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Stimulant therapy in children with attention-deficit/hyperactivity disorder and concomitant long QT syndrome: A safe combination?

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Abstract

BACKGROUND—Attention-deficit/hyperactivity disorder (ADHD) is prevalent in about 11% of children in the United States. As such, ADHD is expected to be present in patients with long QT syndrome (LQTS), a rare, potentially lethal but highly treatable cardiac channelopathy. ADHD-directed stimulant therapy is relatively contraindicated in patients with LQTS because of concern for LQTS-triggered events.

OBJECTIVE—The purpose of this study was to evaluate the ADHD-directed treatment, outcome, and frequency of LQTS-triggered events in patients with LQTS and concomitant ADHD.

METHODS—A retrospective electronic medical record review of 357 pediatric patients with LQTS evaluated between 1999 and 2014 was performed to determine the prevalence of concomitant ADHD and the incidence of LQTS-triggered events in patients with LQTS, with or without concomitant ADHD.

RESULTS—Overall, 28 patients (8%) were diagnosed with LQTS concomitant ADHD. There were no phenotypic differences between patients with LQTS and ADHD, and LQTS alone. ADHD-directed stimulant therapy was stopped or advised against in 19 patients (68%) at the time of first evaluation or after diagnosis. None of the 15 stimulant-treated patients experienced LQTS-triggered events in a combined 56 person-years of treatment. Perhaps paradoxically, there was a statistically lower LQTS-triggered event rate in the stimulant-treated ADHD group compared to the LQTS alone cohort.

CONCLUSION—Among patients with mild- to moderate-risk LQTS, we found a prevalence of ADHD similar to that in the general population, which can be treated effectively and safely with stimulant therapy. Physicians should find reassurance in the low adverse event rate and should weigh the potential effects of suboptimal treatment of ADHD with the theoretical proarrhythmic risk from stimulant medications.

Keywords

Long QT syndrome; Stimulant therapy; Attention-deficit/hyperactivity disorder

Introduction

Congenital long QT syndrome (LQTS) is a cardiac channelopathy that affects approximately 1 in 2000 persons and commonly manifests with symptoms of syncope, seizures, or sudden cardiac death (SCD).^{1–3} However, many patients with LQTS, even those with a positive family history of LQTS or SCD, and/or an LQTS-associated mutation, may never evidence a prolonged QT interval on an ECG or experience an LQTS-triggered episode.⁴ Although patients with LQTS have an increased risk of SCD, the estimation of this risk varies depending on several factors, including QT interval, sex, genetic locus, and specific mutation(s).^{5,6} Studies have shown that the incidence of sentinel cardiac arrest or sudden death ranging between 0.28% and 0.96% per year depending on these risk factors in the first 40 years.⁶ Therefore, the primary management and treatment goal for patients with LQTS is to decrease the risk of an LQTS-triggered SCD.

In contrast, attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder estimated to affect up to 11% of children in the United States.⁷ ADHD is characterized by persistent symptoms of inattention, hyperactivity, and impulsivity, which can interfere with daily function and development.^{7,8} Long-term effects of ADHD are lower grades, lower standardized test scores, and decreased high school completion rates.⁹ The primary management goal is to decrease core symptoms with pharmacotherapy and behavioral therapy to allow for normal function and development. Stimulant medications, such as methylphenidate, significantly reduce core symptoms of ADHD compared with nonstimulant medication or behavioral therapy. However, combined stimulant and behavioral therapy improves academic performance and reduces conduct problems the most.¹⁰

Stimulant medications have had a controversial association with serious cardiac events. In February 2006, the United States Food Drug Administration (FDA) Advisory Committee recommended a black box warning because of case reports of serious cardiac events (stroke, myocardial infarction, and hypertrophy) and sudden death in adults and children.^{11,12} In 2008, the American Heart Association published a statement advocating the use of nonstimulant medication or behavioral therapy before the use of stimulants.¹³ In patients with LQTS, catecholamine release or sympathetic stimulation secondary to exercise, emotions, or exogenous catecholamines have been associated with QT prolongation and torsades de pointes leading to syncope or SCD.^{14,15}

