Sudden arrhythmic death and cardiomyopathy are important causes of sudden cardiac death in the UK: results from a national coronial autopsy database.

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All authors contributed to acquisition of data. MNS, SC and AC contributed to study design. MNS, JW, EZ and BVF contributed to analysis of data. MNS, JW and EZ drafted and approved the paper.

Abstract

Background

Sudden cardiac death (SCD) is defined as natural unexpected death in witnessed cases occurring <1 hour and in unwitnessed cases as last seen alive <24hours. SCD due to ischaemic heart disease (IHD) is frequent in older age groups, in younger people genetic cardiac causes including channelopathies and cardiomyopathies are more frequent.

Purpose

To present the causes of SCD from a large specialist pathology registry.

Methods

Cases were examined macroscopically and microscopically by two expert cardiac pathologists. Criteria used are presented in table 1.

Results

The hearts from 7214 SCD cases were examined between 1994-2021. Sudden arrhythmic death syndrome (SADS), a morphologically normal heart, which can be underlain by cardiac channelopathies, is most common (3821, 53%) followed by the cardiomyopathies (1558, 22%), then IHD (670, 9%). Valve disease (225, 3%), congenital heart disease (213, 3%) and myocarditis/sarcoidosis (206, 3%). Hypertensive heart disease (185, 3%), aortic disease (129, 2%), vascular disease (97, 1%) and conduction disease (40, 1%) are smaller proportions (see figure).

Discussion

This is the largest SCD cohort with autopsy findings ever reported from one country. SADS and cardiomyopathies predominate. This study highlights the importance of the autopsy in SCD which is a significant public health concern in all age groups. Knowing the true incidence in our population will improve risk stratification and develop preventative strategies for family members. There is now a national pilot study integrating molecular autopsy and family screening into the assessment of SCD victims.

Key words: Sudden cardiac death, sudden arrhythmic death syndrome, cardiomyopathy, cause of death, family screening, molecular autopsy.

Introduction

Sudden cardiac death (SCD) is defined as natural unexpected death in witnessed cases as an acute change in cardiovascular status with time to death being <1 hour and in unwitnessed cases as person last seen alive <24hours before being found dead (1). SCD is frequent in older age groups due largely to ischaemic heart disease in USA, Europe and increasing also in China (2) (3) (4). The universal declining autopsy rate is highlighted in many studies and even a recent FIFA report on sudden death in young footballers showed that out of 617 cases from 67 countries , only 127 had an autopsy (5). A recent review within Europe highlighted that up to 40% of SCD in people under 50 years cases did not have an autopsy (6). This study did however emphasise that in the United Kingdom we have a high autopsy rate within our coronial system. It is especially important that SCD in younger people is investigated with autopsy as genetic cardiac causes including channelopathies and cardiomyopathies are more frequent which have important implications for their families (7). These cardiac diagnoses in SCD can only be made at autopsy. The almost universal decline in hospital autopsies has led to significant errors in the cause of death (8). In a recent analysis of USA death certificates from 2018, 34.7% of all death records had an unsuitable underlying cause of death while 19.8% had a nonspecific underlying cause of death (7). Correct death certification is vital to help guide public health service concerns and prevention (9). There is still a role for the autopsy in the 21st century in determining the cause of cardiac death which should guide future public health planning and prevention of further sudden deaths within a family when a specific genetic diagnosis is made.

In the first national autopsy based UK study of people less than 65 year in which Bowker et al, established that the estimated annual frequency of sudden unexpected death due to cardiac causes in adults was 11/100 000 (3481 annual deaths) (10). Not surprisingly, most deaths were due to coronary artery disease but in 4.1% of sudden unexpected deaths no cause was found, and this was the first study to highlight these cases by a name Sudden Adult/Arrhythmic Death Syndrome (SADS). Following this study, a charity funded by bereaved families called Cardiac Risk in the Young (CRY) established with Mary N Sheppard a nationally available service for prospective reporting on the cardiac pathology of SCD. This work enables us to process hearts referred from coroners and pathologists from throughout the UK and report the results within 2 weeks of receipt of the heart. CRY also funded the development and maintenance of a prospective national pathology database based upon mainly on non coronary atherosclerosis causes of SCD. We presented our initial results on 453 cases in 2006 (11). Since then, we have accumulated 7214 cases into this database, the largest series of autopsy sudden cardiac death in the world and wish to expand on our previous series and the evolution of the molecular autopsy which is of vital importance to families and cardiologists who have developed the inherited cardiac conditions speciality within the UK.

