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Cardiac Arrest and Sudden Cardiac Death in the Pediatric Population

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Abstract

Sudden cardiac arrest in children is a rare event. However, sudden cardiac arrest of a child is a devastating event. Clinicians should be aware of conditions associated with sudden cardiac arrest in the pediatric population. This article reviews the most common causes of sudden cardiac arrest in the pediatric population. We review recommendations for screening and diagnosis. We also briefly discuss current management recommendations for the various causes of sudden cardiac arrest in the pediatric population.

Introduction

Sudden cardiac arrest can be defined as unexpected collapse, regardless of physical exertion, in a previously asymptomatic person. Cardiac arrest accounts for 25 to 30 percent of all cases of sudden death in the pediatric population. The annual incidence of pediatric sudden cardiac arrest (PSCA) is 1.7 per 100,000 person-years with a reported range of 0.6 to 7.5 cases per 100,000 person-years. However, despite the low incidence of PSCA, the emotional repercussions for individuals, families and communities are no less devastating.

The purpose of this review article is to provide pediatric and non-pediatric providers with a summary of the most common conditions associated with PSCA. This review provides a brief overview of the various etiologies of sudden cardiac arrest and death in the pediatric population as well as describes diagnostic criteria, pre-disposing risk factors, and briefly reviews management strategies for some of the most common causes of PSCA.

Epidemiology

It is difficult to estimate the incidence of PSCA Factors contributing to our inability to estimate the true incidence include: (1) a lack of mandatory reporting, (2) the absence of a PSCA registry, (3) the presence of reporting bias, (4) inherent difficulties associated with characterizing unwitnessed events and (5) referral bias [1]. According to 2005 Centers for Disease Control (CDC) published vital statistics, approximately 2000 persons under the age of 25 years will die secondary to sudden cardiac arrest [2].

Single center estimates of the incidence of PSCA mirror Centers for Disease Control (CDC) estimates. The current estimated incidence of PSCA is 1.7 cases per 100,000. Studies have also shown a slightly higher incidence of sudden death among athletes versus non-athletes [3,4]. In particular, it is estimated that athletes are 2 times more likely to experience PSCA than non-athletes [5].

There are multiple identified causes of PSCA. In a retrospective study of 103 cases of children who died suddenly, investigators from the Hospital for Sick Children in Toronto found that the majority of autopsy cases were due to myocarditis (35%), hypoplastic left heart syndrome (HLHS) (18%), dilated cardiomyopathy (DCM) (16%), coronary artery anomalies (6%), and aortic stenosis (5%). This study also found that a significant number of cases, 26%, occurred in individuals without prodromal symptoms [6].

Primary conditions associated with sudden cardiac death also include primary arrhythmogenic conditions. Only recently, with greater use of intracardiac devices (ICD) for tracking the delivery of appropriate shocks and better reporting, have we been able to gain more information regarding the incidence of arrhythmogenic causes of PSCA. The most common arrhythmogenic conditions associated with an increased risk of PSCA include long QT syndrome (LQTS), Wolff-Parkinson White (WPW) syndrome (i.e. in the presence of atrial fibrillation), short QT syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome (BS).

PSCA occurs in children under the age of 1 year as well as among individuals 1 to 25 years of age. A prospective single center study from the Oregon Sudden Unexpected Death study found that 76% of cases of PSCA occur in children less than 1 year of age [5] and 90% of these cases met criteria for sudden infant death syndrome (SIDS). Although data is limited, one study found that an identifiable cardiac malformation was only responsible for 4% of PSCA cases in children under 1 year of age [7]. Other studies have suggested that 10 to 15% of SIDs cases and up to 30% of autopsy negative sudden cardiac death cases occur secondary to primary arrhythmia related disorders [8].

Among older children, athletes are most at risk for PSCA [4]. Cardiovascular conditions account for 56% of cases of sudden cardiac arrest among athletes under age 39 years [9]. The majority of cases of PSCA among athletes are due to hypertrophic cardiomyopathy (36%), anomalous origin of the coronary arteries from the opposing sinus (17%), myocarditis (6%), arrhythmogenic right ventricular cardiomyopathy (4%), and ion channelopathies such as long QT and Brugada syndrome (4%) [9]. Conditions (i.e. hypertrophic cardiomyopathy) leading to PSCA among athletes tend to present later, suggesting that there is an age related difference in disease presentation for many of the pre-disposing conditions (Tables 1 and 2).