Although there have been recent large population-based studies for the pediatric population as a whole, information regarding the safety and use of stimulants in children with LQTS is limited. Importantly, all stimulant and many nonstimulant drugs are on the QT drug list of “Drugs to Avoid in Patients with LQTS.”¹⁶ Therefore, our objective was to evaluate our cohort of pediatric patients with LQTS and (1) determine the prevalence of concomitant

ADHD and (2) evaluate the ADHD-directed treatment, outcome, and frequency of LQTS-triggered events in patients with both LQTS and ADHD.

Methods

We performed a retrospective review of the electronic medical records of 357 pediatric patients (18 years) who were clinically and/or genetically diagnosed with LQTS in Mayo Clinic's LQTS/Genetic Heart Rhythm Clinic between the years of 1999 to 2014. For all pediatric patients, the electronic medical record was reviewed for basic demographics, LQTS phenotype, therapy, and LQTS-triggered events. For patients identified to have a concomitant diagnosis of ADHD, additional data were collected on ADHD diagnosis, ADHD-directed therapy, and the duration of treatment. The study was approved by the Mayo Clinic Institutional Review Board.

Outcomes were evaluated to determine the incidences of LQTS-triggered events in patients with LQTS, with or without concomitant ADHD. A LQTS-triggered event was defined as otherwise unexplained syncope or seizure, appropriate implantable cardioverter defibrillator (ICD) shock, documented ventricular arrhythmia, or cardiac arrest after the diagnosis of LQTS was made. Event rate per 100 years was calculated as the total number of cardiac events for the study cohort during the total available follow-up.

For the purpose of our retrospective study and to ensure accurate follow-up and stimulant use, we evaluated treatment follow-up for those diagnosed with concomitant ADHD starting at the patient's evaluation at Mayo Clinic. ADHD treatment-years were defined as years of treatment with a definite and identifiable start time, whereby the end time was considered the last Mayo Clinic follow-up visit. Follow-up for the rest of the pediatric LQTS cohort was defined as the time elapsed from the initial Mayo Clinic evaluation and censored to September 1, 2014.

Statistical analysis was performed using the Student *t* test and Fisher exact test to compare cohort characteristics, and Poisson regression analyses to compare LQTS-triggered event rates. These tests were performed using JMP software (SAS Institute; version 10.0).

Results

The demographics of the pediatric LQTS cohort of 357 patients (178 male [50%]) are given in Table 1. Mean age at diagnosis was 8.2 ± 5.9 years, and mean QTc was 470 ± 52 ms. Overall, 25% of patients had experienced at least 1 LQTS-triggered event before the initial presentation to Mayo Clinic, 67% had a family history of LQTS, and 39% had a family history of SCD. Genetic testing confirmed that 337 (95%) were genotype positive, of whom 169 (47%) had LQT1, 121 (34%) had LQT2, and 34 (10%) had LQT3. LQTS-directed pharmacologic therapy was prescribed for 296 patients (83%; most commonly beta-blockers); 69 (19%) had an ICD, and 68 (19%) had left cardiac sympathetic denervation (LCSD). Mean overall follow-up for the entire cohort was 8.2 ± 4.1 years.

In total, 28 LQTS patients (8%) had been diagnosed with concomitant ADHD (Figure 1 and Table 1; group B), a prevalence similar to that of the general population.⁷ There were 14

male and 14 female patients (mean age at ADHD diagnosis 11.6 ± 3.6 years, mean age at LQTS diagnosis 9.5 ± 4.5 years). Mean QTc was 465 ± 42 ms. Three patients (11%) were symptomatic at diagnosis of LQTS, 20 (71%) had a family history of LQTS, and 11 (39%) had a family history of SCD. All 28 had a positive LQTS genetic test: 12 (43%) had LQT1, 8 (29%) had LQT2, and 4 (14%) had LQT3. There was no specific relationship between the major LQTS genotypes (LQT1, LQT2, and LQT3) and diagnosis of ADHD ($P = .7$, $P = .7$, and $P = .3$, respectively). In this LQTS-ADHD group, 24 patients (86%) were on beta-blocker therapy, 3 (11%) had an ICD, and 4 (14%) had LCSD. Overall follow up was 7.4 ± 3.7 years. Overall, there were no significant phenotypic differences between patients with ADHD and LQTS (group B) and patients with LQTS alone (group A; Table 1).