Material and Methods

All hearts are received fixed in formalin. This is the technique Mary N Sheppard has developed over time to examine the fixed hearts. The surface of the heart is examined and then the coronary arteries are sliced at 2-3mm interval to look for evidence of disease such as significant atheroma, thrombosis, dissection, aneurysm formation or thickening in all branches. All branches should be examined down to the apex of the heart to establish their pathway so as to exclude anomalous coronary artery. The atria are opened before looking at the ventricles. The atria are opened into the appendages. We measure the right atrium between the entrance of the superior and inferior caval vein longitudinally and transversely from the entry of the inferior vena cava to the tip of the right atrial appendage to determine right atrial size. Then we check the tricuspid valve morphology to look for endocarditis, rupture, or congenital abnormalities such as Ebstein’s. The interatrial septum is checked for fatty hyperplasia, the fossa ovalis for a patent foramen ovale and atrial septal defect. The left atrium is measured transversely between the left and right superior pulmonary veins and longitudinally from the atrioventricular junction to the superior edge to determine left atrial size. Then we examine the intact mitral valve for evidence of prolapse up into the left atrium with ballooning or thickening or cordal/papillary muscle rupture up into the left atrium. Once the atrioventricular valves are deemed normal macroscopically, then we slice the ventricles transversely from the apex to mid ventricle at 5mm intervals. The slices are examined for pathology such as hypertrophy, fatty infiltration, fibrosis, and infarction. Lesions can be focal so all levels should be examined carefully. Once the ventricles are deemed to be normal, then measurements can be made at the midventricular level halfway between the atrioventricular junction and the apex of both ventricles. The cavity diameters are measured transversely excluding the trabeculae and papillary muscles. The muscle thickness and epicardial fat of each ventricle is measured in the anterior, lateral, and posterior walls. Septal muscle thickness is measured in the middle of the septum and excludes trabeculae and papillary muscle. In addition, the right ventricular outflow tract is measured 10mm below the pulmonary valve. The epicardial fat measurement should exclude fat around the coronary arteries where it is always prominent. The presence or absence of fibrosis, infarction, or fat in the myocardium is commented on. In the remaining heart the atrium and ventricle is opened laterally extending through each AV valve down to the midventricle slice already made. Each atrium can then be looked at in detail and each appendage checked for thrombi. Both AV valves can be examined in detail and the annulus measured. The lateral left ventricular cut usually separates the anterolateral and posteromedial papillary muscles on either side. From the right midventricle slice cut up into the pulmonary valve. From the left midventricular slice, look up into aortic valve into the outflow tract and see the three leaflets of the aortic valve before cutting through the middle of the anterior leaflet of the mitral valve. Also one can examine the aortic valve from above with a transverse ascending aortic cut. The valves are inspected for calcification and the number of leaflets are noted and annulus measured. The coronary artery ostia are examined in each sinus carefully for anomalous origin. The ascending aorta is examined for evidence of dilatation, intimal atheroma, thickening or dissection and the circumference is measured 20 mm above the valve. Following removal of any clot and attached aorta, the heart is then weighed. We have recently published on expected atrial measurements, ventricular cavity diameters, wall thicknesses, epicardial fat and valvular circumferences depending on age, sex and body measurements and provided a calculator (12).

Cardiac sections

Blocks are taken for histology routinely from the midventricular slice to include anterior, lateral (this will be a lateral cut to include right atrium above and right coronary artery as well as av junction and right ventricle) and posterior right ventricle as well as the right ventricular outflow tract, 10mm below the pulmonary valve. Blocks are taken from the anterior, lateral (to include circumflex artery and mitral valve on lateral cut) and posterior LV as well as anterior and posterior IVS. Sections of coronary artery, atria and conduction tissue are also sampled routinely. Normally, ten sections are examined though more blocks will be taken if specific pathology is found. Significant stenosis or thrombosis of the coronary arteries is serially sectioned for histological analysis if observed. Following processing of the blocks, the slides are stained with haematoxylin and eosin. A picrosirius red is used to highlight fibrosis, if required. This protocol with sampling is similar to one recommended by UK Royal College of Pathologists in which there is a likely cardiac cause of sudden death (13). Table 1 shows our diagnostic criteria for cardiac causes of death and the associated figure shows examples of the histology.

The study has been approved by the London-Stanmore Research Ethics Committee (10/H0724/38).

Results

The CRY Pathology Unit has examined 7456 hearts between 1994 and 2021. Of these, 242 cases are excluded as they had a non-cardiac cause of death. We therefore have 7214 cases with cardiac causes of sudden death. Figure 1 shows the age referral pattern with the wide age distribution with peak in 20-40 age groups but note all age groups are represented. In all age groups the male predominance is striking (Figure 1).

