The spectrum of inheritable cardiac disease in sudden cardiac death: investigation and pathology

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Abstract

Sudden cardiac death in young adults is rarely related to ischaemic or hypertensive heart disease but has increasingly been associated with a number of inheritable conditions including cardiomyopathies, channelopathies and storage disorders. Once other potential causes of death have been excluded, a careful consideration must be given to inheritable cardiac conditions through careful macroscopic and microscopic examination of the heart and where necessary supported by investigation of the potential underlying genetic abnormality. A pragmatic approach to the examination of the heart is given together with the potential inheritable causes to be considered. When appropriate, support should be sought from a special interest cardiac pathologist through the UK Cardiac Pathology Network (UKCPN).

Keywords autopsy; cardiomyopathy; channelopathy; genetics; sudden cardiac death

Introduction

Despite advances in medical screening and diagnostics, every year there continue to be a number of sudden deaths in the under 40 age group which are ascribed to a sudden cardiac arrhythmia in which there is no evidence of underlying ischaemic or valvular pathology and no clinical or other pathological evidence of hypertension. There are a number of underlying conditions which may be the cause of the sudden death including cardiomyopathies, various rhythm disturbances including Brugada syndrome, long QT syndrome and catecholaminergic polymorphic ventricular tachycardia. Some of these diagnoses can be made by the autopsy pathologist, seeking specialist cardiac pathology opinion when necessary, whilst some require genetic screening where possible on material from the deceased but also involves first degree relatives and beyond. Often these deaths are placed together under the title of Sudden Arrhythmic Death Syndrome (SADS) but recent studies using molecular studies on this cohort of patients has identified genetic abnormalities in the ion channels – the so-called channelopathies, in 20–40% of cases, highlighting the importance of undertaking these investigations to screen other family members.[1–3]

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Sudden death – definition

Sudden death has been variously defined as a natural unexpected death occurring within 1 hour of the onset of symptoms in an otherwise healthy individual or where any co-existing disease was not of sufficient severity to have been expected to cause death.[4] Practically many of these deaths occur within the community and are unwitnessed often occurring during periods of sleep and a pragmatic approach is to define the death as sudden and unexpected if the deceased was known to be in good health 24 hours prior to being found.[5] The autopsy provides the first and often the only opportunity to establish the cause of death.

Cardiovascular disease remains the commonest cause of death within the developed world and about 25% would be classified as sudden cardiac deaths. The incidence of sudden cardiac deaths increases dramatically with age. In the young adult age group (<35 year) this has an incidence of 0.01/1000 head of population/year which rises to 2/1000/year at the age of 60 and 200/1000/year in the elderly reflecting the increasing burden of ischaemic, valvular and hypertensive heart disease on the aging population.[6,7]

Autopsies and sudden death

The autopsy in cases of sudden cardiac death will come under the jurisdiction of HM Coroner in England, Wales and Northern Ireland, and the Procurator Fiscal in Scotland. The information provided is often brief, reflecting the circumstances of the death and particularly in younger individuals, there may have been little contact with local medical services either General Practice or Hospital to provide any background information. It may subsequently be appropriate to enquire through friends or families of any prodromal symptoms and if an electrocardiogram even historic has ever been undertaken.

Factors to be considered should include:

- Lifestyle – occupation, pattern of exercise, smoking history and use of illicit drugs.
- Circumstances of death – location, time of day, related to a particular activity and whether witnessed.
- Suspicious circumstances – such as a road traffic collision, immersion.
- All relevant previous medical history with access to ECG recordings, chest radiographs
- Medication history
- Family history – particularly in relation to early or sudden deaths within the family, or any known inheritable diseases.[8]

The autopsy

All cases will require a thorough sequential structured examination to exclude other potential causes as ultimately the diagnosis of a potentially heritable sudden cardiac death will be a diagnosis of exclusion. The investigation of a sudden death in a young person should fall within the repertoire of pathologists undertaking routine autopsies and guidance, particularly where a cardiac cause is suspected can be obtained from Guidelines published by the Royal College of Pathologists (RCPath)[9] or the Association for European Cardiovascular Pathology (AECVP)[8] or by discussion with an experienced cardiac pathologist available through the UK Cardiac Pathology Network website.

