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ORIGINAL ARTICLE

Intellectual and Neurodevelopmental Delays in Pediatric Catecholaminergic Polymorphic Ventricular Tachycardia: Distinct Characteristics and a More Malignant Neurocardiac Phenotype

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BACKGROUND: Marked intellectual and neurodevelopmental delay (INDD) was noted in 6 unrelated patients diagnosed with *RYR2*-related catecholaminergic polymorphic ventricular tachycardia (CPVT) from a single center. Patients exhibited similar distinct phenotypic features not previously described. We aimed to determine the prevalence of INDD in CPVT, compare clinical characteristics between patients with CPVT with and without INDD, and investigate the possibility of a unique neurocardiac CPVT phenotype.

METHODS: Retrospective combined review of patients with *RYR2*-related CPVT diagnosed ≤18 years with and without INDD from a single center and the International Pediatric CPVT Registry. Patients with hypoxic ischemic insult were excluded unless INDD preceded injury.

RESULTS: Among a total of 168 patients, INDD was reported in 19 (11.3% [95% CI, 7.0%–17.1%]). When compared with cases without INDD, patients with INDD exhibited distinct features including (1) younger age at onset of symptoms (median 7.0 versus 10.0 years; P=0.04); (2) higher frequency of atrial tachyarrhythmias (84.2% versus 16.3%, P<0.001); (3) atrial or ventricular tachycardia without adrenergic stimulation (81.3% versus 2.2%, P<0.001, 31.6% versus 4.5%, P=0.001 respectively); (4) cardiac structural changes or systolic dysfunction (36.8% versus 1.3%, P<0.001); and (5) higher incidence of cardiac arrest or sudden death after diagnosis (26.3% versus 2.7%, P=0.001). INDD-related *RYR2* genetic variants clustered within the central and channel domains and may be specific to certain variants.

CONCLUSIONS: This study demonstrates a wider spectrum of *RYR2*-related disease, with a subset associated with extracardiac manifestations. Certain *RYR2* variants may lead to a neurocardiac phenotype with distinct features that are important to recognize, as these patients may be at higher risk.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: arrhythmias, cardiac ■ phenotype ■ polymorphic catecholergic ventricular tachycardia ■ ryanodine receptor calcium release channel ■ tachycardia, ventricular

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WHAT IS KNOWN?

- Cardiac RYR2 (ryanodine receptor 2) associated catecholaminergic polymorphic ventricular tachycardia (CPVT) is a well-described heritable disorder associated with lethal ventricular arrhythmias and cardiac arrest.
- In a study from an international registry, intellectual disability was found to be 2 to 3× more prevalent among RYR2-associated patients with CPVT, although this possible link with neurodevelopmental delays could not be confirmed.

WHAT THE STUDY ADDS

- RYR2-associated CPVT can co-occur with marked intellectual and neurodevelopmental delays in ≈11% of patients, suggesting that neurologic involvement in CPVT is more common than previously recognized.
- In addition to earlier age at symptom onset, compared with those without delays, patients with CPVT and extracardiac manifestations of intellectual and neurodevelopmental delay more frequently had atrial tachyarrhythmias, cardiac structural changes, and systolic dysfunction.
- Specific CPVT variants seem to be associated with co-occurring intellectual and neurodevelopmental delay and may confer a more malignant phenotype associated with a higher risk of cardiac arrest or sudden death even after CPVT diagnosis.

Nonstandard Abbreviations and Acronyms

AT	atrial tachycardia
CPVT	catecholaminergic polymorphic ventricular tachycardia
ICD	implantable cardiac defibrillator
INDD	intellectual and neurodevelopmental delay
IQR	interquartile range
LV	left ventricular
LVNC	left ventricular noncompaction
RYR2	ryanodine receptor 2
SCD	sudden cardiac death
VT	ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a heritable arrhythmia disorder that has been characterized by atrial and ventricular tachycardia (VT) in the absence of structural heart disease.[1–4] CPVT-related arrhythmias typically affect otherwise healthy children primarily during adrenergic stimulation.[2] Although RYR2 (ryanodine receptor 2) is predominantly expressed in cardiac myocytes, it is also expressed in the brain with widespread distribution in the hippocampus and cerebellum.[5] Yet neurological deficits and developmental delays have not historically been associated with pediatric CPVT.

In a large academic center, 6 patients with marked intellectual and neurodevelopmental delays (INDD) were diagnosed with *RYR2*-associated CPVT. These 6 patients demonstrated similar clinical features to each other, all relatively atypical for CPVT, which raised a question of whether they might represent a unique neurocardiac CPVT phenotype. Clinical findings included predominantly atrial tachyarrhythmias (AT) at a young age, and arrhythmias (both atrial and ventricular) occurring without adrenergic stimulation. In addition, myocardial structural changes (left ventricular [LV] trabeculations, noncompaction, dilation, and arrhythmogenic right ventricular cardiomyopathy) or systolic dysfunction were present in most. We hypothesized that these findings were not isolated but rather represented an underrecognized neurocardiac phenotype among pediatric patients with CPVT.

To investigate our hypothesis, we combined the single-center data with the International Pediatric CPVT Registry. The purpose of this study was to determine if the constellation of features, including extracardiac findings, could be related to RyR2 variants and whether these features represented a neurocardiac form of CPVT. We proposed to compare clinical characteristics, presentation, genetics, and outcomes between patients with pediatric *RYR2*-related CPVT, with and without INDD.

