TITLE PAGE

Title

SUDDEN ADULT DEATH SYNDROME AND OTHER NON ISCHAEMIC CAUSES OF
SUDDEN CARDIAC DEATH: A UK EXPERIENCE

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The normal heart in adult sudden death.

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ABSTRACT

Background: While the majority of sudden adult deaths are due to ischaemic heart diseases, other causes are often overlooked and the concept of the structurally normal heart in sudden death has only recently been recognised. Methods: We acted as a referral centre for sudden adult deaths referred to us by UK coroners and prospectively collected pathological data. Results: We reviewed 453 cases from 1994-2003 (278 men (61.4%) and 175 women (38.6%, age range [15-81]). Males predominated in both age groups (≤35 y.o, >35 y.o). More than half of the hearts (n=269, 59.3%) were structurally normal. In the other 40.7 %, cardiac abnormalities were noted which included (i) cardiomyopathies (23%) such as idiopathic fibrosis, left ventricular hypertrophy, hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular dysplasia, (ii) inflammatory disorders (8.6%) including lymphocytic myocarditis and cardiac sarcoidosis, (iii) non atheromatous pathologies of coronary arteries (4.6%), (iv) valve diseases, and (v) miscellaneous and rare causes. Discussion: The concept of the structurally normal heart in sudden death and the need for histological examination in order to detect underlying disease is highlighted. There is a need for the referral of relatives for cardiological/genetic screening in cases of normal hearts found at autopsy.

[199 words]

Acknowledgements:

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INTRODUCTION

Sudden adult cardiac death is due in the vast majority of cases to ischaemic heart disease.[1] In previous UK series this cause ranged between 59% to 86% of sudden death cases in the community. [2] [3] Sudden unexpected cardiac death in the community in which no cause can be found at coroner’s post mortem is increasingly recognised. The proportion of unexplained deaths in one of the earliest studies in Wandsworth in 1988 was 3.4% .[2] In the first national prospective study of sudden death, funded by the British Heart Foundation in the early 1990’s, a very similar figure of 4.1% of unexplained deaths were reported. following detailed examination by three cardiac pathologists.[3] Both these studies advocated identifying these cases by a name, Sudden Adult Death Syndrome (SADS) in order to highlight the problem and deal with it in a similar fashion to sudden infant death and study the aetiology systematically. The concept of the morphologically normal heart in sudden death is of major importance with the emergence of the molecular channelopathies such as Long QT or Brugada syndrome giving rise to lethal cardiac arrhythmias in the last 15 years.[4] Non–ischaemic causes of sudden cardiac death are of major importance because they often include genetic diseases, such as hypertrophic cardiomyopathy, dilated cardiomyopathy and arrhythmogenic right ventricular dysplasia. [5] Following the initial BHF study we acted as a referral centre for sudden cardiac death cases from coroners throughout England and have now completed an analysis of the cases referred for a pathological opinion, often because the referring pathologist did not find a cause of death or was uncertain of the cause of death. The subjects were all older than 15 years and excluded atherosclerotic coronary artery disease (coronary artery stenosis, with or without acute or old myocardial infarction or fibrosis) as a cause of death. This is the first pathological study to evaluate nonatherosclerotic cardiac deaths in the UK population aged over 15 years including elderly subjects.
METHODS

From January 1994 to April 2003, all cases of sudden adult cardiac deaths referred to us were entered in a prospective database which had been referred from coroners throughout England. All the patients had been well until their sudden death with no history of heart disease in the past, apart from the congenital cases and the history of hypertension (elicited from GP notes after left ventricular hypertrophy was reported pathologically). Toxicology (reports were provided by the coroner) was negative in all patients. Details concerning other diseases were obtained from the coroners once they had been in contact with patient’s GPs. For the purpose of the study, ischaemic heart disease cases were excluded. Either histological sections from the myocardium (51% of cases, between 2 and 10 sections per case), a single myocardial transverse section of both ventricles (2%), or whole hearts (47%) were referred by pathologists with permission obtained from the next of kin. The patient’s age, sex, weight and height (when provided), heart weight, thickness of left and right ventricle and overall description were recorded. Where patient’s height and weight were not available, normal cut-off parameters for heart weight was 500 grams in males and 400 grams in females and 15mm for left ventricular thickness. An elastic van Gieson (EVG) stain was performed on selected sections to assess fibrosis.

