

Undiagnosed Heart Disease Leading to Sudden Unexpected Death in Childhood: A Retrospective Study

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KEY WORDS

sudden cardiac death, congenital heart disease, hypoplastic left heart syndrome, myocarditis, cardiomyopathy

ABBREVIATIONS

SUD—sudden unexpected death
 SUCD—sudden unexpected cardiac death
 HLHS—hypoplastic left heart syndrome
 SCD—sudden cardiac death
 CHD—congenital heart disease
 EFE—endocardial fibroelastosis
 ARVC—arrhythmogenic right ventricular cardiomyopathy
 DCM—dilated cardiomyopathy
 HCM—hypertrophic cardiomyopathy
 LCA—left coronary artery

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WHAT'S KNOWN ON THIS SUBJECT: Sudden unexpected death can be the presenting symptom for structural heart disease in childhood.



WHAT THIS STUDY ADDS: This study is the largest pediatric, single-institution, retrospective, autopsy series of sudden unexpected cardiac death. Myocarditis, hypoplastic left heart syndrome, and dilated cardiomyopathy were the most common causes, and there were significant age differences between groups at the time of death.

abstract

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OBJECTIVES: Heart disease accounts for a significant proportion of sudden unexpected deaths among children. We describe here demographic features, pathological conditions, and the frequency of premonitory symptoms in a retrospective series of cases of sudden unexpected cardiac death (SUCD) attributable to undiagnosed structural heart disease.

METHODS: A chart review of autopsies involving children 0 to 17 years of age that were performed at the Hospital for Sick Children (Toronto, Ontario, Canada) between 1984 and 2003 was conducted. Cases of sudden unexpected death within 24 hours after clinical presentation with previously undetected fatal heart disease were included. Cases with multiple or thoracic trauma and chronic or multisystem disease were excluded.

RESULTS: During the 20-year study period, 4926 autopsies were performed. A total of 103 cases (2.1%), involving 51 male patients and 52 female patients 1 day to 15 years of age (mean: 2.9 ± 4.2 years), were diagnosed as having SUCD. The most common diagnoses were myocarditis ($n = 37$ [35.9%]), hypoplastic left heart syndrome (HLHS) ($n = 19$ [18.4%]), dilated cardiomyopathy (DCM) ($n = 16$ [16.5%]), coronary artery anomalies ($n = 6$ [5.8%]), and aortic stenosis ($n = 5$ [4.9%]). There was a significant difference in the mean age of presentation between leading causes of SUCD (6.5 days for HLHS, 1.7 years for DCM, and 5.4 years for myocarditis; $P < .0001$). Of 103 cases, 27 (26.2%) had premonitory symptoms documented.

CONCLUSION: SUCD accounted for 2.1% of all autopsies, and HLHS, DCM, and myocarditis were the 3 most common diagnoses, which presented at increasing ages. *Pediatrics* 2011;128:e513–e520

In 1972, Aherne wrote, "Illness in childhood may be devastatingly rapid and commonly fatal unless diagnosis is quick and accurate and treatment is appropriate."¹ His comments remain pertinent today, and both clinicians and pathologists should know the most frequent causes of sudden unexpected cardiac death (SUCD) and their associated prodromal features. This single-institution pediatric autopsy series is one of the largest contemporary series and reviews morphologically evident causes of SUCD over a 20-year period.

In the developed world, the annual incidence of pediatric SUCD was described recently in a prospective, population-based study as 7.5 cases per 100 000 children,² with the vast majority of cases involving patients with structurally normal hearts. In previously published, retrospective series, the incidence of sudden unexpected death (SUD) resulting from all causes among children varied between 1.3 and 6.2 cases per 100 000 population per year, of which cardiac cases represented up to 25%,^{3–7} ranging from 0.08 to 1.3 cases per 100 000 population.^{4,7} The relative predominance of cardiac causes of death in the pediatric population is reported to increase with age, with heart disease causing 19% of all SUDs in the 1- to 13-year-old age group and up to 30% in the 14- to 21-year-old age group.⁴ It also seems that the frequency of SUCD among adolescents and young adults is increasing, although the reasons are unclear.^{8,9}