External examination

The body should be weighed and the height recorded as these will be relevant to the correlation with the heart weight and wall thickness.[10,11] A record should be made of any dysmorphic features, evidence of injuries and sites of medical intervention that may have occurred during the resuscitation procedure. If a pacemaker or defibrillator are present these should be removed safely according to guidance and sent for interrogation.[12,13]

Internal examination

A full internal examination should be undertaken with a view to excluding other causes of sudden death (Box 1).

In all cases where no specific cause is identified, toxicology should be undertaken and may include blood, urine, vitreous humour, stomach contents and hair depending on the circumstances and history.

Examination of the heart

There are excellent descriptions of the approach to the examination of the heart published by the RCPath[9] and AECVP.[8] In summary:

- Examine and open the pericardium looking for inflammation, adhesions or an effusion.
- Check the anatomical position of the great arteries and transect about 3 cm above the aortic and pulmonary valves.
- Divide the pulmonary veins at the pericardial reflection, the IVC at the level of the diaphragm and the SVC about 2 cm proximal to the right atrium.
- Open the right atrium between the IVC and the apex of the appendage and the left atrium between the pulmonary veins. Inspection should note patency of the coronary sinus, the lining of the cavity and presence of any thrombus. The foramen ovale should be inspected for a defect or evidence of probe patency.
- The tricuspid, pulmonary, mitral and aortic valves can all be inspected from above and any anomalies, defects or evidence of vegetations noted.
- The coronary ostia should be assessed for patency and position. The coronary arteries can be examined by serial transverse slicing, at 3 mm intervals, noting dominance, course, size and patency and should include the first order branches — the diagonals and obtuse marginals. *Calcified arteries may be difficult to slice and may be dissected free and subject to overnight decalcification to assist in assessment.*
- Assessment of the ventricles should be undertaken by a mid-transverse short axis cut. Subsequent slices are made at 1 cm intervals towards the apex. The myocardium should be assessed for thickness, variations in colour or texture, and areas of scarring or discolouration noted.
- The following measurements should be recorded. Total heart weight. Thickness of mid cavity left ventricular wall in the anterior and postero-lateral regions, the right ventricle and the septum — excluding the trabeculae.

Consideration may be given to referral of the heart for a specialist cardiac opinion.[14] This may be done at any time during the examination, but may be done after step 6 above or with the heart intact. However, a thorough examination of the heart, as described above, with good documentation supported by digital images, can mean that only tissue blocks will need to be referred. Under any circumstances, permission of HM Coroner will be required together with the appropriate request forms signed by the relatives as required by the Coroner's Act (1985) and Rules (1988) and the Human Tissues Act (2004).[15,16] In these circumstances, when a potentially inheritable cause for a sudden cardiac death is being considered, it is good practice, to retain material for genetic testing and this should include small pieces of spleen and myocardium (approximately 10 × 5 × 5 mm) to be snap frozen and appropriately stored either locally or at a regional or national genetics centre.

Histological examination

Histology is required in all cases of sudden death and the organs sampled will be at the discretion of the pathologist based on the macroscopic findings. Where a sudden cardiac death is suspected, then the myocardium should be widely sampled to include (Figure 1):

- Anterior left ventricle including left anterior descending artery
- Anterolateral left ventricle
- Lateral left ventricle with branch of circumflex
- Inferolateral left ventricle
- Inferior left ventricle with posterior descending artery
- Septum
- Posterolateral left ventricle and right ventricular outflow tract.
- Any focal lesions
- Atria walls, valves, aorta and conduction system as appropriate.

Initial histological evaluation is undertaken by Haematoxylin and Eosin stained sections, supplemented by connective tissue stains- Elastic Van Gieson and Masson Trichrome, with stains for amyloid as necessary. Additional stains may be required subsequently.[17]

The cardiac histology should be assessed in a sequential fashion.

1. Endocardium — inflammation, thickening — fibrosis, elastosis and smooth muscle cell hyperplasia, overlying thrombus — old or organised.

Other causes of sudden death

Cerebral	Subarachnoid and intracerebral haemorrhage, meningitis.
Respiratory	Airways obstruction, asthma, tension pneumothorax and pulmonary hypertension.
Gastro-intestinal	Haemorrhage
Vascular causes	Aortic dissection, ruptured aneurysm, early onset coronary artery disease.
Shock	Anaphylaxis (consider a mast cell tryptase), septic shock which may be associated with Waterhouse Friedrichsen syndrome.

Box 1