In this review article, we describe the most common conditions associated with PSCA. The purpose of this review article is to provide the pediatric and non-pediatric provider with essential information regarding the most common causes of PSCA. This article will provide a brief overview of the various etiologies of sudden cardiac arrest and death in the pediatric population as well as describe diagnostic criteria,

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Structural Causes (Non-Cardiomyopathy)
Congenital aortic stenosis
Anomalies of the coronary arteries
Valvular disease (excluding aortic valve disease)
Cardiomyopathy
Dilated Cardiomyopathy
Hypertrophic Cardiomyopathy
Electrical
Long QT syndrome
Wolf-Parkinson White syndrome
Other
Myocarditis
Drugs
Primary pulmonary hypertension

Table 1: Common Causes of Sudden Cardiac Arrest in Children less than 1 year of age.

Structural Causes (Non-Cardiomyopathy)
Congenital aortic stenosis
Anomalies of the coronary arteries
Valvular disease (excluding aortic valve disease)
Cardiomyopathy
Dilated Cardiomyopathy
Hypertrophic Cardiomyopathy
Arrhythmogenic Right Ventricular Cardiomyopathy
Restrictive cardiomyopathy
Electrical
Long QT syndrome
Short QT syndrome
Wolf-Parkinson White syndrome
Brugada syndrome
Catecholaminergic polymorphic ventricular tachycardia
Other
Myocarditis
Drugs
Primary pulmonary hypertension
Commotio cordis
Aortic rupture and Marfan syndrome

Table 2: Common Causes of Sudden Cardiac Arrest in Children 1 to 25 Years of Age.

pre-disposing risk factors for sudden cardiac arrest, and briefly review management strategies for some of the most common causes of PSCA. The article describes structural, cardiomyopathy, rhythm disorder related, drug related and other causes of PSCA. The increased risk of PSCA among individuals with congenital heart disease (CHD) is also briefly addressed. However, sudden infant death syndrome (SIDS) and sudden cardiac arrest related to primary pulmonary hypertension, aortic rupture in the setting of Marfan's syndrome, and restrictive cardiomyopathy are not addressed in this review article.

Etiologies of Sudden Cardiac Arrest in the Pediatric Population

Sudden cardiac arrest in the pediatric population is associated with many conditions. Common causes can be classified into the following categories: (1) structural defects (non cardiomyopathy), (2) cardiomyopathy, (3) primary rhythm disorders and (4) other (i.e. drugs of abuse, myocarditis, primary pulmonary hypertension and commotio cordis) (Tables 1 and 2). Structural causes of PSCA include congenital aortic stenosis (AS), coronary artery anomalies, and other valvular related disorders. Cardiomyopathy related causes include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy. Rhythm related causes of PSCA include long QT syndrome (LQTS), short QT syndrome, Wolff-Parkinson-White syndrome (WPW), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT).

Structural Causes of Pediatric Sudden Cardiac Arrest (Non-Cardiomyopathy)

Congenital aortic stenosis

Congenital aortic valve stenosis (AS) accounts for 3-6% of all cases of congenital heart disease [10] and congenital AS accounts for 1-3% of cases of PSCA [11]. Frequently, the diagnosis of aortic stenosis is suspected based upon clinical examination (i.e. detection of a murmur) and confirmed by echocardiography. Non-invasive and invasive imaging techniques used to diagnose this condition include the electrocardiogram, the echocardiogram and cardiac catheterization.

Aortic stenosis can present in infancy. The need for intervention and risk of sudden death is related to the severity of disease at initial presentation [12]. In particular, adult studies have estimated event-free survival for patients with moderate to severe calcification of their aortic valve at 92% at 1 year, 73% at 2 years, 62% at 3 years and 42% at 5 years as compared to 100% at 1 year, 95% at 2 years, 90% at 3 years and 82% at 5 years for patients with no or mild calcification of the aortic valve (P=0.0001) [12].

Children who present with aortic stenosis during the first month of age are more likely to present with severe disease and to require intervention within the first 1 month of life [13-15]. However, among children in whom the diagnosis of aortic stenosis is made after 1 month of age, the severity of disease tends to be milder and the progression of disease, slower [15]. Children with mild forms of the disease at initial presentation typically require treatment after 10 years of age.