According to World Health Organization criteria, SUD is defined as sudden unexpected collapse within 1 hour after the onset of symptoms (witnessed) or subjects being observed alive and symptom-free within 24 hours before an unwitnessed terminal event.^{4,10,11} In previous reports, a cardiac cause was confirmed for one-third of the un-

pected deaths, with an additional one-fourth of unexpected deaths being suspected but not confirmed to be cardiac in origin.^{12,13}

METHODS

A retrospective review of all autopsies conducted during a 20-year period (1984–2003) at the Hospital for Sick Children was performed. Results of a total of 4926 autopsies were reviewed, which included 2422 coroner-referred cases and 2504 cases performed under hospital consent. The Office of the Chief Coroner for Ontario investigates all SUDs that occur in the pediatric population. The majority of these pediatric SUDs occur out of the hospital, and all out-of-hospital pediatric SUDs are investigated, with the inclusion of a complete autopsy. Overall, the Office of the Chief Coroner investigates ~19 500 deaths per year, of which ~6500 (33%) receive autopsies. During the period of the study (1984–2003), 9980 medicolegal autopsies for patients aged 17 years or younger were performed in the Province of Ontario (excluding stillbirths). Of those, 2422 (24%) were performed at the Hospital for Sick Children. Cases of SUD with potentially fatal cardiac pathological conditions that were first diagnosed in the postmortem examination were identified and included in the study. Patients with previously documented heart disease, multiple or thoracic trauma, or chronic or multisystem disease were excluded. Demographic and clinical data were obtained from hospital charts, coroner's warrants, and any additional medical charts or notes available at the time of death. Premonitory symptoms were defined as any complaints against the baseline condition of "being well," as reported by the parents or patients themselves during the 7 days preceding the terminal event and documented in the medical records.

Cardiac diagnoses were categorized into the following groups: structural congenital heart disease (CHD), myocarditis, and cardiomyopathy. The cardiomyopathies were defined on the basis of pathological and phenotypic criteria by using the World Health Organization classification¹⁴ and, if applicable, histologic or molecular evaluation. Myocarditis was diagnosed according to published criteria,^{15,16} with more-recent cases undergoing virologic studies for a panel of common cardiotropic viruses (enterovirus, varicella zoster virus, human herpesvirus 6, 7, and 8, adenovirus, parvovirus B19, herpes simplex virus 1 and 2, cytomegalovirus, and Epstein-Barr virus).

Statistical analyses were conducted by using proprietary statistical software. Data are expressed as mean \pm SD. For comparison of means of normally distributed data, an unpaired Student's *t* test or an analysis of variance was performed. For categorical data, χ^2 and Fisher's exact tests were used. Studies were performed in accordance with the Hospital for Sick Children research ethics board guidelines.

RESULTS

Demographic Characteristics

One hundred three cases of SUCD (2.1% of all autopsies) from the study period were identified. There were 51 male and 52 female subjects, whose ages ranged from 1 day to 15 years (median: 0.6 years; mean \pm SD: 2.9 \pm 4.2 years). The mean \pm SD age for male subjects was 3.1 \pm 4.6 years (median: 0.4 years), and that for female subjects was 2.8 \pm 3.7 years (median: 1.0 years) (*P* = .719). The additional subject characteristics are shown in Table 1. Of note, no patients were documented to demonstrate behavior reported as high risk for SCD, such as use of cocaine or tricyclic agents, bulimia, or anorexia nervosa.¹⁷

