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Long-QT Syndrome and Therapy for Attention Deficit/Hyperactivity Disorder

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Abstract

Introduction—Stimulants are the mainstay therapy for attention deficit/hyperactivity disorder (ADHD) and are associated with adrenergic side effects. There is limited data on the clinical course of patients treated for ADHD who have long-QT syndrome (LQTS), for which β -blockade is the goal of therapy.

Methods—LQTS patients from the Rochester-based LQTS Registry (open-enrollment between 1979–2003; follow-up from 1979 to present) treated with stimulant or non-stimulant ADHD medications (n=48) were compared to a 2:1 age-, gender-, and QTc-duration matched LQTS control group not exposed to ADHD medications (n=96). Kaplan-Meier and Cox proportional hazards regression analyses were used to evaluate risk of cardiac events (syncope, aborted cardiac arrest, and sudden cardiac death) in LQTS patients treated with ADHD medications.

Results—During a mean follow-up of 7.9 ± 5.4 years after initiation of ADHD medication at a mean age 10.7 ± 7.3 years, there was a 62% cumulative probability of cardiac events in the ADHD treatment group compared to 28% in the matched LQTS control group ($p < 0.001$). Time-dependent use of ADHD medication was associated with an increased risk for cardiac events ($HR = 3.07$; $p = 0.03$) in the multivariate Cox model adjusted for time-dependent β -blocker use and prior cardiac events. Subgroup gender analyses showed that time-dependent ADHD medication was associated with an increased risk in male LQTS patients ($HR = 6.80$, $p = 0.04$).

Conclusions—LQTS patients treated with ADHD medications have increased risk for cardiac events, particularly syncope, and this risk is augmented in males. The findings highlight the importance of heightened surveillance for LQTS patients on ADHD medications.

Keywords

long-QT syndrome; congenital arrhythmia; Attention Deficit Hyperactivity Disorder; stimulants; adrenergic side effect

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INTRODUCTION

Congenital long-QT syndrome (LQTS), with a recent prevalence of 1:5000 to 1:2000,^{1,2} is a hereditary channelopathy characterized by prolonged corrected QT interval (QTc) at rest (males >450ms, females >470ms) and predisposition for polymorphic ventricular arrhythmias and cardiac events such as syncope, aborted cardiac arrest (ACA), and sudden cardiac death.^{1,3,4} Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder associated with persistent symptoms of inattention, hyperactivity and/or impulsivity.⁵ There have been reports of serious adverse events with medical therapy from Canada and the United States that have led to vacillating regulatory and policy decisions, resulting in confusion and concern regarding ADHD medication use.⁵⁻⁷ Despite known sympathetic side effects of elevated heart rate and blood pressure, these medications are currently considered relatively safe for the general population, with no associated ECG alterations.⁸ The same generalization, however, may not be appropriate for patients who have cardiovascular conditions such as LQTS, where sympathetic blockade is a major goal of the treatment.

FDA-approved ADHD medications are prescribed for more than 2.7 million children in the United States each year, and the number of newly diagnosed patients with ADHD continues to increase.⁹⁻¹¹ Considering the current dearth of data on the clinical outcome of LQTS patients undergoing ADHD pharmacotherapy, there is a need to better understand the clinical course of these patients to help clinicians and families properly care for this patient population. The present study was designed to: 1) evaluate the clinical course of LQTS patients who are treated with ADHD medications; and 2) assess potential ECG changes during ADHD treatment of patients with LQTS. We hypothesized that LQTS patients who are treated for ADHD would be at greater risk for cardiac events during follow-up compared to those who are not.

METHODS

Study Population

Among subjects of the Rochester-based LQTS Registry,⁴ 144 clinically diagnosed LQTS patients were retrospectively identified for inclusion into this study.

Patients in the ADHD medication group (n=48) were selected based on having started either a FDA-approved stimulant (methylphenidate, dextroamphetamine/amphetamine, lisdexamfetamine, and dexamethylphenidate) or non-stimulant (atomoxetine or guanfacine) medication for ADHD during follow-up. The LQTS Registry did not have specific criteria for the diagnosis of ADHD, but the authors assumed that patients treated with an ADHD medication had the ADHD disorder. The start time of medication use was set as time zero for follow-up in both ADHD and the matched group. To account for stimulant use for other conditions such as depression or narcolepsy, which are typically diagnosed and treated later in life, only patients who began ADHD medication use prior to age 30 were selected. LQTS patients never exposed to ADHD medications (n=96) were randomly selected to match age, gender, and baseline QTc duration of the 48 ADHD LQTS patients in a 2:1 ratio.

All subjects or their guardians provided written informed consent for the genetic and clinical studies. The reported analyses used the LQTS analytic database version 23.

