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Catecholaminergic polymorphic ventricular tachycardia in children—incidence and trends in detection, presentation and management

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/archdischild-2024-328016).

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Received 17 September 2024
Accepted 30 April 2025

To cite: Fitzgerald N, Lawley C, Morrish A, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2024-328016

ABSTRACT

Objective To establish a birth rate for catecholaminergic polymorphic ventricular tachycardia (CPVT) diagnosed in childhood and observe trends in presentation and management.

Design Retrospective cohort study.

Setting The Inherited Arrhythmia Clinic at The Sydney Children's Hospitals Network, a paediatric tertiary referral network, New South Wales (NSW), Australia (2002–2021), where there are 86 000–97 000 live births/year.

Patients Children diagnosed with CPVT aged 0–16 years.

Interventions Clinical data were extracted and evaluated for trends. Using birth year data, the birth rate of CPVT detected in childhood was calculated.

Main outcome measures Birth rate of CPVT detected in childhood in NSW (with post hoc comparison to New Zealand), trends in diagnosis and management, and outcome at last follow-up.

Results 32 children in NSW were diagnosed with CPVT between 2002 and 2021 (0–16 years, median 9 years, 14 (54%) female). Of these, 28 (88%) presented with symptoms (cardiac arrest 20/32, 62.5%) and four (12%) were identified through family screening. Relevant genetic variants were identified in 25/31 (78%). During follow-up (median 4.5 years), symptomatic cardiac events (death n=1) occurred in 10 (33%), largely related to suboptimal adherence or monotherapy beta blocker. In NSW, CPVT was diagnosed during childhood following 1 in 65 000 live births (95% CI 1 in 91 000 to 1 in 46 000). In New Zealand, the corresponding figure was 1 in 84 000 live births (95% CI 1 in 138 000 to 1 in 52 000).

Conclusions The rate of infants born who are later diagnosed with CPVT in childhood is approximately 1 in 65 000 live births. Suboptimal adherence and beta blocker therapy without flecainide appeared related to recurrent cardiac events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a malignant inherited cardiac condition, with a higher lethality than long QT syndrome and hypertrophic cardiomyopathy.
⇒ The annual incidence or population prevalence of CPVT in children remains inexactly defined but has been repeatedly estimated at 1 in 10 000.
⇒ Once diagnosed, effective treatment for CPVT exists.

WHAT THIS STUDY ADDS

⇒ The rate of infants born who are later diagnosed with CPVT in childhood is less than previous estimates.
⇒ Once diagnosed, CPVT treatment failure was associated with medication non-compliance and beta blocker monotherapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Vigilance for CPVT should be maintained following exertional cardiac events in children. Geographical cohorts with unified subspeciality care provide a unique opportunity to calculate population prevalence.

INTRODUCTION

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a malignant inherited cardiac condition, with a higher lethality than long QT syndrome and hypertrophic cardiomyopathy.[1] It most typically presents with exercise or excitement-induced syncope or cardiac arrest in children over the age of 4 years.[2–4]

The diagnosis of CPVT is made by the identification of bidirectional or polymorphic ventricular ectopy and ventricular tachycardia (VT) during exercise or excitement in the presence of a normal resting 12-lead ECG and echocardiogram.[5 6] Diagnosis can usually be supported with genetic testing, and following an unexpected sudden death, this may be the only means of establishing a diagnosis. Heterozygous variants in the cardiac ryanodine (*RYR2*) gene are the most common cause. The annual incidence or population prevalence of CPVT in children remains inexactly defined, with the population prevalence typically quoted as 1 in 10 000 or less.[7] This compares to the relatively well-established prevalence of long QT syndrome at approximately 1 in 2000.[8]

Management options for CPVT have evolved over recent years. Before 2011, management typically included beta blockers, with an implantable cardioverter-defibrillator (ICD) being placed following a cardiac arrest in this group. In 2011, the efficacy of flecainide in suppressing ventricular arrhythmia was recognised[9–11] and, from 2013, evidence was accumulating that ICDs may deliver inappropriate and ineffective shocks and can even

be lethal in this patient group, through sustaining or initiating VT storms.[12–14]

