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Sudden Unexplained Cardiac Arrest in Apparently Healthy Children: A Single Center Experience

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Abstract

Objective—To determine the causes of sudden cardiac arrest (SCA) in apparently healthy children in a single center in the era of primary prevention (screening questionnaire, SQ) and secondary prevention (automated external defibrillator, AED and automated implantable cardioverter defibrillator, AICD).

Study Design—Any child (0–18 year's age) without prior known disease except for attention deficit disorder who underwent out-of-the hospital cardiopulmonary resuscitation was included in the study as SCA. Using retrospective chart review we evaluated the efficacy of the SQ, electrocardiogram (EKG), chest roentgenogram (CXR) and an echocardiogram.

Results—We found 44 out of 6,656 children admitted to intensive care with SCA; an AED was used in 39%, AICD placed in 18% and survival to hospital discharge was 50%. The etiology for SCA was identified in 57% of the cases, mostly in those above one year of age and among these the majority of had a cardiac etiology (50%) while 7% had rupture of an arteriovenous malformation. Stimulant medication use was seen in 11% of the SCA. In the best case scenario of hypothesized primary prevention, a prior SQ, CXR, EKG and echocardiogram may have detected 18%, 9%, 23% and 16% of at-risk cases respectively and 32% may have been detected with EKG and SQ together. Based on a historical control cohort, a positive EKG was significantly higher in children with SCA ($p = 0.014$).

Conclusion—An EKG along with a screening SQ may be more effective in identifying children who are potentially at-risk for SCA than a SQ alone.

Keywords

Stimulants; attention deficit hyperactivity disorder; pseudoephedrine; arteriovenous malformation; sudden cardiac death

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Introduction

Sudden unexplained cardiac arrest (SCA) or death is a rare occurrence in the young, with an incidence between 1.3 and 8.5 per 100,000 patient-years [1, 2]. Even though SCA is rare, such a catastrophe is always unexpected in a previously healthy child. Furthermore, these events not only have devastating impact on the families, but also have a tendency to attract considerable public and media attention. This has led to an increase in screening tools and referrals to cardiologists for sports clearance by schools and for clearance for use of stimulant medications.

Over the last decade there has been increased focus on primary preventive strategies [3] such as (a) screening Questionnaire [4, 5] with utilization of disqualification criteria for participation in physical education and sports, (b) EKG and other investigations; and secondary preventive strategies [3] (a) automated external defibrillator (AED) [6] and (b) automated implantable cardioverter defibrillators (AICD) [7]. Although a screening Questionnaire is currently used for primary prevention of SCA, there is controversy regarding the use of additional testing such as a screening EKG.

In order to answer some of these questions and to learn from the children who had undergone such a tragic event in our region, we evaluated their prior medication history, warning symptoms [8], family history [8], diagnostic studies, any probable etiology, survival and the modes of secondary prevention. We attempted to evaluate the efficacy of a screening Questionnaire [4]. We also evaluated the benefit of additional studies such as electrocardiogram (EKG), chest roentgenogram (CXR) and pediatric transthoracic echocardiogram in assessing children for SCA.

Design and Methods

The study was approved by the institution's Committee for Protection of Human Subjects for a retrospective chart review. The patients were admitted with diagnosis of out-of-hospital SCA to the Children's Memorial Hermann Hospital and University of Texas at the Texas Medical Center at Houston, the only level-one pediatric trauma center in the region with Life Flight services that provides rapid transport of children with high acuity events.

The inclusion criteria were any previously healthy children 0 to 18 years of age with SCA admitted post cardiopulmonary resuscitation in the pediatric intensive care unit in the past 10 years. The SCA definition included children with sudden death cause unknown (ICD-9 code of 798) which also include children with sudden infant death syndrome (SIDS), instantaneous death, sudden unexplained death (SUD) and sudden cardiac death (SCD) (ICD-9 code of 427.5). We included children with attention deficit disorders (ADHD) as they are often treated with stimulant medications. The exclusion criteria included patients with known (a) medical conditions such as congenital heart disease, cardiac disease including arrhythmias, respiratory disease including asthma, genetic syndromes or diseases, renal diseases, seizures or other neurological conditions, malignancies or history of malignancies, metabolic diseases or chronic infectious diseases (b) traumatic death other than commotio cordis but including shaken baby syndrome and neglect (c) homicidal, suicidal, or accidental death including drug overdose and drowning (d) prematurity below 37 weeks of gestation (e) dehydration (f) chronic medications use other than those for ADHD and (g) positive urine drug screen for substance abuse. Besides the consulting cardiologists, for the study, all cases were independently reviewed by 2 pediatric cardiologists and any disagreements resolved by consensus. The children were determined to be on a stimulant if they were taking any stimulant medication for ADHD or pseudoephedrine for an upper respiratory tract infection prior to the arrest. The data were obtained by chart review, and included demographics, medications, prodromal symptoms, personal and family history,