Before their evaluation at Mayo Clinic, many of these patients (19 [68%]) had their stimulant therapy stopped or advised against because of concern for increased risk of serious cardiac events, thus leaving them untreated for their ADHD. Overall, among these 28 patients diagnosed with LQTS and ADHD, 15 had a history of stimulant therapy alone, and 4 had a history of combined stimulant and nonstimulant therapy at the time of the initial Mayo Clinic evaluation (Table 2 and Figure 1). Five patients did not have any pharmacologic treatment of ADHD. The stimulant medications used included methylphenidate (9), dextroamphetamine (6), and dexamethylphenidate (4). Of these 19, follow-up data were available for 15, for a total of 56 years of treatment while undergoing ADHD-directed stimulant therapy and the LQTS-directed treatment program (Figure 1).

Table 3 details the specific LQTS demographics and ADHD treatment information on these 15 patients. Akin to our overall cohort, these 15 showed a mild-to-moderate LQTS phenotype. Overall, there were 9 males (60%; mean age at diagnosis 9.8 ± 4 years, mean QTc 453.6 ± 16 ms). One patient (7%) was symptomatic at diagnosis, 12 had a family history of LQTS (80%), 7 (47%) had a family history of SCD, 1 patient had an ICD (7%), and 3 (20%) underwent LCSD surgery. Further clinical demographics and comparisons to the remainder of the LQTS cohort can be found in Online Supplementary Table 1. No statistical differences between the 2 groups were observed.

Overall, in the stimulant-treated ADHD group ($n = 15$), no LQTS-triggered events occurred during a total of 56 years of follow-up of stimulant-directed therapy, or 0 events per 100 patient-years (95% confidence interval 0–6.6). In contrast, among the majority subset of children with LQTS alone, a total of 163 events occurred for a total of 2735 follow-up years, amounting to an event rate of 6 events per 100 patient-years (95% confidence interval 5.1–6.9). To determine the difference between the 2 groups, a Poisson regression showed a statistically significant lower LQTS-triggered event rate among the patients with both LQTS and ADHD ($P < .01$; Figure 2).

Discussion

Stimulant medications used for the treatment of ADHD have had a controversial association with serious cardiac events. In February 2006, the FDA Advisory Committee recommended a black box warning after submission of about 25 cases of sudden death and 43 cases of serious cardiac events (stroke, myocardial infarction, and hypertrophy) in adults and children

on stimulant therapy reported to the FDA adverse event reporting system.^{11,12} In 2008, the American Heart Association published a statement saying that for patients with heart conditions (including LQTS), “it is reasonable to use stimulants with caution after other methods of treatment for ADHD have been considered or used.” These other methods include nonstimulant medications and behavioral therapy.¹³

However, stimulant medications have shown to have the greatest efficacy in decreasing the core symptoms of ADHD compared to nonstimulants, which is why they are recommended over nonstimulant medications in both the American Academy of Child and Adolescent Psychiatry practice parameters as well as the American Academy of Pediatrics Clinical Practice Guidelines.^{17,18} These recommendations create a clinical dilemma for physicians caring for patients with LQTS and ADHD, because both treating and not treating have significant effects on SCD risk and quality of life for these patients.