Histological criteria for hypertrophic cardiomyopathy (HCM) included myocyte disarray, interstitial fibrosis, vascular changes of small arterioles (thickening of the wall), arrhythmogenic right ventricular dysplasia (ARVD) showed fat and fibrosis throughout the wall of the right ventricle +/- chronic inflammatory infiltrate, left ventricular hypertrophy included hypertrophied myocytes with no fibrosis. Idiopathic fibrosis (IF) showed widespread fibrosis in the left ventricle with no evidence of ventricular wall thinning, dilated cardiomyopathy (DCM) showed a thin walled left ventricle with fibrosis throughout the left ventricle with no coronary artery disease. The final pathological diagnosis was noted and results were categorised into: (a) normal heart
(+- associated diseases), (b) cardiomyopathies, (c) myocarditis, (d) non-atheromatous pathology of the coronary arteries, (e) valvular diseases and (f) other pathologies including disorders of the conduction system.

**RESULTS**

A total of 453 cases of sudden cardiac deaths were retrieved from the database, including 278 men (61.4%) (median age = 32 [15-81]) and 175 women (38.6%) (median age = 31 [15-75]). Two hundred and twenty three (49.3%) were aged ≤35 years (75 women, 148 men) and 230 (50.7%) were aged >35 years (table 1).

(a) **Normal hearts (Table 1)**

Hearts were found to have normal macroscopic and microscopic appearances in 269 cases (59.3%, 162 men, 107 women), representing true sudden adult death syndrome (SADS). There was an equal distribution between subjects younger or older than 35 (53.5% and 46.5% respectively) (table 1). Males predominate in both age groups. In this group of morphologically normal hearts, 13% had reported diseases known to predispose to sudden death. These were epilepsy (n=11), alcoholic fatty liver (n=9), anorexia (n=5), asthma (n=4), diabetes mellitus (n=4), or schizophrenia (n=3).
Table 1: Age and sex distribution of cohort and constitutively normal hearts

<table>
<thead>
<tr>
<th></th>
<th>≤35 y.o</th>
<th>&gt;35 y.o</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OVERALL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>75</td>
<td>100</td>
<td>175</td>
</tr>
<tr>
<td>Males</td>
<td>148</td>
<td>130</td>
<td>278</td>
</tr>
<tr>
<td>Total</td>
<td>223</td>
<td>230</td>
<td>453</td>
</tr>
</tbody>
</table>

|                |         |         |        |
| **NORMAL HEARTS (59.3%)** |         |         |        |
| Females        | 52      | 55      | 107    | (39.8%) |
| Males          | 92      | 70      | 162    | (60.2%) |
| Total          | 144     | 125     | 269    |         |

(b) Cardiomyopaties (Table 2)

Pathologies of the myocardium were found with certainty in 107 patients, representing 23% of all cases (table 2a). Seven cases (as described below) had insufficient tissue sampling for definite diagnosis. Males predominated in both age groups. Left ventricular hypertrophy and idiopathic diffuse cardiac fibrosis made up 55% of the total cardiomyopathy group. Left ventricular hypertrophy without fibrosis or disarray was the commonest pathology, found in 31 subjects, with males predominating in both age groups. Associated diseases found in 14 cases were hypertension (n=9), including 4 cases (4 males, 3 aged less than 35) reported to be of AfroCaribbean origin, and aortic stenosis (n=5). With a similar frequency, idiopathic diffuse left ventricular cardiac fibrosis of the left ventricle was seen in 29 cases (6.4% of the whole series, 27% of the cardiomyopathy group). The majority were men (18/29 cases) with equal distribution.
in both age groups. In 15/29 cases, the heart was macroscopically normal with no evidence of thinning or scarring. In the remaining 14, the heart was hypertrophied. No previous history of hypertension was obtained in these cases. Hypertrophic cardiomyopathy (HCM) represented the third commonest disease of the myocardium in 28 cases. While 23 cases showed the classic hypertrophied left ventricle, in 5 cases the heart was macroscopically normal. Again males predominated with this disease (21/28 cases). Cases were equally distributed between both age groups but more females were diagnosed after the age of 35. Interestingly, one case had associated diffuse lymphocytic myocarditis.