Indications for intervention are less well defined for younger children. Among older adolescents and adults published ACC/AHA guidelines can be used to help guide decisions regarding intervention [16]. Indications for intervention among younger children with aortic stenosis include: a peak systolic velocity of 4 m/s in combination with left ventricular hypertrophy and/or symptoms (i.e. syncope or heart failure) [15]. Bengur et al. found that among individuals with a peak gradient by cardiac catheterization of greater than 50mmHg or a mean gradient by echocardiogram of greater than 27mmHg that intervention is required [17]. However, the second natural history study suggested that approximately 80% of patients with mild stenosis (<25mmHg peak to peak on cardiac catheterization) could be managed conservatively [18]. Guidelines for the evaluation and management of adolescents and young adults with aortic stenosis, published in 2006 listed class 1 indications for intervention to include: (1) symptomatic adolescents and young adults with AS and peak to peak cardiac catheterization gradient of greater than 50 mm Hg, (2) asymptomatic patients with ST and T wave ECG changes at rest or with exercise and peak to peak gradient of >50 mmHg and (3) asymptomatic patients with peak to peak gradient of >60 mmHg [16]. Additional criteria for intervention among adolescents and young adults with AS include: (1) asymptomatic patients with peak to peak gradient (by cardiac catheterization) of >50 mmHg who (1) want to play competitive sports or (2) who want to become pregnant.

Among individuals with congenital valvar aortic stenosis, individuals at greatest risk for sudden cardiac death include those

with symptomatic moderate to severe stenosis [18]. Symptoms of significant aortic stenosis include syncope, chest pain, and exertional dyspnea. However, many patients with significant aortic stenosis are asymptomatic.

Proposed mechanisms for SCA among individuals with AS include severe aortic obstruction resulting in compromised coronary artery perfusion and resultant myocardial ischemia. Ischemic injury of the myocardium is a risk factor for the development of ventricular arrhythmias. Among those with AS and no symptoms at rest (i.e. asymptomatic), exercise testing can be used to assess severity and the need for intervention. Individuals with exercise induced symptoms may be at greater risk for sudden cardiac death. ACC/AHA 2006 guidelines suggest the use of exercise testing in the evaluation of asymptomatic patients with AS, but not in symptomatic patients [16].

Coronary artery anomalies

Children with congenital anomalies of the coronary arteries are at risk for sudden death. Anomalous origin of a coronary artery from the opposing sinus of Valsalva is the second most common cause of sudden cardiac death among young (<30 years of age) competitive athletes [9]. The reported incidence of anomalous coronary artery from the opposing sinus in children is 0.2% [19]. Anomalous origin of the right coronary artery from the left sinus of Valsalva is more common than anomalous origin of the left coronary artery from the right sinus of Valsalva. Although it is more common, anomalous origin of the right coronary artery from the opposing sinus is less frequently associated with sudden cardiac death [20]. However, anomalous origin of the left coronary artery from the right sinus of Valsalva with an interarterial course accounts for the majority of sudden death cases. Basso C et al. found that in 23 out of 27 (85%) cases of sudden death among competitive athletes that there was an anomalous origin of the left main coronary artery from the right aortic sinus. In this same study, only 3 out of the 27 (11%) cases of sudden death had anomalous origin of the right coronary artery from the left aortic sinus [19].

Children with anomalous origin of the left coronary artery from the right sinus of Valsalva and an interarterial course are at greatest risk of sudden death [19-22]. Among individuals with anomalous origin of the left coronary artery from the right aortic sinus and an interarterial course, those with an intramural course are considered most at risk for sudden death [22], however there are case reports of individuals with an intraconal path who developed arrhythmia or died suddenly [22,23]. Among patients with anomalous origin of the coronary artery, death typically occurs during or immediately following exertion [20,24].

Several mechanisms have been proposed to explain the presentation of sudden death among individuals with anomalous origin of the coronary artery from the opposing sinus including the presence of a flap-like orifice that becomes obstructed during peak activity [25] or compression of the artery during peak activity. Unfortunately, one must maintain a high level suspicion with regard to the potential diagnosis of anomalous coronary artery as less than 50% of persons with anomalous origin the coronary artery from the opposing sinus of Valsalva describe symptoms prior to sudden death [26,27]. Symptoms may be related to the length of the intramural segment [28]. Routine diagnostic tests, including ECG, exercise tests and perfusion scans are often not helpful in determining those at greater risk of sudden death [20]. However, age may be helpful in determining those at greatest risk as persons under age 30 years are at greatest risk, while those over the age of 30 years have a lower reported risk of sudden death [29].

Treatment of those most at risk for sudden death includes surgery. Unroofing procedures can be performed in cases in which there is an interarterial and intramural course. It is commonly agreed upon among symptomatic persons with an interarterial and intramural course that surgery is indicated regardless of whether the person has an anomalous origin of the right or left coronary artery. However, in many cases persons are asymptomatic before a sudden death event and the ability to detect an intramural course by diagnostic testing is not always revealing. It is felt, however, that most persons with an interarterial course have an intramural course even if the length of the intramural course varies. Thus, indications for surgery also include the presence of an interarterial course regardless of the absence of symptoms in individuals greater than 10 years of age and less than 30 years of age [29].