The mechanism of action of stimulant medications (methylphenidate or amphetamine salts) is an increase of norepinephrine and/or dopamine by either releasing or inhibiting reuptake of catecholamines at the synapse.^{19,20} In patients with LQTS, catecholamine release or sympathetic stimulation secondary to exercise, emotions, or exogenous catecholamines has been associated with prolongation of the QT interval and torsades de pointes leading to syncope or SCD.^{14,15} Thus, a theoretical concern, backed by initial case reports, has been the rationale against prescribing ADHD-directed stimulants in patients with LQTS. Since 2006, larger population-based studies have evaluated the adverse events of stimulant medications, but no studies have specifically focused on the pediatric population with congenital heart disease or, more specifically, LQTS have been performed.

This patient population is particularly vulnerable to not receive stimulant medications for treatment of their ADHD because of the existing QT warnings associated with these drugs and their underlying heart disease. This was seen in our current study, in which 19 (68%) patients, before their Mayo Clinic evaluation, had their stimulant therapy advised against or discontinued, thus leaving their ADHD untreated.

Herein, we present the largest single-center study evaluating the prevalence of ADHD among patients with LQTS and the use of ADHD-directed stimulant therapy and its effects on LQTS-triggered events in these patients. Similar to the national prevalence of ADHD in the overall population, 28 patients (8%) of our LQTS cohort had been diagnosed with ADHD. When comparing the patients with LQTS and stimulant-treated ADHD to patients with LQTS alone, both cohorts were similar phenotypically with respect to basic demographics, LQTS clinical phenotype, and LQTS-related therapy (see Online Supplementary Table 1). Overall, the entire cohort could be considered a mild- to moderate-risk LQTS cohort based on percentage of symptomatic presentation (25%) and mean QTc (470 ms).

In our study, the 15 patients with LQTS and ADHD treated with ADHD-directed stimulants had no LQTS-triggered events during a total of 56 years of follow-up while on stimulants. Meanwhile, there were 163 LQTS-triggered events for a total of 2735 follow-up years in the patients with LQTS alone, or 6 events per 100 patient-years. However, a few patients with a

very severe LQTS phenotype had multiple LQTS-triggered events/recurrences (>10 events), which could overestimate the event rate in the LQTS alone cohort. Overall, the LQTS-triggered event rate in those who were treated with stimulants was significantly lower than the event rate in the rest of the cohort ($P<.01$; Figure 2).

These findings, although specific to the LQTS population, are similar to those of more recent large population-based studies. Since 2008, several studies have refuted the notion of an increased risk of serious cardiac events secondary to use of stimulant medications, noting instead a low absolute event rate for the greater population.^{21–23} Cooper et al²¹ conducted a large retrospective cohort study of 1.2 million children and young adults treated with ADHD stimulant medications and follow-up of 2.5 million person-years. Their study showed that the point estimate of the relative risk provided no evidence that use of ADHD drugs increased the risk of serious cardiac events in those currently taking ADHD drugs. A systematic review showed that in 6 of 7 studies of children and adolescents, there was no increased risk adverse cardiovascular events. Despite massive sample sizes, they found that because of the very low incidence of serious cardiac events in children, the power needed to detect an association would be extraordinary high.²²

Given that the American Heart Association guidelines denote stimulant-based ADHD therapy as a class IIa recommendation with level of evidence C (“consensus opinion, case studies, or standard of care”), Mayo Clinic’s LQTS Clinic has approached therapeutic decisions based on patient and family autonomy and shared decision making, severity of LQTS, and optimal LQTS therapy and SCD prevention, while striving for the highest quality of life for patients and their families. The impact of possible ADHD stimulant therapy is considered carefully and is discussed with the patient and family instead of dismissing or excluding it right away. In our cohort of patients with congenital LQTS and concomitant ADHD with stimulant-directed therapy, there was no increase in LQTS-triggered events. In fact, we observed a seemingly paradoxical decrease in LQTS-triggered events. Although interpretation of this finding is hampered by small numbers, this could be explained by increased compliance with LQTS therapy motivated by the possibility to then also treat the ADHD. This is not uncommon, having observed a similar effect in our athletic LQTS cohort.²⁴

Study limitations

Inherent to clinical retrospective research, this study has some limitations, such as the tertiary nature of the LQTS clinic and the dependence on data from referral centers. Given the low prevalence of congenital LQTS compounded with the diagnosis of ADHD, it will be hard to gain sufficient power and follow-up. To remedy this for future studies, a nationwide congenital LQTS registry or validation study in a different LQTS cohort from a different institution would strengthen our results. However, at this time, this is the largest cohort of children with LQTS studied on this topic, and the results are important for the management and treatment of the subset with both LQTS and ADHD. Finally, although a comprehensive search was conducted through the database and based on the nature of retrospective chart review, treatment years, diagnosis dates, and LQTS-triggered events were limited to information documented.