Arrhythmogenic right ventricular dysplasia (ARVD) was observed in 10 cases, 6 males and 4 females, and 6/10 cases were diagnosed in the ≤35 age group. Seven were described as having fatty replacement of the right ventricle macroscopically, 1 had a thin right ventricle wall and 2 appeared macroscopically normal. ARVD was seen in association with diffuse lymphocytic myocarditis in one case. Seven additional cases with fatty infiltration of the right ventricle were referred, but we had only limited material in all cases (slides only, no whole hearts) and a diagnosis of ARVD could not be made with certainty because of this limitation. Dilated cardiomyopathy (DCM) was diagnosed in 9 cases, with a female predominance (7/9). In the greater than 35 age group, all cases were female. In retrospect we found 5 cases were associated with heavy alcohol intake, 1 was post partum, 1 had diabetes mellitus, 1 had acute thyrotoxicosis and 1 was post chemotherapy. In one case, a positive family history for dilated cardiomyopathy had been reported.
Table 2: Pathology of the myocardium with a diagnosis of certainty

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>% of group</th>
<th>% of cohort</th>
<th>&lt;35 y.o</th>
<th>&gt;35 y.o</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>LVH</td>
<td>31</td>
<td>28%</td>
<td>6.8%</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>IF</td>
<td>29</td>
<td>27%</td>
<td>6.4%</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>HCM</td>
<td>28</td>
<td>26%</td>
<td>6.2%</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>ARVD</td>
<td>10</td>
<td>9%</td>
<td>2.2%</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>DCM</td>
<td>9</td>
<td>8%</td>
<td>1.9%</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>23%</td>
<td>38</td>
<td>12</td>
<td>35</td>
</tr>
</tbody>
</table>


(c) Myocarditis (Table 3)

Myocarditis occurred in 39 patients (2 already mentioned in association with HCM and ARVD) representing 8.6% of the studied hearts (Table 3). Lymphocytic myocarditis which demonstrated lymphocytes surrounding necrotic myocytes in at least two foci per block of tissue examined was diagnosed in 24 patients and most of these were macroscopically normal hearts in which the histology revealed the cause of death. The majority of cases were found in subjects aged less than 35 (16/24) and of those, 12 were males. Granulomatous myocarditis in which there were well formed granulomas without any eosinophilic infiltrate (cardiac sarcoidosis) was observed in 10 cases, all aged over 35, with a male predominance (8/10). Toxic myocarditis was diagnosed in 5 cases and showed an infiltration of predominantly macrophages and eosinophils in the interstitium (attributed to drugs in two cases and thyrotoxicosis in 1 case).
Table 3: Inflammatory pathologies of the myocardium

<table>
<thead>
<tr>
<th></th>
<th>&lt;35 y.o</th>
<th></th>
<th>&gt;35 y.o</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>Lymphocytic myocarditis</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Granulomatous myocarditis</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Toxic myocarditis</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

(d) Nonatheromatous pathology of the coronary arteries (Table 4).

Nonatheromatous coronary artery diseases were observed in 21 cases (4.6%). Anomalous coronary arteries were observed in 6 cases with both coronary arteries arising from the same coronary ostium in 5 cases and an absent right coronary artery in one case. 5/6 cases were aged under 35. Coronary spasm was diagnosed in 6 patients, where with regional ischaemic damage including contraction band necrosis (n=3/6) or regional acute transmural or chronic myocardial infarction (n=3/6) was observed in association with normal coronary arteries. Cases were found in both age groups. Bridging of the left anterior descending coronary artery (LAD) by muscle was systematically looked for and observed in 4 cases, 3 being in the under 35 year age group. The bridge varies from 20 to 40 mm in length and 2 to 5 mm in depth. Coronary artery vasculitis was found in 3 cases (one associated with an inflammatory pseudotumour of the kidney with IgG paraproteinaemia, one case of eosinophilic vasculitis with possible ChurgStrauss syndrome and one case of giant cell arteritis associated with giant cell aortitis). There were 2 cases of spontaneous dissection of the coronary arteries, both occurring in males.
Table 4: Non-atheromatous pathology of the coronary arteries

<table>
<thead>
<tr>
<th>Pathology</th>
<th>&lt;35 y.o</th>
<th>≥35 y.o</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M  F</td>
<td>M  F</td>
<td></td>
</tr>
<tr>
<td>Anomalous coronary arteries</td>
<td>4  1</td>
<td>1  0</td>
<td>6</td>
</tr>
<tr>
<td>Spasm</td>
<td>2  2</td>
<td>1  1</td>
<td>6</td>
</tr>
<tr>
<td>Bridging of the LAD</td>
<td>2  1</td>
<td>1  0</td>
<td>4</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>0  2</td>
<td>1  0</td>
<td>3</td>
</tr>
<tr>
<td>Spontaneous dissection</td>
<td>1  0</td>
<td>1  0</td>
<td>2</td>
</tr>
</tbody>
</table>

(e) Valvular pathology

Valvular pathology as a cause of death included 9 floppy mitral valves, one cleft mitral valve, 10 aortic stenosis with bicuspid aortic valve in 4 cases, and degenerative tri-leaflet aortic valve calcification in one case.