Currently, data is being collected by the anomalous coronary artery working group. The working group has established a data registry with the sole purpose of: (1) understanding the natural history of anomalous origin of the coronary artery, (2) establishing a multi-center registry to understand the long-term outcomes following surgical intervention, (3) studying the incidence of anomalous coronary artery, and (4) creating a risk stratification model that takes into consideration initial diagnostic findings and the natural history of this anomaly [30].

Acquired coronary artery disease can also occur in children, but is much less common in the pediatric than in the adult population. Within the United States, the most common cause of acquired heart disease among children is Kawasaki's disease [31]. Children with a history of Kawasaki's disease are at risk for the formation of coronary artery aneurysms and stenosis. If untreated, 15 to 25% of children with Kawasaki's disease die secondary to myocardial ischemia [32]. Following treatment, children with a history of Kawasaki's disease are still at risk for sudden death [31]. The estimated prevalence of sudden death among children with a history of Kawasaki's disease and coronary artery aneurysm or stenosis is 16%.

Another form of acquired coronary artery disease associated with sudden cardiac death includes transplant related coronary artery disease. Sudden death occurs in 1 out of 6 pediatric heart transplant recipients [34]. Factors associated with sudden death include: older recipient age, black race, and recurrent rejection within 1 year of age [33]. The development of cardiac allograft vasculopathy (CAV) accounts for approximately 14% of cases of death following pediatric heart transplantation [34].

Cardiomyopathies

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common cause of PSCA [9,35]. The overall prevalence of HCM is 1 in 500 persons, also making it a fairly common disorder [35]. HCM tends to present in older children, and though it rarely presents in younger children, the authors report at least 1 case of presentation during infancy. Cases of HCM may occur sporadically or secondary to the inheritance of particular genetic mutations. There are now over 20 different identified HCM susceptible genes. Specific mutations in the contractile proteins of the sarcomere are associated with the development of HCM. Known genetic mutations associated with the development of HCM include myosin heavy chain 7 (MYH7), tropomyosin 1 (TPM1), myosin binding protein C (MYBPC3), troponin C type 1 (TNNC1), TNNT2, TNNI3, ACTC, MYL2, MYL3, GLA, LAMP2, and PRKAG2 [36]. The most common mutations associated with the development of

HCM include beta-myosin heavy chain (MYH7), cardiac troponin T (TNNT2) and myosin-binding protein C (MYBPC3). Mutations in any of the aforementioned genes are associated with a variable degree of penetrance (i.e. 30- 80%). The sensitivity of commercially available tests for detecting these mutations is 50 to 60% [36]. Prognosis is related not only to disease presentation but to the particular gene mutation.

Sudden death related to hypertrophic cardiomyopathy can occur as early as 1 month of age [37]. The rate of sudden cardiac death is approximately 1% per year [38].

The diagnosis of HCM is usually made by echocardiography. Risk factors for SCD include ventricular septal wall thickness greater than or equal to 30mm, a family history of sudden death, a history of non-sustained ventricular tachycardia, syncope and the development of hypotension in response to exercise. Causes of sudden death in this population include arrhythmia and dynamic left ventricular outflow tract obstruction during peak activity.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is defined as an enlarged and poorly functioning left ventricle. By definition, the left ventricular end-diastolic dimension is greater than 2 standard deviations above the mean for body surface area and the ejection fraction is less than 50% [39,40]. The estimated annual incidence of all cardiomyopathies in children under the age of 18 years is approximately 1.13 cases per 100.000 children [39]. DCM accounts for 50% of all pediatric cases of cardiomyopathy [39] with an annual incidence of 0.57 cases per 100,000 children [41]. Like other forms of cardiomyopathy, the diagnosis is made by echocardiography.

DCM may occur secondary to ischemia, infection, metabolic conditions, endocrine related disorders, toxins, infiltrative diseases or may be inherited. Cases of DCM not due to infection, toxin exposure or other previously mentioned causes are described as idiopathic. Twenty to 50% of idiopathic cases have a genetic origin [40]. Of the genetic causes of DCM, there are now at least 20 known mutations. Lamin A/C mutations are a relatively common genetically inherited cause of DCM. The presence of a lamin A/C mutation is associated with a higher risk of arrhythmia related SCD [42]. Sudden cardiac death secondary to DCM may occur via a variety of mechanisms, including progressive bradycardia, electromechanical dissociation, pulmonary embolism, and ventricular arrhythmia.