Sudden arrhythmic death syndrome in which the heart is morphologically normal is the most common cause of death (3821, 53%) followed by the cardiomyopathies (1558, 22%), then ischaemic heart disease (670, 9%). Valve disease which mainly are aortic stenosis and mitral valve prolapse (225, 3%), congenital heart disease (213, 3%) and myocarditis/sarcoidosis (206, 3%) are the next most common and made up similar proportions. Hypertensive heart disease (185, 3%), aortic disease mainly acute thoracic dissection (129, 2%) vascular disease including ruptured peripheral aneurysms and vasculitis (97, 1%) made up smaller proportions of the cohort. Other cardiac disease (70, 1%) include tumours, transplant, and amyloidosis. Conduction disease (40, 1%) is reserved for cases of Wolff-Parkinson-White or total heart block diagnosed clinically where often no pathological abnormality or focal fibrosis is detected in examination of the SA and AV nodal tissue. The causes of SCD are shown in Figure 2.

SCD occurs almost twice as commonly in males compared to females (4398 vs 2285, 1.9:1). This persists in most conditions underlying SCD and is noted particularly in SADS, cardiomyopathies and ischaemic heart disease (Figure 1).

SADS is seen in all age groups but is more frequent in under thirty-five age group while cardiomyopathies predominate in over thirty-five age group (Figure 1). Ischaemic and hypertensive heart disease is also more common in over thirty-five age group. When looking at children under age fifteen, SCD is mainly due to SADS (258, 61%), cardiomyopathy (68, 16%) and congenital heart disease (37, 9%).

Looking at the cardiomyopathies as a group, the pathological phenotype idiopathic hypertrophy (479, 31%) is the most frequent followed by arrhythmogenic (291,19%), hypertrophic (284, 18%) and dilated (253, 16%) cardiomyopathies. Obesity cardiomyopathy was present in 11%. All are male predominant and mainly older thirty-five age group (Figures 1 and 3).

Since 2013, the importance of taking of genetic material at autopsy was promoted by cardiologists and clinical geneticists, the so called molecular autopsy has evolved (14,15). We developed a protocol for taking a small 1cm square of fresh spleen and putting it in a solution to preserve DNA called RNAlater. Since 2013 the number of spleens has risen from 21 in 2013 to 306 in 2021, reflecting that over half the hearts are coming with material suitable for genetic analysis which is continuing into 2022 (Figure 1).

Discussion

This study reflects the pathological phenotypes present in mainly non ischaemic causes of SCD. It is well recognised that ischaemic heart disease is the most common overall cause of SCD which includes our previous study (10,16–18). This autopsy series focuses mainly on the non-ischaemic causes of SCD. Therefore, this study does not reflect the true incidence of this cause of SCD in the UK population. A large study from northern Finland of 4031 mainly older patients between 1998 and 2012 showed that while ischaemic heart disease still predominated, it is reducing in incidence while obesity related, alcohol related and hypertensive heart disease are increasing (19). We do emphasise that in younger patients the finding of significant coronary atheroma points towards the possibility of familial hypercholesterolaemia so should be commented on by the pathologist and the family screened accordingly (20).

This is the largest SCD cohort with autopsy findings ever reported in the literature from one country in which all cases have been autopsied and in which SADS and Cardiomyopathies predominate. Comparison of SCD incidences between countries is difficult due to different age groups, autopsy rates, population as well as regions selected and study designs. Nationwide studies in Denmark, Australasia and Ireland (16,21–24) have been done but not in such a wide age group and not all had autopsies. Even within a national legal framework there can be dramatic regional variation in autopsy rates as shown in Denmark in 2012 (25).

Sudden Adult Death Syndrome /Sudden Arrhythmic Death Syndrome (SADS)

The number of SADS which are also labelled as unexplained sudden cardiac death cases with negative autopsy and toxicology findings, varies widely depending on age and study type and numbers (Figure 4). Previous studies have found sudden arrhythmic death syndrome in 6-40% of cases (16,21,23,24,26–28). All these studies confirm that SADS is more common in younger age group. Males are more at risk for SCD in all the above studies and our study also confirms this. Our high rate of 53% of unexplained/SADS may be due to referral bias as more unexplained cases are more likely to be referred for a second opinion but we also believe that SADS is underreported as a study we undertook previously showed an overdiagnosis of cardiac pathology especially HCM and ACM in normal hearts (29). Some of the observed differences will be due to small scale studies, regional variation, varied age ranges, select study populations and the absence of specialist examination. SADS is mainly due to inherited channelopathies in the majority of cases with predominant entities being Brugada syndrome, long Q-T and catecholaminergic polymorphic ventricular tachycardia (CPVT)(30)(31) and there are now clinical guidelines for their investigation in families (32). It is thus essential that the pathologist correlates the normal heart and negative toxicology (the negative autopsy) and advises family cardiological screening. The combination of post mortem genetic testing and family screening identifies an inherited cardiac condition in 39% of individual’s diagnosed with SADS further highlighting the importance of advising family screening and genetic testing (31).