METHODS

Recruitment and Study Population

This retrospective cohort study included patients diagnosed with *RYR2*-related CPVT from 2 separate cohorts. Cohort 1 included all patients diagnosed with CPVT at Texas Children's Hospital between January 1, 2000 and October 1, 2022 identified via an electronic health record query. Cohort 2 was comprised of patients from the International Pediatric CPVT Registry, affiliated with the Pediatric and Congenital Electrophysiology Society, and coordinated at British Columbia Children's Hospital in Vancouver, Canada. Patients in the International Pediatric CPVT Registry diagnosed with CPVT ≤18 years of age, and their first-degree relatives, were enrolled in the registry. Eligibility of patients for inclusion in the registry was determined based on expert consensus criteria and verified by 2 independent personnel (D.K. and S.S). This study first provides descriptions and clinical details of patients with INDD in cohort 1, as such data are not always available in a registry database. Second, the 2 cohorts were combined, and data are presented from the combined cohort. For the purposes of this study, the term total cohort refers to combined data from both cohorts 1 and 2. Due to the rarity of CPVT and the potential to inadvertently reidentify patients included in the cohort based on available data, data is not available on request. Patients in cohort 1 were included under a retrospective waiver of consent. Patients in cohort 2 provided written consent for registry inclusion. This study was approved by the Institutional Research Boards at Baylor College of Medicine (protocol H-58658),

British Columbia Children's Hospital (protocol H14–00301), and participating registry sites.

Inclusion and Exclusion

For this study and for inclusion into the total cohort, patients harboring a pathogenic/likely pathogenic *RYR2* variant or a variant of uncertain significance (VUS) in *RYR2* with a phenotype consistent with CPVT were eligible. Patients with a VUS in *RYR2* without sufficient evidence to confirm a CPVT phenotype were excluded. In addition, patients with a known phenotype consistent with calcium release deficiency syndrome[6] or an *RYR2* variant with functional data confirming loss of function were excluded. To minimize potential selection bias, patients in cohort 1 were excluded if their first presenting symptom was death after cardiac arrest. This ensured consistency with the recruitment protocols used by the International Pediatric CPVT Registry, which enrolls living patients (at the time of initial consent) from various sites.

Intellectual Disability and Neurodevelopmental Disorders

Intellectual disabilities were defined as limitations in both intellectual functioning and adaptive behaviors (conceptual, social, and practical abilities). Patients who demonstrated delays in multiple domains were considered to have global developmental delays. Neurodevelopmental delays included autism spectrum disorder and significant learning or motor disorders.[7] Patients with INDD and a history of cardiac arrest were only included if it was determined that their INDD was present before arrest and not a result of hypoxic ischemic insult.

Data Collection Variables

Demographics included sex, race and ethnicity, age at genetic diagnosis, age at first symptom, age at first cardiac evaluation, and proband status. The patient was considered a proband if they were the first in their family to be diagnosed. Racial and ethnic classification for patients in the registry was categorized as mutually exclusive White, Hispanic, Black, Asian, or other. For the purposes of this study, the ethnicity and race of cohort 1 patients were reclassified based on registry classifications to mirror the following categories: non-Hispanic White were categorized as White and those classified as Hispanic White was classified as Hispanic.

Clinical data included typical features consistent with CPVT and distinct features not generally associated with CPVT. Typical features included the presence of adrenergic bidirectional or polymorphic VT, a history of syncope, aborted cardiac arrest/sudden cardiac death (SCD), or familial history of confirmed genotype or phenotype consistent with CPVT. Family history of CPVT was defined as a first-degree relative with a confirmed pathogenic/likely pathogenic *RYR2* variant or a phenotype consistent with CPVT (eg, aborted cardiac arrest, syncope with evidence of adrenergic stimulation), if relatives were unavailable for genetic testing.

Distinct CPVT features considered were AT, VT, or cardiac arrest occurring without a known preceding adrenergic-stimulating event. AT included atrial tachycardia or atrial fibrillation. The presence of AT, or VT, was ascertained from available Holter monitors, exercise stress tests, telemetry, or electrophysiology studies, including drug challenge (eg, epinephrine). Atrial tachycardia was defined as ≥3 consecutive atrial ectopic beats, and ventricular arrhythmias were defined as frequent premature ventricular contractions, couplets, bidirectional couplets, or bidirectional or polymorphic VT ≥3 beats. Details regarding whether documented AT or VT events occurred during adrenergic stimulation were obtained from the primary electrophysiologists. Structural changes on echocardiography were also considered atypical and distinct. For the purposes of this article, structural changes included prominent LV trabeculations or LV noncompaction (LVNC), ventricular dilation, arrhythmogenic cardiomyopathy, and systolic dysfunction. Systolic dysfunction was defined as an ejection fraction <55% or shortening fraction <35%. Due to neurological considerations, seizure history was investigated.

Genetic Testing

Genetic testing varied by center and was predominantly panel tests for CPVT. In some patients, comprehensive arrhythmia panels or exome sequencing was performed. Inheritance pattern was defined as de novo if both parental genetic testing was negative. For the purposes of this study, a patient's *RYR2* variant was presumed to be inherited if family history was consistent with CPVT phenotype, including cases in which relatives were not available for genetic testing (eg, died after a cardiac arrest). *RYR2* variant location was categorized based on 4 established hotspots: hotspot 1 (amino acids 44–466), 2 (2246–2534), 3 (3778–4201), or 4 (4497–4959).[8] When available, functional data for variants were reviewed. The following CPVT-related genes were documented if identified on genetic testing reports: *CASQ2*, *CALM1*, *CALM2*, *CALM3*, *TRDN*, and *TECRL*.