TABLE 1 Subject Characteristics

	Subjects, <i>n</i> (%)	Age, Range (Mean)	Cases With Preceding Symptoms, <i>n</i> (%)	Comments
Myocarditis	37 (21 M/16 F) (35.9)	10 d to 14 y (62 mo)	15 (40.5)	1 death occurred during exercise
HLHS	19 (10 M/9 F) (18.4)	2–16 d (7 d)	2 (10.5)	
DCM	16 (7 M/9 F) (16.5)	2 wk to 142 mo (19.9 mo)	5 (31.3)	1 death occurred during exercise
Combined with EFE	11/16 (68.8)			
Aortic stenosis	5 (4 M/1 F) (4.9)	3 d to 34 mo (7.5 mo)	1 (20.0)	
Transposition of great arteries	4 (3 M/1 F) (3.9)	2 h to 9 d (2.6 d)	0 (0.0)	3 deaths occurred within first 24 h after delivery
Atrioventricular septal defect	3 (1 M/2 F) (2.9)	1 mo	2 (66.7)	
ARVC	3 (1 M/2 F) (2.9)	69 mo to 15 y (125 mo)	0 (0.0)	1 death occurred after exercise
Other cardiomyopathies ^a	6 (0 M/6 F) (5.8)	1–147 mo (29.8 mo)	1 (16.7)	1 death occurred after exercise
Coronary artery anomalies	6 (5 M/1 F) (5.8)	1–149 mo (46.3 mo)	1 (16.7)	Previous exertional syncope was only premonitory symptom for 1 patient in this group
Other causes	4 (3 M/1 F) (3.9)	3 d to 4 wk (16.5 d)	0 (0.0)	1 case each of situs inversus totalis, tetralogy of Fallot, total anomalous pulmonary venous drainage, and coarctation of aorta
Total	103 (50 M/53 F) (100)	2 d to 15 y (35 mo)	27 (26.2)	

M indicates male; F, female.

^a HCM, restrictive cardiomyopathy, left ventricular noncompaction, or histiocytoid cardiomyopathy.

Pathological Conditions

Causes of SUCD

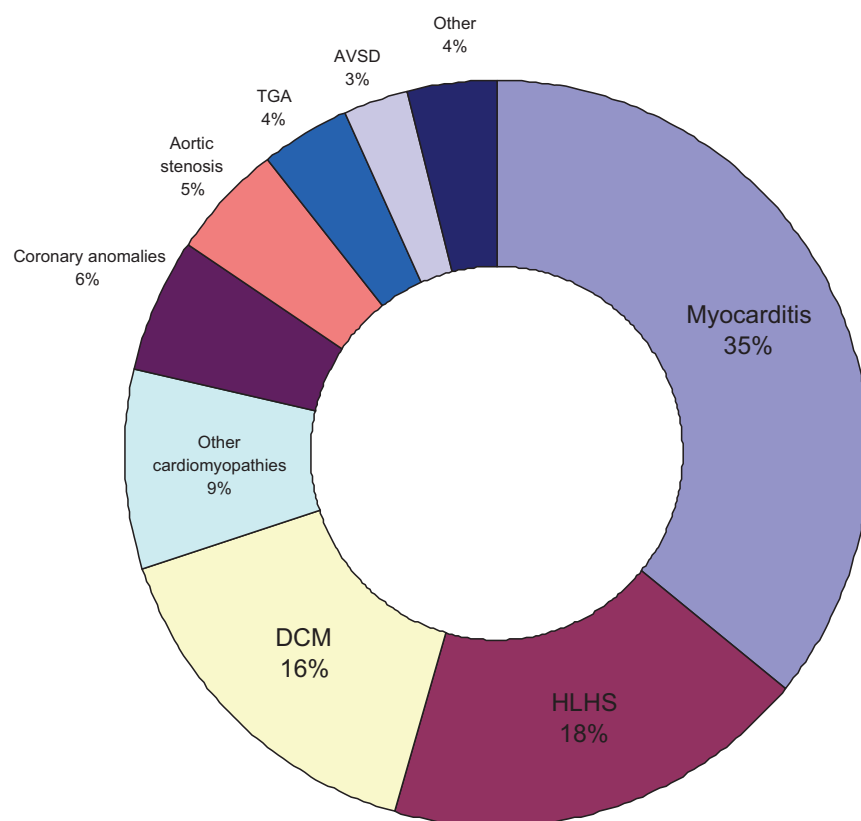
The causes of SUCD identified in autopsy examinations are outlined in Fig 1. In descending order of frequency, these were myocarditis ($n = 37$