Cardiomyopathies

Our study identified cardiomyopathies in 22% of SCD cases and all with a male predominance and older age group. Other studies show cardiomyopathies range from 15-30% of SCD cases (16,17,22,23,26–28). It is vital to diagnose these entities correctly as most have a genetic cause and the family must undergo cardiological screening and genetic testing (33).

 When looking specifically at the types of cardiomyopathies within the cardiomyopathy category there is wide variation between our study and others. We report idiopathic hypertrophy in 32%, with ACM in 19%, HCM in 18% and DCM in 16% and obesity related cardiomyopathy in 11%. Danish study found higher proportion of idiopathic hypertrophy in 60%, ACM in 29%, DCM in 7% and HCM in 4% (22). The Irish study identified much higher proportion of HCM at 49%, idiopathic hypertrophy in 34% with DCM making up 9% and ACM 6% (23). The Italian study identified a much higher proportion of ACM at 55% with 27% being HCM and 18% being DCM with no cases of idiopathic hypertrophy (28). HCM has been reported in 36% of 842 SCD in young USA Athletes with again male predominance (34). In a Finnish study of non ischaemic cardiac deaths cardiomyopathy made up 80% of cases (35). This variation between national studies merits further investigation. The entity of idiopathic left ventricular hypertrophy is only now being included in SCD studies and on family follow up does not appear related to HCM (36). The entities of idiopathic cardiac fibrosis and obesity related cardiomyopathy also need further study.

Cardiomyopathy made up a greater proportion of SCD in those over 35 years in our study. This was also observed in the Danish and Swiss studies particularly with regard to idiopathic left ventricular hypertrophy (17,21). One exception to this is ACM which presents with SCD more commonly in less than 35 year olds (17,21) which is also noted in our cohort.

The underlying causes of the cardiomyopathy include genetic and metabolic conditions. Genes implicated in cardiomyopathy have increased considerably recently. A recent consensus guideline published by European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society and Latin American Heart Rhythm Society highlights the complexity of this rapidly advancing field with numerous genes associated with each cardiomyopathy (37).

HCM is well recognised to be caused by mutations in sarcomere protein genes however it may also be mimicked by Fabry’s and Danon diseases (38). The HCM heart, which displays myocyte disarray on histology, may also be of a normal weight with hypertrophy in around 30% of cases (39).

The dilated cardiomyopathy phenotype has diverse aetiology including metabolic causes such as inborn/mitochondrial, alcohol, diabetes and drugs and genetic such as Lamin A/C. A genetic cause is found in approximately 40-50% of cases of dilated cardiomyopathy (40).

ACM is now recognised to be a biventricular disease and can affect solely the right or left ventricle as well as affecting both ventricles. It is diagnosed by the presence of fibrosis in an epicardial distribution which is frequently admixed with fat. Historical reports had labelled cases with solely fat present in the right ventricle as ACM however it is now recognised that fatty infiltration of the right ventricle is a normal finding (12,41).

Idiopathic hypertrophy, which is recognised to be distinct from HCM, is diagnosed on the basis of an increased heart weight in the absence of myocyte disarray (36). We have recently published on the relationship between body measurements, sex, and cardiac parameters including heart weight highlighting that the female heart has a lower weight, smaller atria and smaller ventricular wall thickness and cavity size but greater epicardial fat thickness (12). The paper provides a calculator to give expected measurements according to age, sex, height and weight.

Valve disease

Valve disease is a well-recognised cause of sudden cardiac death incorporating entities such as aortic calcific stenosis, mitral valve prolapse and endocarditis. Other series have also highlighted it as a cause of SCD occurring at a range of less than 1% up to 16% (17,26,28). Mitral valve prolapse is important to identify as it can have a genetic aetiology and therefore screening should be advised in blood relatives. Post mortem studies have shown myocardial fibrosis occurs most commonly in the posterior wall (42). Endocarditis is a rare cause of SCD occurring in those with normal valves, valvular disease and following valve replacement surgery and is frequently not diagnosed prior to autopsy (43).