Outcomes

The primary outcome was time-to-first cardiac event. A CPVT-related cardiac event was defined as a composite variable of SCD, aborted cardiac arrest, syncope associated with adrenergic stimulation, or appropriate implantable cardiac defibrillator (ICD) shock(s). As not all syncope may be CPVT-related and not all ICD shocks reflect life-threatening events, we separately evaluated cardiac events that only included aborted cardiac arrest or death. As cardiac events after diagnosis warrant concern, we first assessed the proportion of patients who had cardiac events at any point in time (before or after diagnosis) and then limited the analysis to cardiac events occurring after CPVT diagnosis.

Statistical Analysis

Descriptive statistics were used, using median and corresponding interquartile ranges (IQR) to describe the total cohort. The prevalence of INDD phenotype in the total cohort was calculated with corresponding 95% binomial confidence limits. Characteristics among those with and without INDD were compared using χ^2 and Fisher exact test for categorical variables, where appropriate. Wilcoxon rank-sum test was used to identify differences in continuous variables by groups. To evaluate time-to-first postdiagnosis cardiac event (or arrest) following diagnosis based on INDD status, Kaplan-Meier curves were generated and compared using log-rank test. Time zero was defined as the age at clinical CPVT diagnosis. Patients

were censored according to age at first postdiagnosis event (or arrest) or age at last follow-up. A $P<0.05$ was considered statistically significant. Due to the exploratory nature of this investigation, *P* values were not adjusted for multiple comparisons. Analyses were performed using Stata statistical software (Stata/IC v16.1, College Station, Texas).

Sensitivity Analysis

Because not all INDD may have been reported to the registry, we performed an exploratory sensitivity analysis to assess whether clinical characteristics associated with INDD (eg, AT or VT without adrenergic stimulation, systolic dysfunction) were seen among other patients with variants in the same exon as INDD subjects, but not reported to have INDD.

RESULTS

Description of Cohort 1 Patients With INDD

Within cohort 1, there were 22 patients with *RYR2*-related CPVT diagnosis, 6 of whom were diagnosed with INDD. Detailed histories and data regarding these patients are provided in the Supplemental Material (see Additional Data on Cohort 1 Patients). All 6 patients with INDD had cognitive deficits and delays in developmental milestones, particularly walking and speech. In 4 patients, with presumed isolated AT, the CPVT diagnosis was delayed because VT was diagnosed after AT. In 2 patients, genetic testing was performed due to global developmental delays, and *RYR2* was identified incidentally.

In 5 patients, nonadrenergically mediated AT was noted on Holter monitoring before ventricular tachyarrhythmias were documented. The median age at the time of AT diagnosis was 5.8 years (range, 1.7–12.2 years). Three patients were diagnosed with AT before age 5 years (1.7 years, 3.9 years, and 4 years). AT was documented at rest and with adrenergic stimulation. The median age at first documentation of VT was 12 years (range, 7–19 years). VT without adrenergic stimulation was documented in 3 of 6 (50.0%) and with adrenergic stimulation (eg, epinephrine drug challenge or treadmill) in 5 of 6 (83.3%). The single patient without VT was nonambulatory and unable to perform exercise stress testing. Sinus node dysfunction was present in 2 of 6 (33.3%). Both subjects with sinus node dysfunction underwent pacemaker implantation.

LV trabeculations (not meeting noncompaction criteria) were reported as prominent in 2 of 6 (33.3%) and mild in 1 of 6 (16.7%). LVNC was reported by echocardiogram or cardiac magnetic resonance imaging in 2 of 6 (33.3%). Thus, in 5 of 6 (83.3%), increased trabeculations or LVNC were reported on echocardiogram or MRI. In addition, ventricular dilation (1 LV, 2 biventricular) was diagnosed in 3 of 6 (50.0%) and systolic dysfunction in 2 of 6 (33.3%, 1 LV, 1 biventricular). One patient was diagnosed with arrhythmogenic cardiomyopathy.[9]

Three patients with INDD had a significant cardiac event after CPVT diagnosis, 2 of whom have been previously reported.[9,10] Two patients suffered witnessed cardiac arrests. A 17-year-old male with a history of longstanding AT, syncope, left cardiac sympathetic denervation, and severe biventricular dysfunction collapsed while standing in the hospital bathroom. He was on sotalol at the time of his arrest. He subsequently underwent heart transplantation and was found to have arrhythmogenic cardiomyopathy based on pathological examination of his explanted heart.[9] The second patient had an arrest at age 19 years while compliant on atenolol and flecainide. At the time of arrest, she was not on nadolol as her CPVT diagnosis had not yet been confirmed. She was resuscitated and underwent subsequent left cardiac sympathetic denervation but continues to have AT with ICD discharges. The third patient had an ICD, bilateral sympathectomy, and was on flecainide and nadolol. She was lost to follow-up and was found deceased in bed at age 24 years. An autopsy was not performed, and her cause of death remains unknown.[10]

Three patients with INDD had formal neurodevelopmental testing. The first was a severely delayed, nonambulatory, noncommunicative 5-year-old male. Formal testing at age 5 years assessed him to be developmentally equivalent to a 9- to 10-month-old child.

The second patient was a 9-year-old ambulatory female with moderate-severe developmental delays. She was able to walk with an uncoordinated gait but was unable to run and could speak in short sentences. Formal intelligence quotient testing (Leiter-3) at age 8 years revealed an intelligence quotient of 63 (less than second centile) and comprehension and functional skills at less than first centile, with an overall age equivalent of 2 to 3 years. The third patient was a 13-year-old female with mild-moderate developmental and speech delays. Formal neurodevelopmental testing at age 13 years revealed significant deficits in fine motor skills and dexterity (less than first centile for age) and low end of low-average visuomotor integration and expressive language (difficulty with word finding) skills with an intelligence quotient of 86. Three of the remaining affected patients were young adults with no history of formal neurodevelopmental testing. Two of these individuals were reported to have skills comparable to those of 5- to 6-year-old children based on subjective assessments by parents and physicians. Formal neurocognitive and developmental testing was not available for cohort 2 patients or cohort 1 subjects without INDD.