[35.9%]), hypoplastic left heart syndrome (HLHS) ($n = 19$ [18.4%]), dilated cardiomyopathy (DCM) ($n = 16$ [16.5%]), coronary artery anomalies ($n = 6$ [5.8%]), and aortic stenosis ($n = 5$ [4.9%]). There were significant

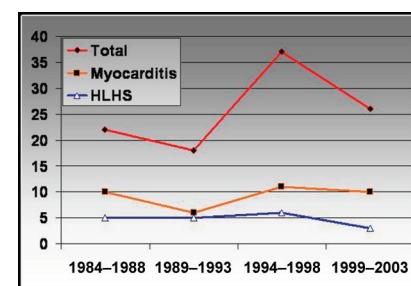
differences in the mean age of presentation among the 3 most frequent causes of SUCD, that is, 6.5 ± 3.9 days for HLHS, 1.7 ± 3.0 years for DCM, and 5.4 ± 4.2 years for myocarditis ($P < .0001$). With regard to trends in disease occurrence over time, the absolute numbers of myocarditis cases and HLHS cases remained similar in each 5-year period during the 20-year study period ($P = .25$, not significant), except for a slight decrease in the number of HLHS presentations in the past few years (Fig 2).

Myocarditis

Of the 37 cases of myocarditis, 20 occurred in female patients and 17 in male patients, with ages ranging from 10 days to 14 years (mean \pm SD: 5.4 ± 4.15 years; median: 5 years). Histologic

**FIGURE 1**

Causes of SUCD attributable to undiagnosed heart disease, as identified in autopsy examinations ($N = 103$). TGA indicates transposition of the great arteries; AVSD, atrioventricular septal defect.

**FIGURE 2**

Numbers of presentations over time for each of the 3 major diagnostic groups.

examination revealed a predominantly lymphocytic infiltrate for 29 patients (78%) and a mixed infiltrate with both lymphocytes and neutrophils for 5 patients (13.5%). The remaining 3 patients had either eosinophilic or histiocytic infiltrates. Postmortem virologic studies were performed in 24 cases (65%), with only 3 positive results (2 positive culture results for coxsackie B5 virus and 1 positive polymerase chain reaction result for human herpesvirus 7).

Dilated Cardiomyopathy

Of the 16 cases, 7 involved male patients and 9 female patients. The age range was 2 weeks to 11.8 years (mean \pm SD: 1.7 ± 3.0 years; median: 7 months). Eleven patients (68.8%) had the additional finding of endocardial fibroelastosis (EFE). No associated cardiac tumors, infective endocarditis, or primary pericardial disease was identified in the cases of DCM.

Other Cardiomyopathies

A heterogeneous group of cardiomyopathies included arrhythmogenic right ventricular cardiomyopathy (ARVC) ($n = 3$ [2.9%]), histiocytoid cardiomyopathy ($n = 2$ [1.9%]), and 1 case each of hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy, and isolated left ventricular noncompaction (Table 2).

Structural CHD

The most common entity in this group of conditions was HLHS, which oc-

curred in 19 cases (18.4% of all diagnoses; 10 male subjects and 9 female subjects). The age range was 2 to 16 days (mean: 7 days; median: 5 days). Other cardiac defects, totaling 18 cases (17%), included coronary artery anomalies ($n = 6$), aortic stenosis ($n = 5$), transposition of the great arteries ($n = 4$), and atrioventricular septal defect ($n = 3$). Of the 4 infants with transposition of the great arteries, 3 died within 24 hours after birth; 2 were born in the hospital and died within a few hours, whereas 1 was born at home. The latter patient was brought to the emergency department with cyanosis but collapsed and died within a few hours. The coronary artery anomalies included 1 case of left coronary artery (LCA) origin stenosis with evidence of myocardial infarction, 1 case of both right coronary artery and LCA ostial stenosis, 1 case of anomalous origin of the LCA from the main pulmonary artery, 1 case of anomalous origin of the LCA from the right aortic sinus of Valsalva, and 1 case of premature coronary atherosclerosis in a 12-year-old male patient. As reported previously,¹⁸ an unusual case of a papillary fibroelastoma of the mitral valve with extension into and occlusion of the LCA ostium was included with the coronary anomalies.