Congenital disease

SCD in individuals with congenital heart disease occurs frequently (44). It has been observed to account for a similar proportion of SCD in other specialist cardiovascular pathology series (45). Frequently there is ventricular fibrosis in these individuals which is thought to account for their SCD. However, a small portion of individuals do not reveal a substrate for arrhythmia. Sequential segmental analysis and the “morphological method” are important for describing these complex cases which should be examined in a specialist centre (46). Anomalous coronary arteries which is included under this category are also a well-established cause of SCD (47).

Myocarditis and sarcoidosis

Myocarditis has been reported in 4-10% of autopsy cases in other series and has noted to be more common in males compared to females similar to our study (23,24,28,48). Cardiac sarcoidosis cab be a challenge to diagnose because of focal lesions. It is important to sample conduction tissue in cases of sarcoidosis as it is frequently involved and can result in heart block (49). It tends to occur in older individuals when compared to myocarditis.

Aortic and vascular

Aortic dissection and rare vascular causes including peripheral ruptured aneurysms and vasculitis are recognised within other studies which agree with our findings that it is a minor cause and generally found in less than 10% of cases (23,24,27,28). It is important to advise screening in younger individuals with aortic dissection as it is frequently familial (50).

Conduction disease

Conduction system abnormalities are not mentioned in most other studies but have been noted in 9% of cases in the Italian study (28) and 2% in one of the Danish studies (21). These are higher proportions than within our cohort.

The concept of the molecular autopsy

The first such diagnosis was made in 1999 when a diagnosis of Long Q-T was made in a fatal drowning. We have now proven that molecular testing with sample collection during autopsy in SCD is valuable in yielding a diagnosis (30,31). Considering that SADS and cardiomyopathies accounts for a significant number of sudden deaths in young people and that epidemiological, clinical and now post-mortem genetic analyses all suggest a lethal cardiac channelopathy or cardiomyopathy mutation, the molecular autopsy should be viewed as the standard of care for the post-mortem evaluation of SCD (51,52). Already pathologists within the UK are doing this by obtaining samples of spleen and fixing in RNAlater this avoiding the need for freezing tissue and excellent quality DNA can be extracted. Both the Royal College of Pathologists and European Association of Cardiovascular pathology have included this in their guidelines (53,54).

Summary

 This study highlights the importance of the autopsy in SCD which is a significant public health concern in all age groups. It is important to verify the causes of SCD by autopsy as death certification alone can be inaccurate and autopsy imaging is not yet reliable enough in detecting specific cardiac disease. We need to know the true incidence of conditions leading to SCD because especially in younger age group it is largely due to genetic causes in 75% of cases. Multiple studies show that family members of young SCD victims are at risk of preventable cardiac disease. Knowing the true incidence with autopsy in a population will improve risk stratification and develop preventative strategies for family members. Already we have established the molecular autopsy in a national pilot study of SCD which is being undertaken with NHS England, Genomics England, British Heart Foundation and CRY in which all the genetic testing will be undertaken within the NHS.

Limitations

While we get over five hundred cases annually in UK, we obviously do not get all cases of SCD in UK and ischaemic heart disease is not the focus of this study which mainly deals with non ischaemic causes.

Data availability

Data will be made available upon reasonable request to the corresponding author.

Conflicts of interest

We have no conflicts of interest to declare.

Acknowledgements

Cardiac Risk in the Young fund the Cardiac Risk in the Young Cardiovascular Pathology Laboratories.

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Figure legends

Figure 1. Demographics and numbers of referrals to the CRY cardiovascular pathology laboratories from 1994-2021. The upper left panel shows the age and sex distribution of the referrals with females in red and males in blue. The upper right panel shows the cause of death broken down by sex with females in red and males in blue. The lower left panel shows the causes of death broken by under and over 35 with less than 35 year olds in red and over 35 year olds in red (SADS=sudden arrhythmic death syndrome, CM=cardiomyopathy, IHD=ischaemic heart disease, CHD=congenital heart disease, HHD=hypertensive heart disease).

Figure 2. Pie chart of causes of death. The causes of sudden cardiac death from 7214 referrals to the CRY cardiovascular pathology laboratories from 1994-2021. Sudden arrhythmic death syndrome (SADS) and cardiomyopathy (CM) account for 75% and are imperative to identify and advise family screening as they can be heritable.

Figure 3. Pie chart of cardiomyopathies. The breakdown of the 1558 sudden cardiac deaths with cardiomyopathy. Idiopathic hypertrophy was most common. Arrhythmogenic cardiomyopathy (ACM), hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) made up similar proportions. Obesity cardiomyopathy (OCM) was less common (CM=cardiomyopathy).

Figure 4. The proportions of sudden arrhythmic death syndrome (SADS) and cardiomyopathy from worldwide studies. This graph highlights the profound variability that exists between studies conducted in different countries from around the world.