New South Wales (NSW) is Australia's most populous state, with a population of approximately 8 million people. Of these, around 1.5 million are children aged 0–16 years.[15] Over the past three decades, the state's birth rate has gradually increased from approximately 86 000 to 97 000 births per year.[16–22] Inherited arrhythmias are managed across two tertiary referral paediatric cardiac centres in Sydney, which operate as one network (The Sydney Children's Hospitals Network, SCHN). A third, smaller children's hospital in Newcastle, NSW, collaborates closely with SCHN. A multidisciplinary paediatric cardiac-genetic inherited arrhythmia service was established in NSW in 2013. In New Zealand, there is a single cardiac inherited disease network and national registry of inherited heart conditions and sudden death investigations (the Cardiac Inherited Disease Group, CIDG).[1] From 2007 onwards, this included CPVT.

This study sought to describe the trends in the rate of detection of CPVT in children in the state of NSW and to extrapolate the rate of paediatric CPVT detected in childhood. As a secondary outcome, trends in the mode of presentation, subsequent management and outcomes were reviewed and compared by era of initial management.

METHODS

A retrospective cohort study was performed at SCHN reviewing the 20-year period from 1 January 2002 to 31 December 2021. All consecutive paediatric patients (0–16 years of age, as these children could only have been managed through SCHN in NSW) diagnosed with CPVT on clinical grounds, cascade family screening or following investigation of sudden unexplained death were included for analysis. Standard criteria, in keeping with current guidelines, were used to confirm the diagnosis, including use of exercise testing when possible and incorporating results of genetic testing.[5] Structural and congenital heart diseases were excluded with echocardiography (or on autopsy). Data for deceased children diagnosed with CPVT were obtained from the well-established NSW collaborative molecular autopsy programme.[23 24]

Extracted data included baseline demographics, clinical presentation details, diagnostic methods, results of genetic testing, treatment types and symptoms during follow-up. A symptomatic cardiac event in follow-up was defined as syncope, cardiac arrest or death after commencement of pharmacological therapy and was deemed synonymous with treatment failure. Inappropriate ICD discharge was defined as an ICD shock delivered in the absence of VT or ventricular fibrillation. Data on other ICD complications (infection, lead or device misplacement or lead fracture) were also collected. To reduce the risk of bias, for those cases missing data for a specific variable, this was annotated, and the case was included for other variables where the data were available.

Subgroup analysis of early (first year after diagnosis) management strategy based on era of diagnosis (group 1 ('historical'): CPVT 2002–2014; group 2 ('contemporary'): CPVT 2015–2021) was performed, with the timepoint defined by evidence-based institutional change in practice relating to ICD use and programming and choice of medication.[9–12 14] Data collection was performed by NF, CL, AM (SCHN) and AT (New Zealand) from existing medical records and internal departmental databases.

Statistical analyses were performed using SPSS V.25 and SAS 9.4. Descriptive statistics were presented as frequencies with percentages for categorical variables and mean with SD or, when abnormally distributed, median with IQR for continuous variables. Subgroup analysis by era of diagnosis was performed using Pearson's χ^2 test for categorical variables and t-test for continuous variables. The rate of paediatric cases of CPVT detected per year in NSW over the study period was calculated. Subsequently, using birth year data, the rate of infants born between 1993 and 2015 who were later diagnosed with CPVT in childhood was calculated.[16–22] Using the Poisson distribution, the 95% CI for this annualised birth rate of infants later diagnosed with CPVT in childhood was established, and using a Poisson regression analysis, the trend by year was evaluated. This process was repeated using New Zealand data 2007–2021 as a post hoc comparison. The level of statistical significance was set at p value <0.05.

RESULTS

32 children were diagnosed with CPVT during the study period; the youngest was 2 months and the oldest was 16 years, median 9.6 years (IQR 5.5 years). 14 (44%) of the children were female and the median age at first symptomatic event was 9.3 years. Six children had a family history of sudden death at age less than 40 years. Two children (6%) presented with sudden death (via forensic services), 20 (62.5%) with out-of-hospital cardiac arrest, six (19%) with syncope and four (13%) were asymptomatic and identified through family screening.

