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Prevalence of early-onset atrial fibrillation in congenital long QT syndrome

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Abstract

BACKGROUND—The prevalence of atrial fibrillation (AF) in the young (age <50 years) is 0.1%, or 1:1,000 persons. Mutations in KCNQ1-, KCNH2-, and KCNA5-encoded potassium channels and SCN5A-encoded sodium channels have been reported in familial AF. A mechanism of atrial torsade has been suggested to occur in patients with congenital long QT syndrome (LQTS).

OBJECTIVE—The purpose of this study was to determine the prevalence of AF in patients with congenital LQTS.

METHODS—History of documented AF was sought from two independent cohorts. One cohort consisted of 252 consecutive patients (146 females and 106 males, average age at diagnosis 23 ± 16 years, QTc 465 ± 51 ms) with genetically proven LQTS seen at Mayo's LQTS Clinic. The second cohort consisted of 205 consecutive patients (133 females and 72 males, average age at testing 23 ± 16 years, QTc 479 ± 51 ms) with a positive FAMILION genetic test (PGxHealth) for LQTS.

RESULTS—Early-onset AF was documented in 8 (1.7%) of 457 patients, including 6 (2.4%) of 252 patients seen at Mayo and 2 (1%) of 205 patients with a positive FAMILION test. Five (2.4%) of 211 patients with LQT1-susceptibility mutations had documented AF, compared to 0 of 174 patients with LQT2, 1 of 59 patients with LQT3, 1 of 1 patient with Andersen-Tawil syndrome, and 1 of 34 patients with multiple mutations. The average age at diagnosis of AF of the six patients evaluated at Mayo was 24.3 years (range 4–46 years). Early-onset AF (age <50 years) was significantly more common in patients with LQTS compared to population-based prevalence statistics ($P < .001$, relative risk 17.5).

CONCLUSION—Compared to the background prevalence of 0.1%, early-onset AF was observed in almost 2% of patients with genetically proven LQTS and should be viewed as an uncommon

but possible LQT-related dysrhythmia. Clinical complaints of palpitations warrant thorough assessment in patients with LQTS.

Keywords

Atrial fibrillation; Long QT syndrome; Tachyarrhythmias; Ion channels

Introduction

Congenital long QT syndrome (LQTS) affects 1:2,500 persons and was first described as the Jervell and Lange-Nielsen syndrome and Romano-Ward syndrome in the late 1950s and early 1960s.^{1–3} The trademark dysrhythmia underlying the symptomatic LQTS patient is torsade de pointes, a potentially lethal ventricular arrhythmia.⁴ To date, 11 distinct LQTS-susceptibility genes have been discovered. However, mutations in the three most common LQTS subtypes, *KCNQ1*-mediated LQT1, *KCNH2*-mediated LQT2, and *SCN5A*-mediated LQT3, account for 75% of clinically definite LQTS.

Multiple genetic mutations have been reported recently in patient familial forms of atrial fibrillation (AF). In 2003, Chen et al⁵ reported a family with early-onset AF that had a gain-of-function mutation in the *KCNQ1*-encoded potassium channel. A second gain-of-function mutation in *KCNQ1* associated with AF and a short QT interval was reported in 2005 by Hong et al.⁶ Gain-of-function mutations in *KCNH2*-encoded potassium channels,⁷ loss-of-function mutations in the atrial-specific *KCNK5*-encoded Kv1.5 potassium channel,⁸ and loss-of-function mutations in the *SCN5A*-encoded sodium channel⁹ have been reported recently in familial AF.

The incidence of early-onset AF (age <50 years) is 0.62 cases per 1,000 person-years for men and 0.19 cases per 1,000 person-years for women.¹⁰ The prevalence of AF in this age bracket is approximately 0.1%.^{11–14} Notably, early-onset AF has been reported in approximately 20% of patients with Brugada syndrome.¹⁵ However, the prevalence of documented AF in patients with genetically proven LQTS is unknown. The purpose of this study was to determine the prevalence of AF in two large cohorts of patients with LQTS.

Methods

The medical records of two distinct cohorts of patients with genetically proven LQTS were reviewed for a history of AF. The reviewers (JNJ and DJT) were blinded at all times to the patients' genotypes. The first cohort consisted of 252 consecutive patients (146 females and 106 males, average age at diagnosis 23 ± 16 years, QTc 465 ± 51 ms) with genetically proven LQTS seen at Mayo's LQTS Clinic between 1998 and 2006. These patients underwent genetic testing by denaturing high-performance liquid chromatography and/or direct DNA sequencing at the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory. The second cohort consisted of 205 consecutive, unrelated patients (133 females and 72 males, average age at testing 23 ± 16 years, QTc 479 ± 51 ms) who had a positive FAMILION genetic test for LQTS.

