Sudden Cardiac Death not Related to Coronary Atherosclerosis

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ABSTRACT

Sudden cardiac death (SCD) accounts for approximately 300,000 cardiac events in the United States each year, representing an overall incidence of 0.1–0.2% per year. Although the vast majority of these may be attributed to coronary atherosclerosis, a wide variety of nonatherosclerotic-related cardiac diseases have been associated with SCD. This review highlights three general categories of cardiac disease not related to atherosclerosis: the cardiomyopathies, inflammatory myocardial diseases, and ion channel disorders. The important role played by genetics in some of these cardiovascular diseases is presented as well as toxic and drug-related etiologies.

Keywords. Cardiomyopathy; myocarditis; molecular genetics; sudden cardiac death; toxicology.

INTRODUCTION

Cardiovascular disease is one of the major public health problems in the Western hemisphere and is the most common cause of death in developed countries. Sudden cardiac death (SCD) accounts for approximately 300,000 cardiac events in the United States each year, representing an overall incidence of 0.1–0.2% per year (Myerburg et al., 1997). Eighty percent of SCD cases may be ascribed to coronary atherosclerosis and its sequelae acute and healed myocardial infarction, another 15% to the various cardiomyopathies, with the remainder attributed to a wide diversity of causes. The World Health Organization (WHO) defines sudden death as death within 24 hours of symptoms, a time interval that allows for inclusion of cases of acute myocardial infarction. We prefer to use the time limit of 6 hours, as the histologic features of acute myocardial infarction are not evident within this time frame.

Once coronary artery disease has been excluded in a case of SCD, there is often the misconception amongst pathologists that the lesion responsible for the death resides in the specialized conduction system, yet anatomic abnormalities of the conduction system rarely provide any useful information in the evaluation of SCD. Rather, the pathologist should be aware of the many other types of cardiac diseases and their associated pathologic features that may be responsible for a SCD. For example, cardiomyopathies, abnormal origin of a coronary artery, congenital heart disease, cardiac tumors, valvular heart disease, and inflammatory processes such as sarcoid are among the many cardiac causes of sudden unexpected death.

It is beyond the scope of this brief review to detail the entire retinue of non-atherosclerotic related cardiac diseases involved in SCD. Instead we highlight some of the more common nonvascular causes of SCD such as the cardiomyopathies and inflammatory myocardial diseases because of their importance to the practicing pathologist and clinical relevance. Included here also are the relatively obscure, but intriguing ion channel disorders, which despite showing no anatomic abnormalities at autopsy demonstrate disease-causing mutations, many of which have only recently been elucidated. Additionally, toxic and drug related aspects of SCD are presented. It should be mentioned, that in some cases of sudden death the precise anatomic substrate is never identified.

CARDIOMYOPATHY AND SUDDEN DEATH

Cardiomyopathies are a major cause of morbidity and mortality at all ages. They are defined by the World Health Organization as “diseases of the myocardium associated with cardiac dysfunction” and are classified into four major groups: hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. An additional category referred to as “specific” cardiomyopathies, which encompasses a wide variety of specific cardiac or systemic disorders, has also been included in the classification scheme (Richardson et al., 1996). The cardiomyopathies may be either inherited or acquired. In the last 20 years, advances in molecular genetics have improved our understanding of the pathogenesis of cardiomyopathies by identifying underlying gene mutations that lead to myocardial disease. While many cardiomyopathies result from a single gene defect and are therefore inherited in a predictable Mendelian fashion, the resultant disease phenotype may be clinically and pathologically diverse.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a well-recognized cause of SCD with sudden unexpected death occurring most frequently in young persons. Although the disease may occur at any age, most patients are in their 30s or 40s at the time of diagnosis and in 16% of cases the diagnosis is first made at autopsy (sudden death) (Codd et al., 1989).