modes of resuscitation and secondary prevention, types of consultations, results from the diagnostic studies to identify the etiology of the sudden event, including CXR, echocardiogram, EKG, electrophysiology study, MRI, cardiac catheterization, cardiac tomography scan and others when available. We used the pre-participation Questionnaire[4] that includes history of certain symptoms, some medical history and family history of certain diseases to identify children who are potentially at risk for SCA. The patient history was used to fill the screening Questionnaire on each patient. The children who did not have the pertinent history for the Questionnaire were not included in the analysis. We estimated the incidence of a positive pre-event EKG, CXR or an echocardiogram based on the findings on the studies done post-event.

Statistical Analysis

Descriptive analysis of the data was performed and results expressed as means (with standard deviation) and median (with range) for normal or non-normal distributed continuous data, respectively. Questionnaire data [4] was used to identify individuals that could potentially have been categorized as “at-risk” for SCA had a pre-event screening been performed. To evaluate if the proportion of individuals thus identified in the SCD cohort was different from proportion of positive imaging studies in the pediatric population, the frequencies of these potentially “at-risk” children were compared to previously reported frequencies in published data [9]. Statistical significance was assumed at a two-sided Type I error probability of 0.05

Results

This study included a large multiethnic patient population of 6,656 children admitted to a tertiary care intensive care unit from January 2000 to December 2009. There were total of 44 patients with SCA who were included in this study (table 1) with a prevalence of 0.7% of admissions to the pediatric ICU. In our study the inpatient survival to hospital discharge was 50% in SCA patients and the survival was higher in children 1–18 year age group compared to the infants. An etiology was less evident in infants in comparison to older children.

Cardiac causes of sudden unexplained cardiac arrest

Probable causes of SCA were found in about 57% of patients overall although a cause was rarely identified in infants (table 1). The majority of these had a cardiac etiology (50%). Thus, etiology for 43% of the SCA was not determined. Primary arrhythmias on post-event electrophysiology testing were documented in 4 children including, junctional ectopic tachycardia, right ventricular outflow tract tachycardia, left ventricular outflow tract and catecholaminergic polymorphic ventricular tachycardia. A primary long QT syndrome (LQTS) was diagnosed in 2 children (one with a positive genetic testing); secondary LQTS was noted in 3 children. The determination of primary and secondary long QT syndrome was made by an electrophysiologist and several EKGs were used to document the disease after correction of all the electrolytes and recovery from the event. Wolff Parkinson White syndrome (WPW) was determined in 6 patients (4 children underwent ablation of the accessory pathways; one child was transferred to a different facility upon parental request and one child died). Of the children ablated for WPW, one child had a retrograde pathway along with an anomalous right coronary artery anatomy from the left sinus.

Arteriovenous malformations associated with sudden unexplained deaths

An AVM rupture in the brain is a rare etiology for SCA and was also noted in our study population (table 2). In one patient, who died before confirmatory diagnosis, the autopsy report documented rupture of AVM as a high possibility for cause of death. A positive family history was noted in one patient whose father died suddenly at the age of 44 years

and the father's autopsy report showed a ruptured abdominal aneurysm. In another child with AVM (not included in this study because he presented with seizures but no SCA), the CT scan showed intracerebral hemorrhage and the AVM rupture was confirmed with magnetic resonance angiograms and vascular angiograms; there was also a positive family history of AVMs in this child (paternal grandfather and 2 paternal aunts who were all deceased). Thus, 50% of the children with AVM had a positive family history of AVMs. Coil embolization of AVMs was performed in those who survived the SCA.

Other possible risk factors for sudden unexplained cardiac arrest

Antecedent use of stimulant medications was noted in 5 (11%) children (table 3) although their cause and effect with respect to SCA were unknown. Antecedent psychotropic medication use was documented in 2 of the 3 children with secondary LQTS and included the following: clonidine, lithium, escitalopram, citalopram and sertraline; all these medications except for clonidine are associated with secondary LQTS. No antecedent EKG was available in these 3 children. We found significantly higher number of infants dying during sleep when compared to older children and 40% of the older children dying while exercising. We noted antecedent upper respiratory infection in 9 (20%) of the children. We evaluated seasonal distribution of the SCA and found no relationship with different seasons in our area.