Symptoms

Of all 103 patients, only 27 (26.2%) had any premonitory symptoms (Fig 3). Symptoms were categorized as fol-

lows: influenza-like illness ($n = 15$), fever alone ($n = 2$), abdominal pain ($n = 2$), chest pain and shortness of breath ($n = 2$), intermittent cyanosis ($n = 2$), feeding difficulties ($n = 2$), headache ($n = 1$), and 1 episode of previous exertional syncope ($n = 1$).

Of the patients for whom myocarditis was confirmed subsequently, a substantial proportion ($n = 15$ [40.5%]) reported symptoms before the terminal event. The majority of cases were described as influenza-like illness ($n = 11$ [30%]). In contrast, two-thirds of patients with DCM were without symptoms; only 5 (31.3%) of 16 patients described influenza-like illness ($n = 4$) or abdominal pain ($n = 1$). Two (10.5%) of 19 patients with HLHS had feeding difficulties before the terminal event. Only 4 deaths (3.8%) occurred during or immediately after exercise (DCM, ARVC, and isolated left ventricular noncompaction).

DISCUSSION

Overview

In this study, we describe the occurrence of undiagnosed structural cardiac and myocardial disease resulting in SUCD in a large autopsy series of children and adolescents. A classification of the cardiac causes of sudden death was proposed previously,¹² that is, structural CHD; coronary artery anomalies or acquired diseases; inflammatory and noninflammatory cardiomyopathies; disorders of generation, propagation, or maintenance of

TABLE 2 Cardiomyopathies Other Than DCM

	<i>n</i>	Age	Gender	Preceding Symptoms	Comments
HCM	1	1 mo	F	Yes	—
Histiocytoid cardiomyopathy (rare mitochondrial disorder)	2	3 mo; 20 mo	2 F	No	—
Restrictive cardiomyopathy	1	5 mo	F	No	—
Isolated EFE	1	3 mo	F	No	—
Isolated noncompaction of left ventricle	1	147 mo	F	No	Death occurred after exercise
ARVC	3	69 mo; 13 y; 15 y	1 M/2 F	No	1 patient died after exercise; 1 patient had associated myxomatous degeneration of mitral valve

M indicates male; F, female.

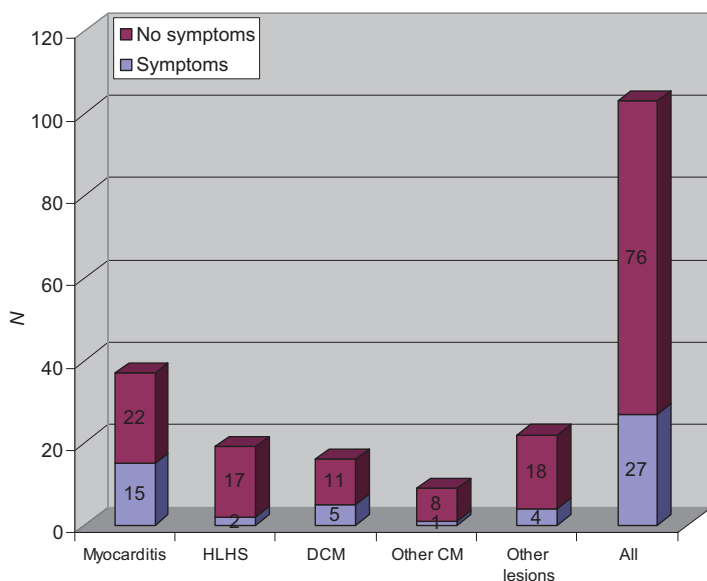


FIGURE 3
Incidences of premonitory symptoms according to diagnosis. CM indicates cardiomyopathy.

normal rhythm; mitral valve prolapse; and cardiac tumors.

