

## 25th Anniversary of the International Long-QT Syndrome Registry : An Ongoing Quest to Uncover the Secrets of Long-QT Syndrome

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## 25th Anniversary of the International Long-QT Syndrome Registry

### An Ongoing Quest to Uncover the Secrets of Long-QT Syndrome

Arthur J. Moss, MD; Peter J. Schwartz, MD

Today, it is exceptional to find a major cardiology congress without a session devoted to the long-QT syndrome (LQTS), but it was quite different 25 years ago when the minuscule knowledge about LQTS was paralleled only by the minute number of investigators interested in what seemed to be little more than a medical oddity. Partly by chance, the two of us had actually and independently developed a rather burning interest and curiosity for this often lethal hereditary disorder that is spiced by several unique features.<sup>1-4</sup> We joined forces with the goal of unraveling this mysterious disease by establishing a prospective International Registry for LQTS. The main objectives were those to gain insight into the natural history, clinical course, and efficacy of current and novel therapies. When molecular biology techniques matured to the point of making possible the identification of disease-causing genes and disease-causing mutations, what became essential was the availability of numerous and well-developed clinical pedigrees providing clear separation between “affected” and “nonaffected” individuals. This is what the Registry was able to provide and where it played a decisive role in sharing with molecular biologists the ideal material for their analysis.

In 1979, when the Registry was established, it did not escape us that this long-term project was likely to contribute to a better understanding and management of LQTS. Quite frankly, however, we did not anticipate the explosion of knowledge that would result from the genetic and molecular findings of the 1990s and the central role that the Registry, with its well-defined clinical phenotypes and family pedigrees, would play in uncovering the secrets of this disorder. Additionally, we could not have fathomed the now clear evidence that LQTS indeed represents a paradigm for the understanding of sudden cardiac death in more common cardiac diseases.

#### Objectives

Our primary objective with the International LQTS Registry was to gain insight into the natural history and clinical course of this hereditary repolarization disorder so that more effective

therapy could be rendered to prevent the syncope and sudden death events that frequently accompanied LQTS.

#### Impact

The International LQTS Registry has enhanced our knowledge base of an infrequently occurring cardiac disorder, and it has become a paradigm for studying such conditions. The diagnostic criteria for LQTS have been established.<sup>5</sup> The cardiologists associated with the Registry continue to offer physicians from around the world an opportunity to obtain advice on how to manage their LQTS patients. This exchange between the Registry cardiologists and physicians became a mutually beneficial interaction because these physicians also contributed clinical data to the Registry by willingly completing enrollment and yearly follow-up data forms. This approach allowed us to gather information on an impressive number of patients and, of crucial importance for the subsequent genetic developments, on first- and second-degree family relatives. Over the years, the growing knowledge in LQTS was shared with the profession through scientific publications, chapters in cardiology textbooks, personal communications, and recently, an Internet-based virtual LQTS symposium (<http://lqts-symposium.org>).

Subsequently, similar types of registries were established by interested investigators for other uncommon cardiac disorders, including hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and Brugada syndrome. It is gratifying to know that the International LQTS Registry helped to pave the way for scientific progress in the difficult field of uncommon diseases.

#### Molecular Genetics

By the early 1990s, molecular biology had made impressive progress. The new genetic techniques, especially linkage analysis and detection of DNA sequence differences, were offering a realistic potential for the identification of disease genes and disease-causing mutations. There was only one limiting step, and not a small one. These techniques, as powerful as they were, still depended for their success on the availability of well-developed clinical pedigrees. Carefully

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studied large family trees with clear separation between affected and nonaffected individuals were essential. This is where the Registry, with its many large families and myriad of small families together with a quantitative QTc diagnostic marker and well-defined clinical phenotypes, played a decisive role in offering molecular biologists ideal material on which to perform their analyses.

It was on this background that Keating and associates made their fundamental discoveries.<sup>6–10</sup> It seems fair to say that in modern cardiology, few findings have had such fruitful consequences as the identification of the first 3 LQTS genes (*KvLQT1* [LQT1], *hERG* [LQT2], and *SCN5A* [LQT3]). Merit is often not disjointed from good luck. The first series of genes identified with LQTS were all encoding cardiac ion channels, and it is fortunate that techniques already existed that allowed for functional evaluation of the mutant genes by cellular expression studies. These studies provided the evidence on how a specific mutation, by altering cardiac electrophysiology and the balance between inward and outward currents, was affecting the cardiac action potential, thus explaining how these mutations result in the lengthening of ventricular repolarization coded as QT prolongation.