Description of Total Cohort, Including International Pediatric CPVT Registry

Based on findings in cohort 1, this study next evaluated and combined findings from the International Pediatric CPVT Registry. A total of 168 pediatric patients met the

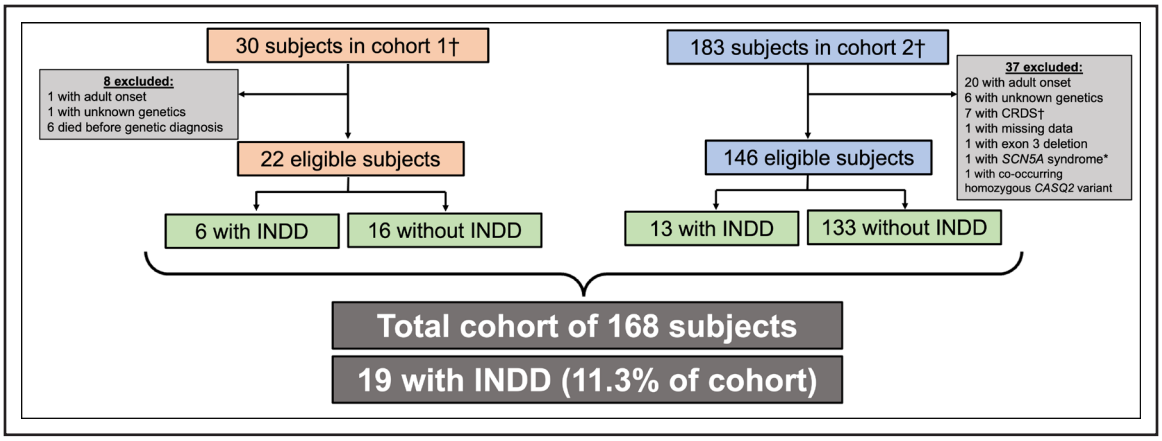

Figure 1. Selection of final cohort.
Cohort 2 was comprised of patients included in the International Pediatric Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Registry, excluding those seen at Texas Children's Hospital. CRDS indicates Calcium release deficiency syndrome; and INDD, intellectual and neurodevelopmental delay. *One patient was found to have an *RYR2* variant but was phenotypically more consistent with *SCN5A* syndrome. †Cohort 1 was comprised of patients evaluated at Texas Children's Hospital.

inclusion criteria, including 22 from cohort 1 (Texas Children's Hospital) and 146 from cohort 2 (International Pediatric CPVT Registry; Figure 1). Six patients were found to have INDD from cohort 1 (n=6/22, 27.3%) and 13 from cohort 2 (n=13/146, 8.9%). Therefore, the prevalence of INDD in the total CPVT cohort was 19 of 168 (11.3%, 95% CI, 7.0%–17.1%). In the total cohort, the median age at first CPVT-related symptom was 9.0 years (IQR, 6–13 years). The most common presenting symptom was syncope in 82 (48.8%), followed by cardiac arrest in 36 (21.4%), and other (near-syncope, seizures, palpitations) in 11 (6.6%). A total of 39 (23.2%) patients were asymptomatic and diagnosed through familial screening or incidental genetic findings.

When comparing characteristics by INDD status, sex was not associated (P=0.20; Table). Patients with INDD were more likely to be probands (n=18/19, 94.7% versus n=101/129, 67.8%, P=0.02) and exhibited CPVT-related symptoms at an earlier age (7 years [IQR, 4–10 years]) compared with those without INDD (10 years [IQR, 6–14 years]; P=0.04). There was no difference in seizures between patients with INDD and without INDD (11.1% versus 14.3%, P=1.00). Clinical characteristics of patients can be found in the Table.

Arrhythmias and Cardiac Structural Changes

Among patients with INDD for whom activity during AT was known, most (n=13/16, 81.3%) had documented AT without adrenergic stimulation, as compared with patients without INDD (n=3/135, 2.2%; P<0.001). In addition, patients with INDD more frequently had VT at rest compared with patients without INDD (n=6/19, 31.6% versus n=5/112, 4.5%, P=0.001).

When examining the total cohort, prominent trabeculations or LVNC were diagnosed in 7 of 19 (36.8%) patients with INDD compared with 2 of 149 (1.3%) patients without INDD (P<0.001). In addition, systolic dysfunction was significantly higher among patients with INDD (26.3% versus 2.7%; P=0.001).

Cardiac Events

When evaluating all CPVT-related cardiac events that occurred at any time (before and after diagnosis), the frequency of events did not differ by INDD status (INDD n=14/19, 73.7% versus non-INDD n=109/149, 73.2%; P=1.00). When limiting analyses to only events after CPVT diagnosis (median postdiagnosis follow-up of 6.0 years [IQR, 3.0–11.0 years]), patients with INDD demonstrated more frequent cardiac events (7/19, 36.8%) compared with patients without INDD (34/149, 22.8%), although difference in risk bordered on statistical significance (log-rank P=0.05; Figure 2). There was no difference in treatment (antiarrhythmic therapy, sympathetic denervation, and ICD) between the INDD and non-INDD groups (Table).