Hypothesized primary prevention of sudden cardiac arrest in children

A detailed history for the Questionnaire [4] such as symptoms and family history was available for 33 (75%) of patients. Based on the data entered into the Questionnaire, 18% children had information that would potentially have labeled them as "at-risk for SCA" prior to the event. For e.g. there were documented antecedent symptoms in older children of palpitations and syncope and these were marked as positive in the Questionnaire. CXR data was available for all patients. EKG data was available for 25 (57%) of patients. Echocardiogram data was available for 27 (61%) of patients. In the best case scenario, a prior Questionnaire, CXR, EKG and thorough pediatric transthoracic echocardiogram may have detected 18%, 9%, 23% and 16% of at-risk cases respectively (table 4). There were 32% at-risk children who may have been detected by a pre-event Questionnaire and EKG together. We compared these findings to a historical cohort [9] in a previously published study of 60 consecutive children that had been evaluated by a pediatric cardiologist for cardiac symptoms or signs and found to have no heart disease upon a physical examination. Subsequent imaging studies of these children identified one CXR (2%), 3 EKGs (5%) and 12 echocardiograms (7%) that were positive for any heart disease [9]. Based on a historical control cohort [9], a positive EKG was significantly higher in children with SCA ($p = 0.014$) (table 4).

Discussion

Cardiac disease remains the primary cause of SCA in apparently healthy children[10, 11] as confirmed by our study and can be due to several causes including coronary artery anomalies[12], infectious[13] and non-infectious cardiomyopathies, and arrhythmogenic substrates [10]. In this era of advanced imaging, autopsies [14] alone may not provide an insight into the cause of SCA since many of the arrhythmogenic substrates account for one third of autopsy-negative sudden unexplained deaths in children. However, addition of genetic testing [15] and metabolic evaluation can improve the yield of an autopsy. Although cardiac disease make up a significant portion of the etiology for SCA as reported in literature, a ruptured AVM has also been identified as a possible cause of SCA [16]. With improving imaging capabilities, an AVM is perhaps being diagnosed more often and accounted for 7% of SCA in our study. Regarding secondary prevention, we found that an

AED was used in 39% patients during resuscitation and 18% received an AICD for malignant arrhythmias or cardiomyopathies. The inpatient survival to hospital discharge in our center was 50% for SCA.

Children less than a year of age had significantly higher incidence of SCA or SIDS during sleep, lower detection of an etiology for SCA and a lower survival rate when compared to older children in our study. Compared to the younger children, about 40% of the older children in our cohort had an event while exercising. These findings are consistent with earlier reports of SCA being observed in competitive athletes [17] and SIDS being observed during sleep [18].

We noted antecedent upper respiratory infection in 9 (20%) of the children in our cohort. We included an upper respiratory tract infection as a possible associated risk factor for SCA because of the following reasons: firstly these infections are associated with use of over the counter medications that may contain stimulants like pseudoephedrine and secondly it may be associated with a subclinical myocarditis. Furthermore, upper respiratory tract infections have been associated with SCA in infants [19, 20] and older children. Winter months have been associated with SIDS although one study did not find any seasonal variation [19]. Many conditions can cause seasonal variation in SCA in children including discontinuation of physical education and decreased use of stimulant medications for ADHD during summer breaks, higher incidence of viral infections and swaddling during winter months and so on. We did not find any seasonal predilection for SCA in our study.

Our study found 11% of the SCA had stimulant use prior to event, including stimulants like pseudoephedrine and medications for ADHD. We included pseudoephedrine under stimulants since it is a sympathomimetic amine like ephedrine and has also been associated with SCA in children [20]. We found that 7% of the SCA were related to stimulants use for ADHD, and although cause and effect were not established between the two, 100% of them had an additional cardiac abnormality. Children with ADHD who died suddenly had congenital junctional ectopic tachycardia, hypertrophic cardiomyopathy and secondary long QT syndrome most likely related to additional psychotropic medications. These 3 diseases would have most likely been able to be diagnosed by a pre-event EKG. The stimulant medication with prevalence of use in 2%–18% of the children in the general population [21], has central and peripheral catecholaminergic effects and has been documented in the literature as a possible contributor of acute mortality in children [3, 20, 22–24]; however, one very large study has shown an elevated but statistically non-significant hazard ratio of SCA [25]. Stimulant use and abuse can lead to a statistically significant increase in heart rate [26, 27], blood pressure [26, 27] and cardiomyopathies, all increasing the risk for arrhythmias and sudden cardiac arrest [24]. Stimulants also have the potential of abuse amongst children, especially as performance-enhancing drugs among athletes [28] and hence SCA due to the use of stimulants are perhaps under-diagnosed and under-reported. The Food and Drug (FDA) review of patients taking stimulant medications for the treatment of ADHD followed the report of 25 cases of sudden cardiac death in patients treated with methylphenidate (7 children and 1 adult) and with amphetamine (12 children and 5 adults) and another 54 people who had serious cardiovascular events during the period 1999–2003. A review by FDA of the cardiovascular risks associated with the use of stimulants in children and adults did not find increased risk except for those with underlying heart disease, and for them, a black box warning was included on pharmaceutical package inserts. These findings by FDA are confirmed by our study.