Data Collection and Endpoints

On enrollment, routine clinical and ECG information was obtained from birth to the participants' enrollment age, and ongoing clinical information and ECG parameters were obtained when possible at yearly intervals thereafter. Measured parameters on the first recorded ECG included QT and R-R intervals in milliseconds, with QT corrected for heart rate by Bazett's formula ($QT_c = QT / \sqrt{RR}$).¹² The baseline QTc interval was expressed in continuous form and dichotomized at 500ms. Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical history, ECG findings, therapy, and endpoints during follow-up. Time-dependent ADHD medication use included starting date as well as discontinuation and restarting dates when applicable, similar to the documentation of time-dependent β -blocker therapy.

The primary endpoint of the study was the first occurrence of a cardiac event, defined as syncope, aborted cardiac arrest, or LQTS-related sudden cardiac death during the follow-up period. The secondary endpoint was the occurrence of death.

Statistical analysis

Baseline and follow-up clinical characteristics of the study population were evaluated using the Chi-squared test for categorical variables and the Wilcoxon signed-rank test for continuous variables. The cumulative probabilities of occurrence of cardiac events by ADHD medication use, gender, genotype status and subgroups were assessed using Kaplan-Meier survival analyses, and significance was tested by the log-rank test. The same Kaplan-Meier analyses were used to assess mortality. Follow-up was from the time at which a patient started stimulant or non-stimulant medication in the ADHD group and the same time point was used to begin follow-up in the matched group.

Multivariate Cox proportional hazards regression models were used to evaluate the independent association of time-dependent ADHD medication use and clinical factors with the occurrence of cardiac events during follow-up. Time-dependent influence of ADHD medication use refers to the risk of developing a cardiac event during the time LQTS patients are on the ADHD medication when compared to LQTS patients not receiving ADHD medication. Stratification of the multivariate model by matched group inherently accounted for age, gender, and QTc duration. Other pre-specified covariates in the total population included time-dependent β -blocker therapy and occurrence of cardiac events prior to ADHD medication start time. Subgroup analyses were performed separately for males and females.

Statistical analyses were performed using SAS software version 9.3 (SAS institute Inc, Cary, North Carolina). A 2-sided 0.05 significance level was used for hypothesis testing.

RESULTS

Study Population

A total of 48 patients affected with LQTS were treated with either stimulant or non-stimulant drugs approved for ADHD treatment: 44 on stimulants, 4 on non-stimulants, and 4 on both at one point in time. Ninety-six patients were randomly selected based on matching them to ADHD-treated patients by age, gender, and baseline QTc duration prior to ADHD medication starting time. Of the study population, 44% (n=64) were diagnosed with genetically confirmed LQTS (LQT1:32, LQT2:23, LQT3:8).

The average follow-up time was 6.9 ± 5.5 years for ADHD patients and 8.4 ± 5.2 years for matched patients. The matched ages and baseline QTc durations were also similar (Table 1). LQTS treatments and the frequency of cardiac events were similar between the ADHD and matched groups prior to start time of ADHD treatment.

Influence of ADHD pharmacotherapy in LQTS

LQTS therapy between the groups was similar during follow-up, with the majority of patients in both groups receiving β -blockers and a few had ICDs. A total of 35.4% of the patients in the ADHD group experienced cardiac events after beginning ADHD treatment compared to 15.6% in the matched group ($p=0.007$ [Table 2]). In both groups, cardiac events were dominated by syncope. There were 2 deaths in the study population (1/48 ADHD group; 1/96 matched group).

At 5 years of follow-up, the heart rate of LQTS patients taking ADHD medications was, on average, 11 beats/min faster than that of the matched control patients (Table 2). There was no significant difference in QTc duration between the two groups.

During 15 years of follow-up, there was a 62% cumulative probability of occurrence of cardiac events in the ADHD treatment group compared to 28% in the matched LQTS control group ($p<0.001$ [Figure 1]), with similar event rates between LQTS types 1–3 ($p=0.67$). The cumulative probability of syncope events was also higher in the ADHD treatment group compared to the matched cohort ($p=0.003$, [Figure 2]). Time-dependent use of stimulant and non-stimulant ADHD medication was associated with an increased risk for cardiac events (HR=3.07; 95% CI 1.09–8.64; $p<0.03$ [Table 3]) in the multivariate proportional hazards model adjusting for time-dependent β -blocker use and prior cardiac events, and stratifying by matched groups. Similar results were seen when comparing only patients taking stimulants with the control group (HR=2.57; $p=0.04$) with adjustment for relevant covariates.

In male LQTS patients (n=90, ADHD males=30, matched LQTS males=60), time-dependent ADHD medication was associated with over a 6-fold increased risk for cardiac events compared with the matched control group, but no significantly increased risk was observed in females (Table 3). Within the ADHD medication group (n=48), gender, QTc duration, time-dependent β -blocker use and prior cardiac events were not shown to be significant independent contributors to increased cardiac event risk during follow-up.

