High Prevalence of Neurodevelopmental Disorders in Pediatric Long QT Syndrome: A Single Centre Experience

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Abstract

Background: Long QT Syndrome (LQTS) is a rare familial ion channelopathy that may result in syncope, cardiac arrest and sudden death. Ion channel gene variants have been implicated in neurodevelopmental disorders (NDDs), however the link between LQTS and NDDs in children is not well characterized. **Methods:** This retrospective observational cohort study included patients diagnosed with LQTS at <19 years of age with an NDD diagnosis, prospectively enrolled in an inherited arrhythmia registry at a tertiary hospital between April 2015- June 2021. Patients with hypoxic ischemic injury were excluded. Demographics, genetics, therapy and outcomes were evaluated. **Results:** Among 106 LQTS patients in the registry, we identified 15 (14%) with NDDs. Eleven (73%) of 15 patients were male compared with 4 (27%) females (p=0.02). Thirteen (87%) were *KCNQ1*-positive, with mean age at LQTS diagnosis of 6.6 years (SD: 4.3) and baseline QTc of 446ms (SD: 24). Eight (53%) patients had attention deficit hyperactivity disorder, followed by 4 (27%) with learning/communication disorder, 3 (20%) with autism spectrum disorder and 2 (13%) with motor disorder. Nine of 15 (60%) patients received an NDD diagnosis 4.4 (SD: 2.1) years post-LQTS diagnosis; 4 (27%) pre-LQTS diagnosis, and 2 (13%) were unknown. Thirteen (87%) patients were treated with Nadolol monotherapy, 1 (7%) with flecainide and 1 (7%) with lifestyle modifications only. Five (33%) patients were taking a concomitant psychostimulant for their NDD, and none experienced arrhythmic events on therapy. LQTS-related event was experienced by 1 (7%) patient over a mean follow-up of 5.7 (SD: 3.9) years. **Conclusion:** The prevalence of NDD in LQTS patients (14%) was higher compared to the general population (4.5-9%). Larger studies investigating the link between *KCNQ1*, other LQTS-related genes and NDDs are warranted.

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Conflicts of Interest: None

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Results: Among 106 LQTS patients in the registry, we identified 15 (14%) with NDDs. Eleven (73%) of 15 patients were male compared with 4 (27%) females (p=0.02). Thirteen (87%) were*KCNQ1* -positive, with mean age at LQTS diagnosis of 6.6 years (SD: 4.3) and baseline QTc of 446ms (SD: 24). Eight (53%) patients had attention deficit hyperactivity disorder, followed by 4 (27%) with learning/communication disorder, 3 (20%) with autism spectrum disorder and 2 (13%) with motor disorder. Nine of 15 (60%) patients received an NDD diagnosis 4.4 (SD: 2.1) years post-LQTS diagnosis; 4 (27%) pre-LQTS diagnosis, and 2 (13%) were unknown. Thirteen (87%) patients were treated with Nadolol monotherapy, 1 (7%) with flecainide and 1 (7%) with lifestyle modifications only. Five (33%) patients were taking a concomitant psychostimulant for their NDD, and none experienced arrhythmic events on therapy. LQTS-related event was experienced by 1 (7%) patient over a mean follow-up of 5.7 (SD: 3.9) years.

Conclusion: The prevalence of NDD in LQTS patients (14%) was higher compared to the general population (4.5-9%). Larger studies investigating the link between *KCNQ1* , other LQTS-related genes and NDDs are warranted.

Keywords: Long QT syndrome, pediatric, channelopathies, neurodevelopmental disorders, intellectual disability, autism, ADHD

Introduction

Long QT Syndrome (LQTS) is an ion channelopathy characterized by a prolonged corrected QT interval (QTc) on an electrocardiogram and a structurally normal heart with risk of malignant arrhythmias and sudden cardiac death[1]. The majority of LQTS cases can be categorized into three common subtypes (LQTS1-3) associated with variants in *KCNQ1* , *KCNH2* and *SCN5A* genes, respectively[2]. Ion channel dysfunction in the brain, like in the heart, may alter ion channel excitability, which may potentially lead to neurological manifestations[3]. The clinical and pathological link between cardiac ion channel mutations and comorbid epilepsy and LQTS, has been previously evaluated[4]. However, studies investigating the potential association between LQTS and neurodevelopmental disorders (NDDs) are limited. The aim of this study was to evaluate the prevalence and clinical phenotype of pediatric LQTS patients with NDDs.