All surviving children had normal resting ECGs. Of the 28 children with symptoms (syncope, cardiac arrest, sudden death) prior to a diagnosis of CPVT, 21 (75%) experienced events while active (four of these while swimming), two (7%) while using a computer, one while unwell, one after a head injury and one while at rest. In two (7%) children, the activity at the time of symptoms was unclear. Of the 31 children who underwent genetic testing (one child's family declined), relevant genetic variants were found in 25 (78%). The two most common genes affected were *RYR2* in 19 patients (61%) and calsequestrin in three patients (10%). Of the 18 (58%) children where information on the inheritance of the genetic variant was available, 11 (61%) were de novo. There was no documented paternal inheritance of an *RYR2* variant in this cohort. Participant demographics and results of genetic testing are summarised in table 1.

Median follow-up was 4.5 years (IQR 2.6 years). At the last follow-up, 19/29 (65%) of surviving children had an ICD implanted. 10 children experienced one or more symptomatic cardiac events following diagnosis, including one death (see online supplemental table 1). Lack of medication adherence was postulated as the likely cause of the event in six (60%) cases, and monotherapy beta blockade was considered a possible cause in three (30%) cases. Three children were prescribed a beta-1 selective beta blocker, which may also have been contributory.[25] One child experienced VT during their initial admission following out-of-hospital cardiac arrest, while undergoing medication titration (beta blocker and flecainide). During the study period, six (20%) children received an appropriate ICD therapy and four (13.3%) received an inappropriate shock. Other complications such as lead fracture or displacement were seen in five (17%) children.

When looking at the cohorts based on management era, the contemporary cohort (2015–2021) saw more diagnoses made in the context of family screening, a trend towards less use of ICDs and an increase in the use of flecainide as part of the initial management (first year after diagnosis). While the average age of diagnosis in the contemporary cohort was younger (7 years vs 10 years in the historic cohort), this did not reach

Table 1 Demographic information for children diagnosed with CPVT in NSW, 2002–2021

Demographics	n (%)
Number of patients	32
Female	14 (43.8)
Family history of SCD <40 years	6 (18.8)
Age (years) at:	
First event (median; IQR)*	9.3 (5.7–11.1)
Diagnosis (median; IQR)	9.6 (5.6–11.1)
Mode of presentation	
Cardiac arrest	20 (62.5)
Sudden cardiac death	2 (6.2)
Syncope	6 (18.8)
Family screening (asymptomatic)	4 (12.5)
Activity at time of initial presentation†	
Physically active	21 (75.0)
Playing on computer	2 (7.1)
Other	3 (10.8)
Unknown	2 (7.1)
Method of diagnosis	
Primarily clinical	24 (75.0)
Genetic investigation‡	8 (25.0)
Relevant genetic variant location (heterozygous unless specified)	
RYR2	19 (59.4)
CASQ2	3 (9.4)§
CALM1	1 (3.1)
CALM2	1 (3.1)
TECRL¶	1 (3.1)
No relevant abnormality	4 (12.5)
Testing declined	1 (3.1)

*Denominator: 28 children with a symptomatic event prior to diagnosis (four asymptomatic children identified through family screening were excluded).
†In four children, this physical activity was swimming.
‡Three children were identified via cascade family screening using genetic testing for a known pathogenic or likely pathogenic variant; two children were identified via molecular autopsy in the setting of sudden unexplained death; and three children were identified after an exertional cardiac arrest.
§All were related and heterozygous for a pathogenic variant in *CASQ2* (c.539A>G, p.Lys180Arg).
¶Compound heterozygote: one variant pathogenic, one variant of uncertain significance.
CALM, calmodulin; *CASQ2*, calsequestrin; CPVT, catecholaminergic polymorphic ventricular tachycardia; NSW, New South Wales; *RYR2*, cardiac ryanodine; SCD, sudden cardiac death; *TECRL*, trans-2,3-enoyl-CoA reductase-like.

statistical significance. Figure 1 summarises the treatments used in surviving children in the first 12 months following diagnosis, by era of diagnosis.