### LQTS and Drug-Induced QT Prolongation

In 1982,<sup>11</sup> we highlighted the role of drug-induced QT prolongation in delayed ventricular repolarization disorders. We pointed out that flagrant QT prolongation and syncope can occur at ordinary therapeutic doses of quinidine and raised the possibility that “quinidine therapy may exacerbate an underlying repolarization abnormality, possibly a subclinical forme fruste of idiopathic LQTS with incomplete expression.”

Concurrent with the advance in the molecular genetics of LQTS and the realization that reduction in the  $I_{Kr}$  current involving mutations in the *hERG* gene was responsible for LQT2, drug-induced QT prolongation involving terfenadine, cisapride, and other medications surfaced with documented torsade de pointes and sudden death. The similarity of acquired drug-induced prolongation of ventricular repolarization with the LQT2 form of LQTS was appreciated. The information acquired from the Registry about the cellular and molecular mechanisms involved in ion channel currents contributed to our enhanced understanding of drug-induced repolarization disorders.

### Findings From the Registry

The Registry, with its expanding number of genotyped families, has provided an opportunity to study the clinical aspects and explore the genotype-phenotype relationships in this unique cardiovascular disorder. The first publication of findings from the Registry occurred in 1985 when we highlighted the risk factors for cardiac events in 196 LQTS patients.<sup>12</sup> By 1991, we expanded the prospective study of the clinical course of this disorder to 1016 affected individuals in 328 LQTS families.<sup>13</sup> Important findings from the Registry during the past decade have included the following: age- and sex-related differences in the clinical manifestations of LQTS<sup>14</sup>; influence of pregnancy on the risk for cardiac events in LQTS<sup>15</sup>; ECG T-wave patterns in genetically distinct

forms of LQTS<sup>16</sup>; clinical course of LQTS by genotype<sup>17</sup>; the spectrum of mutations in LQTS genes<sup>18</sup>; increased risk associated with mutations in the pore region of the *hERG* gene<sup>19</sup>; role played by physical exercise, emotions, arousal, and rest/sleep as triggers and facilitators for syncope and sudden cardiac death in LQT1, LQT2, and LQT3<sup>20–22</sup>; effectiveness of  $\beta$ -blocker therapy, particularly in patients with LQT1 and LQT2 genotypes<sup>23</sup>; potential gene-specific usefulness of sodium channel blockers (mexiletine and flecainide) in the treatment of patients with the LQT3 mutations<sup>24,25</sup>; life-saving benefit from the implanted defibrillator in high-risk LQTS patients<sup>26</sup>; and left cardiac sympathetic denervation in the management of high-risk LQTS patients.<sup>27</sup>

We initially thought that the clinical benefit of left-sided sympathectomy might have come from either a correction of a hypothesized left-sided dominance of sympathetic innervation or, in the case of a yet undefined “myocardial abnormality” (subsequently found to be represented by the mutations in cardiac ion channel genes), from removal of an arrhythmogenic trigger. Our current view is that the second hypothesis was correct and that the benefit of left cardiac sympathetic denervation reflects primarily the interruption of the major source of norepinephrine release at the ventricular level.

Key to the success of the International LQTS Registry was our good fortune to have an outstanding group of committed multidisciplinary investigators who have been associated with the program through several decades.

### Limitations

All registries have limitations. From the beginning we pre-specified the data to be collected, but the initial data collection reflected our limited understanding of the disorder. As we gained more insight into LQTS and its clinical and genetic heterogeneity, we expanded the type and extent of collected data, especially during yearly follow-ups. Our experience with sophisticated data management grew as the Registry expanded. Early on we recognized the need for biostatistical and statistical-genetic expertise. Although we collected prospective data and based our primary analyses on prespecified hypotheses, several of our important secondary studies involved retrospective analyses with the need to control for relevant covariates. The Registry utilized observational data, with all the potential problems of bias. Because the time origin was usually birth when doing clinical course studies, we appreciated the need for proportional-hazard survivorship analyses using time-dependent end points for syncope, aborted cardiac arrest, and death. Randomized placebo-controlled clinical trials are not practical when dealing with a rare cardiac disorder with relatively infrequent cardiac events, and therefore we learned to control for various types of bias as best we could through statistical adjustment techniques when evaluating the safety and efficacy of  $\beta$ -blocker, left cardiac sympathetic denervation, and implanted defibrillator therapies.

### Challenges for the Future

Additional new genes and new genetic mechanisms need to be uncovered, modifier genes that explain the variable ven-

tricular repolarization duration and/or the variable severity of clinical manifestations in individuals with the same mutation have yet to be identified, gene-specific and mutation-specific therapy is presently in its infancy, and the brain-heart connection with regard to emotional triggers of cardiac events needs more neurophysiologically based investigations. Our quest for uncovering the secrets of LQTS continues.

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