Characteristics of Long QT Syndrome Probands who had Aborted Cardiac Arrest Prior to Diagnosis

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Introduction

The prevalence of congenital Long QT Syndrome (LQTS) is estimated to be 1 in 2,000 in Caucasians[1]. This corresponds to 3,328 individuals on the island of Ireland[2,3]. The Sudden Cardiac Death (SCD) rate in LQTS patients on treatment has decreased from 1.3%/yr in 1985 to 0.05%/yr in 2017[4]. Adrenergic blockade, QT-prolonging drug avoidance and defibrillation of secondary malignant arrhythmia are key contributors to this reduction. LQTS has been found to be the primary cause in 21% of resuscitated sudden cardiac arrests in Cardiac Inherited Disease and is the leading cause of such[5].

Methods

This retrospective study was undertaken to profile cases of aborted cardiac arrest (ACA) in LQTS probands attending the Family Heart Screening Clinic (FHSC). Information has been gathered at the clinic between February 2007 and June 2020. In the FHSC proband database there are 212 LQTS probands who, by family screening, have revealed a total of 656 LQTS patients. 27 LQTS probands presented with an aborted cardiac arrest.

This group of 27 was selected by inclusion of individuals who had a primary presentation of arrhythmia and cardiac arrest with prolonged QTc detected and subsequent LQTS diagnosis. Four cases were excluded as, on review of documentation surrounding the presentation and further follow-up, the QTc prolongation was deemed to have been more likely to have occurred secondary to another cause of arrest. The primary causes of arrest and QTc prolongation in one of these four probands was pulmonary embolism, in another it was acute decompensation of Aortic Regurgitation. In the third of these four the arrest was bradycardic, and in a fourth the QTc was prolonged due to LBBB and the arrest was deemed to not have been caused by this QT-prolongation.

Results and Interpretation

Characteristics

Of the 27 probands, there were 17 females and 10 males. The overall average age of presentation with ACA was 38 years old. The average in the male population was 27 years old. The average age for females was 44 years old.

Of the 27 probands, none had a prior diagnosis of LQTS and as such were not receiving anti-adrenergic prophylaxis.

Precipitants

5 had been on drugs to be avoided in LQTS[6] at the time of arrest. Those drug prescriptions/combinations were as follows:

1. Domperidone
2. Fluoxetine, Haloperidol
3. Metronidazole
4. Clarithromycin, Levofloxacin, Sotalol
5. Escitalopram, Tamoxifen

Other precipitating factors demonstrated in our subgroup included diarrhoea (n=1; LQT1), swimming (n=2; LQT1, LQT2), running (n=1; LQT3), undergoing alcohol detoxification (n=1; KCNQ1), initiating a bar fight (n=1, not genetically typed), undergoing treatment for a RTI (n=1, VUS in SCN5A).

Genetic Studies

Seventeen out of the 27 (63%) had genetic testing undertaken while 10 did not. The variants detected are stratified in accordance with American College of Medical Genetics classifications.

The studies revealed Pathogenic (P) or Likely Pathogenic (LP) variants in 11 of the 17 patients. Two of these 11 had further Variants of Unknown Significance (VUS).

Outside of the 11 P and LP variants, 2 probands had genetic studies which came back with single VUSs. One occurring in SCN5A and the other in KCNQ1.

4 were deemed to be negative.

Of the 11 P or LP variants:
5 were in SCN5A (LQTS3) they were 4 P, 1 LP.
4 were in KCNQ1 (LQTS1), they were 2 P, 2 LP.
1 was in KCNE1 (LQTS5), this was LP.
and the last was in KCNH2 (LQTS2), this was P. (See Figure 1.)

Two probands included above also had VUSs which co-occurred with their aforementioned variants. These were as follows:
Alongside a P variant in SCN5A, 3 x VUS in KCNE1, KCNE2, RYR2 were detected in proband affected with cardiac arrest as a young child.
Alongside a LP variant in KCNE1, 1 x VUS in SCN5A was detected in a proband affected with cardiac arrest in late adulthood.

A notable finding among a number of cases was the variability of a proband's QTc at different clinical presentations. Variability in QTc at different time points is evident. For example, 2 female patients aged 52 and 45 had QT intervals >600ms at the time of arrest that had normalised by the time of discharge.

Of the 27 LQTS ACA probands, 22 had ICDs implanted after the arrest. Of the probands who did not have ICD implanted, two had life-limiting complications associated with their ACA. A third fatally arrested in hospital following abortion of first the first cardiac arrest. A fourth had their ACA prior to widespread implantation of ICDs (1991) and has been successfully managed with Beta-Blockade alone . The fifth had been given 3 QT-prolonging drugs at the time of ACA and has been successfully managed with Beta-Blockade and QT-prolonging drug avoidance.

