Addressing the diagnostic and therapeutic challenges in inheritable arrhythmia syndromes: with emphasis on the pediatric population
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Inheritable arrhythmia syndromes are a highly heterogeneous group of diseases, contributing significantly to sudden cardiac death in young individuals with structurally normal hearts. The accurate diagnosis of these conditions is challenged not only by the disease characteristics such as variable penetrance and expressivity, but also by the relative paucity of literature on some of the rarer disease groups. Advances in molecular cardiology in the past 2-3 decades have undoubtedly revolutionized the process of confirming a clinical diagnosis; however, it has to be recognized that genetic testing is a “rapidly evolving tool”, requiring prudent application and cautious interpretation. Moreover, the utilisation of the test is restricted by time and cost considerations, as well as limited availability; hence, the clinical assessment of patients has to be precise with an aim to optimize the use of available resources and to ensure a high diagnostic yield.

Once diagnosed, the intensity of treatment in affected individuals is almost always directly related to the severity of manifestations. Therapeutic dilemmas particularly arise when confronted with the extreme forms of the disease, namely, the severe forms which tend to be therapy-resistant, and the asymptomatic seemingly-healthy cases. Polytherapy, combining pharmacological and device therapies, is usually required in the former, while regular evaluations and/or a single drug would suffice for the latter group. Other criteria in determining the therapeutic strategies are the aim of treatment (primary prophylaxis versus secondary prevention of arrhythmias), age of the patient at diagnosis (infancy and early childhood versus adults), and family history (positive for sudden cardiac death in the young versus negative history). Having said this, it also has to be highlighted that the concept of personalized management is currently in vogue, whereby treatment is being tailored to suit individual patients rather than groups of diseases. The studies in this thesis were performed with an aim to address these critical hurdles in the effective management of patients with congenital long QT syndrome (LQTS) and loss-of-function sodium channelopathies.

Chapter 1 gives a general introduction to inheritable arrhythmia syndromes with a special focus on the current state-of-affairs in the management of LQTS and loss-of-function sodium channelopathies. The genotype-phenotype correlations, the diagnostic modalities, the risk stratification strategies and the treatment options currently available, are discussed in this chapter. Following the general introduction and outline of the thesis, chapters 2-5 address the diagnostic and therapeutic aspects of LQTS, and chapters 6-8 deal with current management issues in children with loss-of-function sodium channelopathies.

Part 1: Congenital Long QT Syndrome

Chapters 2-4 are a series of studies addressing the issue of how best to predict the presence of LQTS in a patient, with the current clinical diagnostic tools. At the basis of these studies is the need to cleverly and clearly identify those patients that are most likely to benefit from genetic testing, particularly, probands presenting with atypical
features, and asymptomatic relatives of mutation carriers. In the future, we hope to apply the findings of these studies not only in diagnosis but also in risk stratification of affected patients.

In Chapter 2, we performed a prospective study on 41 children with clinical suspicion of LQTS to evaluate the role of the epinephrine challenge test in predicting mutation carriership. Although the test was safely performed in children, epinephrine test positivity had a poor correlation with genotyping in this cohort, despite its proven ability to predict LQTS and to discriminate LQTS types 1, 2 and 3 in adults. The response to epinephrine however enabled better therapeutic decisions in many of the cases in this study, especially in those with a negative test result.

Chapter 3 describes the derivation and validation of a simple exercise-based algorithm for identifying LQTS. In this study, differential QT response during exercise was exploited to predict LQTS carriers among 69 first-degree relatives of probands with an established diagnosis of LQTS. A simple 3-step screening algorithm was derived based on resting corrected QT interval, 4-minute recovery corrected QT interval, and 1-minute recovery corrected QT interval. Among patients with a nondiagnostic resting QTc, 4-minute recovery QTc ≥445 ms was a good predictor of disease, while a prolonged 1-minute recovery QTc was common in the LQT1 subtype. Subsequent external validation in an independent cohort of 152 patients demonstrated a high degree of accuracy for predicting LQTS carriers, and a moderate degree of accuracy for predicting LQTS subtype compared with genetic testing as a gold standard. This screening algorithm has potential application as an interim test while formal genetic results are awaited or as a diagnostic test in centers where genetic testing is unavailable. Together with the established diagnostic criteria for LQTS, exercise test definitely has a role in increasing the yield of genetic testing.5

In clinical practice, physicians often see patients referred for suspected LQTS but with borderline or near-normal QTc. Whether or not to subject such cases to genetic testing is a difficult call, particularly in centers with no/limited access to a laboratory capable of performing the test. While Holter monitoring is frequently employed in the clinical evaluation of LQTS patients, the role of maximum Holter QTc in predicting mutation carriership has not been evaluated before. As described in Chapter 4, we analyzed the maximum Holter QTc of 111 unrelated probands referred for LQTS genetic testing, and found that among patients with low to intermediate Schwartz score and normal range resting QTc, all those with Holter QTc ≤450 ms were genotype-negative; i.e. normal Holter QTc is 100% effective in ruling-out mutation carriership in patients with nondiagnostic resting QTc. Though the study was limited by a relatively small patient cohort, the findings are significant and appear to have a role in situations where genetic testing is restricted in availability and/or feasibility.