Since there was only one death in each of the matched treatment and non-treatment groups, there were too few death events for treatment-related death analysis.

We also assessed the risk of cardiac events by ADHD medication while excluding those who were both on stimulant and non-stimulant medication, as a sensitivity analysis, and confirmed similar results (HR=3.20, 95% CI: 0.92–11.07, p=0.069).

DISCUSSION

In this study, ADHD pharmacotherapy was associated with a 3-fold increase in non-fatal cardiac events when compared to LQTS patients not receiving these medications. These findings suggest that it is the ADHD medications that are contributing to the increased risk since the cardiac event rate was similar between the two groups during a number of years before starting the ADHD medication.

The history of ADHD medication use has been controversial and complicated by the removal and reinstatement of extended-release mixed amphetamine salts,^{6,13} as well as the consideration by three different FDA advisory committees to include a black-box warning for ADHD stimulants.¹⁴ Subsequent clinical trials of healthy children and adult patients have demonstrated statistically significant but not clinically important elevations in heart rate (4–10 bpm) and blood pressure (1–5 mmHg) with ADHD stimulant and non-stimulant use.^{15–24} Despite an increased likelihood of emergency ward and physicians' office visits due to cardiac symptoms (syncope, tachycardia, and palpitations),²⁵ ADHD medications are now viewed as relatively safe for healthy children and adults.^{5,8–10,26,27}

In this study, there was a 3-fold increased likelihood for cardiac event occurrence in the group of LQTS patients on ADHD medications compared to the matched LQTS control patients. This risk was increased to over 6-fold in male LQTS patients treated for ADHD. The overall increased cardiac risk was not unexpected in the LQTS patient population considering the sympathomimetic side effect profile of ADHD medications. A similar increase in the risk of cardiac events has been associated with other sympathomimetic medications such as β -agonist therapy for treatment of asthma in LQTS patients.^{28,29}

There was no significant difference in QTc duration between the two groups in this study during follow-up, which is consistent with previous ADHD trials in healthy subjects.³⁰ In this study of LQTS patients, ADHD medication was associated with an 11 bpm higher average heart rate at 5 years of follow-up, a finding consistent with an increased sympathomimetic state in these patients. It is therefore possible that, given common arrhythmia triggers in LQTS such as noise/emotion and exercise,³¹ cardiac events are more likely to occur in this group because their thresholds for events have been lowered by ADHD pharmacotherapy.

There now exist non-stimulant ADHD medications such as atomoxetine and guanfacine for those who could not tolerate the first-line stimulant therapy. However, case reports documenting fatal cardiac events and seizures associated with atomoxetine use and overdose have been reported.^{32–34} Atomoxetine, as a selective norepinephrine reuptake inhibitor, increases overall availability of norepinephrine that has been shown to result in elevations in

heart rate and blood pressure.^{35,36} This drug has also been reported to inhibit hERG current *in vitro*,³⁷ the potassium (I_{Kr}) current implicated in LQT2. Non-stimulants were therefore included in the primary analysis and findings were similarly significant in the alternative analysis that contains exclusively patients on stimulants and matched patients. However, even though 2 out of 4 patients who used only non-stimulants had cardiac events, we cannot draw conclusions on non-stimulant use alone because of the small numbers of patients and events.

Various risk stratification studies have shown that LQTS patients are at increased risk for cardiac events depending on the patient's age, gender, clinical history, ECG parameters,^{38–43} and genetic subtypes of LQTS.^{44,45} For instance, LQT1 males are at a greater risk for cardiac events during childhood and adolescence.⁴⁶ In the current study, the fact that only 48 LQTS patients received ADHD medications meant that there was insufficient power to assess the effect of genetic subtype on risk from exposure to these drugs.

LIMITATIONS

Because only 48 LQTS patients received ADHD medications, we could not assess the effect of genetic genotype on risk. Since only 4 patients were taking non-stimulant ADHD drugs, we cannot draw definitive conclusions about the risk of these medications (even though 2 of the 4 patients taking them experienced cardiac events). Finally, there were too few death events for treatment-related death analysis.

In this study, transient loss of consciousness was categorized as syncope when there was abrupt onset and offset of the event, thus suggesting an arrhythmic event. However, there was a potential that the transient loss of consciousness was a vasovagal event that could be associated with the drug and not specifically related to LQTS. We cannot definitively answer the causation question of whether it is the ADHD medication that is exacerbating the clinical course of ADHD patients with LQTS or whether it is the ADHD condition itself since the matched control group did not have ADHD. The fact that the pre-medication event rates were similar between the two groups, however, makes it likely that the ADHD medication played a major role in the current findings. Furthermore, annual surveys may be limited in capturing clinical events since remote events may not always be remembered.