There was no difference in overall frequency of aborted cardiac arrest or SCD between groups (INDD n=7/19, 36.8% versus non-INDD n=49/149, 32.9%; P=0.73). When analyses were limited to cardiac arrest after CPVT diagnosis, those with INDD were at significantly higher risk of aborted cardiac arrest and SCD after diagnosis compared with patients without INDD (INDD n=5/19, 26.3% versus non-INDD n=3/149, 2.0%, log-rank P<0.001; Figure 3). Noncompliance was suspected in 1 of 5 patients with INDD compared with 2 of 3 patients without INDD who experienced aborted cardiac arrest or SCD after diagnosis.

Two patients experienced SCD after CPVT diagnosis. The first was the INDD female previously discussed. The second patient was a female without INDD who experienced SCD at age 27 years while driving under circumstances thought to be adrenergically stimulated.

Table. Clinical Characteristics of Patients With and Without INDD

Variable	N	Patients with INDD (n=19)	Patients without INDD (n=149)	*P* value
Sex	168			0.20
Male		7 (36.8%)	78 (52.4%)	
Female		12 (63.2%)	71 (47.7%)	
Race and ethnicity	168			0.002*
White		8 (42.1%)	105 (70.5%)	
Hispanic		7 (36.8%)	13 (8.7%)	
Asian		0 (…)	14 (9.4%)	
Black		0 (…)	3 (2.0%)	
Other/unknown		4 (21.1%)	14 (9.4%)	
Median age at first symptoms (IQR)	129†	7.0 (4.0–10.0)	10.0 (6.0–14.0)	0.04*
Median age at first cardiac evaluation (IQR)	167	10.5 (4.7–12.6)	11.0 (6.8–13.9)	0.58
Median age at clinical diagnosis (IQR)	162	10.0 (4.0–12.0)	9.0 (4.0–13.0)	0.91
Median age at genetic diagnosis (IQR)	165	10.5 (4.0–15.0)	12.6 (7.4–15.2)	0.91
First CPVT-related symptom	168			0.09
Cardiac arrest		2 (10.5%)	34 (22.8%)	
Syncope		12 (63.2%)	70 (47.0%)	
Other		3 (15.8%)	8 (5.4%)	
Asymptomatic		2 (10.5%)	37 (24.8%)	
Any cardiac events (before or after diagnosis)	168	14 (73.7%)	109 (73.2%)	1.00
Cardiac events only after diagnosis	168	7 (36.8%)	34 (22.8%)	0.25
Any cardiac arrest (before or after diagnosis)	168	7 (36.8%)	49 (32.9%)	0.73
Cardiac arrest only after diagnosis	168	5 (26.3%)	3 (2.0%)	<0.001*
Any documented AT	160	16 (84.2%)	23 (16.3%)	<0.001*
Any documented VT	168	16 (84.2%)	100 (67.1%)	0.13
History of syncope	168	13 (68.4%)	74 (49.7%)	0.15
History of seizures	165	2 (11.1%)	21 (14.3%)	1.00
Distinct phenotypic characteristics				
AT without adrenergic stimulation	151	13 (81.3%)	3 (2.2%)	<0.001*
VT without adrenergic stimulation	131	6 (31.6%)	5 (4.5%)	0.001*
Cardiac arrest without adrenergic stimulation	52	2 (50.0%)	8 (16.7%)	0.16
Trabeculations or left ventricular noncompaction	168	7 (36.8%)	2 (1.3%)	<0.001
Arrhythmogenic right ventricular cardiomyopathy	168	1 (5.3%)	0 (…)	…
Systolic dysfunction	168	5 (26.3%)	4 (2.7%)	0.001
Genetics				
Proband status	168	18 (94.7%)	101 (67.8%)	0.02*
Family history of CPVT	147	3 (16.7%)	66 (51.2%)	0.01*
De novo *RYR2* variant	126			0.01*
De novo		11 (78.6%)	44 (39.3%)	
Inherited		3 (21.4%)	68 (60.7%)	
RYR2 ACMG/AMP classification	168			0.16
Variant of unknown significance		11 (57.9%)	63 (42.3%)	
Likely pathogenic		1 (5.3%)	3 (2.0%)	
Pathogenic		7 (36.8%)	83 (55.7%)	
Functional hotspot location	168			0.001*
Hotspot 1 (amino acids 44–466)		1 (5.3%)	41 (27.5%)	
Hotspot 2 (amino acids 2246–2534)		2 (10.5%)	22 (14.8%)	
Hotspot 3 (amino acids 3778–4201)		8 (42.1%)	25 (16.8%)	
Hotspot 4 (amino acids 4497–4959)		8 (42.1%)	28 (18.8%)	

(*Continued*)

Table. Continued

Variable	N	Patients with INDD (n=19)	Patients without INDD (n=149)	*P* value
No hotspot		0 (…)	33 (22.2%)	
Other CPVT-related variant	168	3 (15.8%)	2 (1.3%)	0.01*
Therapy	168			
β-blocker		18 (94.7%)	142 (95.3%)	1.00
Flecainide		14 (73.7%)	77 (51.7%)	0.09
Left cardiac sympathetic denervation		4 (21.1%)	23 (15.4%)	0.51
Implantable cardioverter defibrillator		5 (26.3%)	58 (38.9%)	0.29

ACMG indicates American College of Medical Genetics; AMP, Association for Molecular Pathology; AT, atrial tachycardia; CPVT, catecholaminergic polymorphic ventricular tachycardia; INDD, intellectual and neurodevelopmental delay; IQR, interquartile range; and VT, ventricular tachycardia.

*Indicates values that met statistical significance with a $p < 0.05$

†Thirty-nine asymptomatic patients were excluded from this count. Patients with unknown data were excluded from the total count of each respective variable.

She had been consistently compliant with her nadolol and flecainide regimen.