Based upon data from the Pediatric Cardiomyopathy Registry, it is estimated that the 5 year incidence of SCD among children with DCM is 3% [41]. Ilina et al. 2011 reported that DCM is the cause of sudden death in 16.5% of PSCA cases. However, it should be noted that in twenty percent (56 out of 280) of all reported cases of death among children with DCM, the cause of death was unknown [41]. Predictors of sudden cardiac death secondary to DCM include (1) age at diagnosis of < 14 years, (2) increased left ventricular end diastolic dimension (i.e. 1.2 to 1.3 fold increase in risk for each unit increase in Z-score above the mean), (3) greater left ventricular posterior wall thickness to end diastolic dimension ratio, and (4) the use of anti-arrhythmic therapy within 1 month of diagnosis [41].

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular dysplasia (ARVC) is an inherited disorder of the heart muscle. The estimated prevalence of ARVC is 1 in 2000 to 1 in 5000 [43]. ARVC occurs secondary to defects in cellular adhesions proteins, known as desmosomes. Defects in the desmosomes, including desmoplakin result in fibrofatty replacement of the myocardium [46]. Children with ARVC present with ventricular tachycardia of a left bundle branch block morphology (LBBB) and right ventricular enlargement. The first clinical sign of disease may be cardiac arrest.

The diagnosis of ARVC can be difficult to make. Identification of clinical criteria may aid in the diagnosis [43,45]. According to revised 2010 guidelines, major criteria include severely decreased right ventricular function, the presence of a localized right ventricular aneurysm, evidence of a depolarization abnormality, the presence of epsilon waves by electrocardiogram, evidence of fibrofatty replacement of the myocardium and confirmed family history [45]. Minor criteria include (1) mild global myocardial dysfunction, (2) mild segmental right ventricular dilation, (3) regional right ventricular hypokinesia, (4) evidence of late potential on signal average ECG, (5) inverted T waves in the right precordial leads (V2 and V3) in persons > 12 years of age, (6) frequent ventricular extrasystoles (>1,000 per 24 hours), (7) a family history of premature death (age < 35 years), and (7) a (clinical) family history. A clinical diagnosis of ARVC can be made if there are at least 2 major criteria, 1 major and 2 minor or 4 minor criterion [45].

Cardiac MRI has become more frequently used in the diagnosis of ARVC. However, use of this imaging modality is often associated with overdiagnosis of ARVC [43]. Another modality currently used in the diagnosis of ARVC is endocardial voltage mapping. This technique can be used to identify areas of myocardial atrophy and fibrofatty replacement of the myocardium. The voltage mapping generates low amplitude electrograms for more accurate detection of abnormal myocardial regions [43]. Sudden death is related to the development of ventricular arrhythmia and progressive congestive heart failure among children with ARVC.

Known mutations associated with ARVC include DSP, PKP2, DSG2, DSC2, and TMEM43. However, genetic testing is only positive for 40-50% of cases [46].

Non-Structural, Arrhythmia Related Causes of Pediatric Sudden Cardiac Arrest

Long QT Syndrome

The estimated prevalence of long QT syndrome (LQTS) is 1 in 2534 Italian-persons [47]. Knowledge of the true prevalence of disease among broader populations is limited. Studies identifying cases of long QT syndrome excluded infants with QTc intervals <470 msec [47]. Estimating the true prevalence of LQTS is limited by the lack of widespread genetic testing, the presence of genotype positive-phenotype negative cases [48], and incomplete knowledge regarding additional genomic rearrangements associated with this condition [49].

LQTS is an inherited channelopathy characterized by mutations in potassium and sodium ion channels. Alterations in the potassium and sodium channels result in ventricular repolarization abnormalities and a predisposition toward the development of ventricular arrhythmias. There are now at least 12 disease causing mutations identified that have been found to be associated with LQTS. Commercially available genetic tests detect approximately 75 to 80% of cases [50].