We found that based on a historical cohort of apparently healthy children without SCA, the prevalence of an abnormal EKG was significantly higher in those with SCA. Also findings from our study suggest that all 3 (100%) children on stimulants for ADHD may have

benefitted from obtaining an EKG prior to starting the medications. A recent metanalysis has shown that an EKG has high sensitivity for mass screening in asymptomatic children with detectable causes of SCA such as hypertrophic cardiomyopathy, LQTS and WPW [29]. Current recommendations by American Academy of Pediatrics [3, 30, 31], FDA's Pediatric Advisory Committee [32] and American Academy of Child and Adolescent Psychiatry [33] do not include an EKG for screening a child prior to starting stimulants for ADHD or participation in sports. The American Heart Association recommends that obtaining an EKG prior to starting the stimulants a reasonable option and further recommends a cardiology consult if there are any red-flags on history, physical examination or the EKG [34]. Although it is an important first-step, a screening questionnaire alone is not enough to separate the low-risk from the high-risk children. Based on our findings, an EKG along with the screening Questionnaire [4] would improve detection of at-risk children than a Questionnaire [4] alone. We would recommend confirming these findings with a large prospectively conducted study.

We further recommend addition of history of the following known risk factors to the screening questionnaires: use of all medications including non-prescription drugs and supplements, Kawasaki disease [35], attention deficit disorder, psychiatric disorder and a family history of aneurysms and AVMs. Currently recommended screening Questionnaires [3, 4] are incomplete in some of this important data.

Limitations of the study

This was a retrospective study involving a review of medical records and hence there are many of the limitations of such a study, including reporting bias. We did not have access to information regarding the history of exposure to nicotine, either as substance abuse or as a second-hand exposure. For deaths among infants, we did not have data on maternal age or fetal exposure to substance use. We could not confirm the sleep position of those children who died during sleep. Details concerning stimulant medications regarding duration of use prior to arrest and so forth was unknown. There was also lack of genetic, metabolic and toxicology tests (besides the urine drug screen) on all the patients. We excluded children who died at scene or were dead on arrival to emergency department and hence the data are limited to those children who were resuscitated initially and admitted to the pediatric ICU. The study included children from a large metropolitan area and hence the results may not be generalizable to other demographic locations. We may have overestimated the incidence of a positive pre-event EKG, CXR or an echocardiogram based on the findings on the studies post-event. For example, a distinctive finding of WPW syndrome can be intermittently absent on EKGs on the same child but we considered it to be positive if we found a positive EKG post-event. Similarly a CXR can easily miss early cardiomyopathy or myocarditis; however if the CXR was positive post-event then we considered it as positive for pre-event diagnosis. Lastly, we did not have a randomized control group for the Questionnaire or imaging studies. Hence, the study lacks sensitivity analysis.

Conclusions

Predominantly, the etiology of SCA in apparently healthy children appears to be cardiac in origin. A screening Questionnaire along with an EKG appears to be a more effective strategy for detecting at-risk children for sudden unexplained cardiac arrest in comparison to a screening Questionnaire alone.