(f) Other pathologies

(i) Conduction system

The conduction system was examined in 7 cases. There was one case of fat and fibrosis in the atrioventricular (AV) node in a 43 year old female who had a documented history of arrhythmias during life (paroxysmal supraventricular tachycardia, atrial fibrillation and complete heart block), one case of tuberous sclerosis in a 41 year old female with multiple ventricular lipomata and a lipoma in the AV node and 2 cases of lipomatous hypertrophy of the inter-atrial septum, one associated with fatty infiltration of the AV node. In three cases of cardiac sarcoidosis, epithelioid and giant cell granulomas were found in the AV node.
(ii) Congenital heart disease

There were 6 cases of surgically corrected complex congenital heart diseases (2 repaired atrial septal defects with right and left ventricular hypertrophy, one repaired tetralogy of Fallot, one repaired ventricular septal defect with right ventricular hypertrophy, two more complex cases with dextrocardia in one patient and corrected atrioventricular septal defect in another). All these had been operated on many years previously and there was no indication of clinical deterioration prior to sudden death. At autopsy apart from the surgical corrections and congenital anomalies, there were no specific new findings to explain the sudden death in each case. The pathologists had referred them because of their complexity and surgical correction.

(iii) Miscellaneous

Very rare causes of sudden death included idiopathic thrombotic thrombocytopenic purpura associated myocardial necrosis (n=2), lipoma in the left coronary ostium (n=1) causing obstruction of the left main stem, small benign tumour (AV nodal mesothelioma) (n=1) and metastatic adenocarcinoma to the myocardium (n=1).

DISCUSSION

A substantial proportion of persons experience sudden death as the first and only clinical expression of underlying coronary artery disease and pathologists are familiar with this in their coronial practice. However there are few large reports on sudden cardiac deaths due to non atheromatous causes or where no cause is found. Reports of non-atheromatous causes of sudden cardiac death tend to concentrate on a limited age group of subjects aged less than 35-40, including athletes.[6][7][8][9] The current study differs in that it explores sudden cardiac death in a wider age group (15-81 y.o.) and describes a large proportion of macroscopically and
microscopically normal hearts and non-atheromatous causes of sudden cardiac death in which pathologists were uncertain of the cause of death or wished for confirmation of the diagnosis. Almost 60% of our cases had a macroscopically and microscopically normal heart with an equal distribution between subjects younger than 35 and older than 35, emphasising that this entity can occur in all age groups and not just in the young or athletes. The male predominance is also remarkable. This group is a much higher figure compared to the Italian study of 273 cases of sudden deaths in young patients (≤35 years old) in whom 16/273 had a 12 normal heart, giving a rate of 6%.[8] A 21% rate of normal hearts in unexplained death was observed in a Swedish study [9] in the same age group In a French study in 1996 of 1000 sudden death autopsies in adults under 65 years of age, 12.3% had normal hearts [10] and 15.8% in an American series in 14-40 years old group.[6] We included all our cases less than 40 years for comparison and show that 60% had a normal heart. The frequency of hearts with “no finding” decreased with age in the Virmani study in 2001, 30% in the 14-20 age group, 21% in 21-30 age group and 9% in the 31-40 age group.[7] In our series, almost half of the normal hearts were found in subjects older than 35 year, a fact not established in the literature which has in the past emphasised sudden death in younger age groups. The high proportion of normal hearts in the present study may be explained by the selective and biased referral pattern by pathologists who found nothing at autopsy or were uncertain of the cause of death; another explanation may be the poor sampling in some cases (as seen for 7 cases of suspected ARVD) and the fact than slides rather than whole hearts were referred in 51% of cases with limited sampling of the right ventricle.