A clinical history of AF was obtained in the Mayo cohort directly by a physician specializing in LQTS (MJA). A patient was considered to have a history of AF if a prior diagnosis of AF from a physician was noted in the available medical record. In several patients, the diagnosis of atrial fibrillation was made once they had received an implantable cardioverter-fibrillator (ICD) for LQTS. In these cases, the ICD detected the abnormal rhythm.

Patients in the FAMILION cohort did not have a direct clinical history taken by any of the authors but were referred for testing, mostly by heart rhythm specialists throughout North America. The physician requesting a FAMILION test for a patient was asked to complete a phenotype questionnaire. These historical questions were reviewed blindly and anonymously, counting any patient for whom the practitioner had marked the check box for AF. The authors inferred that any phenotype check box being marked was an accurate statement and assumed documentation of reported findings. The completion rate of the questionnaires was 89%. FAMILION tests were performed by PGxHealth, LLC (New Haven, CT, USA). This study, including analysis of anonymous, de-identified questionnaire information from PGxHealth, was reviewed and approved by the Mayo Clinic Institution Review Board.

Statistical analyses were performed with the assistance of the Center for Patient-Oriented Research at Mayo Clinic (Rochester, MN, USA). All continuous variables are reported as mean $\pm$ SD. Proportions were analyzed and compared using a two-tailed Fisher exact test. Means were analyzed using the independent groups T-test for means. A binomial test was used to evaluate the frequency of AF in the LQTS population relative to AF in the young (<50 years).

A single author (JNJ), who was blinded to both genotype and AF history, manually measured all QT intervals, and the heart rate corrected QT interval (QTc) was calculated using the standard Bazett formula.¹⁶ In a small percentage of patients (9% [19/205]) in the FAMILION cohort, QTc was reported by the ordering physician but an attached ECG was not available for manual measurement. In these cases, the reported QTc values were used. In addition, QTc for a number of FAMILION patients (36/205 [18%]) was neither reported nor available for review.

Results

Table 1 details some of the demographic features of the two independent cohorts composing the study population. The two cohorts were similar with regard to male/female composition and age at genetic testing. QTc was slightly longer among the patients from the FAMILION cohort compared to patients in the Mayo cohort (479 vs 465 ms, $P < .005$).

Overall, early-onset AF was documented in 8 (1.7%) of the 457 patients and was more common in males (6/178 [3.4%]) than in females (2/279 [0.7%], $P = .06$). This frequency is significantly higher than the expected 0.1% prevalence of AF in the young ($P < .001$). The relative risk of a patient with LQTS having AF prior to age 50 years compared to population-based norms is 17.5 (confidence interval 2.2–139.6). The distribution of positive AF cases included 6 (2.4%) of 252 patients seen at Mayo Clinic and 2 (1%) of 205 patients with a positive FAMILION test. AF was slightly more common among patients with LQT1 compared to the two other most common LQTS subtypes. Genotype-specific analysis revealed that 5 (2.4%) of 211 patients with LQT1-susceptibility mutations had AF compared to 0 of 174 LQT2 patients, 1 of 59 LQT3 patients, 1 of 1 patient with Andersen-Tawil syndrome, and 1 of 34 patients with multiple mutations (Table 2). The average age at diagnosis of AF of patients in the Mayo cohort was 24.3 years (range 4–46 years). The age at onset of AF for the FAMILION cohort (Table 2, cases 1 and 3) was not stated explicitly but could be estimated at <1 year and <15 years based on their age at the time of LQTS genetic testing indicating very-early-onset AF.

Figure 1 shows the location of the mutations found in the five patients with mutations in *KCNQ1*. Four of the patients had missense mutations, and one had a four-nucleotide deletion resulting in a frameshift mutation. All mutations were absent in more than 2,500 references

alleles and involved highly conserved residues that localized to key structure–function domains. The patient with Andersen-Tawil syndrome had a single, loss-of-function missense mutation (T75M) in the proximal portion of the *KCNJ2*-encoded Kir2.1 potassium channel (Figure 2). The patient with type 3 long QT syndrome had a previously published, gain-of-function, missense mutation (E1784K) in the C-terminal region of the *SCN5A* protein (Figure 3). The patient with multiple genetic variants (patient 6) was diagnosed with LQTS at birth and had onset of AF at age 4 years. Mutation analysis revealed compound heterozygosity involving both *KCNH2* and *SCN5A* (Figure 4). Functionally, the pathogenic mutation in the sodium channel most likely is N275K-*SCN5A* rather than A572D. The former had a classic LQT3 molecular/cellular phenotype with accentuated late sodium current, whereas A572D was wild type (data not shown). His ECG on presentation showed both AF and a prolonged QT interval (Figure 5).