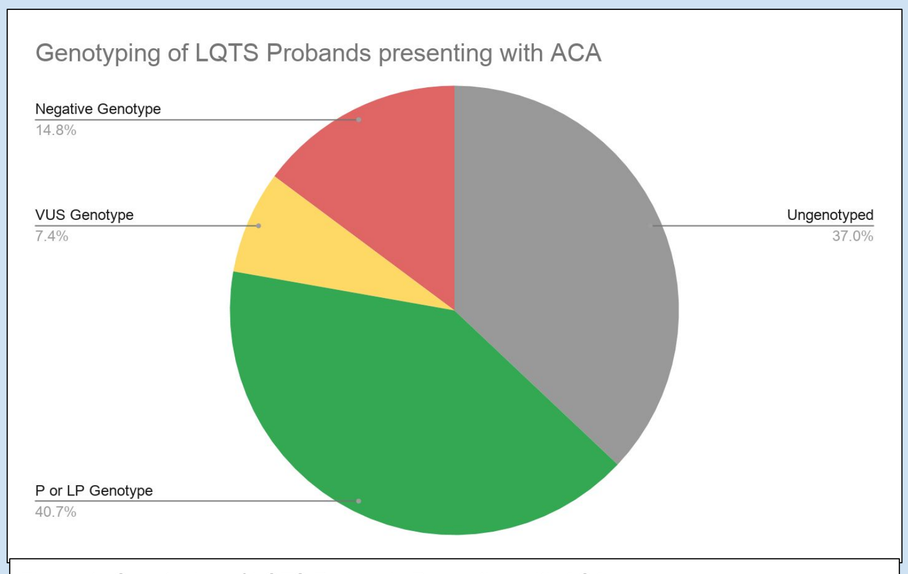

Figure 1. *Genotyping of LQTS Probands Presenting with ACA*

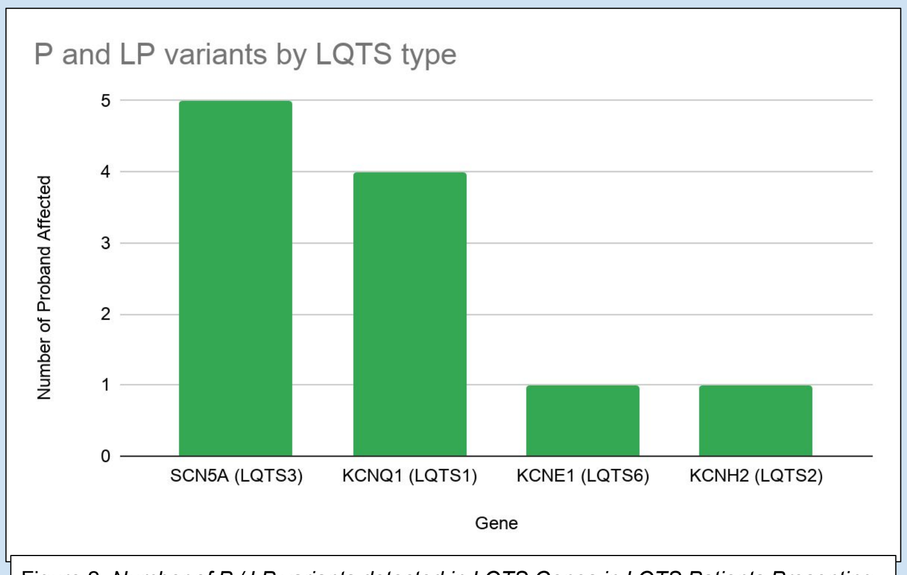

Figure 2. *Number of P / LP variants detected in LQTS Genes in LQTS Patients Presenting with ACA.*

Conclusions

This retrospective review of a single centre experience demonstrates genetic diagnosis in 65% of cases where sought in a post-ACA LQTS proband subgroup. Detection of P and LP variants enables family screening for the affected gene. We saw increased prevalence of LQT3 among ACA sufferers; that QT-prolonging drug use was the most commonly recognized modifiable precipitator of cardiac arrest in this group.

We have described the proportions of types of LQTS in our 17 gene-tested ACA proband subgroup. The genetic variant frequencies showed an increased proportion of LQT3 (45%) in our ACA LQTS proband subgroup compared to LQT3 prevalence (5-10%)[7]. For a larger data set, it would be important to include non-proband patient information, and include non-aborted cardiac arrests.

Consideration could be given to the volume of VUS demonstrated in our population and as such these detections should be published by the relevant labs so as to tease out pathogenicity or benignness. This allows for informative engagement between clinician and genetic testing results. (Model of engagement may pay attention should be emerging evidence of the polygenic model of ICC[8].)

ICD insertion is generally undertaken in survivors of ACA with LQTS at this clinic.

References

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