The average annualised birth rate of infants who were later diagnosed with CPVT during childhood was 1.4 per year (95% CI 0.98 to 1.97). Using NSW birth rate data,[16–22] the rate of infants born who were later diagnosed with CPVT in childhood was estimated at 1 in 65 000 (95% CI 1 in 91 000 to 1 in 46 000). Using Poisson regression analysis, the number of infants born who were later diagnosed with CPVT in childhood was found to be increasing by year (ratio 1.0895, 95% CI 1.0214 to 1.1620, p=0.0092), with a fairly static overall NSW birth rate. Figure 2 graphically presents the number of children diagnosed with CPVT by year and by year of birth, against the NSW birth rate data.

Following this analysis, the NSW clinicians contacted the New Zealand Cardiac Inherited Disease Group. New Zealand has a population of just over 5 million people, compared with approximately 8 million in NSW. Annual birth rate from 1996 to 2018 varied between 54 021 and 64 341 (mean 58 971).[26] Data were available on all CPVT cases identified during childhood (0–16 years) over a 15-year period (2007–2021) (online supplemental figure 1A). 16 cases of paediatric CPVT were diagnosed, with year of birth ranging from 1996 to 2018 (online supplemental figure 1B). Two (13%) were diagnosed after sudden death by molecular autopsy, 10 (62%) presented with symptoms (including eight with cardiac arrest) and four (25%) were detected through family screening. 14 of the 16 cases (88%) carried a likely causative variant in *RYR2*. By the same methodology, this equated to an average annualised birth rate of infants later diagnosed with CPVT in childhood in New Zealand of 0.7 per year (95% CI 0.43 to 1.14), or 1 in 84 000 live births (95% CI 1 in 138 000 to 1 in 52 000).

DISCUSSION

This study represents the largest single population-based report on paediatric CPVT. Using the known catchment population and published birth data from NSW, the rate of infants born who are later diagnosed with CPVT in childhood is estimated as 1 in 65 000 live births. Median age at presentation for those who were symptomatic prior to diagnosis was 9.3 years (IQR 5.4 years, range 2 months to 16 years) and was with cardiac arrest during activity, most typically exercise. Where inheritance was known (n=18), most cases were genetically de novo, with the causative variant in the *RYR2* gene.

This NSW cohort of children with CPVT has some remarkable differences to that published in the paediatric multicentre CPVT registry. That registry report from 2018 contained 236 subjects below 19 years of age, from 28 centres.[3] Genetic underpinnings were similar in both cohorts, with relevant *RYR2* genetic variants found in 61% of the paediatric CPVT cases in NSW and 60% of those in the registry. A paucity of paternal inheritance of *RYR2* variants has also been reported previously.[27] There were two cases of calmodulin (*CALM*)-associated CPVT. There was evidence from 2012 onwards of its potential role in CPVT,[28] and it was tested for internationally by most laboratories routinely over the next 2–3 years. In the present cohort, this genetic diagnosis was made in 2014 and 2020, respectively. The median age at diagnosis in NSW was 9.6 years, compared with 12.6 years in the registry.[3] Additionally, 63% of children presented with survived cardiac arrest in NSW compared with 28% in the registry; registry data report the majority of those diagnosed after symptoms as presenting with syncope.[29 30] The NSW cohort was thus detected on average 3 years earlier and was twice as likely to have been detected following cardiac arrest rather than syncope. We speculate that this represents both the success of early resuscitation response in NSW and the successful use of diagnostic algorithms, including genetic testing, once patients have reached the intensive care unit.[31] Conversely, the reason for a lower proportion of diagnoses following syncope is at this time unclear. It is potentially as a result of the lower age at diagnosis compared with the registry data. However, the possibility exists that arrhythmic syncope is being underinvestigated, leading to underdiagnosis of CPVT in children.

