ADC Online First, published on September 30, 2014 as 10.1136/archdischild-2014-306864

Must every child with long QT syndrome take a beta blocker?

Kathryn E Waddell-Smith,[1,2,3] Nikki Earle,[2,3] Jonathan R Skinner[1,2,3,4]

[1]Green Lane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand
[2]Department of Cardiology, University of Auckland, Auckland, New Zealand
[3]Department of Child Health, University of Auckland, Auckland, New Zealand
[4]Cardiac Inherited Disease Group, Auckland City Hospital, Auckland, New Zealand

Correspondence to
Dr Jonathan Skinner, Green Lane Paediatric and Congenital Cardiac Services, Starship Children's' Hospital, Private Bag 92024, Auckland 1142, New Zealand;
jskinner@adhb.govt.nz

Received 28 May 2014
Revised 15 September 2014
Accepted 16 September 2014

ABSTRACT

Long QT syndrome is the most commonly recognised cause of sudden cardiac death in children. With a prevalence of 1 in 2000, family screening is identifying large numbers of hitherto asymptomatic gene carriers in the community, about a third of whom have a normal QT interval. The mainstay of treatment is long term uninterrupted beta blocker therapy, a treatment with many potential side effects. This article reviews the evidence and suggests a cohort who may, after assessment in a specialised cardiac-genetic clinic, be spared this treatment because of very low baseline risk. These are asymptomatic boys and prepubertal girls with a heart rate corrected QT interval persistently less than 470 ms who do not indulge in high risk activities (especially swimming) and do not have a missense mutation in the c-loop region of the KCNQ1 (long QT 1) gene.

INTRODUCTION

Long QT syndrome (LQTS) with a population prevalence of 1 in 2000[1] is the most commonly recognised cause of sudden cardiac death in children.[2–4] It causes syncope and sudden death from malignant ventricular arrhythmia. It can be misdiagnosed as epilepsy,[5] cause drowning in a strong swimmer,[6] be difficult to differentiate from benign syncope[7] and may present first with sudden unexpected death at all ages.[2 8 9]

Screening of families of those affected is identifying large numbers of hitherto asymptomatic gene carriers in the community.[10 11] As more and more presymptomatic individuals with milder forms of the condition are identified, we must now ask how aggressively we should treat such people.

The mainstay of therapy in LQTS is the prophylactic, regular and uninterrupted use of beta blockers.[12] However, beta blockers are not an entirely benign medication, and long term adherence in adults tends to be very poor, with 20%–25% having stopped them within 1 year.[13 14] Reported side effects include dyspnoea, fatigue and dizziness,[14] nightmares,[15] cold digits and tired legs.[16] Precipitation of asthma is feared, as are the occasional idiosyncratic reactions such as drug rashes or hair loss. While depression, insomnia and impotence have been reported, these side effects, and others, are disputed by evidence from placebo controlled trials.[17]

Having to take a medication can cause tension between the anxious parent and the child. The child is reminded constantly that he or she is different from unaffected siblings and peers. There may also be fiscal implications. There is fear that intermittent use of beta blockers may make the risk of cardiac arrest higher, through the blocked beta receptors being transiently upregulated for a period after stopping the medication.

It is thus clear that the decision to start a beta blocker is not a small one. Must every gene positive child take a beta blocker?

REVIEW OF THE EVIDENCE

Types of LQTS

While 15 genotypes of LQTS have been recognised to date, the vast majority are types 1, 2 or 3,[10] or are part of the 20%–25% in whom a genotype cannot be identified. Since evidence is sparse for the others, we will confine the discussion to these three genotypes. Phenotypic features of the three commonest genotypes are shown in table 1.