Genetics

Among 14 of 19 patients in whom inheritance status was known, a majority (n=11/14, 78.6%) harbored de novo variants (Table), whereas 3 INDD cases had inherited variants (R420W, E2405K, and I4588T). The mother harboring the R420W variant and father (mosaic for E2405K) did not have reported INDD. The mother with I4588T did have a history of cognitive delays. The neurodevelopmental challenges, distinct clinical characteristics, and associated genotype among patients with INDD are reported in Table S1.

Seventeen distinct *RYR2* variants were reported among the total cohort of patients with INDD (Figure 4). Among these patients with INDD, 84.2% of variants were localized to either hotspot 3 (amino acids, 3778–4201) or 4 (amino acids, 4497–4959). Of the 3 subjects with variants in hotspot 1 or 2, 2 were inherited from parents without INDD history. Among patients without INDD, 27.5% of variants were in hotspot 1 (amino acids, 4–466; $P<0.001$). Of note, although a majority of variants associated with INDD clustered within the central domain (hotspot 3) and channel domains (hotspot 4) of the *RYR2* gene, not all variants within these hotspots were associated with INDD phenotype. A schematic of the *RYR2* exons containing the variants associated with INDD can be found in Figure S1. The most commonly observed *RYR2* variant among patients with INDD was a heterozygous pathogenic V4771I variant (n=5 patients), 3 of whom reported INDD. The 2 remaining patients without reported INDD harboring this variant were from unrelated families in the registry. Although neither subject had documentation of INDD in medical charts, when primary electrophysiologists were questioned, both subjects were suspected to have some cognitive impairment. Patients with INDD were

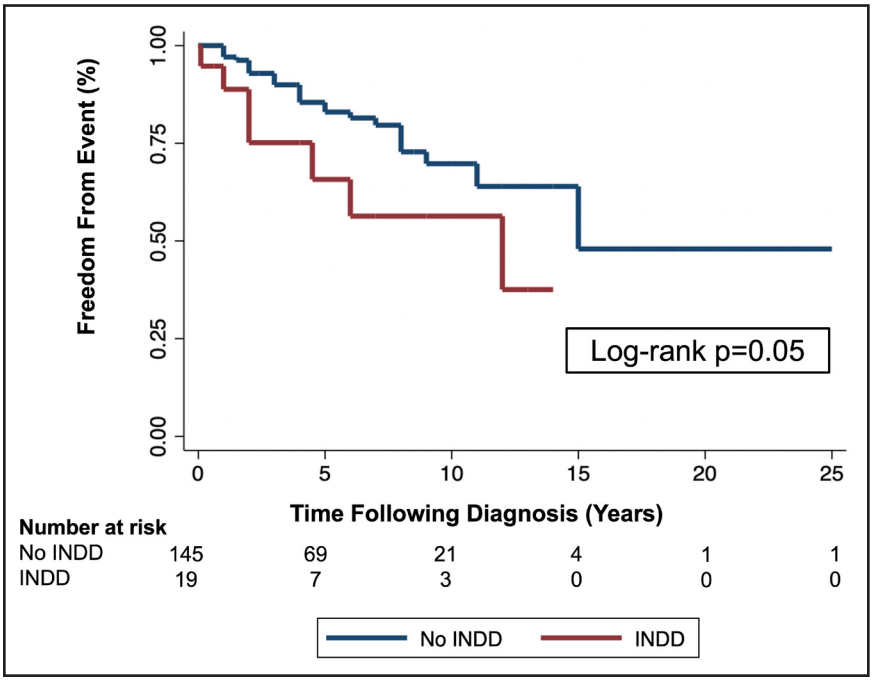

Figure 2. Freedom from all cardiac events after diagnosis.
Cardiac events evaluated included aborted cardiac arrest, sudden cardiac death, appropriate implantable cardiac device shock, or arrhythmia-induced syncope. There were 4 individuals without intellectual and neurodevelopmental delay (INDD) whose age at last follow-up was at genetic diagnosis and, therefore, were not included in Kaplan-Meier evaluation.

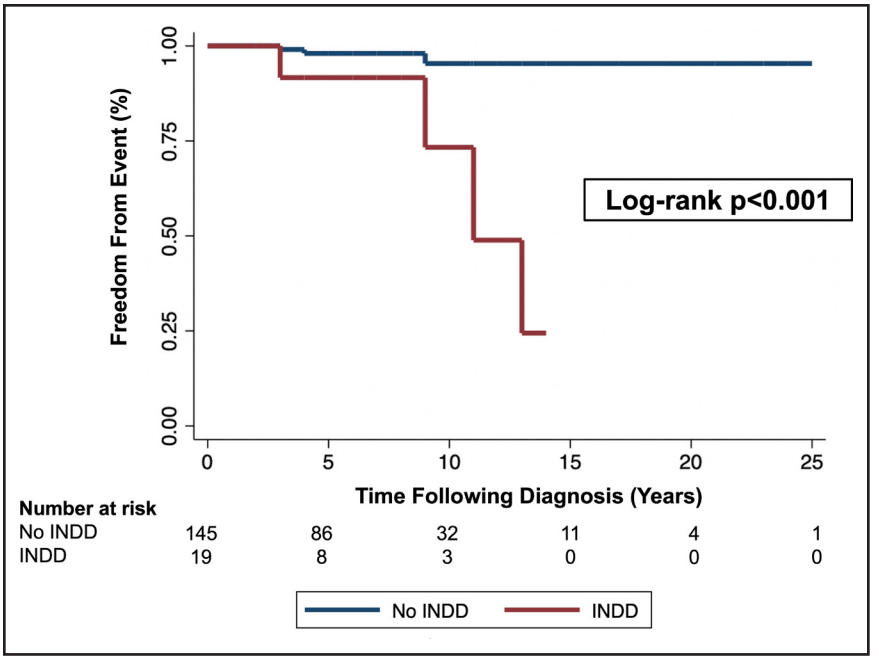

Figure 3. Freedom from cardiac arrest after diagnosis.
There were 4 individuals without intellectual and neurodevelopmental delay (INDD) whose age at last follow-up was at genetic diagnosis and therefore were not included in Kaplan-Meier evaluation.

more likely to have multiple CPVT-related variants compared with patients without INDD (INDD n=3/19, 15.8% versus non-INDD n=2/149, 1.3%; *P*=0.01). These variants, shown in Table S1, were felt to be benign, at least in isolation. Whether these variants may be modifying the phenotype could not be elucidated.