Observation from the New Zealand CIDG suggests that cardiac arrest due to long QT syndrome is decreasing, while that due to CPVT is increasing.[1] This presumably is due to the effectiveness of family screening and protective therapies in long QT

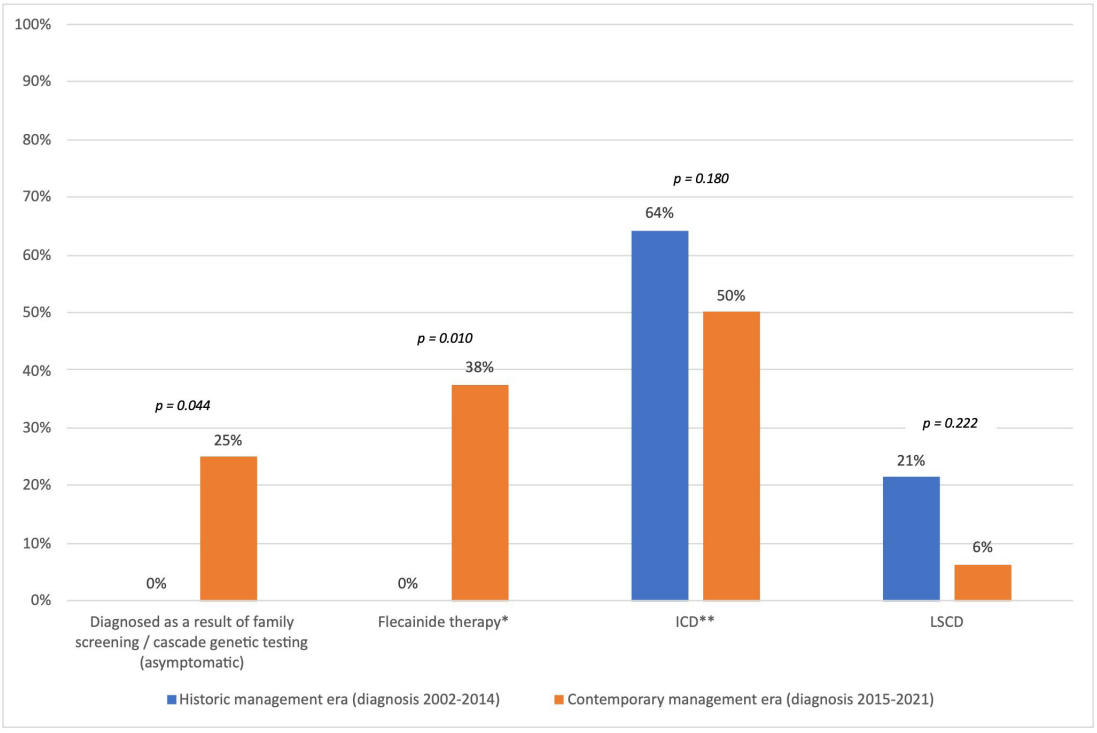

Figure 1 Reason for diagnosis and treatment used in the first year, following diagnosis, for surviving children with a diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT), by era of diagnosis. P value from Pearson's χ^2 test; asymptomatic significance, two sided. *All children were also on beta blocker therapy in both eras. **Date of implant data is missing for n=2 patients (patients 31 and 32). ICD, implantable cardioverter-defibrillator; LSCD, left sympathetic cardiac denervation.

syndrome, against the high proportion of de novo cases in CPVT which continue to present.[1 32] Our experience in NSW is very similar, with provisional data demonstrating that CPVT is now the most common cause of VF cardiac arrest in children.[33]

Exertional collapse in childhood warrants further investigation. In the case of a cardiac arrest or sudden death during exertion, multidisciplinary review is essential, including paediatric cardiology and clinical genetics.[34] Awareness of CPVT during childhood cardiac arrest among first responders is critical, as early management with epinephrine may be counterproductive or even dangerous by sustaining catecholamine drive and causing or sustaining a VT storm.[35] Early use of opioids, sedation and general anaesthesia may be very effective.

Previous studies showing that flecainide, in combination with beta blockers, is remarkably effective at suppressing life-threatening cardiac events have led to a reduced prescription of ICD therapy.[9–12 14 36] However, a focus on adherence is essential given that poor adherence was the dominant cause of cardiac events during follow-up, in keeping with international work.[37] From this NSW cohort, 10 patients (one-third of the cohort) had a recurrent event and there was one death over a median of 4.5 years of follow-up. In over half of these cases, poor adherence to therapy was an identifiable factor, and although some had an event while on beta blockers alone, including beta-1 selective beta blockers.[25] Three were prescribed flecainide, and one was certainly taking it (although this child was in the early postarrest phase with treatment titration underway). The internationally recognised problems with ICDs in this group of patients were also seen, leading to a trend towards reduction in the number being prescribed an ICD due to the increased confidence in the combined beta blocker and flecainide therapy. Within the last 5 years in NSW, ICDs were not prescribed in this paediatric CPVT cohort when combined beta blocker and flecainide therapy suppressed VT on exercise testing, and adherence was felt to be assured.