On gross examination, the heart is typically enlarged to twice normal weight. The mean heart weight in a series of 40 autopsied cases was 634 grams (Roberts et al., 1977).
The hypertrophy is secondary to ventricular thickening and may occur almost anywhere in the ventricular mass, but is most often found in the interventricular septum (Figure 1). Heart weight may occasionally be normal or only slightly increased, an observation that has been linked in some cases with troponin T mutations (Moolman et al., 1997). Microscopically the most characteristic feature is myofiber disarray characterized by disorganized branching myocytes. Other features include myocyte hypertrophy, interstitial fibrosis, and intramural coronary artery thickening. Diagnostic confusion often exists in making the distinction between a true hypertrophic cardiomyopathy and cardiac hypertrophy. Proper sectioning in a case of suspected hypertrophic cardiomyopathy entails sectioning in the short axis plane or from endocardium to epicardium in the transverse plane. Histologic review of multiple cross-sections from the ventricular septum is required demonstrating myofiber disarray of at least 5% cross-sectional area (Maron et al., 1981).

It has been shown that approximately 50–60% of HCM cases are familial with an autosomal dominant pattern of inheritance. Currently, 14 genes and over 150 different mutations have been identified (Scheffold et al., 2005). The structural deformities of hypertrophic cardiomyopathy result from mutations in genes that encode sarcomeric proteins, most commonly beta myosin heavy chains. High risk mutations include the beta myosin heavy chain (MYH7) mutations (R403Q, R453C, G716R and R719W) (Ackerman et al., 2002). A diagnosis of HCM mandates genetic counseling with serious implications for family members and thus should be reserved only for cases fulfilling the diagnostic criteria.

**Arrhythmogenic Right Ventricular Dysplasia**

Arrhythmogenic right ventricular dysplasia (ARVD) is a genetic cardiomyopathy often presenting with sudden cardiac death, particularly in adolescents and young adults. In Italy, ARVD is the most frequent cause of sudden death in young athletes. The mean age for patients dying suddenly is usually in the third decade (Nava et al., 1988; Corrado et al., 1997). Although the name implies a purely right-sided disease process, involvement of the left ventricle has been shown to occur in >75% of cases and rare cases are reported to affect the left ventricle exclusively (De Pasquale and Heddle, 2001).

The heart is generally normal in size or slightly enlarged. Grossly the right ventricle may show focal myocardial wall thinning to 2 mm or less, aneurysm formation, and cavity dilatation. Additionally, the left ventricle may show subepicardial scars on gross examination (Gallo et al., 1992). The histologic features of ARVD include transmural fatty infiltration of myocardium, fibrosis and inflammation, principally lymphocytes (Figure 2). Fat infiltration of the right ventricle is usually considered a mandatory finding for the diagnosis, but the diagnosis should not be based only on the presence of fat because normal hearts may show a certain degree of fatty infiltration in the right ventricle. We have shown that it is not unusual to see fat infiltration occupying over 50% of myocardial area in the anterior wall of the right ventricle in trauma victims (autopsy control subjects; Burke et al., 1998). The pathologic criteria for ARVD remain controversial and there is not yet a universal agreement about the definitive diagnostic features.
ARVD is a genetic cardiomyopathy that has been associated with mutations of plakoglobin, plakophilin, and desmoplakin genes (Norman et al., 2005). These genes encode desmosomal proteins which are involved with cell adhesion. Loss of normal desmosomal structure is considered a crucial event in the pathogenesis of ARVD, but the precise mechanisms underlying the development of disease are as yet unknown.

**Left Ventricular Noncompaction**

Ventricular noncompaction, also known as left ventricular noncompaction (LVNC), is a rare form of cardiomyopathy believed to result from an unexplained arrest in cardiac development. LVNC has been reported as a cause of sudden death in both children and adults (Oechslin et al., 2000). Recently we reviewed the clinical and pathological characteristics of 14 pediatric cases, 9 of which had a history of sudden death (Burke et al., 2005). Since the diagnosis is often made initially at autopsy, pathologists should be aware of the diagnostic features. Grossly the left ventricular wall demonstrates deep recesses extending to the inner half of the ventricle occurring most prominently in the midventricle to apex. The recesses show variable patterns including anastomosing broad trabecula, coarse trabecula resembling multiple papillary muscles, and fine interlacing bundles that may only be appreciated microscopically. The histologic features of LVNC are distinct, characterized by anastomosing muscle bundles forming irregular, large branching staghorn recesses in the endocardium. Another pattern shows spongy parenchyma with compressed invaginations that are not grossly apparent. Marked endocardial fibroelastosis with prominent elastin deposition is present as well.