EVIDENCE OF THE EFFECTIVENESS OF BETA BLOCKERS

No randomised trial of any therapy for LQTS has ever been performed. However, the international LQTS registry has produced a series of observational research studies demonstrating a reduced risk among those who take beta blockers.[9 18–20] The greatest benefit occurs among those with the highest baseline risk, particularly those who have had recent syncope, or a very long QT interval. Further risk stratification can be made according to genotype, gender and age (see table 1). Those at highest risk are boys and adult women with a long QT interval, and anyone with a history of syncope. Beta blockers reduce sudden death most profoundly in exercise related syncope in long QT type 1.[21]

While it may be a logical presumption that beta blockers reduce risk of sudden death in those with a normal QT interval, no study has yet proven this to be the case, possibly because the baseline risk is so low (0.13%/year).[22] This has urged many to prescribe beta blockers to anyone who is a gene carrier, regardless of a normal QT interval.

EXPERT CONSENSUS GUIDELINES

A recent international expert consensus document gives a confusing message regarding patients with a normal corrected QT interval (QTc) and no symptoms. It states that 'Beta-blockers are **clinically indicated** in LQTS, including those with a genetic diagnosis and normal QTc, unless there is a contraindication such as active asthma'.[23] However, elsewhere in the document, it states that 'Beta blockers **are recommended** in individuals with a repeated QTc greater than or equal to 470 ms' but only that 'Beta-blockers **can be useful** in patients with a diagnosis of LQTS who are asymptomatic with QTc less than or equal to 470 ms'.[23]

We consider that 'can be useful' and 'clinically indicated' deliver quite different messages.

To cite: Waddell-Smith KE, Earle N, Skinner JR. *Arch Dis Child* Published Online First: [*please include* Day Month Year] doi:10.1136/archdischild-2014-306864

Table 1 Characteristic features of the three commonest genotypes of long QT syndrome

	Gene	Ion channel	Typical triggers for events	Higher risk groups	Overall risk reduction by beta blockers
LQT1	*KCNQ1*	IKr	Activity, swimming	Males aged 5–20 years	+++
LQT2	*KCNH2*	IKs	Startle, sleep	Females >12 years	++
LQT3	*SCN5A*	INa	Sleep/rest	Infants/adult males	+

+++, Very good; ++, good; +, moderate.

Figure 1 shows data from the New Zealand long QT registry,[10] and reveals that 36% of gene positive individuals have a QTc less than 470 ms; 43% of the cohort are children or youth (<25 years) and 16% are under 11 years of age.

GENOTYPE POSITIVE INDIVIDUALS WITH A NORMAL QT INTERVAL

Figure 2 is reproduced from an international LQTS registry study.[22] The population of 1861 genotype positive individuals was divided into the 25% with a normal QTc (<440 ms) and compared with those with a prolonged QTc and their unaffected family members. By the age of 40, 4% of individuals with a normal QTc had experienced a life threatening event. *However, there were no life-threatening arrhythmias in the first 10 years of life*.

EVIDENCE IN CHILDREN

Another report from the same authors studied 3015 children from 1 to 12 years of age.[18] Overall, beta blockers reduced risk of cardiac arrest or sudden death by 53%.[18] Of the 875 who were genotyped, 127 (15%) had a QTc <450 ms, of whom none had cardiac arrest.

Of the 437 with QTc 450–500 ms, including those with symptoms, 1% had cardiac arrest or sudden death.

Thus, in all children with LQTS, including those with symptoms, aged ≥1 with a QTc 450–500 ms, continuous beta blockade given to 200 children for 11 years will be expected to avoid one cardiac arrest, while potentially not preventing the other.

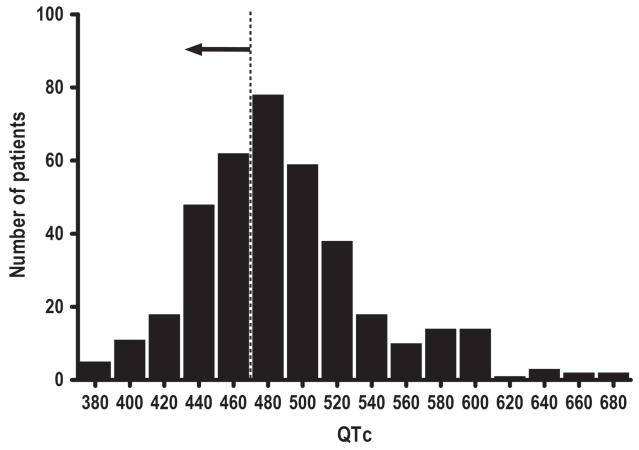

Figure 1 Heart rate corrected QT intervals (QTc; corrected using the Bazett formula (QTc=QT/square root R-R interval)) among 383 genotyped individuals in the New Zealand long QT registry.[10] The arrow points to the 36% with QTc <470 ms, where guidelines allow for discretion in treatment with beta blockers (see text).

