrollment of patients into the Registry. Presently, there are over 1,000 LQTS families enrolled in the International Registry involving over 2,500 affected family members.

The first of many medical publications from the International LQTS Registry occurred in 1985 when there were 196 patients with the LQTS enrolled in the study.⁹ Relevant risk factors for transient loss of conscious and SCD were identified. Surgical sympathetic ganglionectomy and beta-blocker therapy were each associated with a significant reduction in life-threatening events during follow-up. This publication significantly advanced clinical interest in the LQTS. A second major publication from the International Registry in 1991 involved over 1,000 patients with longer follow-up -- further highlighting the clinical features, risk factors, and the efficacy of appropriate therapy in this disorder.¹⁰

Genetic Aspects of LQTS

The Human Genome Project began in the late 1980s. A major breakthrough in understanding the LQTS occurred with a seminal genetic linkage study published by Dr. Mark Keating and associates in 1991.¹¹ Working with a large LQTS family from Utah, Keating, et al. compared DNA marker distributions in affected family members having overt QT prolongation and in unaffected family members with normal QT intervals. A DNA marker on chromosome #11 (H-ras-1 locus) was tightly linked to and associated with the prolonged QT interval in affected subjects, but not in normal family members. Dr. Keating concluded that a “mutation at a single genetic locus on the short arm of chromosome 11 predisposes individuals in this family to QT prolongation, ventricular arrhythmias, and sudden death.” This was a very important finding and set the stage for further genetic studies in other LQTS families to identify specific gene mutations responsible for their disorder. In brief, this linkage analysis was a prelude to the identification of disease genes and disease-causing mutations.

During the next 5 years the Keating group moved from linkage analyses to specific identification of disease-causing mutations that helped elucidate the mystery of the LQTS disorder.^{12, 13} To do this, Keating and associates required investigations of well-developed clinical pedigrees of LQTS families involving both affected and unaffected family members. Dr. Keating contacted and collaborated with Dr. Moss, and families from the International LQTS Registry were made available to him for genetic studies. At that time, the Human Investigation Committee had become operational at the University of Rochester Medical Center, and the family studies were approved; the subjects in the chosen families provided informed consent for the blood samples needed for the genetic investigations. Quickly, the Keating group identified 3 different LQTS genes called LQT1, LQT2, and LQT3, with the numerical sequence related to the order of their discovery. Each gene encoded a different ion channel that influenced and regulated the flow of specific potassium or sodium ions across the cell membranes of the heart. It is the movement of these ions and others into and out of the heart muscle cells that regulates the electrical and mechanical activity of each heartbeat. Altered function of the ion-channel as a result of a specific mutation in an ion-channel gene

is responsible for the prolonged QT interval. Thus, the LQTS came to be known as an ion-channelopathy disorder.

Presently, approximately 100 different mutations have been identified in the LQT1 gene, with somewhat fewer mutations identified to date in LQT2, and considerably fewer in LQT3 genotype. Various mutations in one of these 3 genes accounts for about 75 percent of the patients who are seen presently with the LQTS,¹⁴ with LQT3 mutations being the most virulent.¹⁵ The clinical presentation of patients with LQTS also appears to be different by genotype, with LQT1 patients experiencing their events mostly during physical activity, LQT2 patients having an increased frequency of cardiac events triggered by emotional stress and in reaction to sudden loud noises, and LQT3 patients have most of their events during relative inactivity.¹⁶ Since the first three LQTS genes were identified in the mid-1990s, a total of thirteen additional long QT syndrome genes have been reported, and more are anticipated. These genes have been labeled LQT4 thru LQT16, and mutations in these genes account for about 5 percent of the identified patients with the LQTS. In about 20 percent of patients with the clinical LQTS disorder, a gene mutation has not been identified at the present time in genetic testing.