Methods

We retrospectively assessed patients diagnosed with LQTS at <19 years of age, who were prospectively enrolled in an inherited arrhythmia registry at a tertiary hospital between April 2015- June 2021. Patients with hypoxic ischemic injury were excluded. Data on demographics, baseline QTc on stress test and during recovery, genetics, comorbid NDD diagnosis and treatments was extracted from the registry. Ethical approval was obtained from The University of British Columbia, Children's and Women's Health Centre of British Columbia Research Ethics Board (H15-00898).

Categorical data are reported as counts and frequencies (%) and continuous data as mean +/- standard deviation (SD). Sex differences within the group were determined using Fisher's exact test.P <0.05 was

considered significant.

Results

A total of 106 LQTS patients were prospectively enrolled in an inherited arrhythmia registry, between April 2015- June 2021. Of these patients, 15 (14%) had a NDD. Eleven (73%) of 15 NDD patients were male and 4 (27%) were female (p=0.02) with a mean age at LQTS diagnosis of 6.6 years (SD: 4.3) (Table 1). Seven (47%) were Canadian First nation, 5 (33%) Caucasian, 2 (13%) Greek, and 1 (7%) unknown. Fourteen (93%) patients had a positive family history of LQTS, with 1 (7%) unknown. The following NDD diagnoses were reported: 8 (53%) with ADHD, 4 (27%) with learning/communication disorder, 3 (20%) with ASD and 2 (13%) with motor disorder (Table 2). Nine (60%) patients received an NDD diagnosis 4.4 (SD: 2.1) years post-LQTS diagnosis; 4 (27%) pre-LQTS diagnosis, and 2 (13%) with unknown dates of diagnosis. Mean baseline QTc was 446ms (SD: 24) and 499ms (SD: 17; n=10) during stress test recovery. Of the 15 patients, 13 (87%) were *KCNQ1* -positive, with 5 (38%) carrying founder variant p.V205M. Locations of LQTS associated*KCNQ1* variants found in this cohort are presented in Figure 1. Nadolol monotherapy was prescribed in 13 (87%) patients, followed by flecainide in 1 (7%) and 1 (7%) patient was managed with lifestyle modifications only. Five (33%) patients were taking a concomitant psychostimulant and experienced no arrhythmic events on therapy. LQTS-related event rate was experienced by 1 (7%) patient over a mean follow-up of 5.7 (SD: 3.9) years after LQTS diagnosis. This patient experienced syncope/pre-syncope and was therapy compliant.

Discussion

In our cohort, pediatric patients diagnosed with LQTS had a higher prevalence of NDD (14%) compared with the general population (4.5-9%)[5, 6]. A previous study reported similar prevalence of NDDs (12%) in neonatal LQTS[7]. Interestingly, contrary to our findings, studies have reported lower rates of NDDs in LQTS-1 compared with other LQTS types[4, 7]. Previous studies have reported a link between other inherited arrhythmia syndromes and NDDs. In catecholaminergic polymorphic ventricular tachycardia, associated with variants in the cardiac ryanodine receptor type 2, 8% of patients were reported to have an intellectual disability[8]. LQTS-8, or Timothy Syndrome, associated with variants in the cardiac L-type calcium channel, is characterized by a multi system disorder including cardiac arrhythmias and autism in over 80% of patients[9]. It is suggested that these ion channels play a role in regulating neuronal gene expression, neurotransmitter levels, neuronal hyper-excitability and in subsequent neurodevelopmental disorders[10].