CONCLUSIONS

The results of this study indicate that there is a time-dependent increased risk for cardiac events, primarily syncope, in the LQTS study population during ADHD pharmacotherapy, and particularly in male patients. In light of these findings, ADHD medications should be prescribed for LQTS patients only when dysfunctional symptoms clearly require therapy. LQTS patients who require ADHD medication should receive the lowest effective dose and undergo close follow-up.

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Figure 1. Cumulative Probability of First Occurrence of Cardiac Events in the Study Population by ADHD Medication

The values in parentheses are Kaplan-Meier estimates of the cumulative probability of a first occurrence of cardiac events comparing LQTS patients treated with ADHD pharmacotherapy versus age-gender-QTc-matched control LQTS patients.

Figure 2. Cumulative Probability of First Occurrence of Syncope in the Study Population by ADHD Medication

The values in parentheses are Kaplan-Meier estimates of the cumulative probability of a first occurrence of syncope comparing LQTS patients treated with ADHD pharmacotherapy versus age-gender-QTc-matched control LQTS patients.

TABLE 1

Baseline Clinical Characteristics Prior to Starting the ADHD Drug

Clinical Characteristics	ADHD Subjects N=48	Matched Subjects N=96	P-value
Enrollment Age (yrs)	12±6	10±8	0.21(matched)
Female gender	18(38)	36(38)	1.00(matched)
Average follow-up time (yrs)	6.9±5.5	8.4±5.2	0.06
ECG, mean ± SD			
Baseline QTc (ms)	471±41	471±42	0.95(matched)
Maximum QTc (ms)	493±50	486±53	0.25
Baseline Heart Rate (bpm)	87 ± 27.9	89.4 ± 21.6	0.49
LQTS Therapies, n (%)			
β-Blocker	13(27.1)	34(35.4)	0.32
Pacemaker	0(0)	5(5.2)	0.17
ICD	4(8.3)	8(8.3)	1.00
LCSD	0(0)	0(0)	
Cardiac Events, n (%)			
Any Cardiac Event	12(25.0)	23(24.0)	0.89
Syncope	11(22.9)	23(24.0)	0.89
ACA	1(2.1)	2(2.1)	1.00
Genotype Data, n (%)			
Genotype-positive	17(35.4)	47(49.0)	0.72
Unknown	31(64.6)	49(51.0)	
LQT1	4(30.8)	28(71.8)	0.01
LQT2	6(40.0)	17(53.1)	0.40
LQT3	6(40.0)	2(12.5)	0.11

ACA= aborted cardiac arrest; ICD= implantable cardioverter-defibrillator; LCSD= left cervical sympathetic denervation; LQTS= long-QT syndrome; LQT1=long QT syndrome type 1; LQT2= long-QT syndrome type 2; LQT3= long-QT syndrome type 3; SD= standard deviation; QTc= corrected QT interval.

TABLE 2

Follow-Up Therapy and Events after Starting ADHD Therapy and the Equivalent Start Time in the Matched Control Subjects

	ADHD Subjects	Matched Subjects	P-value
LQTS Therapies, n (%)			
β-Blocker	29(60.4)	54(56.3)	0.63
Pacemaker	1(2.1)	0(0)	0.33
ICD	13(27.1)	16(16.7)	0.14
LCSD	0(0)	0(0)	
ADHD Medication, n (%)			
Stimulants	44	0	
Non-Stimulants	4	0	
Both	4	0	
Cardiac Events, n (%)			
All Cardiac Events	17(35.4)	15(15.6)	0.007
Syncope	14(29.2)	13(13.5)	0.02
ACA	2(4.2)	1(1.0)	0.26
LQTS Death	1(2.1)	1(1.0)	1.00
ECG at 5.2 yrs follow-up			
Mean HR (bpm)	72.9 ± 11.0	61.7 ± 13.6	0.01
Mean QTc (ms)	469 ± 35	472 ± 38	0.39

Abbreviations as in Table 1.

TABLE 3

Hazard Ratio for Risk of First Cardiac Event in Study Population and in Gender Subgroups

	HR	95% CI	p-Value
STUDY POPULATION (n=144)			
Time-dependent ADHD therapy	3.07	1.09–8.64	0.03
Time-dependent β -blocker therapy	0.43	0.11–1.58	0.20
Prior Cardiac Event	1.89	0.47–7.66	0.38
SUBGROUPS			
Females (n=54): Time-dependent ADHD therapy vs. Controls	1.11	0.38–3.23	0.84
Males (n=90): Time-dependent ADHD therapy vs. Controls	6.80	1.13–40.91	0.04

HR=hazard ratio for first cardiac event in ADHD patients vs. matched group; CI= confidence interval. Each gender subgroup was adjusted for time-dependent beta-blocker use and prior cardiac events.