The long QT syndrome in South Africa

P.A. Brink* and V.A. Corfield#

*Department of Medicine, University of Stellenbosch, South Africa
#US/MRC Centre for Molecular and Cellular Biology, University of Stellenbosch, South Africa

Address for correspondence:
Prof Paul Brink
Internal Medicine
University of Stellenbosch
PO Box 19063
Tygerberg
7505
South Africa

Email:
pab@sun.ac.za

ABSTRACT **The long QT syndromes (LQTS) are Mendelian inherited conditions where syncope and sudden death are due to precipitous occurrence of polymorphic ventricular tachycardia. In South Africa a number of white, some coloured and some Asian individuals have been identified but, interestingly, not a single black person and neither has it been reported from Africa. With over 400 known causal-mutations, mostly in cardiac ion channel-genes, it is unlikely to be absent in African populations. LQTS is notorious for going undiagnosed or misdiagnosed, perhaps even more so in Africa. Amongst persons of Afrikaner descent the KCNQ1 A341V-mutation represents a founder effect. The availability of 170 living individuals sharing the same mutation has made it possible to study factors modifying risk. A blunted autonomic response has been shown to decrease risk of attacks.** SAHeart 2008; 5:160-163

The long QT syndrome (LQTS) is recognized by episodes of syncope or sudden death and a prolonged QT interval corrected for heart rate, the QTc, on an ECG. Other important features on an ECG lie in the variable shape of the T wave. Episodes of transient loss of consciousness (TLOC) result from polymorphic ventricular tachycardia (torsade de pointes) and a family history of sudden unexpected death or the diagnosis of LQTS in close relatives is often present. Reviews covering the background in the text are available[1-3] and references are given selectively or if of specific South African (SA) relevance.

GENETICS

Classically, an autosomal dominant inherited form of LQTS, the Romano-Ward syndrome (RWS) and an autosomal recessively inherited form associated with neuronal deafness, Jervell and Nielsen-Lange syndrome (JNLS), have been described. Today RWS and JNLS are overarching terms for a group of diseases genetically and phenotypically quite diverse. At least eight genes with more than 400 causal-mutations have been associated with LQTS. Defective cardiac ion channels or proteins involved in modulating ion currents form a common theme and, barring two instances, the LQTSs are associated with a pure cardiac phenotype. Andersen-Tawil syndrome (KCNJ2; LQT7), firstly, is a disease with periodic skeletal muscle paralysis and anomalies such as low-set ears, cleft palate and limb defects. Secondly, Timothy syndrome (CACNA1C; LQT8) is associated with short stature, syndactyly, baldness at birth and teeth abnormalities.

The three ionic currents most commonly involved in lengthening of the cardiac action potential and explaining QT prolongation are I_{Ks}, I_{Kr} and I_{Na}. Genes involved are:

1. I_{Ks} current: KCNQ1 (LQT1) and KCNE1 (LQT5), encoding co-operating protein units for a K^+ channel, with defects in either causing RWS or JNLS;

2. I_{Kr} current: KCNH2 (LQT2) and KCNE2 (LQT6), similarly encoding co-operating protein units for a K^+ channel with defects causing RWS;

3. I_{Na} current: SCNA5 (LQT3) encoding a Na^+ channel with defects causing RWS.

In JNLS individuals are either homozygous for KCNQ1 mutations or compound heterozygotes for KCNQ1 and KCNE1.

BIO-ELECTRIC PHENOMENA

Both in LQT1 (I_{Ks}) and LQT2 (I_{Kr}) repolarization is retarded in some cardiac cell types, ergo a prolonged QT-interval on the surface ECG.

K^+ flows are either too late or too little. LQT3 (I_{Na}), represent a "gain of function" with inappropriately large amounts of Na^+ flowing into the cell over a prolonged time and thus prolonging the action potential. Arrhythmogenic substrate derives from excessive differences created in repolarization potential between different cell types in different areas of myocardium leading to re-entry potential.

Interestingly, switching of roles, i.e. gain of function of I_{Ks} and I_{Kr}, lead to the short QT syndrome and loss of function of I_{Na} to Brugada syndrome, all being other disorders associated with polymorphic ventricular tachycardia.

GENE-ASSOCIATED CLINICAL DISEASES

KCNQ1 (LQT1): Episodes of TLOC are commonly exercise related in ±70% of cases.[4] Four associated ECG patterns are an infantile pattern, a broad-based T wave, a normal-appearing T wave and a late-onset normal-appearing T wave pattern.[5]

KCNH2 (LQT2): Attacks have commonly been correlated with emotional events (sudden fright / noise), but with significant proportions also exercise and sleep or rest related.[4] Four common ECG patterns all with bifid T-waves have been described ranging through the obvious and the subtle with the second component appearing in various places on the T or U wave.[5]

SCNA5 (LQT3): The great majority of attacks occur during rest or sleep without arousal.[4] ECG features are late-onset peaked/biphasic T waves or an asymmetrical peaked T wave.[5]

MANAGEMENT

One needs to differentiate between acquired, for example, drug mediated, and inherited forms of QT prolongation. Information on drugs that cause torsade de pointes, prolong the QT interval or are specifically contraindicated in LQTS are maintained at Arizona CERT (http://www.qtdrugs.org). Even "acquired" QT prolongation could be the result of an inherited predisposition uncovered by medication.[6]

Treatment entails avoiding offending drugs and situations associated with attacks. The mainstay is ß-blocker treatment and, especially useful in LQT1, a partial left-sided sympathectomy.[1] Pacemakers, or commonly nowadays an implanted cardioverter-defibrillator (ICD) which has a pacing mode, can be used if bradycardia, important either as a primary manifestation of the disease or related to ß-blocker use, is problematic. In individuals deemed high risk of suffering sudden death an ICD will act as a safety net, but the decision to implant should not be taken lightly as significant device-associated risk exists.

