

EDITORIAL COMMENT

# Evolution in Managing Long QT Syndrome

## From Registries to Centers of Excellence\*



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Forty years ago, the number of patients diagnosed as affected by long QT syndrome (LQTS) was very small (1), and even the best cardiology centers had seen only a handful of them. Almost nothing was known about the natural history and the response to therapy. As evidence, we may recall that Dirk Durrer (a pioneer of cardiac electrophysiology) wrote to Conor Ward (of the Romano-Ward syndrome) “I am pessimistic about the possibility to control the syndrome in any way,” and that in the early 1970s, one of the initially favored therapies was digitalis (1). Therefore, the only way to understand these aspects, critical for any “newly discovered” disease, was to establish an International Registry (2-4).

Besides paving the way to the genetic discoveries (4), the fruits of the LQTS registry were truly significant. They showed, for instance, that the risk for major cardiac events (syncope, cardiac arrest, and sudden death) is higher when the QT interval is longer, when a syncope has already occurred, and among women especially after puberty, and that  $\beta$ -blocker therapy is very effective (5,6). The registry was the only way to make progress at a time when the diagnosed cases were so few, but it contained the germ of a problem. Moss in the United States and Schwartz in Europe, but covering also Asia and Africa, were sending out forms to the many physicians who had either published 1 or a few cases or had inquired

for advice; the completed forms were returned to Rochester, were the source for analysis, and were regularly updated. Over the years, the system was significantly refined, but the critical limitation (i.e., the fact that the specific drugs used and their dosages represented the nonuniform approach by so many individual doctors) unavoidably remained. Indeed, a major limitation common to all registries is that the critical and in-depth analysis of the events surrounding a breakthrough event, including a sudden death, is not always possible or complete, because it is hampered by the distance between those who analyze the data and the doctor(s) responsible for managing the patient at the time of the event.

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In this issue of the *Journal*, Rohatgi et al. (7) from Mayo Clinic present their experience as a leading center for LQTS in the United States. This retrospective study covers the period from 1999 to 2015 and provides uniquely useful information on 606 LQTS patients, 98% of whom were genotype positive. Their report contains a substantial number of data, all meaningful, but some of which seem worthy of specific mention because of the effect that they should have, in our opinion, on medical management.

Genetic testing in this large cohort confirmed, with striking precision, the first report indicating that 5% of LQTS are carriers of multiple LQTS-associated mutations (8), and that this group has a higher arrhythmic risk. This concept has been largely underestimated, and it is common practice almost everywhere to screen family members just for the disease-causing mutation found in the proband. In 2003, we had pointed out that this practice, albeit cost-saving and very reasonable, may favor

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an important error (8). We quote here what we wrote then:

*Molecular screening and clinical management should be affected by the realization that within LQTS families some individuals may carry more than a single mutation. When facing family members with different clinical manifestations, to ignore the possibility of an additional mutation might lead to inadequate therapy or to the failure to identify family members who are genotype-negative for the first mutation but who are carriers of a second LQTS mutation. This, in turn, would lead to a misdiagnosis of “unaffected by LQTS” with dangerous implications (8).*

We stand by what we wrote in 2003, and at our center in Milan, it is our policy to always consider these possibilities. The confirmation by Rohatgi et al. (7) that a second mutation should be expected in 1 out of 20 LQTS families should become part of the clinical approach.

During the last few years, especially at meetings, the possibility has been voiced that men, especially LQT3 patients, might be less protected by  $\beta$ -blockers than women. The present study dismisses that possibility by stating clearly that there were no differences between men (4%) and women (2%) in breakthrough events, not even when subdividing the 3 main genotypes.

Finally, Rohatgi et al. (7) confirm a very important concept that has progressively been accepted but that, when not accounted for, can still lead to misguided conclusions in the interpretation of therapeutic results. We refer to the extremely high clinical severity associated with a cardiac event in the first year of life, to which we had first called attention in 2009 (9) and which was rapidly confirmed by the International Registry (10). It had indeed been the high incidence in early deaths among LQT3 infants that, given also the small number of LQT3 patients, had led to the guideline-supported (11) but ill-advised recommendation to consider implantable cardioverter-defibrillator implants even in primary prevention for LQT2 and LQT3 patients. This in turn had led to the dreadful consequence that the majority of LQT3 patients who received an implantable cardioverter-defibrillator were asymptomatic, as we have shown (12), and would have had a much better quality of life if they had been more simply treated with  $\beta$ -blockers (9,13). The data from the Mayo Clinic Center are unequivocal. Among their symptomatic patients, 27 (16%)

experienced their sentinel event during the first year of life; when compared with those who became symptomatic after the first year of life (139; 84%), they had much worse outcomes with a higher risk for recurrences despite treatment (67% vs. 17%;  $p < 0.0001$ ). Moreover, 4 of the 5 children with the worst outcomes (3 cardiac transplants and 2 sudden deaths) had their initial event during the first year of life! The take-home message, when coupled with our earlier reports (8,9), could not be clearer: *when assessing the efficacy of any therapy, do not include patients with events in the first year of life.*

The group working at the Mayo Clinic under the guidance of Mike Ackerman deserves to be congratulated for this important contribution. Indeed, the experience at our own center, where for 40 years we have been seeing 3 to 4 LQTS families every day, is very similar, and we concur with almost all of their findings. Nowadays, when the number of LQTS patients has increased beyond expectation, the most useful messages for clinical management come from the largest referral centers where clinical investigators with long-standing personal experience can analyze the effect of a uniform approach, both in terms of drugs and of interventions. We wish to stress the significant implication of their mortality data: 3 per 1,000 individuals. This means that, when treated well and by experts, LQTS should no longer be considered a disease with a high risk for sudden death. Once again, our experience is similar. This important result does not come by chance; in our opinion, besides the greater accuracy in risk stratification provided by genetic analysis, an important role is played by a very experienced team with a uniform approach, and especially by the fact that 80% of the Mayo patients return every 1 to 2 years and that 95% of our patients return every year (even after 40 years) for a complete visit and assessment. This is what allows both us and the Mayo group to identify early on changes in arrhythmic risk and tailor the therapy to the evolving needs of the individual patient.

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