Conclusion

This is the first and largest study to determine the prevalence and outcome of patients with LQTS and concomitant ADHD. Among patients with LQTS, the prevalence of ADHD is similar to that of the general pediatric population. For those with LQTS and ADHD who were treated with stimulants, no LQTS-triggered events were observed. Therefore, current guideline recommendations advising against stimulant therapy for all children with LQTS, despite its severity, may be too strict and may be causing suboptimal treatment for ADHD, and may be safe for those with mild- to moderate-risk LQTS. Physicians should weigh the potential long-term effects of suboptimal treatment of ADHD with the theoretical proarrhythmic risk from stimulant medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix: Supplementary data

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.hrthm.2015.04.043>

ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
FDA	Food Drug Administration
ICD	implantable cardioverter-defibrillator
LCSD	left cardiac sympathetic denervation
LQTS	long QT syndrome
SCD	sudden cardiac death

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CLINICAL PERSPECTIVES

For clinicians, taking care of children with long QT syndrome (LQTS) and concomitant attention-deficit/hyperactivity disorder (ADHD) and balancing the risks and benefits of ADHD-directed stimulant medications (most of which are contraindicated in patients with LQTS) has been difficult and controversial. Our study is the first to show the outcomes of children with mild- to moderate-risk LQTS treated with ADHD-directed stimulant therapy for their ADHD. We found that many children with LQTS and ADHD had their stimulants discontinued or not started because of concerns for cardiac events. However, in our study, we found that among patients who continued stimulant treatment, there was no increase in LQTS-related cardiac events. This finding shows that ADHD-directed stimulant therapy in children with mild- to moderate-risk LQTS and ADHD may be safe, and current guidelines based on expert opinion may be too strict.

Figure 1.

Study cohort. Flowchart showing the study cohort and several subsets (based on diagnosis or treatments) compared throughout the study. ADHD = attention-deficit/hyperactivity disorder; LQTS = long QT syndrome.

Figure 2. Comparison of attention-deficit/hyperactivity disorder (ADHD) therapies and long QT syndrome (LQTS) adverse event rate. Bar diagram shows the event rate in patients with LQTS and ADHD treated with stimulants (*left*) compared to patients with LQTS alone (*right*).

Table 1

Cohort demographics and comparisons between patients with LQTS and ADHD, and LQTS alone

	Entire cohort	LQTS alone (group A)	ADHD (group B)	P value
No. (%)	357	329 (92)	28 (8)	
Gender male/female (% male)	178/179 (50)	164/165 (50)	14/14 (50)	.1
Median age at diagnosis (years)	8.2 ± 5.9	8.1 ± 6.0	9.6 ± 4.5	.1
Mean QTc (ms)	470 ± 52	470 ± 53	465 ± 42	.5
Symptomatic presentation	90 (25)	87 (26)	3 (11)	.07
Family history of LQTS	240 (67)	220 (67)	20 (71)	.7
Family history of SCD	137 (39)	126 (38)	11 (39)	.3
LQTS genotype				
LQT1	169 (47)	157 (48)	12 (43)	.7
LQT2	121 (34)	113 (34)	8 (29)	.7
LQT3	34 (10)	30 (9)	4 (14)	.3
Other (4, 5, 8, 12, mixed 1 and 2)	13 (4)	9 (3)	4 (14)	.01
Genotype negative or unknown	20 (5)	20 (6)	0 (0)	.1
Medical therapy	296 (83)	272 (83)	24 (86)	.8
ICD	69 (19)	66 (20)	3 (11)	.3
LCSD	68 (19)	64 (19)	4 (14)	.6
Follow-Up (years)	8.3 ± 4.1	8.3 ± 4.1	7.4 ± 3.7	.2

Values are given as no. (%) or mean ± SD, unless otherwise indicated. ADHD = attention-deficit/hyperactivity disorder; ICD = implantable cardioverter-defibrillator; LCSD = left cardiac sympathetic denervation; LQTS = long QT syndrome; SCD = sudden cardiac death.