IMPORTANCE OF A WARNING SYNCOPE

Combining two registry studies,[18 22] it appears likely that almost all children have a warning syncope prior to a cardiac arrest. The initial presentation of syncope elevates their risk of subsequent cardiac arrest by 27 times in girls and 3–6 times in boys,[18] therefore moving them from the asymptomatic group to a group where beta blockers are strongly recommended. Thus, cardiac arrest is rare in asymptomatic children with a QTc less than 500 ms, certainly much less than 1%.

What of the very rare presentation of sudden death with a normal QT interval? A recent discovery into the effect of the position of mutations within the gene may explain this.

POSITION AND TYPE OF MUTATION IN THE CARDIAC ION CHANNELS

Mutations in the transmembrane portion of the cardiac ion channels seem to produce more severe disease in both long QT 1 and 2 as discussed below.

Long QT 1 (KCNQ1)

Approximately 15% of LQT1 subjects have a missense mutation in the transmembrane C-loop domain of the ion channel protein formed by *KCNQ1*.[24] The increased risk associated with C-loop mutations is most marked in females and is independent of the QT interval.[25] *In vitro* studies showed that the induction of torsades de pointes by adrenaline is abolished by beta blockers. Among patients, the life-saving benefit of beta blockers in the entire cohort of 860 patients was explained entirely by the effect among these 15% of patients with a c-loop mutation.[24] Thus, from the other point of view, *they were unable to demonstrate a survival benefit from beta blockers in the 85% of long QT 1 patients without a missense C-loop mutation*.

So, there is a small group of long QT 1 patients who must have beta blockers, probably from birth and probably for life, regardless of the QT interval. These are missense mutations in *KCNQ1* within the C-loop residues 171–195 and 242–262.

In the New Zealand cohort, we have identified 21 patients with missense C-loop mutations (14 female patients). Examples include R174H, R178 T and R243C.[10] We have contacted them and their clinicians and advised beta blockade, even when the QT interval is normal.

Long QT type 2 (KCNH2)

Long QT type 2 is a killer of adult women (or girls over 12), typically at night or after a startle and in the first year after giving birth.[20 26] There is thus a particular imperative to ensure beta blockade in young women with a long QT interval. Males are less severely affected unless they carry a mutation in the pore-loop region, part of the transmembrane portion.[27] There is however no evidence that these are especially responsive to beta blockade, and our practice is to use the QT interval or presence of symptoms to guide advisability of beta blockers in LQT2.

Long QT 3 (SCN5A)

Long QT3 is relatively uncommon (9%)[10] and quite different. Cardiac events tend to occur in the absence of adrenaline stimulus, during the night.[28] Leak of sodium across the ion channel results in prolongation of the QT interval. Beta blockers may have a place[29] as may sodium channel blockers such as mexiletine.[30] Pause related QT prolongation suggests pacemakers have

