The advent of genetic testing and the implantable cardioverter-defibrillator (ICD) have so revolutionized the outlook for patients with long QT that the cardiac community needs to revise its thinking about long QT syndrome (LQTS). This is the underlying message of a report by Etheridge et al. (1) in this issue of the Journal.

Etheridge et al. (1) studied 128 children with LQTS. About one-half of their patients were probands (47%) and the rest (53%) were identified during screening in relatives of probands. A significant aspect of their report is the number of nonprobands, a rather unique and underreported group. After acknowledging the caveats of any clinical retrospective study, their conclusions are that certain types of probands need to revise its thinking about long QT syndrome (LQTS). This is the underlying message of a report by Etheridge et al. (1) in this issue of the Journal.

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As with other studies, they show that KCNQ1 is the most common mutation responsible for LQTS. Of the 51 patients successfully genotyped, KCNQ1 mutations were seen in 30 and no one with an isolated KCNQ1 mutation received an ICD. Despite this (and probably because 98% of the total population was on beta-blockers, there was no death in any patient with a known KCNQ1 mutation treated with beta-blockers. The only death in the KCNQ1 group was in a patient who presented with sudden death and was found to have the mutation posthumously. Villain et al. (2) previously reported 122 patients with long QT. They also had no deaths in KCNQ1 mutation patients on beta-blockers and no deaths in patients diagnosed because of their family history.

In the study by Etheridge et al. (1), patients with KCNH2 and SCN5A forms of LQTS did receive ICDs, and many of those with the former had appropriate shocks. The only other death in their cohort was an infant whose genetic subtype was not known.

This study raises a number of interesting issues, mainly related to perception of risk in LQTS and to the indications for an ICD in the current era. Along with previous articles, theirs emphasizes the differences between the 3 most common forms of LQTS. Discounting 1 patient with a compound mutation (KCNQ1 and SCN5A), all ICDs were placed either for KCNH2 or SCN5A mutation patients. Despite this, there were no deaths in the KCNQ1 group. This finding supports the previous reports of Villain et al. (2) and Priori et al. (3,4), who showed that KCNQ1 patients have a lower rate of cardiac events both before and after initiation of beta-blocker therapy compared with KCNH2 and SCN5A.

There are significant disadvantages to having an ICD in childhood, including implantation difficulties secondary to the relatively large size of leads and generator, a greater length of time for which ICD protection is needed (with consequent lead problems with the need for multiple surgeries and lead revisions), a greater incidence of inappropriate shocks, and potentially greater psychological problems from having an ICD (5–8).

Current ICD implantation guidelines justify the use of ICDs in a large number of patients with LQTS. One of the class I indications is “cardiac arrest due to ventricular tachycardia or ventricular fibrillation not due to a transient or reversible cause.” Another is “spontaneous sustained ventricular tachycardia in patients without structural heart disease not amenable to other treatments.” One of the class IIb indications is “familial or inherited conditions with a high risk for life-threatening ventricular tachyarrhythmias such as LQTS” (9).

What are the deficiencies of the report by Etheridge et al. (1)? First, their cohort, although large for a pediatric study, is small. Only 30 genotyped KCNQ1 patients are reported. Their mean follow-up is <5 years. It is unclear what was the mean QT in the KCNQ1 patients and how many of them had an excessively prolonged QT (a QTc >500 has been shown to be associated with higher risk). One possible extrapolation of the study by Etheridge et al. (1) is that our indications for ICD placement in KCNQ1 patients need to be more stringent. However, their study does not answer the question of what to do with a patient presenting with cardiac arrest. Should an ICD be placed while awaiting genetic test results, or should one prescribe beta-blockers and wait for the test result in the hope that the patient has a KCNQ1 mutation and will therefore be unlikely to need an ICD?

Of 128 patients, a positive genetic diagnosis was available in only 51 (40%). Because the genotype has such a significant impact on prognosis and management, genetic testing for LQTS needs to be more widely performed. There is currently only one company (Familion, PGxHealth, New Haven, Connecticut) performing this test, and the cost of the test is not covered by many insurance companies. If a positive diagnosis of KCNQ1 mutation makes it likely that a patient may not need an ICD, this could be an important
inducement for insurance companies to pay for the genetic test because the cost could be offset by savings from not using an ICD.

In KCNQ1 patients, regardless of symptom severity at presentation, it may be preferable to initiate beta-blockers and reserve ICD use for those who have a risk of sudden death despite beta-blockade, those who are intolerant of beta-blockade, or those who have other contraindications to their use. Intrinsic to this is the problem of defining the adequacy of beta-blockade. Exercise tests and epinephrine challenge testing may help determine the adequacy of beta-blockade (10). Compliance also may be a significant factor in young people, particularly in infants who require frequent dosing (3 to 4 times daily) and in teenagers. For teens in particular, it is hard to remember to take a medication that may make you feel bad for a condition that does not. These aspects call for intensive monitoring with frequent outpatient visits, dosage adjustments, and counseling to maximize the efficacy of drug therapy.

It is possible that patients diagnosed incidentally as part of a family screening effort may have less risk than probands as noted by Villain et al. (2). Etheridge et al. (1) found no difference in need for ICD implantation based on the patient’s presentation despite the fact that probands had a significantly longer QTc compared with nonprobands. More studies are needed to assess this question.

Despite the good news regarding KCNQ1 patients from this study, we need to be cautious in our recommendations. This study, after all, is a small one, and it will be wise to use caution in extrapolating this to the entire population of KCNQ1 patients. Other previously described indicators of high risk, including symptoms despite beta-blockade and an excessively prolonged QTc (>500 ms), may be reasons to implant ICDs despite a positive genetic diagnosis of KCNQ1 mutation.

The biggest message of this report may be that long QT is no longer a single disease. Although known for some time, the differences in prognosis and management between KCNQ1 mutation and KCNH2 and SCN5A mutations are so significant that management without knowing the genotype may amount to working in the dark.

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