Congenital Cardiovascular Malformations

With modern diagnostic and surgical techniques, most cases of structural CHD are identified early and can be treated in specialized centers. However, our retrospective series demonstrates that unrecognized structural CHD continues to be a potential cause of SUD among infants and children.

Recently published data suggest that, among infants, sudden infant death syndrome is a more common cause of death than undiagnosed structural CHD. Furthermore, it has been proposed that a proportion of sudden infant death syndrome cases may be related to primary arrhythmogenic disorders.^{2,5,19} Among all subjects 0 to 18 years of age, however, structural CHD and myocardial disease remain more important causes of SUCD than primary arrhythmogenic disorders.^{5,20,21}

In our series, structural CHD was seen less frequently than cardiomyopathies or acquired diseases (36% vs 64% of all cases). Because the former cases

predominantly involved infants with lesions that can be addressed surgically, this remains an important diagnostic concern that was highlighted previously.²² Råsten-Almqvist and Rajs⁵ reported that cardiovascular malformations accounted for 3.8% of SUDs in an infant group, and they showed that two-thirds of deaths occurred in the absence of a premortem diagnosis. Duct-dependent systemic outflow obstructive lesions and transposition of the great arteries were the most frequent congenital lesions in our series, which confirms previously published data^{12,23} and emphasizes the importance of prenatal screening for CHD.

Myocardial Disorders

Among the cases of myocardial disease identified in this series, myocarditis was by far the most common (0.75% of all pediatric deaths and 35.9% of SUCD cases). This again is consistent with the previously published literature.^{4,17,21,23–25} The mean and median ages of patients with myocarditis were 5.4 and 5 years, respectively, which confirms that myocarditis is more likely to cause SUCD in older

children. This is in accordance with the findings of Weber et al.²⁵

In our series, conventional histopathological criteria were used to establish the diagnosis of myocarditis.^{16,26} Reports have demonstrated limitations of the light-microscopy criteria (the Dallas criteria), pointing out that milder inflammatory changes may go undetected.²⁷ Others have noted that inflammatory changes in the myocardium may be focal and frequently are located close to the conducting system,⁵ leaving certain areas of the myocardium unaffected. These are clearly important limitations to the sensitivity of endomyocardial biopsy for the diagnosis of myocarditis; however, the detection of myocarditis in autopsy specimens is aided by the increased amount of tissue available for histologic analysis. In our series, postmortem virus-isolation studies were performed in 24 cases (65%), with a very low detection rate (3 cases [12.5%]). Therefore, we consider the presence of viral pathogens or DNA in the myocardium only to support a diagnosis of myocarditis. Low virus identification rates also may reflect the fact that molecular techniques were less established in the earlier years of this case series. No cases of bacterial or parasitic myocarditis were identified. In the National Australian Childhood Cardiomyopathy Study,²⁸ SUD was the presenting feature for 4.8% of 184 patients. Of note, 8 of the 9 patients who died suddenly fulfilled the postmortem diagnostic criteria for myocarditis.

Of interest, EFE12 was identified in nearly 70% of DCM cases in our series, all of which involved subjects who were younger than 2 years at the time of death. The association of congenital EFE and cardiomyopathy with prenatal mumps virus exposure has been reported,²⁹ and it has become less common since the initiation of widespread immunization in the 1970s. Although

EFE is noted frequently in the presence of chronic myocarditis, systemic outflow tract obstruction, or congenital heart block,^{30,31} its significance as a marker of DCM severity remains unclear.