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Abbreviations

ADHD	Attention deficit disorder
AED	Automated external defibrillator
AICD	Automated implantable cardioverter defibrillator
AVM	Arteriovenous malformation
CXR	Chest roentgenogram
EKG	Electrocardiogram
LQTS	Long QT syndrome
MRI	Magnetic Resonance Imaging
SCA	Sudden Cardiac Arrest
SIDS	Sudden infant death syndrome
WPW	Wolff-Parkinson-White Syndrome

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Table 1

Demographic and clinical information on the children with sudden cardiac arrest

	Child < 1 year age	Child 1–18 years age	Total
n	19	25	44
Male Gender, n (%)	12 (63)	20 (80)	32 (73)
Age in years; median (range)	0.25 (0.02 – 0.92)	14 (3 – 17)	7.5 (0.02 – 17)
Race, n (%)			
Caucasian	8 (42)	9(36)	17(39)
African American	4 (21)	4 (16)	8 (18)
Hispanic	3 (16)	8 (32)	11 (25)
Others	4 (21)	4(16)	8 (18)
Related to Exercise, n (%)	NA	10 (40)	10 (23)
Related to Sleep, n (%)	9 (47)	1 (4)	10 (23)
Defibrillation, n (%), Total	5 (26)	18 (72)	23 (52)
In-Hospital	1 (5)	5 (20)	6 (14)
AED	4 (21)	13 (52)	17 (39)
Died, n (%)	15 (79)	7 (28)	22 (50)
AICD, n (%)	0	8 (32)	8 (18)
Autopsy, n (%)	0	2 (8)	2 (5)
LQTS, n (%)	0	5 (20)	5 (11)
Primary	0	2 (8)	2 (4)
Secondary	0	3 (12)	3 (7)
WPW syndrome, n (%)	0	6 (24)	6 (14)
Arrhythmias, n (%)	0	4 (16)	4 (9)
Cardiomyopathy, n (%)	2 (11)	4 (16)	6 (14)
HOCM	0	2 (8)	2 (4)
DCM	2(11)	0 (0)	2 (4)
LVNC	0	2 (8)	2 (4)
Coronary artery anomaly, n (%)	0	1 (4)	1 (2)
Ruptured AVM, n (%)	0	3 (12)	3 (7)
Unknown, n (%)	17 (90)	4 (16)	21 (48)

n, number; AED, automatic external defibrillator; AICD, automatic implanted cardioverter-defibrillator; AVM, arteriovenous malformation; LQTS, long QT syndrome; WPW, Wolff Parkinson White syndrome; HOCM, Hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; LVNC, left ventricular non compaction; NA, not applicable

Table 2

Arteriovenous malformations identified in children with sudden cardiac arrest

	Age, years	Gender	Ethnicity	Resuscitation measures	Symptoms prior to event	Family history of AVM	Imaging
1	6	M	Hispanic	CPR	HA	No	CT
2	9	M	Caucasian	CPR, Defibrillation	HA, vomiting	Yes	CT, MRA, Angiograms
3	10	M	Hispanic	CPR, Defibrillation	HA, vomiting	No	CTA, Angiograms

AVM, arteriovenous malformation; M, male; CPR, cardiopulmonary resuscitation; HA, headache; CT, computed tomography scan; MRA magnetic resonance angiogram; Angiograms; vascular catheterization with selective angiograms

Table 3

Stimulant medications use in children with sudden cardiac arrest

	Age, years	Gender	Race	Stimulant Medication	Exercise Related	URI	Final Diagnosis
1	11	M	Caucasian	Methylphenidate	Y	N	Congenital JET
2	10	M	Caucasian	Methylphenidate *	N	N	Secondary LQTS, VT
3	16	M	Caucasian	Methylphenidate	Y	N	HOCM
4	3	M	Hispanic	Pseudoephedrine	N	Y	VF
5	0.25	M	Caucasian	Pseudoephedrine	N	Y	SIDS

M, male; Y, yes; N, no; JET, junctional ectopic tachycardia; LQTS, long QT syndrome; VT, ventricular tachycardia; HOCM, hypertrophic cardiomyopathy; VF, ventricular fibrillation; SIDS, sudden infant death syndrome.

* Was also concomitantly on clonidine, lithium, escitalopram

Table 4

Hypothesized efficacy in primary prevention of sudden cardiac arrest in apparently healthy children

	Child < 1 year age	Child 1–18 years age	Total	p value
n	19	25	44	
Positive family history, n (%)	0	5 (20)	5 (11)	NA
Positive screening questionnaire, n (%)	0	8 (32)	8 (18)	NA
Positive CXR, n (%)	2 (11)	2 (8)	4 (9)	0.160
Positive EKG, n (%)	0	10 (40)	10 (23)	0.014
Pediatric TTE, n (%)	2 (11)	5 (20)	7 (16)	0.196

n, number; NA, not available; CXR, chest roentgenogram; EKG, electrocardiogram; TTE, transthoracic echocardiogram; p value based on based on a historical control cohort