Although β-blockers clearly dominate the scenario of treatment in LQTS, it became obvious that a significant proportion of cases had breakthrough cardiac events under therapy. In an attempt to strike at the root of the myth that all β-blockers are equally efficacious in arrhythmia-protection in LQTS, we designed the multicenter
study described in Chapter 5. On comparing 382 LQT1/LQT2 patients treated with propranolol, metoprolol and nadolol, we discovered that due to a combination of QTc-reducing and late-sodium channel blocking properties, propranolol and nadolol were much more effective in preventing breakthrough cardiac events in previously symptomatic patients. As the risk of suffering symptom recurrence was four times higher with metoprolol than with propranolol and nadolol, we propose that metoprolol is best avoided in symptomatic LQT1 and LQT2 patients.

In summary, the key messages in the management of LQTS are:

- In the diagnosis of LQTS, the yield of genetic testing can be substantially increased by corroborating the findings of family history, symptom history and resting ECG with QTc derived from exercise test and Holter recording. The role of the epinephrine test in diagnosing LQTS in the pediatric population is limited; however, a negative test enables the confident decision to withhold therapy in the atypical cases.

- In the treatment of symptomatic LQTS patients, propranolol and nadolol are preferred over metoprolol due to their efficacy in preventing breakthrough cardiac events and thereby sudden cardiac death.

Part 2: Loss-of-Function Sodium Channelopathies

A decade ago, loss-of-function sodium channelopathies, failed to even feature in the differential diagnoses of sudden cardiac arrest in previously healthy children. It was the study by Probst et al. that attracted widespread interest in the occurrence of these diseases in young children. In Chapter 6, we report a unique case of a 4-month old girl with aborted cardiac arrest and recurrent ventricular arrhythmias, in relation to fever and vaccination. The diagnosis of an SCN5A mutation, in the patient, her sibling, and their father, and the subsequent treatment strategies employed, are described in detail in this chapter. The tachycardia-related ventricular arrhythmias in the infant precluded the use of implantable cardioverter defibrillator; however, β-blocker therapy in high dosage, together with fever-controlling measures, has provided adequate protection from severe ventricular arrhythmias in the siblings.

Consecutively, we embarked on a multicenter study to look into the diagnostic and therapeutic aspects of the entire spectrum of loss-of-function sodium channelopathies in children. In the study described in Chapter 7, there were 33 pediatric cases of loss-of-function sodium channelopathies. Interestingly, life-threatening arrhythmias and sudden cardiac death occurred predominantly during infancy in this cohort; and prolonged conduction intervals were seen frequently on the ECG of these children, in comparison to the much rarer Brugada ECG pattern. Upon diagnosis, general and/or specific treatment measures were being effectively used in arrhythmia-prevention in these patients. Aggressive antipyretics and ECG monitoring during fever episodes and during and after vaccinations, avoidance of potentially harmful drugs, antiarrhythmic medication such as β-blockers, and implantable cardioverter defibrillators, were the common therapeutic strategies employed.
Studying this unique patient series has provided the following significant insights:

- The spectrum of loss-of-function sodium channelopathies may manifest even in infants and very young children, and severe symptoms are not uncommon in this age group.
- Genotyping has a role in risk stratification, with truncation mutations, severe missense mutations, and compound mutations implying a higher risk.
- Fever management plays a significant role in managing affected patients; apart from aggressive antipyretic use, infants and children have to be monitored for rhythm disturbances during fever episodes and during and after vaccinations.
- Pharmacological therapy, either alone or in combination with device therapy, is effective in prevention of sudden cardiac death in the majority of cases.

Idiopathic ventricular fibrillation is a diagnosis of exclusion, and is rarely reported in infants. Recently, idiopathic ventricular fibrillation has been identified to be associated with previously undetected channelopathies and with early repolarization syndrome. In Chapter 8, we report the occurrence of sudden cardiac arrest in two infants, both of whom did not show any evidence of an underlying cause for the arrest, during a thorough cardiac and extracardiac evaluation. Both patients went on to receive an implantable cardioverter defibrillator for secondary prevention and were clinically stable. In fact, one of the children developed dilated cardiomyopathy at the age of 19 months, 10 months after the initial event. Thus, careful and frequent monitoring proved very useful in these unique cases.

### Future Directions

The adage “bench to bedside” seems to be perfectly exemplified by the inheritable arrhythmia syndromes, with research into basic sciences such as molecular biology and cellular functional studies, feeding and guiding day-to-day patient management. This trend has to be protected and preserved, and this delicate balance maintained, while encouraging and expanding the scope of scientific collaboration. Although genetic testing has become the cornerstone in diagnosing affected patients, continuous attempts are being made to refine the existing clinical diagnostic tools and to design newer techniques, in order to be able to strengthen and support the process of diagnosis. Understanding the diversity in these diseases and identifying the disease modifiers are the prime targets of research groups; the variability in patient/disease response to treatment forms another major area of future research. Studies are especially warranted on the aspect of loss-of-function sodium channelopathies as potential causes of fever (and vaccination) related arrhythmias and sudden deaths in previously undiagnosed infants and young children.
Conclusions

This thesis has addressed some of the most pressing issues and challenges in the management of congenital long QT syndrome and loss-of-function sodium channelopathies, with a special focus on the pediatric population. With inheritable arrhythmia syndromes emerging as an important piece in the puzzle of sudden unexplained death, the findings of the studies described here have relevant implications in different spheres of clinical practice, namely improved awareness, accurate diagnosis and effective treatment.

References