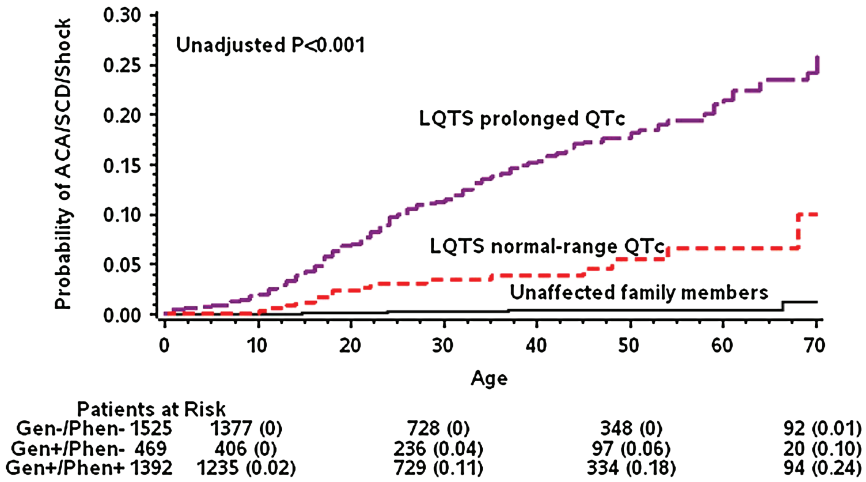

Figure 2 Kaplan–Meier cumulative probabilities of aborted cardiac arrest (ACA) or sudden cardiac death (SCD) comparing 469 genotype positive individuals with a 'normal' QTc (<440 ms) with 1392 with a QTc above 440 ms, and unaffected relatives.[22] Note the lack of life-threatening events in the first 10 years in those with a QTc<440 ms. (Goldenberg *et al*,[22] figure 2. Reproduced with permission from Elsevier).

a role in this type of LQTS. This group is especially difficult to manage and advice from long QT specialist is strongly advised in each case, though a resting QTc below 440 ms does infer very low risk.[22]

CHANGE OF RISK AT PUBERTY

Prior to puberty, girls are at lower risk than boys,[22 31] and having long QT 2 is a lower risk than 1 or 3.[22 31] Risk in boys correlates closely with the QT interval, but in girls, prior syncope is the only useful indicator.[18] At the age of 10–12 years, boys are 8 times more likely to have a cardiac arrest than girls.[19]

Between age 13 and 18 years, the gender risk equalises, and over the age of 18, it is higher in women, and long QT type 2 carries the highest risk.[19] This rise in risk for female patients around puberty probably relates to increased oestrogen levels.[32]

IMPORTANCE OF REPEATED QT MEASUREMENT

In assessment of risk, it has been shown that one should use the longest QTc recorded on a 12-lead ECG.[33] While exercise testing can help reveal phenotype, we do not yet know how to prognosticate with this information. We recommend obtaining several 12-lead ECGs, even if only days apart, to assign a level of risk. Serial normal QT measurements on follow-up provide ongoing reassurance during childhood.

PSYCHOSOCIAL FACTORS AND RISK TAKING BEHAVIOUR

Even though young children with a normal QT interval are at very low risk, some activities pose a special risk. Swimming and possibly high level competitive sport pose a particular risk, especially in long QT type 1.[6] A transient syncope on land is usually not fatal, but the opposite is true under water. If an asymptomatic genotype LQT1 child with a normal QT interval must swim, then it seems prudent to reduce that possible risk with beta blockers, even though absolute risk is low. Automated external defibrillators can also provide a level of practical reassurance in those at higher risk.[34]

THE WISHES OF THE CHILD AND THE FAMILY

Risk of sudden arrhythmic death is based on the assessment of probabilities, and no one can ever give a 100% guarantee, irrespective of treatment. An open discussion of these probabilities, and the pros and cons of treatment, should be had with the family so that a rational joint decision can be made. This is based on the best available data and incorporates the child's wishes as far as practicable.

If a child and the family, having been thoroughly informed, want to take beta blockers, their decision should be supported. If beta blockers are commenced, the family must understand the importance of continuous supply and adherence.

CHOOSING BETA BLOCKERS

If beta blockers are given, a long acting, single daily preparation will optimise adherence. Nadolol and controlled release propranolol are examples.[35] If metoprolol is used, it should be a controlled release, once daily form.[35] The lack of a once daily infant preparation makes adherence more difficult and is another reason to be more circumspect about starting beta blockers in this age group.