Sensitivity Analysis

After controlling for *RYR2* exon location, differences in neurocardiac features observed between groups were similar, suggesting that the presence of INDD was not exon-specific (Table S2). When evaluating cardiac arrests at any time, patients with and without INDD did not differ by time-to-cardiac arrest (Figure S2; *P*=0.63).

Two patients with INDD were noted to have autism spectrum disorder and inherited *RYR2* variants (R420W and E2405K), where neither genotype-positive parent demonstrated any neurological or developmental deficits, raising questions whether these variants were associated with INDD. As such, a sensitivity analysis was performed, removing these 2 patients (Table S3). All comparisons and statistical tests were repeated to assess for potential skewing of results by the inclusion of these 2 patients. After excluding these 2 subjects, patients with INDD had a higher risk of cardiac events after diagnosis compared with patients without INDD (*P*=0.04; Figure S3). Analyses of postdiagnosis arrests remained significant (*P*<0.001; Figure S4).

DISCUSSION

In this retrospective multicenter study, our findings suggest there is a subset of patients with *RYR2*-related CPVT with a neurocardiac phenotype that includes INDD. In this study, INDD affected at least 11% of children with *RYR2*-associated CPVT, a higher prevalence compared with the 1% to 3% prevalence reported in the general population.[7] This rate is also higher than the 8.1% of INDD reported in primarily adult patients with CPVT.[7]

The observed distinct CPVT neurocardiac phenotype among pediatric patients with INDD included the following: (1) younger age at the onset of CPVT-related symptoms; (2) an early predominance of AT; (3) presence of AT and VT with and without adrenergic stimulation; (4) higher risk of structural changes and cardiomyopathy that may progress with age; and (5) a higher risk of cardiac arrest or sudden death after diagnosis when compared with patients without INDD.

The earlier age at presentation for children with INDD is important because these *RYR2* variants are often incidental findings in patients without high pretest probability for CPVT. We believe incidental findings of rare, novel, or de novo *RYR2* variants among children with cognitive or developmental delays should trigger cardiac evaluation for neurocardiac CPVT, particularly if the variant falls in hotspot 3 (3778–4201) or 4 (4497–4959).[11]

We also found that patients with INDD were more likely to have AT diagnosed at young ages, even in the absence of VT, and importantly, the AT occurred without adrenergic stimulation, which is highly unusual in a disorder that has been historically characterized by adrenergically stimulated arrhythmias. Indeed, AT without adrenergic stimulation was documented in more than two-thirds of the patients with INDD and should be considered as a diagnostic tool for identifying CPVT in this cohort. Based on findings, cardiac evaluation