The diagnosis of LQTS is made based upon the presence of a prolonged QT interval (> 450msec in males and > 460msec in females), abnormal T wave appearance by ECG, symptoms, family history and genetic testing [51]. Persons with LQTS may present with syncopal events during periods of stress, emotion, loud auditory stimuli, or

relative bradycardia (i.e. during sleep or rest). In patients with LQTS, evidence of a prolonged QT interval may also be associated with abnormal T waves on the ECG. In 80% of suspected LQTS cases there is an identifiable genetic abnormality and genetic testing may be useful in confirming the diagnosis. Indications for genetic testing include (1) to aid in diagnosis when based upon clinical findings, the diagnosis remains uncertain, (2) to identify other affected family members, and (3) to provide prognostic information associated with the identification of particular gene mutations [48]. In cases in which there is borderline prolongation of the QTc interval, exercise testing may also be helpful [52].

Approximately 25% of persons with LQTS types 1, 2, and 3 have normal QTc intervals [32]. A recent study found that even among individuals with a normal QTc interval but genetic evidence of LQTS that there was a significantly higher risk of sudden cardiac death. However, although this risk was higher than the risk for SCD within the general population, the total risk was low (i.e. estimated 4%) [48].

Among young athletes, SCD related to LQTS is estimated at 0.5% to 8 % [53,54]. One of the risk factors associated with sudden cardiac arrest in those with LQTS is a more prolonged QTc interval [55]. Those at greatest risk for SCD include individuals with a QTc interval >550msec [56]. Studies have shown that among 18 year olds with a QTc >550msec, 20% will experience SCA by age 40 [56]. Among individuals with LQTS, additional risk factors for PSCA include (1) males between the ages of 5 and 20 years of age with LQTS type 1, (2) females with LQTS type 2 and (3) young adult males with LQTS type 3 [56]. Individuals with a prior history of syncope may also be at greater risk for sudden cardiac death. A prior history of syncope is associated with a 27 fold higher risk of SCD in girls and a 6 fold higher risk in boys [55]. Post partum women with prolonged QT intervals and males with LQTS type 3 and slower heart rates are at increased risk of sudden death [55].

Wolff parkinson white (WPW) syndrome

Wolff Parkinson White (WPW) electrocardiographic pattern implies the presence of preexcitation or delta wave with a short PR interval on ECG. Isolated ventricular preexcitation refers to the presence of an abnormal ECG pattern in the absence cardiovascular symptoms. Such patients are also referred to as "asymptomatic WPW". WPW syndrome on the other hand refers to patients with WPW pattern on ECG accompanied by cardiovascular symptoms. The pre-excited pattern on ECG is secondary to antegrade conduction down an accessory pathway.

The estimated prevalence of Wolff-Parkinson White syndrome (WPW) is 1 to 3 per 1000 persons [57]. Sudden cardiac death in children with WPW is uncommon with an estimated rate between 0 and 15 cases per 1000 patient-years [57]. The mechanism of sudden death in patients with WPW syndrome is rapid antegrade conduction, in the setting of atrial fibrillation, over the accessory pathway and includes the development of ventricular fibrillation. Identified risk factors for sudden cardiac death among individuals with WPW include: younger age (< 30 years), male gender, history of AF, prior syncope, associated congenital or other heart disease, the presence of multiple accessory pathways [57] and familial WPW. The "shortest pre-excited R-R interval (SPERRI)" during an invasive EP study can be used to assess risk. An SPERRI of < 220-250 msec during atrial fibrillation is the best discriminator of those at risk for VF [56].

Recently, the Pediatric and Congenital Electrophysiology Society (PACES) and Heart Rhythm Society (HRS) expert consensus statement was published. The PACES/HRS consensus statement addressed the management of young, asymptomatic patient with a WPW electrocardiographic pattern. The expert panel, authors of the consensus statement, suggested that all asymptomatic persons with a WPW pattern by ECG, who have persistent manifest pre-excitation, should undergo an exercise stress test. All patients with persistent or uncertain loss of manifest pre-excitation should undergo a diagnostic transesophageal or an intracardiac electrophysiology study. The group found that it is reasonable to consider catheter ablation in patients with a SPERRI in atrial fibrillation < 250 msec. Patients in this category are at high risk of SCD (Class IIA). Similarly patient with inducible SVT have a class IIB indication for catheter ablation.

Brugada syndrome (BS)

Brugada syndrome was first described by Pedro and Josep Brugada in 1992 [58] and occurs in 1 in 2000 persons. It is an inherited disorder and in most cases, Brugada syndrome is due to a mutation in the SCN5A gene [59]. Other known genetic mutations associated with BS include SCN1B, GPD1L, KCNE3, CACNA1C, SCN3B, and ACNB2. Known mutations are detected in 25-40% of cases [60]. Among persons with normal cardiac structure, BS is responsible for 4-12% of all cases of sudden cardiac death and affected individuals die secondary to the development of ventricular arrhythmia [61].