The genetic findings also provided explanation why deafness was associated with only a small proportion of patients affected with the LQTS. The more common form of LQTS occurs without deafness when the child receives only one mutant copy of a gene from one of the parents, a genetic disorder reflecting autosomal dominant inheritance. Deafness is present only when the affected patient receives two mutant LQT1 mutations, one from each parent. The double mutation impairs electrical conduction in the auditory nerves with resultant deafness, and it also is associated with greater prolongation of the QT interval and a more severe form of the LQTS with an increased risk for SCD.¹⁷ This double mutation resulting in deafness involves autosomal recessive inheritance, and it frequently occurs in marriages of blood-related individuals, such as first or second cousins, with each affected parent transmitting one copy of the LQT1 mutation to their child.

The genetic underpinning of the LQTS has revolutionized the clinical understanding of this disorder. It is important to identify LQTS patients who are at high risk of having serious life-threatening heart events so that appropriate preventive therapy can be initiated. In the past, this risk stratification of patients exclusively utilized clinical features such as a history of a prior passing out spell, the duration of QT prolongation on the ECG, and the age of the patient with adolescence being a high-risk period for cardiac arrhythmic events. The risk by gender has been less than clear cut, although some studies showed that post-adolescent females were at higher risk for cardiac events than age-matched males. During the past 10 years, there has been an explosion in the genetic study of patients with the LQTS involving many academic centers throughout the world, with several of the centers actively collaborating with investigators in the International LQTS Registry. Specific genetic mutations associated with LQT1¹⁸ and LQT2¹⁹ have been reported with reduction in 1st cardiac events by 74% and 63%, respectively, with anti-adrenergic therapy involving mostly beta-blockers.

With extensive clinical and genetic information now being accumulated in patients with the LQTS, the efficacy of targeted therapies with beta-blockers,^{20, 21} surgical ganglionectomy,²² and devices such as the implantable defibrillator²³ are being more closely evaluated in patients with this disorder. In addition to the major LQTS genes, it is now appreciated that inherited modifier genes can influence the expression of the major gene effect on the heart, thus explaining variation in the QT interval in family members with the same major gene mutation.²⁴ Preliminary studies suggest that some of the gene mutations associated with the LQTS may also contribute to certain forms of epilepsy. One pharmaceutical company, Gilead Sciences, Inc., is currently developing and testing the effectiveness of targeted, innovative medications that counter the ion-channel dysfunction related to mutations involved in patients with the LQTS.

LQTS Genetics and Related Disorders

The ion-channel dysfunction due to specific LQTS gene mutations is providing new insight into complex rhythm disorders associated with common heart conditions. Remarkable interactions and collaborations involving patients, clinicians, and basic scientists have taken place over the past 45 years since the first effective therapy for LQTS was identified in 1970. The current ongoing world-wide investigations of this syndrome are now advancing the fundamental knowledge and understanding of the electrical activity of the heart, and possibly other excitable tissues and organs in the body.^{25, 26} New potential medical therapies for treatment of a spectrum of disorders related to ion-channel dysfunction appear promising.^{27, 28}

Conclusion

The story of the LQTS involved a chance interaction that took place in 1957 when Dr. Moss was shown a unique series of ECGs with a prolonged QT interval in a young deaf boy whose recurrent syncope culminated in SCD. Who could have predicted that this clinical experience would lead to innovative and effective new therapy for a patient with the LQTS several years later and the subsequent formation of the International LQTS Registry, which has stimulated interactions among and between patients and physicians and has enhanced collaborations involving clinical, genetic, and basic-science investigators? The net result has been a significant improvement in the diagnosis, treatment, and outcome of patients with the LQTS and an overall advancement in the science of medicine – two of the many satisfactions that physicians can experience in the clinical practice of medicine.

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Abbreviations

LQTS	Long QT syndrome
SCD	Sudden cardiac death

US	United States
VT	Ventricular tachycardia

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Figure 1.

Electrocardiograms, Lead 2, of first patient treated with left cervicothoracic sympathetic ganglionectomy surgery for long QT syndrome.⁵

In A, taken on October 18, 1968, one day after the patient's first syncopal episode, the QT interval is 0.64 second. In B (April 20, 1970), 83 minutes after local left stellate-ganglion block, the QT interval is 0.46 second. In C (April 29, 1970), 40 minutes after local right stellate ganglion block, the QT interval is 0.72 second. In D (November 5, 1970), six months after left cervicothoracic sympathetic ganglionectomy, the QT interval is 0.44 second. From:

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