ARVC was relatively uncommon in our series, occurring in only 3 cases (2.9%), which is in agreement with the literature.⁶ Two cases of histiocytoid cardiomyopathy were identified in our series, and SUD frequently is a presenting feature.^{32–36}

Our series demonstrated that undiagnosed HCM caused SUCD in only 1 case (<1% of all SUCD cases), which is at odds with the widely held perception of HCM being the “single most common disorder causing sudden cardiac death in people younger than 35 years.”^{37,38} This perception arose from reported autopsy data on a selected cohort of young competitive athletes,³⁹ which may not be representative of the general pediatric population. HCM detected before the age of 14 years may carry a somewhat worse overall prognosis in adolescence and early adulthood⁴⁰; however, it frequently is amenable to treatment and does not commonly require cardiac transplantation. In support of this, no disproportionate age distribution of SUD was identified in a large nonreferred cohort of patients with HCM,⁴¹ and no overwhelming predominance of HCM was reported by authors studying SUD in general pediatric and young adult populations.^{4,17,19,42,43}

Coronary Artery Lesions

Six of our cases fell into this category, with 4 (3.8%) being grouped under the umbrella of “anomalies of coronary ostia.” SUCD associated with coronary artery anomalies has been described for children of all ages and young adults; most commonly, SUCD is caused by an anomalous LCA origin from the right aortic sinus.^{12,19} Other

common anomalies associated with SUCD include an ectopic origin of the LCA from the pulmonary artery, an anomalous right coronary artery origin from the left aortic sinus, a “high-take-off” coronary ostia, or an ostial origin at a commissure.¹⁸ One case (0.97%) each of an anomalous LCA origin from the right aortic sinus and an anomalous LCA origin from the pulmonary artery were detected in this series. Of note, we encountered no cases of Kawasaki disease-related coronary artery lesions in this cohort, although this condition has been identified as the leading cause of acquired heart disease among children in the developed world and an important cause of SCD.^{12,44}

Symptoms

Although some investigators suggested that as many as 50% of victims of SCD may actually have unrecognized antecedent symptoms,¹⁷ this incidence varies, reflecting the limitations of retrospective assessment.^{45,46} In our series, a significant number of families gave a record of premonitory symptoms; this was most prominent in cases of myocarditis (40.5%). Influenza-like symptoms preceding myocarditis have been described commonly, whereas signs of heart failure may be subtle or undetectable.^{17,21}

In contrast, symptoms were uncommon among children who died as a result of DCM, and no symptoms heralding death were observed for any of the patients with coronary artery anomalies. Similarly, exercise immediately before collapse and death occurred for only 3.8% of the subjects in our series, whose postmortem diagnoses included myocarditis, DCM, ARVC, and left ventricular noncompaction. This small proportion of exercise-related deaths may in part reflect the absence of genetic arrhythmogenic diagnoses in this cohort.

Risk stratification for SUD among apparently healthy youths has become a topic of debate over the past decade. It is complex, costly, and possibly unattainable for the general pediatric population.^{47–49} Adolescents participating in competitive athletic activities may be amenable to preparticipation screening. However, practices vary widely, and consensus is lacking regarding the extent of testing and the means of implementation.⁵⁰

Study Limitations

This was a retrospective study performed at a single institution; therefore, referral bias may play a role in the reported frequency of the heart diseases reported. The study does not address the issue of sudden arrhythmic death in children, because such cases were not included in the cohort. Similarly, subjects older than 15 years were not represented in the study. Furthermore, data on the presence of premortem symptoms were not collected in a standardized fashion, and findings were based on the information that was available to the pathologist at the time of the autopsy. Finally, data collection for this study did not entail approaching family members or family physicians; therefore, the number of cases with a positive family history of SUD is not known.

CONCLUSIONS

This study, being the largest pediatric autopsy series published to date, reinforces the findings of previous reports with respect to the broad range of structural cardiac anomalies encountered. Lacking the power of epidemiological studies, it nevertheless convincingly indicates that unrecognized structural CHD and myocardial disease remain significant causes of SUCD in children. Most deaths are not preceded by recognized symptoms heralding demise.

Given the importance of undiagnosed myocarditis and DCM in our

series, we highlight the need for a systematic expert autopsy examination directed at detecting focal changes within the myocardium, especially those localized around the

specialized conducting tissue. We now consider genetic testing for cardiomyopathy or ion channel disease to be an important adjunct for diagnosis. Attaining a specific diagnosis

is extremely important for the surviving family members and also may inform policy decisions regarding the screening processes indicated for heart disease in young people.

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