Table 2**LQTS and ADHD treatment**

No. of patients with ADHD	28
Mean age at ADHD diagnosis (years)	11.5 ± 3.6
ADHD treatment n	
Stimulants only	15 (54)
Combination	4 (14)
Nonstimulants	4 (14)
None	5 (18)
ADHD medication not started, paused, or discontinued because of LQTS diagnosis before Mayo Clinic evaluation	19 (68)
Total years of stimulant therapy	55.7

Values are given as no. (%) or mean ± SD, unless otherwise indicated. ADHD = attention-deficit/hyperactivity disorder; LQTS = long QT syndrome.

Table 3

Individual LQTS and ADHD characteristics of the stimulant-treated LQTS cohort

Case	M/F	Gene	Mutation	Symptom at				FHX LQTS	FHX SCD	FHX ICD	LCSD	Beta-blocker therapy	Age at ADHD diagnosis (years)	ADHD treatment	Years on ADHD therapy	LQTS event
				Age at LQTS diagnosis (years)	QTc (ms)	diagnosis (age at event)	diagnosis (age at event)									
1	M	<i>KCNQ1</i>	E115G	10	448	N	N	Y	N	N	N	None	10	Stim	4	0
2	F	<i>KCNQ1</i>	G168fs/68	9	444	Syncope (9)	N	Y	N	N	N	Nadolol	6	Stim/NS	7	0
3	F	<i>KCNQ1</i>	G269S	14	453	N	N	N	Y	N	N	Nadolol	13	Stim	1	0
4	M	<i>KCNQ1</i>	G269S	6	467	N	N	Y	Y	N	Y	Nadolol	6	Stim	1	0
5	M	<i>KCNQ1</i>	A344A	6	480	N	N	Y	Y	N	Y	Nadolol	15	Stim/NS	2.5	0
6	F	<i>KCNQ1</i>	Q356X	8	460	N	N	Y	Y	N	N	Nadolol	13	Stim	1	0
7	M	<i>KCNQ1</i>	I567T	10	476	N	N	N	N	N	N	Nadolol	7	Stim	5	0
8	M	<i>KCNQ1</i>	A590T	16	437	N	N	N	N	N	N	Nadolol	10	Stim	6.5	0
9	M	<i>KCNH2</i>	N33T	3	418	N	N	Y	N	N	N	Nadolol	8	Stim	0.2	0
10	M	<i>KCNH2</i>	Q376sp	3	458	N	N	Y	Y	Y	Y	Nadolol	9	Stim/NS	0.3	0
11	M	<i>KCNH2</i>	G1036fs/81	15	460	N	N	Y	Y	N	N	Nadolol	12	Stim	3	0
12	F	<i>SCN5A</i>	E1784K	9	447	N	N	Y	Y	N	N	None	9	Stim	9	0
13	F	<i>KCNE1</i>	S28L	13	465	N	N	Y	N	N	N	Nadolol	11	Stim	5	0
14	M	<i>KCNE1</i>	S28L	13	456	N	N	Y	N	N	N	Nadolol	14	Stim	1.5	0
15	F	<i>SNTA1</i>	A257G	12	436	N	N	Y	N	N	N	None	10	Stim/NS	7	0

ADHD = attention-deficit/hyperactivity disorder; FHX = family history; ICD = implantable cardioverter defibrillator; LCSD = left cardiac sympathetic denervation; LQTS = long QT syndrome; NS = nonstimulant; SCD = sudden cardiac death; Stim = stimulant.