Discussion

The prevalence of AF in the young (age <50 years) is estimated at 0.1%, or 1:1,000 persons (derived from Framingham, Olmsted County, and ATRIA studies).^{11–14} In this study, early-onset AF was observed in almost 2% of patients with genetically proven LQTS, including 3% of males with LQTS. Patients with LQTS had a relative risk of 17.5 for having AF diagnosed before age 50 years compared to population norms. Using the binomial test, the prevalence in the general population would have to be greater than 1:132 (or 0.75%) for our LQTS cohort not to be statistically different. Interestingly, the observed prevalence of AF in these two independent cohorts of patients with LQTS occurred in patients with an average age <20 years, mirroring the AF prevalence expected from a postretirement (age 65–69 years) population.^{11,14}

The diagnosis of AF in young patients with LQTS but no evidence of other structural heart disease theoretically can be labeled as “lone AF.” Most studies consider individuals with lone AF to account for approximately 10% to 20% of all AF patients.¹⁷ With this classification, our findings of increased risk for AF in LQTS patients would be even more statistically significant ($P < .00001$).

In 2003, Kirchhof et al¹⁸ reported that patients with LQTS had altered atrial electrical conduction and were at increased risk for polymorphic atrial tachyarrhythmias than were patients with known AF as well as controls. The duration of polymorphic atrial tachyarrhythmia was longer in LQTS patients than in patients with investigator-induced AF as well as patients with persistent AF. In addition, atrial action potential durations were longest in LQTS patients with polymorphic atrial tachyarrhythmia compared to other AF patients. Intriguingly, P waves during episodes of polymorphic atrial tachyarrhythmia were reported to have an undulating nature, not unlike those seen in ventricular fibrillation.^{18,19} These observations prompted the speculation that an atrial torsade mechanism mediated the susceptibility for AF. Notably, atrial torsade de pointes was first described nearly a decade ago in a canine model of Andersen-Tawil syndrome in which cesium-mediated block of Kir2.1 potassium channels induced atrial early afterdepolarizations that precipitated polymorphic atrial tachyarrhythmia and subsequent degeneration into AF.²⁰

Accepting the caveat of small sample size of LQTS/AF-positive subjects, this study identifies a trend for greater AF susceptibility among patients with type 1 LQTS. Five of 8 patients with genotype-positive LQTS and documented AF had probable or already proven loss-of-function mutations in *KCNQ1*. Two percent of patients with LQT1 had early-onset AF compared to no patients with LQT2. Of note, in contrast to LQT1-associated loss-of-function mutations in *KCNQ1*, gain-of-function mutations in *KCNQ1* were among the first published mechanisms underlying familial AF.⁵

Given the observations reported by Kirchhof et al¹⁸ and Satoh and Zipes,²⁰ it is tempting to speculate that dysfunction of the *KCNQ1*-encoded I_{Ks} potassium channel, which is critical for phase 3 repolarization, could result in enhanced susceptibility for atrial torsade. We previously reported an anecdotal case (not included in either cohort here) of early-onset AF (age 19 years) in an LQT1-positive female.²¹ Notably, her AF was completely suppressed by mexiletine pharmacotherapy. Perhaps in the setting of defective I_{Ks} potassium currents, the amount of physiologic late sodium current provides sufficient substrate for polymorphic atrial tachyarrhythmias. Development of other therapy options for patients with both LQTS and AF will be crucial, considering that many pharmacotherapeutic choices for AF treatment are contraindicated in patients with genetically proven LQTS. In fact, AF control with amiodarone attempted elsewhere for one of the patients in this cohort resulted in a profound VT/VF storm requiring multiple external defibrillator therapies and emergent sternotomy and extracorporeal membrane oxygenation.