The clinical presentation of BS varies by age. Symptoms of BS include palpitations and dizziness [59,61]. Most affected persons present with symptoms during the fourth decade of life. However, children as young as 1 year of age may present with symptoms and are subsequently diagnosed with BS [61]. Among adults, BS most commonly occurs in men (70%), while among children, there is no gender difference [61].

Persons with BS present with classic electrocardiogram (ECG) findings. There are 3 different types of ECG patterns in Brugada syndrome. In general, ECG findings associated with BS include coved or saddle-back ST segment elevation in leads V1-V3 that may be most notable during a febrile illness. In most cases and among 2 out of the 3 types, there is also evidence of incomplete right bundle branch block and T wave inversion.

Type 1 BS findings include coved-type ST segment elevation of > 2mm in more than 1 of the right precordial leads, followed by negative T waves. Type 2 BS is characterized by > 2mm J point elevation in the right precordial leads and positive or biphasic T waves. Type 3 BS can present similar to Type 1 and Type 2 Brugada but with < 1mm ST segment elevation [60]. Type 1 ECG findings are considered to be the most specific BS findings.

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is another rare cause of sudden death among persons with structurally normal hearts. The estimated prevalence of CPVT is 1 in 10,000 persons [62]. CPVT is an inherited disorder. Autosomal dominant forms of this condition are associated with mutations in the ryanodine receptor gene (RYR2). Autosomal recessive forms of the condition also exist and are associated with mutations in calsequestrin (CASQ2) [63]. Genetic testing is sensitive in 65-75% of cases [63]. In either case, CPVT is thought to be related to perturbations in the normal handling of intracellular calcium and increased diastolic leak of calcium from the

sarcoplasmic reticulum (SR) in response to increased catecholamine activity.

Catecholamime activity leads to beta adrenergic receptor activation and premature calcium release from the sarcoplasmic reticulum among individuals with CPVT. Elevated cytosolic calcium levels result in an inappropriate influx of sodium into the cell leading to depolarization of the cell during diastole. Depolarization of the cell membrane leads to the generation of a "delayed-after-depolarization" leading to the development of ventricular arrhythmias [64].

Individuals with CPVT typically present with symptoms during adolescence. CPVT is associated with sudden death during stress or with physical exertion. The diagnosis may be made during exercise testing. During exercise testing, ectopy occurs more readily. Persons often develop "bidirectional" ventricular tachycardia with beat to beat variation in the QRS axis (180 degree change in the QRS axis with each beat). If left untreated, CPVT is fatal in 30-50% of patients [63].

Other

Drugs

Use of particular illicit and non-illicit drugs can be associated with an increased risk of sudden death in children. Anti-arrhythmic drugs (i.e. flecainide), antipsychotic drugs (i.e. thioridazine, olanzapine), antihistamines, antimalarials (e.g. halofantrine), and quinolone antibiotics (e.g. moxifloxacin) are all associated with prolongation of the QT interval and most (but not all) with the development of *torsade de pointes* and sudden death The reader is referred to www.longqtdrugs.org for a list of medications that place susceptible individuals (i.e. those with a prolonged QT interval) at risk for sudden death. Similarly, drugs associated with increased risk of sudden among individuals with Brugada syndrome can be found at www.brugadadrugs.org.

Illicit drugs use has also been associated with PSCA. Cannabis (i.e. marijuana) use is associated with an increased risk of myocardial infarction particularly during the first 1 to 2 hours after use. The proposed relative risk of infarction is increased by 3.2 in the first hour. In the second hour, the relative risk is 1.7 [65]. Other agents associated with sudden death include agents such as cocaine [66], other sympathomimetic agents and psychotropic drugs [67].

Myocarditis

Myocarditis can also result in sudden cardiac death secondary to fatal arrhythmias. Investigators from the Hospital for Sick Children in Toronto found that 35% of cases of PSCA occur secondary to myocarditis. Arrhythmias can occur in both the acute or healing phase of the illness [68]. Sudden death occurs secondary to the development of arrhythmias. Due to the risk of arrhythmia, competitive sports participation is usually prohibited during the initial six months of convalescence [69].

Commotio cordis

Commotio Cordis is sudden cardiac arrest secondary to ventricular fibrillation as a result of direct blunt trauma to the chest wall. If the trauma occurs during the vulnerable phase of ventricular repolarization (i.e. 15-30 milliseconds prior to the peak of T wave) then the trauma can result in a potentially fatal arrhythmia [70,71]. Precordial blows are moderate in force and can be secondary to direct collision between the athletes or by a projectile such as baseball or hockey puck [70]. Commotio cordis has a high fatality rate and survival has been reported in only 15% of cases with prompt on field resuscitation and defibrillation [72].