**INFLAMMATORY MYOCARDIAL DISEASES**

Myocarditis is defined as inflammation of the myocardium and may be attributed to a number of causes including infectious, toxic and idiopathic. Examples of inflammatory myopathies include lymphocytic myocarditis (viral), hypersensitivity myocarditis, giant cell myocarditis, toxic myocarditis, infectious myocarditis and sarcoidosis.

**Lymphocytic Myocarditis**

Viral, or lymphocytic myocarditis, is seen more commonly in cases of neonatal and childhood SCD, and may follow a recent viral syndrome. Gross examination of the heart is typically unrevealing. Histologically the inflammation is usually diffuse and consists primarily of lymphocytes macrophages, and occasional neutrophils with associated evidence of myocyte damage (Figure 3). In cases of SCD, it is presumed that the lesion(s) acts as an inflammatory nidus for an arrhythmia, usually ventricular tachyarrhythmias. In North America, enteroviruses, in particular Coxsackieviruses are common agents producing myocarditis,
although adenovirus, cytomegalovirus and herpes simplex have also been associated with lymphocytic myocarditis. Up to the present time, the most useful and rapid technique for detecting virus in cases of suspected viral myocarditis is polymerase chain reaction (PCR). In one study, PCR analysis detected a viral genome in 68% of endomyocardial biopsies showing lymphocytic myocarditis from a pediatric population (Martin et al., 1994). Besides viruses, a large number of other pathogens have been associated with infectious myocarditis including bacteria, fungi and parasites. The gross and histologic features of infectious myocarditis vary depending on the etiologic agent and the stage of the disease.

**Hypersensitivity Myocarditis**

Hypersensitivity myocarditis is a rare cause of SCD. More than 20 drugs have been implicated as possible etiologic agents in hypersensitivity myocarditis with penicillin, sulfonamides and methyldopa being the most common. Table 1 lists some of the drugs associated with hypersensitivity myocarditis. Although often asymptomatic, hypersensitivity myocarditis may cause congestive heart failure, arrhythmias, and rarely sudden death. Most cases of hypersensitivity myocarditis are diagnosed at autopsy, therefore the true prevalence of nonlethal cases is unknown. The histopathologic features of hypersensitivity myocarditis include interstitial and perivascular chronic inflammatory infiltrates consisting of lymphocytes, plasma cells, and macrophages, with a prominence of eosinophils. There is little associated necrosis and no scarring.

**Toxic Myocarditis**

In addition to eliciting a hypersensitivity myocarditis, some drugs may be directly toxic to the myocardium and produce what is referred to as toxic myocarditis, characterized histologically by edema, neutrophil infiltration and necrosis, sometimes with contraction band necrosis. Endothelial swelling and vasculitis may be present as well (Figure 4). Etiologic agents in this category include catecholamines, arsenicals, venoms, paracetamol and chemotherapeutic agents. Differentiating features of toxic and hypersensitivity myocarditis are presented in Table 2.

**Giant Cell Myocarditis**

Giant cell myocarditis is a rare disease of unknown etiology most commonly seen in adults 20–50 years old. Clinically it usually presents as sudden onset of congestive heart failure and is rapidly fatal in most cases. The histopathologic features include widespread, often serpiginous, myocardial necrosis with chronic inflammation including multinucleated giant cells. The giant cells are usually seen at the margins of
necrosis and have been shown to be derived from the histiocyte (Litovsky et al., 1996).

**Sarcoidosis**

Most patients with cardiac sarcoidosis have clinically apparent systemic involvement, but in some patients the heart may be the primary site. The clinical manifestations are determined by the extent and location of involvement and may include conduction defects, ventricular arrhythmias, congestive heart failure, mitral regurgitation, and sudden death. Cardiac sarcoidosis is a focal disease involving the myocardium in decreasing order of frequency: left ventricular free wall, base of the ventricular septum, right ventricular free wall, and atrial walls (Roberts et al., 1977). Grossly the heart may display scarring in a distribution not typical for ischemic disease, also involving the epicardial surface. The histologic features of cardiac sarcoid are similar to those of extracardiac sarcoid consisting of noncaseating granulomas, histiocytes, giant cells, lymphocytes and plasma cells. Special stains must be performed to rule out the presence of fungi and acid-fast bacilli.