In our cohort, those affected with an NDD were most often male. This observation is consistent with previous reports which report a younger age of LQTS presentation among males[11]. There was no clear association between variant localization in *KCNQ1* and NDD (Figure 1). This finding would suggest that LQTS patients with a*KCNQ1* variant irrespective of the variant localization are at risk of NDDs. The localization of *KCNQ1* mutations warrants further investigation among LQTS patients with NDDs.

None of our patients experienced any cardiac events on concomitant psychostimulant medications as has been reported previously in patients with LQTS and ADHD[12]. This is reassuring since LQTS patients are advised to avoid taking stimulants due to their QT interval prolonging effects (www.crediblemeds.org). However, other studies have reported higher cardiac events rates compared with our cohort[4, 7]. This is possibly because of differences in phenotypic profiles between the cohorts, especially because they comprised of younger, mostly infantile populations at LQTS presentation[4, 7].

Over half of the LQTS patients received their NDD diagnosis with a delay of 4-years post-LQTS diagnosis suggesting the need for multidisciplinary care in LQTS. Psychological consultation is imperative in the management of patients diagnosed with an inherited arrhythmia syndrome such as LQTS[13]. The presence of psychological support may potentially help in an earlier NDD diagnosis and improve prognosis through early behavioural intervention[14].

Our study was limited by its retrospective nature and small sample size. Future prospective studies investigating the relationship between LQTS and NDDs with larger cohorts are warranted.

Conclusion

The incidence of NDDs was higher in this cohort of LQTS patients compared to the general population. The low incidence of cardiac events while on concomitant psychostimulants was reassuring. Earlier diagnoses, psychological support and behavioural intervention in LQTS patients with NDDs could lead to improved clinical outcomes.

References

1. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ Arrhythm Electrophysiol 2012;5:868-877.

2. Wilde AAM, Amin AS, Postema PG. Diagnosis, management and therapeutic strategies for congenital long QT syndrome. Heart 2022;108:332-338.

3. Goldman AM, Glasscock E, Yoo J, Chen TT, Klassen TL, Noebels JL. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci Transl Med 2009;1:2ra6.

4. Miyazaki A, Sakaguchi H, Aiba T, Kumakura A, Matsuoka M, Hayama Y, Shima Y, Tsujii N, et al. Comorbid Epilepsy and Developmental Disorders in Congenital Long QT Syndrome With Life-Threatening Perinatal Arrhythmias. JACC Clin Electrophysiol 2016;2:266-276.

5. Miller AR, Masse LC, Shen J, Schiariti V, Roxborough L. Diagnostic status, functional status and complexity among Canadian children with neurodevelopmental disorders and disabilities: a population-based study. Disabil Rehabil 2013;35:468-478.

6. Arim RG, Garner RE, Brehaut JC, Lach LM, MacKenzie MJ, Rosenbaum PL, Kohen DE. Contextual influences of parenting behaviors for children with neurodevelopmental disorders: results from a Canadian national survey. Disabil Rehabil 2012;34:2222-2233.

7. Moore JP, Gallotti RG, Shannon KM, Bos JM, Sadeghi E, Strasburger JF, Wakai RT, Horigome H, et al. Genotype Predicts Outcomes in Fetuses and Neonates With Severe Congenital Long QT Syndrome. JACC Clin Electrophysiol 2020;6:1561-1570.

8. Lieve KVV, Verhagen JMA, Wei J, Bos JM, van der Werf C, Roses INF, Mancini GMS, Guo W, et al. Linking the heart and the brain: Neurodevelopmental disorders in patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2019;16:220-228.

9. Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R, Napolitano C, Schwartz PJ, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism.Cell 2004;119:19-31.

10. Schmunk G, Gargus JJ. Channelopathy pathogenesis in autism spectrum disorders. Front Genet 2013;4:222.

11. Locati EH, Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Lehmann MH, Towbin JA, Priori SG, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. Circulation 1998;97:2237-2244.

12. Rohatgi RK, Bos JM, Ackerman MJ. Stimulant therapy in children with attention-deficit/hyperactivity disorder and concomitant long QT syndrome: A safe combination? Heart Rhythm 2015;12:1807-1812.