In considering the use of data from this work to estimate the rate of CPVT detected in children, it is pertinent to consider cases that may have escaped notice. It is anticipated that the rate of clinical detection in children may continue to rise; some children with syncope may have been missed, and there will also be subclinical carriers of pathogenic genetic variants, particularly in *RYR2*. *RYR2* rare variants occur in approximately 3% of the general population and in 60% of clinical CPVT cases[38]; CPVT remains primarily a clinical diagnosis. Some children may have died without a molecular autopsy—although NSW has a remarkably positive history with respect to the investigation of young sudden death. The use of panel testing in some instances in previous molecular autopsy series may mean that very rare cases due to *CALM* variants may not have been captured.[23 24] It would seem unlikely that a significant number would have been missed, particularly since most syncope and deaths in the setting of CPVT occur during activity and are witnessed, given resuscitation if required and investigated in hospital.[30] This is unlike the overall more common nocturnal sudden death in young people, exceptionally rare in CPVT and not encountered in this cohort, where molecular autopsy tends to be less diagnostic.[24] Additionally, using the birth rate alone does not account for other influences on paediatric population size such as migration and mortality; an alternate approach would be to calculate annualised incidence using population-based data.[15] In practice, this resulted in an incredibly small number given that the age at presentation varies, so the population at risk includes all children,[15] and is felt to be less informative than the calculation of the birth rate of infants later diagnosed with CPVT in childhood, noting the genetic underpinnings of this condition. It is emphasised that this work provides an estimate only. However, the