**Sudden Cardiac Death in the Absence of Autopsy Findings**

In some patients, the underlying defect responsible for a sudden cardiac death is not found on gross, microscopic, or even ultrastructural examination of the heart. Autopsy studies of cardiac death subjects have shown that structural cardiac abnormalities are absent in 5 to 8 percent of cases (Priori et al., 2002). With recent advances in molecular biology, it has become apparent that a proportion of these deaths are due to mutations in cardiac ion channels that may lead to ventricular arrhythmias and sudden death. The underlying gene defects alter the electrical activity in the heart predisposing the patient to fatal cardiac arrhythmias, without any morphologic changes seen in the myocardium. Such disorders of ion channels are sometimes referred to as “cardiac channelopathies”—examples of these include long Q-T syndrome (LQTS) and Brugada syndrome.

The long QT syndrome (LQTS) is characterized by QT prolongation on the ECG and a susceptibility to fatal torsades de pointes ventricular tachyarrhythmias. Clinically the patients are prone to syncope and fainting, often precipitated by physical or emotional stress such as fright. LQTS can be divided into inherited and acquired forms. Both an autosomal dominant form, Romano Ward syndrome and an autosomal recessive variant with deafness called Jervell and Lange-Nielsen syndrome have been identified (Sarkozy and Brugada, 2005). Onset of symptoms typically occurs in the first two decades of life, but in females may occur later in life. Six LQT syndromes have been defined thus far, designated LQT1 through LQT6, based on the order in which they were discovered. The culprit genes have been identified as constituents of the potassium and sodium channel subunits as well as ankyrin, a protein responsible for anchoring ion channels to the cellular membrane. Specific mutations carry different risk profiles. LQT1 and LQT2 carry the highest risk for arrhythmias while LQT3 may have fewer cardiac events,
but when present tend to be more lethal (Wilde and Bezzina, 2005).

The acquired form of LQTS results from administration of drugs that prolong the action potential. In the last decade, the single most common cause for the removal of a drug from the market has been the prolongation of the QT interval associated with torsades de pointes (Rodén, 2004). Drugs that have been associated with LQTS include antiarrhythmics, tricyclic antidepressants, phenothiazines, antihistamines and others. Many of these drugs remain on the market because of a very low incidence of fatal arrhythmia and because the benefit of the drug is believed to outweigh the risk.

Brugada syndrome is characterized by right bundle branch block with ST-segment elevation in the right precordial leads and is associated with sudden death (Brugada and Brugada, 1996). Sudden death can occur at any age including very young children. Brugada syndrome is familial in about one third of patients with an autosomal dominant pattern of inheritance. The SCN5A gene has been implicated in the disorder with the mutation leading to a loss of Na⁺ channel function (Wilde and Bezzina, 2005).

Other causes of sudden cardiac death with a morphologically normal heart include “commotio cordis” caused by blunt impact to the anterior chest sometimes reported during sports activities. Depending on the sport, the impact may result from objects such as baseballs, hockey pucks, or cricket balls (Maron et al., 1981). Occult Wolff–Parkinson White syndrome, a disorder impossible to diagnose at autopsy may also result in a sudden cardiac death with an apparently normal heart. Coronary artery vasospasm may represent an underestimated cause of such deaths as well.

CONCLUSION

Sudden and unexpected cardiac deaths frequently become the subject of pathologic investigations to determine the cause of death. Although the vast majority of these may be ascribed to coronary atherosclerosis, there are many other potential causes of a sudden cardiac death. In the majority of cases only detailed pathologic examination of the heart in conjunction with meaningful clinical-pathologic correlation allows the pathologist to determine the underlying disease process leading to death. When no anatomic abnormality is present at autopsy it may be of benefit to archive DNA for genetic studies if an ion channel disorder is suspected. Finally, recent advances in the field of molecular genetics have expanded our understanding of the etiology and classification of many of the aforementioned cardiac diseases. These new techniques not only augment our diagnostic capabilities, but also highlight the importance of molecular diagnostics in identifying new disease-causing mutations.

REFERENCES


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