CONCLUSIONS

Beta blockers are generally recommended in LQTS where the QTc in greater than or equal to 470 ms.[23] However, even being extremely cautious, there are groups of asymptomatic LQTS gene-carrying children in whom beta blockers may be considered non-essential because they are at very low risk. After assessment in a specialised cardiogenetics clinic where all the above issues have been given expert consideration,[23] we suggest beta blockers are not essential if:

1. The QTc is consistently less than 470 ms and
2. The patient does not have a C-loop missense LQT1 mutation and
3. The patient does not take part in high risk activities (particularly swimming) and is either
4. A preschool boy OR
5. A prepubertal girl.

Including the above factors, a QTc below 440 ms infers even lower, 'nominally zero' risk.[22] If treatment is started, men may look forward to being gradually withdrawn from beta blockade at age 20 or so if they remain asymptomatic and the QT interval is not prolonged.

QT prolonging drugs must be avoided (http://www.crediblemeds.org) and every child should remain under periodic specialist review. A trusting clinical partnership can develop, such that borderline decisions can be made together with the child and family as circumstances change.

Finally, we should make it clear to our patients that research is changing this field rapidly, and so our advice may also change. We recommend that every such patient should be offered to be

part of a clinical registry, with every managing clinician contributing to and learning from it.

Contributors The paper is not under consideration elsewhere and none of the paper's contents have been previously published. There are no conflicts of interest to declare. All authors have contributed, read and approved the current manuscript.