Congenital heart disease and pediatric sudden cardiac arrest (CBS)

Children with congenital heart defects, repaired and unrepaired, are at risk for sudden death. A detailed description of congenital defects and risk of sudden cardiac death is beyond the scope of this manuscript. However, Silka MJ et al. estimated that the long term risk of sudden cardiac death among those with particular congenital heart defects is 25 to 100 times the risk of sudden cardiac death in the general population [73]. In this study, the highest risk of sudden death occurred among individuals with a history of left sided obstructive lesions (i.e. aortic stenosis) and cyanotic defects (i.e. d-TGA). For additional details, the reader is referred to this reference [73].

Screening

At the present time, there are no widely accepted screening guidelines to identify children at greatest risk for sudden cardiac death [74]. Debate exists on both sides as to the effectiveness of a screening program [74]. Arguments in support of the adoption of a large-scale screening program include the opportunity to reduce the incidence of sudden cardiac death in children. However, those who oppose immediate adoption of a screening program site a lack of (1) knowledge regarding the true incidence and prevalence of predisposing conditions, (2) understanding of the adequacy of screening tests in recognizing disease, and (3) effective treatment options even if the conditions are recognized early. Furthermore, the potential for false-positive results and the impact of false-positive results on individuals and families must be considered. For more information regarding specific recommendations made by the working group on "screening for sudden cardiac death in the young", the reader is referred to Kaltman JR et al. [74].

The American Academy of Pediatrics (AAP) recently released a policy statement regarding pediatric sudden cardiac arrest [75]. In this statement, the AAP acknowledges the importance of recognition, assessment, standardization of practice, treatment and advocacy for the prevention of PSCA. The newly released statement calls for recognition by health providers of the warning signs and symptoms of common causes of SCA. The statement also emphasizes the importance of asking the "right" personal and family history related questions, use of a standardized physical examination assessment form and the need to eliminate process variation. Early referral of patients suspected of having conditions that place them at risk for sudden cardiac death is also emphasized.

Screening electrocardiogram (ECG)

The use of a screening ECG has been proposed to help identify children at greatest risk for sudden death. Currently, there is no formal recommendation for the use of the screening ECG in the United States. To date, only two countries, Italy and Japan, have recommended performing screening electrocardiograms. However, the importance of diagnosing at risk patients, particularly during the asymptomatic stage of a disease process, is well recognized.

The 3 most common conditions associated with characteristic ECG findings and sudden cardiac death in the pediatric population are hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS) and Wolff-Parkinson White syndrome (WPW). Another channelopathy associated with characteristic ECG findings and sudden

death, although much less common, is Brugada syndrome [58]. Recently published study, described the sensitivity, specificity, negative predictive value and positive predictive value of routine ECG screening for identification of HCM, LQTS and WPW [76]. This study reported that the NPV for detecting HCM and LQTS was high. However, the PPV varied considerably by sensitivity, specificity and true prevalence of disease [76]. Recent American Heart Association guidelines do not recommend routine ECG assessment [77].

Treatment

The treatment of conditions associated with PSCA varies. Primary prevention of sudden cardiac death includes medical therapy, device therapy such as automated intracardiac defibrillator and pacemaker placement, activity restriction, avoidance of particular medications and family education. A detailed review of all treatment options for each condition is beyond the scope of this review article.

In patients not previously identified as high risk, secondary prevention is as important as primary prevention. Secondary prevention involves a "chain of survival." The "chain of survival" includes early symptom recognition, early emergency medical system (EMS) activation, effective bystander CPR, early defibrillation and provision of advanced hospital care [78].

Conclusion

Sudden cardiac arrest, in the pediatric population, is a devastating event that occurs secondary to a variety of conditions. Fortunately, conditions responsible for PSCA are rare. However, the devastating risk of PSCA looms. Unfortunately, while our knowledge regarding the features of the various etiologies is growing, there is still much to learn. Current policies and guidelines acknowledge the need for screening; however, no widespread screening protocol has been shown to be effective or validated for use. While there are ongoing efforts to characterize the prevalence and risks stratify common causes of PSCA, information is limited. The lack of data registries and the limited number of prospective studies has contributed to our inability to address this need. Providers are encouraged to maintain a high index of suspicion and to perform the necessary tests for diagnosing children most at risk. Primary prevention measures, including early recognition and secondary prevention measures are essential.

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