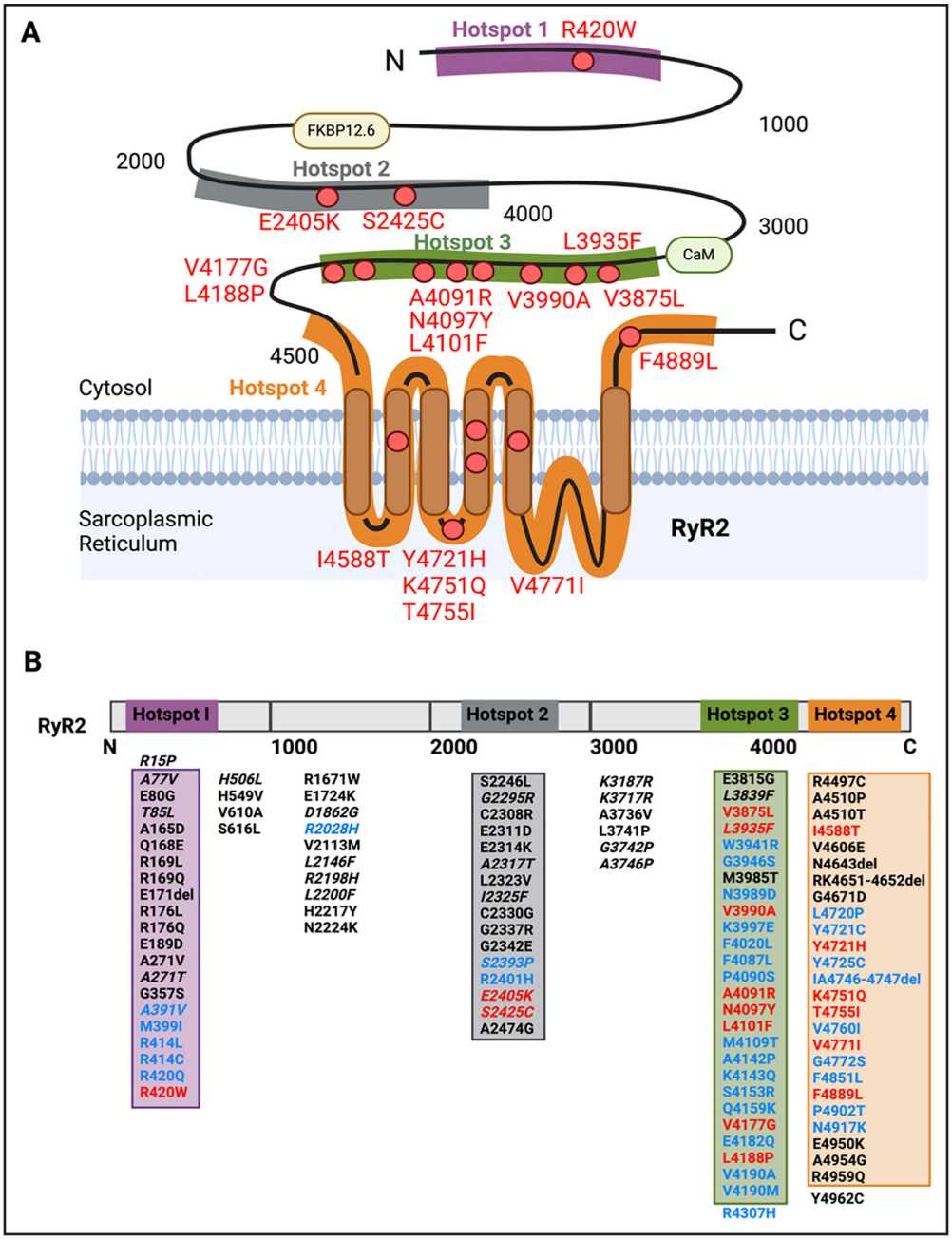

Figure 4. Schematic of *RYR2* (ryanodine receptor 2) variants associated with intellectual and neurodevelopmental delay (INDD). **A**, Red circles indicate catecholaminergic polymorphic ventricular tachycardia (CPVT) variants associated with INDD and their location in the cytosolic and transmembrane regions of *RYR2*. **B**, Diagram of full-length *RYR2* including CPVT variant hot spots, cytosolic and transmembrane regions, protein domains, and molecular binding sites. Variants of uncertain significance (VUS) are shown italicized. Variants associated with INDD are in red. Variants not associated with INDD but share the same exon as a variant associated with INDD are in blue. Variants that are neither associated with INDD nor in the same exon as a variant associated with INDD are shown in black.

should include a Holter monitor evaluating the presence of arrhythmias without adrenergic stimulation, with an awareness of CPVT diagnosis, even if VT is not yet seen.

This study also identified a higher frequency of structural abnormalities among patients with CPVT with INDD, including ventricular dilation, LVNC, and arrhythmogenic cardiomyopathy. Prominent trabeculations were commonly reported, and systolic dysfunction was observed in more than one-third of patients with INDD. Therefore, it is our recommendation that serial echocardiograms be performed during follow-up with consideration for cardiac magnetic resonance imaging.

The distinct clinical characteristics associated with INDD in this cohort of patients almost exclusively clustered among specific *RYR2* variants in later exons within hotspots 3 (3778–4201), or 4 (4497–4959). In this pediatric study, 3 subjects (R420W, E2405K, and S2425C) had variants outside of these hotspots. It is not

clear whether *RYR2*-gain of function is a spectrum with varying degrees of neurological and myocardial involvement among all variants or whether these findings are isolated to specific variants. Our data suggest that this phenotype may be variant-specific; however, further studies are needed to definitively address the genotypic influence on the presence of an INDD phenotype.

Lastly, similar to Lieve et al[7] we also found patients with INDD demonstrated a more malignant phenotype. Compared with those without INDD, children with INDD not only had a higher likelihood of experiencing earlier cardiac events, but were also more likely to experience a cardiac arrest or sudden death after diagnosis while compliant on standard medical therapy. Thus, further studies are needed to determine optimal treatment strategies.

Clinical Implications

Assessing the presence of INDD in pediatric CPVT should be an important component of clinical evaluation and workup. In addition, CPVT should be considered among those with INDD found to have rare or de novo *RYR2* variants, even without cardiac symptoms. Adopting a standardized approach to evaluate neurodevelopmental status among patients with CPVT will be important to identify this potentially higher-risk cohort. Although many patients with INDD did have profound delays that are recognizable (eg, nonambulatory, noncommunicative, expressive, and communicative function at a 5–6-year age level), the spectrum of delays may vary, with some demonstrating milder features. This study could not compare or define the delays as there were limited objective data for all subjects. This suggests that future standardized detailed assessments may be helpful in answering these questions.

Limitations

We were limited by our small sample size, nature of multicenter registry, which results in missing data in variables of interest, and different approaches in evaluation and diagnosis among centers. This study may have underestimated the true prevalence of INDD because the International Pediatric CPVT Registry was not focused on INDD data collection. Patients with mild delays may not have been identified in cardiac evaluation, whereas patients who have apparent INDD may have neurological problems that are not necessarily related to CPVT. The large prevalence of INDD at Texas Children's Hospital may be due to referral bias or a heightened awareness of this neurocardiac phenotype and subsequent screening for neurodevelopmental delays in patients.

Conclusions

This study identified an 11% prevalence of intellectual and neurodevelopmental delays among children with *RYR2*-associated CPVT, with INDD variants clustering in hotspots 3 and 4. These features may be more common than previously thought and are likely underestimated based on the data presented. In addition to neurocognitive deficits, these patients exhibit distinct characteristics, including younger age at CPVT presentation, high prevalence of atrial arrhythmias and arrhythmias occurring without adrenergic stimulation, development of cardiomyopathy and systolic dysfunction, and a higher likelihood of experiencing breakthrough cardiac arrest. Overall findings highlight the need for tailored diagnostic and management strategies to optimize patient outcomes in this population.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S4

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