Competing interests JRS receives salary support from Cure Kids. NE is funded by the Auckland Medical Research Foundation. KEW-S is funded by the New Zealand Heart Foundation.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Schwartz PJ, Stramba-Badiale M, Crotti L, *et al*. Prevalence of the congenital long-QT syndrome. *Circulation* 2009;120:1761–7.
2 Skinner JR, Crawford J, Smith W, *et al*. Prospective, population-based long QT molecular autopsy study of postmortem negative sudden death in 1 to 40-year-olds. *Heart Rhythm* 2011;8:412–19.
3 van der Werf C, Hofman N, Tan HL, *et al*. Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: the experience of a tertiary referral center in The Netherlands. *Heart Rhythm* 2010;7:1383–9.
4 Tester DJ, Medeiros-Domingo A, Will ML, *et al*. Cardiac channel molecular autopsy: insights from 173 consecutive cases of autopsy-negative sudden unexplained death referred for postmortem genetic testing. *Mayo Clin Proc* 2012;87:524–39.
5 MacCormick JM, McAlister H, Crawford J, *et al*. Misdiagnosis of long QT syndrome as epilepsy at first presentation. *Ann Emerg Med* 2009;54:26–32.
6 Albertella L, Crawford J, Skinner JR. Presentation and outcome of water-related events in children with long QT syndrome. *Arch Dis Child* 2011;96:704–7.
7 MacCormick JM, Crawford JR, Chung SK, *et al*. Symptoms and signs associated with syncope in young people with primary cardiac arrhythmias. *Heart Lung Circ* 2011;20:593–8.
8 Arnestad M, Crotti L, Rognum TO, *et al*. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. *Circulation* 2007;115:361–7.
9 Goldenberg I, Moss AJ, Bradley J, *et al*. Long-QT syndrome after age 40. *Circulation* 2008;117:2192–201.
10 Earle N, Crawford J, Smith W, *et al*. Community detection of long QT syndrome with a clinical registry: an alternative to ECG screening programs? *Heart Rhythm* 2013;10:233–8.
11 Theilade J, Kanters J, Henriksen FL, *et al*. Cascade screening in families with inherited cardiac diseases driven by cardiologists: feasibility and nationwide outcome in long QT syndrome. *Cardiology* 2013;126:131–7.
12 Vincent GM, Schwartz PJ, Denjoy I, *et al*. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment "failures". *Circulation* 2009;119:215–21.
13 Gislason GH, Rasmussen JN, Abildstrom SZ, *et al*. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006;27:1153–8.
14 Kalra PR, Morley C, Barnes S, *et al*. Discontinuation of beta-blockers in cardiovascular disease: UK primary care cohort study. *Int J Cardiol* 2012;167:2695–9.
15 Dimsdale JE, Newton RP. Cognitive effects of beta blockers. *J Psychosom Res* 1992;36:229–36.
16 Lewis RV, Jackson PR, Ramsay LE. Side-effects of beta-blockers assessed using visual analogue scales. *Eur J Clin Pharmacol* 1985;28(Suppl):93–6.
17 Barron AJ, Zaman N, Cole GD, *et al*. Systematic review of genuine versus spurious side-effects of beta-blockers in heart failure using placebo control: recommendations for patient information. *Int J Cardiol* 2013;168:3572–9.
18 Goldenberg I, Moss AJ, Peterson DR, *et al*. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. *Circulation* 2008;117:2184–91.
19 Hobbs JB, Peterson DR, Moss AJ, *et al*. Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome. *JAMA* 2006;296:1249–54.
20 Sauer AJ, Moss AJ, McNitt S, *et al*. Long QT syndrome in adults. *J Am Coll Cardiol* 2007;49:329–37.
21 Goldenberg I, Thottathil P, Lopes CM, *et al*. Trigger-specific ion-channel mechanisms, risk factors, and response to therapy in type 1 long QT syndrome. *Heart Rhythm* 2011;9:49–56.
22 Goldenberg I, Horr S, Moss AJ, *et al*. Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. *J Am Coll Cardiol* 2011;57:51–9.
23 Priori SG, Wilde AA, Horie M, *et al*. HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes: Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* 2013;10:1932–63.
24 Barsheshet A, Goldenberg I, O-Uchi J, *et al*. Mutations in cytoplasmic loops of the KCNQ1 channel and the risk of life-threatening events: implications for mutation-specific response to beta-blocker therapy in type 1 long-QT syndrome. *Circulation* 2012;125:1988–96.
25 Costa J, Lopes CM, Barsheshet A, *et al*. Combined assessment of sex- and mutation-specific information for risk stratification in type 1 long QT syndrome. *Heart Rhythm* 2012;9:892–8.
26 Seth R, Moss AJ, McNitt S, *et al*. Long QT syndrome and pregnancy. *J Am Coll Cardiol* 2007;49:1092–8.
27 Migdalovich D, Moss AJ, Lopes CM, *et al*. Mutation and gender-specific risk in type 2 long QT syndrome: implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome. *Heart Rhythm* 2011;8:1537–43.
28 Schwartz PJ, Priori SG, Spazzolini C, *et al*. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95.
29 Calvillo L, Spazzolini C, Vullo E, *et al*. Propranolol prevents life-threatening arrhythmias in LQT3 transgenic mice: implications for the clinical management of LQT3 patients. *Heart Rhythm* 2014;11:126–32.
30 Ruan Y, Liu N, Bloise R, *et al*. Gating properties of SCN5A mutations and the response to mexiletine in long-QT syndrome type 3 patients. *Circulation* 2007;116:1137–44.
31 Wedekind H, Burde D, Zumhagen S, *et al*. QT interval prolongation and risk for cardiac events in genotyped LQTS-index children. *Eur J Pediatr* 2009;168:1107–15.
32 Sedlak T, Shufelt C, Iribarren C, *et al*. Sex hormones and the QT interval: a review. *J Womens Health (Larchmt)* 2012;21:933–41.
33 Goldenberg I, Mathew J, Moss AJ, *et al*. Corrected QT variability in serial electrocardiograms in long QT syndrome: the importance of the maximum corrected QT for risk stratification. *J Am Coll Cardiol* 2006;48:1047–52.
34 Johnson JN, Ackerman MJ. Return to play? Athletes with congenital long QT syndrome. *Br J Sports Med* 2013;47:28–33.
35 Chockalingam P, Crotti L, Girardengo G, *et al*. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. *J Am Coll Cardiol* 2012;60:2092–9.

Must every child with long QT syndrome take a beta blocker?

Kathryn E Waddell-Smith, Nikki Earle and Jonathan R Skinner

Arch Dis Child published online September 30, 2014
doi: 10.1136/archdischild-2014-306864