THE SOUTH AFRICAN EXPERIENCE WITH LQTS

Of 46 index cases (multiple affected from a single family count as one; LQTS total 200+) that came to our attention most are white (84.8%), some of mixed descent (10.9%) and Asiatic (4.3%) (updated).[7] No black persons have been referred to or identified by us and a PUBMED search produced no reports from Africa other than our own.[7] In contrast, African Americans are not uncommon amongst LQTS populations.[3] Remarkably out of 39 white index individuals 23 (59%) have the same KCNQ1 A341V mutation in the transmembrane region of the protein. This is the result of a founder effect amongst the Afrikaners which could be traced to a couple married in approximately AD 1730.[8,9] Of the other cases mutations have been detected in KCNQ1, KCNH2 and KCNE1 (Durrheim, unpublished results). No case of JNLS has come to our attention and screening of children with neuronal deafness at schools for the deaf is ongoing (Hofmeyr, unpublished results).

In the first 51 symptomatic cases of the KCNQ1 A341V mutation that we identified 40% were misdiagnosed as epilepsy, 31% undiagnosed and only 29% diagnosed.[10] In the UK it has been estimated that as many as 20% of epilepsy diagnoses are wrong, TLOC being either due to arrhythmic events or pseudo TLOC.[11] In Africa a range of possibilities for undiagnosed LQTS exist, ranging from lack of meaningful communication (time available, language and cultural barriers) and the high burden of infectious disease, malnutrition and trauma causing premature death[12] and camouflaging rare diseases.

THE KCNQ1 A341V (A341V) SOUTH AFRICAN FOUNDER EFFECT & CLINICAL SCIENCE

By offering the opportunity to observe phenotypic differences influenced by environmental or genetic factors other than the primary mutation, the founder effect permitted investigation of modifying influences[9] in LQT1 in 22 families (166 living mutation carriers) as described below.

Severity of the A341 mutation

Compared to LQT1 individuals from an international database with many different mutations, A341V-carriers were more symptomatic[9,13]

and experienced more LQTS related death.[13] By age 40 years 79% of A341V-carriers were symptomatic vs. 30% in the international registry.[9] This high degree of symptoms is a mutation-specific effect and not the result of environment or genetic modifiers in the SA A341V group as risk was the same in other ethnic groups.[13] Furthermore, comparing A341V to non-A341V LQT1 carriers, A341V-carriers were more likely to have had events (75% vs. 24%), were younger at first event (6 vs. 11 years), and had a longer QTc (485±43 vs. 465±38 ms). A341V patients also had more events even when on ß-blocker therapy.

The explanation for severity may partially reside in that A341V has a moderate dominant-negative effect and not a pure loss of function in patch clamp experiments.[9] However, this does not tell the whole story as arrhythmic risk remained higher when the A341V carriers were compared with KCNQ1 mutations with a strong dominant negative effect and with mutations within the C- and N-terminals of the protein.[13]

Influence of the QTc and the autonomic nervous system on disease severity

Lower heart rates (HR) were associated with lower risk of attacks[9,14] in persons with QTc <500ms. With a QTc >500ms virtually everybody had episodes consistent with this being recognized as a major risk predictor.[15] Most asymptomatic individuals were found in the group with a QTc <500ms and HR <60bpm. The association with low HR led us to propose that other markers of autonomic response could be important and we investigated baro-receptor sensitivity (BRS). The BRS was lower in asymptomatic than symptomatic A341V carriers. A341V carriers with both lower HR and BRS were less frequently symptomatic than those with different patterns (20% vs. 76%). Thus lower resting HR and "relatively low" BRS are protective factors in KCNQ1-A341V carriers, which goes contrary to the experience with post myocardial infarction (MI) subjects where lower degrees of BRS had been associated with a higher frequency of sudden death.[16] A plausible underlying mechanism preventing arrhythmias in LQT1 is that a blunted autonomic response averts rapid HR changes when IKs is reduced. Thus a physiological risk modifier with opposing effects in different arrhythmogenic substrates has been identified.

Pregnancy risk

Historic information of 115 pregnancies in 36 women with the A341V (LQT1) mutation was obtained with unaffected sisters as controls.[17] Likely LQTS related events at any time in life; the nine-month interval preceding pregnancy, pregnancy and labour and the nine-month post partum interval were compared. LQT1-affected pregnant women were at low risk for cardiac events and had no events when ß-blockers were used. Higher than expected risk post partum in an earlier systematic study in non-genotyped LQTS[18] could possibly be explained by the unrecognized presence of LQT2.[19] Furthermore, in our study there were no excess risks of miscarriage and no segregation distortion. The tendency to bradycardia of LQTS possibly leads to misdiagnosis of fetal distress in a number of cases and may also partly explain an excess of Cesarean sections in carriers. Beta-blockers had no serious neonatal complications and remain recommended during pregnancy.

In similar vein, general surgery and anesthesia, based on information at our disposal but not formally analyzed, seems not to carry excessive risk.

CONCLUSIONS

Studies of LQTS in South Africa are scientifically fertile because of the presence of a founder effect. Information gained will help to manage LQTS-afflicted individuals. The possibility of LQTS should be entertained in women and children with an incidentally discovered QTc ≥470ms and QTc ≥450ms in men, bizarre repolarization patterns, unexplained syncope, and/or a family history of sudden unexpected death.

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