13. Ingles J. Psychological Issues in Managing Families with Inherited Cardiovascular Diseases. Cold Spring Harb Perspect Med 2020;10:

14. Darling SJ, Goods M, Ryan NP, Chisholm AK, Haebich K, Payne JM. Behavioral Intervention for Social Challenges in Children and Adolescents: A Systematic Review and Meta-analysis. JAMA Pediatr 2021;175:e213982.

Tables

Table 1. Demographics of long QT patients included.

Patient	Sex	Ethnicity	Age at LQTS diagnosis (years)	Family history of LQTS (+/-)
1	M	Canadian First Nation	7	+
2	F	Caucasian	11	+
3	M	Canadian First Nation	0.33	+
4	M	Canadian First Nation	4	+
F	F	Canadian First Nation	0	+
6	M	Canadian First Nation	9	unknown
7	M	Canadian First Nation	unknown	+
8	M	Canadian First Nation	8	+
9	M	Caucasian	unknown	+
10	M	Unknown	7	+
11	M	Greek	8	+
12	M	Caucasian	3	+
13	F	Caucasian	4	+
1	M	Greek	10	+
15	F	Caucasian	15	+

M=Male; F=Female; LQTS= Long QT syndrome

Table 2. Clinical data of long QT patients with neurodevelopmental delays.

Patient	LQTS Gene	Variant	QTc on stress test during recovery	NDD	Cardiac symptoms during follow-up	Treatment at last follow-up	Treatment at last follow-up	Durati of Follow (years)
						For LQTS	For NDD	
1	*KCNQ1*	R591H	480	ADHD	Presyncope, syncope	Nadolol 60 mg	Concerta 36mg	5
2	*KCNQ1*	C.477+1 G>A	480	ADHD	asymptomatic	Nadolol 40 mg	Concerta 18 mg	1
3	*KCNQ1*	V205M	unknown	ASD	asymptomatic	Nadolol 20 mg		5
4	*KCNQ1*	V205M	unknown	Motor disorder	asymptomatic	Nadolol 40 mg		8
5	*KCNQ1*	V205M	500	Motor disorder, Global developmental delay	asymptomatic	Nadolol 40 mg		14
6	*KCNH2*	R582C	unknown	ADHD, Learning disorder	asymptomatic	Nadolol 40 mg	Intuniv	8

Patient	LQTS Gene	Variant	QTc on stress test during recovery	NDD	Cardiac symptoms during follow-up	Treatment at last follow-up	Treatment at last follow-up	Durati of Follow (years)
7	*KCNQ1*	V205M	500	Global developmental delay	asymptomatic	Nadolol 80 mg		4
8	*KCNQ1*	V205M	Unknown	ADHD, Communication disorder	asymptomatic	Nadolol 40 mg		3
9	*KCNQ1*	R594Q	530	ADHD, Learning disorder, Global developmental delay	asymptomatic	Nadolol 60 mg		7
10	*KCNQ1*	R518X	500	ADHD, Motor disorder, ASD	asymptomatic	Nadolol 40 mg	Guanfacine 3mg Vyvanse 40mg	6
11	*KCNQ1*	W305L	500	ASD	asymptomatic	Nadolol 30 mg		2
12	*KCNQ1*	V254M	500	ADHD	asymptomatic	Nadolol 40 mg		10
13	*KCNJ2*	R67W	480	Global developmental delay, ADHD	asymptomatic	Flecainide 75mg		10
14	*KCNQ1*	W305L	520	Communication Disorder	asymptomatic	Nadolol 40 mg		2
15	*KCNQ1*	K362R	unknown	Global developmental delay with microencephaly	asymptomatic		Clobazam 100mg	6

ADHD= attention deficit hyperactivity disorder; Autism Spectrum Disorder; LQTS= Long QT syndrome; NDD= neurodevelopmental delay

Figure 1. Schematic of KCNQ1 and associated variants reported in our LQTS + NDD cohort.