Although clinically detectible AF seems more common in Brugada syndrome (estimated at 20%¹⁵) than observed here for LQTS, we anticipate that the 0.7% (females) to 3.4% (males) prevalence underestimates the true frequency of AF among patients with LQTS. There is a significant potential for underreporting as well as underdetection in this study. Although a direct history and chart review is the ideal form of historical data collection, this was possible only for the Mayo cohort. The FAMILION cohort depended on completion of the phenotype questionnaire of the test referral form by the practitioner or assistant. Some practitioners (approximately 11%) either did not check any boxes in the history section or neglected to fill out the entire page. We are forced to speculate that either the patients truly had no history or that the practitioners simply did not complete the section.

Besides the distinct possibility of underreporting, under-detection of AF among patients with LQTS is likely as well given that detection of paroxysmal AF can be quite difficult. Clinically, the chief symptoms stemming from ventricular torsade that have been considered an LQTS-precipitated cardiac event include syncope, seizures, and/or sudden death.^{22,23} Palpitations have been dismissed generally as totally unrelated to LQTS. It is intriguing to ponder now whether or not patients with LQTS are experiencing palpitations secondary to their LQTS substrate, albeit through atrial torsade-precipitated paroxysmal AF.

Conclusion

Early-onset AF (age <50 years) was observed in approximately 2% of patients with genetically proven LQTS, a significantly higher frequency than population-based frequency estimates of early-onset AF. Due to underreporting and underdetection, this concomitant expression of AF in LQTS likely is an underestimate. AF should be viewed as an uncommon but possible LQT-related dysrhythmia. Rather than being dismissed as unrelated, palpitations in patients with LQTS warrant closer scrutiny.

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Figure 1.
Summary of KCNQ1 (LQT1) mutations in the patient cohort. Localization of mutations identified in the *KCNQ1* gene in patients with both atrial fibrillation and long QT syndrome.

KCNJ2 (ATS1)

Figure 2.
Summary of KCNJ2 (Andersen-Tawil syndrome [ATS1]) mutations in the patient cohort. Shown is the localization of a mutation identified in the *KCNJ2* gene in one patient with both atrial fibrillation and Andersen-Tawil syndrome.

Figure 3. SCN5A (LQT3) mutation found in patient 7. Shown is localization of a single mutation identified in the *SCN5A* gene in one patient with both atrial fibrillation and Long QT Syndrome.

Figure 4. *KCNH2* and *SCN5A* mutations found in patient 6. Shown is localization of the mutations identified in the *KCNH2* and *SCN5A* genes in one patient with both long QT syndrome (diagnosed at birth) and atrial fibrillation (diagnosed at age 4 years). * = uncommon polymorphism; ^ = pathogenic mutation.

Figure 5.
ECG recorded from patient 6, a young boy who presented at birth with long QT syndrome and at age 4 years with atrial fibrillation.

Table 1

Demographics of genotype-positive long QT syndrome cohorts

	Total cohort	Mayo cohort	FAMILION cohort
No. of patients	457	252	205
Age at genetic testing (years)	23 ± 16	23 ± 16	23 ± 16
Sex (male/female)	178/279	106/146	72/133
Average QTc at diagnosis (ms)	471 ± 50	465 ± 51	479 ± 51

Values are given as number or mean ± SD.

Table 2
Demographics and specific mutation information for patients with atrial fibrillation and long QT syndrome

Patient no.	Cohort	Sex	Age at diagnosis of LQTS (years)	QTc (ms)	Age at onset of AF (years)	Genotype	Exon	Nucleotide	Amino acid
1	FAMILION	M	15	NA	<15	LQT1	51	19 C>T	P7S
2	Mayo	M	13	420	18	LQT1	3	Del572-576	L191fs/90 [†]
3	FAMILION	F	1	479	<1	LQT1	5	692 G>A	R231H
4	Mayo	M	31	482	31	LQT1	5	704 T>A	I235N
5	Mayo	M	33	422	33	LQT1	7	964 A>G	T322A
6	Mayo	M	1 day	570	4	LQT3	7	825 C>A	N275K [†]
						SCN5A	12	1715 C>A	A572D ^{*†}
7	Mayo	M	44	521	46	LQT3	4	INS "GCGCGGGCG" 569-570	INS GAG 189-190
						KCNH2	28	5350 G>A	E1784K [†]
8	Mayo	F	14	418	14	LQT7	1	224 C>T	T75M [†]

NA = not available.

* A572D-SCN5A is not a pathogenic LQT3-causing mutation but an uncommon polymorphism of uncertain functional significance.

[†] In vitro functional phenotype has been established.