Sudden death with a morphological normal heart is a very important negative finding at autopsy.[3] Genes have been identified for several disorders responsible for arrhythmias and
sudden death. These genes all encode ion channels and are referred to as channelopathy genes, and the proteins that regulate electrical activity are not detectable morphologically at the time of post mortem. Diagnosis can only be made by ECG investigation during life. The occurrence, of sudden death with a normal heart should therefore prompt referral of close relatives to a specialist cardiologist for genetic screening. In a recently completed study of 147 first-degree relatives of 32 people who died of SADS, 109 (74%) underwent cardiological assessment; seven (22%) of the 32 families were diagnosed with inherited cardiac disease and four with long QT syndrome.[12] This study emphasises that it is important to screen families for genetic conditions in sudden cardiac death cases. However, although we systematically advise genetic screening of relative in cases of sudden adult death with a morphologically normal heart, one limitation of the current study is the lack of genetic results or information of family history in this group of structurally normal heart. We need to study in more detail these cases.

All types of cardiomyopathies including HCM, DCM and ARVD have an underlying genetic mutation in many cases and cardiomyopathies are responsible for sudden cardiac death in nearly 25% of our cases, representing a significant figure. Their diagnosis can be difficult in view of the variation in phenotypic expression of these entities. HCM can present with sudden death and macroscopically normal heart as this study also demonstrates. The male predominance in this entity in both age groups emphasizes that sudden death can occur in older patients with this condition.

LVH was male-predominant and also affected older age group in our study. Note the link with hypertension in 9 cases which emphasises that detailed study of general practitioner records in sudden deaths may reveal underlying causes as well as racial differences. While left ventricular hypertrophy is accepted as a cause of sudden death, its definition is controversial and should be
ideally related to the body mass index of the deceased. In current routine coronial work, the weight and height of the deceased may not be recorded and the heart weight is assessed in isolation. One of the drawbacks of the current study is the absence of body mass index data in most cases and the evaluation of LVH on arbitrary cut off points as these values may be normal in tall and overweight individuals.[21]

Normal hearts macroscopically can show microscopic abnormalities as our study also highlights. In the Italian study[8] amongst the 28% of the hearts that were macroscopically normal, 79% on histological examination disclosed concealed pathologic substrates, as also described in a recent French study (out of 1930 unexplained sudden deaths, 200 had pathological evidence of ARVD[18]), emphasizing that histological examination and sampling is essential even in normal appearing hearts.

The proportion of sudden death with a normal heart and associated diseases was 13% in our series. Sudden death has also been reported in epilepsy without clinical evidence of status epilepticus[13], in asthma without clinical evidence of status asthmaticus[14], in anorexia[15], schizophrenia[16] in patients with alcoholic fatty liver without an alcoholic cardiomyopathy.[17] As arrhythmias have been documented during life in patients suffering from these conditions, cardiac arrhythmias are thought to be the mode of death. This 13% rate is by no means accurate and is probably an underestimate due to lack of detailed clinical data in each case. We need to study the clinical history of all these cases further.

Normally we do not check the conduction system in sudden cardiac death. Abnormalities including abnormal conduction bundles, fibrosis and fatty infiltration have been described but
their role in causing death is controversial.[25] In the current study the conduction system was only examined if clinically indicated in particular if the subject was known to suffer from arrhythmias during life and this yielded positive findings. Interestingly the Italian study reported 24 cases of conduction system diseases, and most of the patients had clinical evidence of arrhythmias during life.[8]

Many other studies confirm anomalous coronary arteries and bridging as a cause of sudden death.[26][27] The role of coronary artery spasm is more controversial but has been linked to sudden death and survival after cardiac arrest.[28][19] Vasculitis can affect the coronary arteries locally. This emphasises that detailed study of all the coronary arterial system is essential in cases of sudden cardiac death. Finally we included congenital heart disease because there is an established link to fatal arrhythmias in the absence of symptoms and clinical deterioration at which no new findings are seen. [30]

CONCLUSION

The non-atheromatous causes of sudden cardiac death present a diagnostic challenge for coroners and pathologists. The finding of a normal heart is an important negative finding in the investigations as it warrants referral of living relatives to a specialist cardiologist and genetic screening. As macroscopically normal hearts can have microscopic disease, histological analysis is mandatory to make a specific diagnosis. Today with many questioning the role of the autopsy in modern medicine[31], this study emphasises its importance and central role in helping families come to term with death in a previously “healthy “relative. Detailed and precise cardiac findings
will be important for these families in terms of health screening, genetic counselling, health insurance and treatments such as drugs and implantable defibrillators.
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Aurélie Fabre and Mary N Sheppard

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