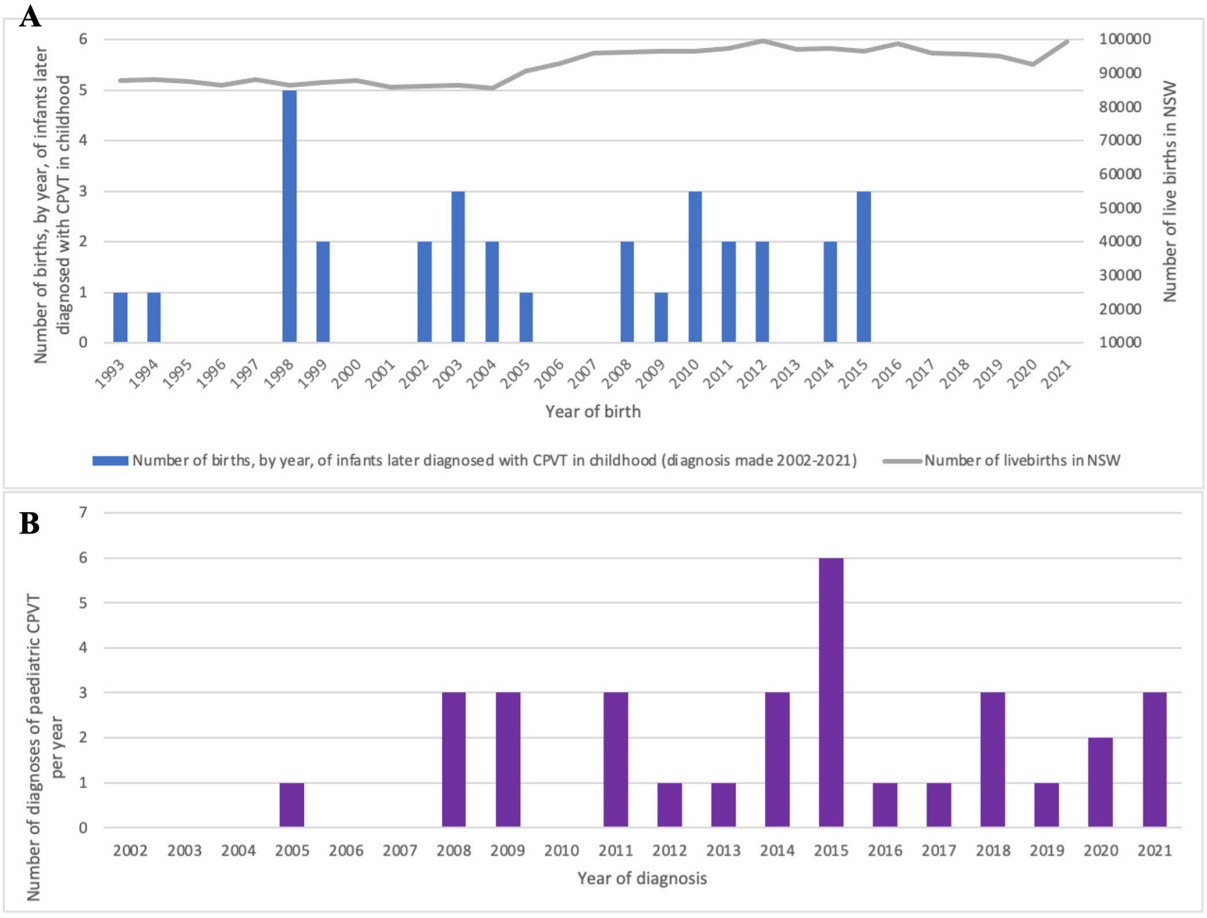

Figure 2 Thirty-two cases of paediatric catecholaminergic polymorphic ventricular tachycardia (CPVT) diagnosed in New South Wales (NSW) between 2002 and 2021, represented by (A) year of birth alongside the number of live births in NSW, and (B) year of diagnosis. *Birth data sourced from NSW Mothers and Babies Reports, 1996–2021.[16–22]

data from New Zealand, with a slightly lower detection rate but overlapping CIs with the NSW data, confirm that this study is unlikely to be a significant underestimate of the true birth rate of CPVT presenting in childhood. Other limitations of this work include those intrinsic to retrospective cohort studies.

If we accept that the birth rate of infants later diagnosed with CPVT in childhood in this study approximates to the true prevalence of clinical CPVT in children, it will still not equal the overall population prevalence since this estimate does not incorporate those born with CPVT who are diagnosed in adult life. Presentation after the age of 18 years is less common than in children. Reviewing international registry data on *RYR2*-related CPVT, 477 were 18 years old or younger and 343 were over 18 (a ratio of 1.4:1).[25] The adult cases from this series include less severely affected individuals with more familial, rather than de novo, causative genetic variants, often detected through family screening; 200 (58%) of the adults were asymptomatic versus 148 (31%) of children. In estimating the overall population prevalence of CPVT, these adults would need to be included. Assuming a current ratio of 1.4:1 children diagnosed to every adult, an overall estimate of diagnosed CPVT population prevalence would be approximately 1 in 46 000. To give a perspective, this is 20 times less common than long QT syndrome (1 in 2000).[8] While the data are not perfect, to our understanding, this study is the closest anyone to date has come to a meaningful real-world estimate based on verifiable data.

CONCLUSIONS

From this study, CPVT was diagnosed in childhood in approximately 1 in 65 000 live births. Two-thirds presented with cardiac arrest or sudden death. Using extrapolated registry data to include adult cases, the overall prevalence is estimated to be approximately 1 in 46 000 live births. Long-term outcomes may be improved by a focus on achieving adherence to dual medical therapy with non-selective beta blockers and flecainide.

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Acknowledgements The study team would like to thank Ms Liz Barnes (biostatistician, The University of Sydney) for her statistical support in establishing population-based estimates and Ms Nikki Earle for her support as part of the Cardiac Inherited Disease Group, New Zealand.

Contributors JRS and CT conceptualised the study. NF, CML, AM and AT collected the data. NF and CML undertook initial data analysis with interpretation assisted by LM, HA, CT and JRS. NF and CML undertook draft manuscript preparation, assisted by JRS. All authors reviewed the results and approved the final version of the manuscript. CML and JRS act as guarantors for this work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Sydney Children's Hospitals Network Human Research Ethics Committee (SCHN 2021/STE02841) and the New Zealand Health and Disability Ethics Committee (AKX/02/00/107/AM03). A waiver of consent was approved.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Not applicable.

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