Review Article

Sudden Unexplained Death in Sleep in Adults: Autopsy Challenges

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Abstract

Sudden and unexplained death of young adults has remained an important and challenging aspect to the Forensic Pathologists. The aetiology of sudden death in sleep is varied and includes cardiac conduction abnormalities, sleep apnoea due to either upper respiratory or lower respiratory disorders, etc. A syndrome popularly known as Bruguda Syndrome, an autosomal dominant disease with incomplete penetrance where mutation in the SCN5A, gene encoding the alpha subunit of the cardiac sodium channel, & electrocardiographically characterized by a distinct ST segment elevation in the right precordial leads. The syndrome is associated with a high risk for sudden cardiac death in young and otherwise healthy adults, and less frequently in infants and children. The victims are typically young men, median age 30-34 years, all in apparent good health, who die within minutes of the onset of distress during sleep. 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. In fact recent advances in the field of molecular genetics have expanded our understanding of the aetiology and classification of many of the cardiac diseases.

Key Words: Sudden cardiac Death, Ventricular fibrillation, Bruguda Syndrome, molecular Investigation

Introduction

Sudden Unexplained Death in Sleep(SUDS) was first described in the medical literature of the Philippines[1] in 1917 and these deaths were popularly known there as *bangungut*—a Tagalog word meaning 'to rise and moan in sleep'.The major difficulties interpreting epidemiological data on sudden death are the lack of standardization in death certificate coding and the variability inthe definition of sudden death. Sudden death has been defined as natural, unexpected fatal event occurring within 1 hour from the onset of symptoms in an apparently healthy subject or whose diseasewas not so severe as to predict an abrupt outcome.[2] Sudden death is estimated to account for nearly 450,000 deaths annually in the United States of America, which represents a prevalence of 0.1 percent in the general population.[3] Ventricular tachyarrhythmia (either ventricular fibrillation or ventricular tachycardia) are responsible for disordered ventricular contraction resulting in sudden death in most of the cases. Coronary artery disease (CAD) is the major underlying substrate responsible for sudden death - in fact, majority of such events are the presenting manifestation of previously quiescent CAD.[4] Myocardial diseases such as dilated cardiomyopathy and hypertrophic cardiomyopathy along with primary electrical diseases of the heart such as long QT syndrome, Brugada syndrome, idiopathic ventricular fibrillation, *etc*. account for about 15-20 per cent of sudden deaths.[4]

Furthermore recent advances in the field of molecular genetics have expanded our

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understanding of the aetiology of many lethal and heritable channelopathies leading to fatal arrhythmias, such as congenital long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) andBrugada syndrome (BrS) which is an autosomal dominant form of cardiac arrhythmia with a typical electrocardiographic (ECG) pattern of ST segment elevation in leads V1 to V3, and incomplete or complete right bundle branch block[5] linked to mutations in the SCN5A gene encoding for the alpha-subunit of the cardiac sodium channel;[6,7] thus actually forensic pathologists play acrucial role in such circumstances because an accurate post- mortem diagnosis of the causes of SCD is of particular importance to establish pre-emptive strategies to avoid other tragedies among relatives.[8]

It is less satisfactory in forensic practice where autopsies may be requested on patients whose deaths were not witnessed, occurred during sleep or at an unknown time before their bodies were discovered. Under the latter circumstances, it is probably more satisfactory to assume that the death was sudden if the deceased was known to be in good health 24 hours before death occurred.[9]

Sudden deaths in sleep of healthy young adults mostly occur out of hospitals and are usually investigated where medical legal systems exist.[10] Forensic pathologists are responsible for determining the precise cause of sudden death but there is considerable variation in the way in which they approach this increasingly complex task. The wide range of uncommon pathology is especially apparent in reports from referral centres.[11,12]

Problems faced by Forensic pathologists:

- In most cases the death occurred without any antecedent history of illness
- The victim was found dead in bed during sleep
- Obtaining a detailed history of medical illness and previous medical records may sometimes be cumbersome and inaccurate due to faulty and negligent maintenance of records
- Autopsy findings sometimes remain obscure with only non-specific findings of asphyxia
- Evaluation of families with history of sudden unexplained death with involvement of a cardiologist, clinical geneticist, genetic counsellor, and Forensic Pathologist a multi-disciplinary approach is still far from becoming a reality

Methods of investigation:

Several book chapters, professional guidelines, and articles have described how pathologists should investigate sudden death.[13,14] Despite these guidelines, there is little consistency between centres, even in individual countries. Forensic investigation of sudden death involves 4 steps:[15]

1. Circumstances of death and clinical information relevant tothe autopsy;
2. Autopsy examination and histology;
3. Laboratory tests;
4. Formulation of a diagnosis: main findings at post-mortem investigation

Finally, a forensic report including a clinic-pathologic summary is written by the autopsy surgeon. At this stage it is critical to establish or consider:

- whether the death is attributable to a cardiac disease or to other causes of sudden death;
- the nature of the cardiac disease, and whether the mechanism was arrhythmic or mechanical;
- Whether the cardiac condition causing sudden death maybe inherited, requiring screening and counselling of the next of kin;

The possibility of a toxic drug abuse or poisoning must be ruled out

Importance of circumstances of death and clinical information relevant to the autopsy:

- Visit to the scene of death is important with

careful examination of theclothing and effects of the deceased.

- Interrogation of the family members, physician of the team which attempted resuscitation
- Although most of such deaths occur at home however any preceding symptoms of difficulty in breathing chest pain, syncope, dizziness are important
- Information regarding age, gender, occupation, habits (smoking, alcohol consumption), exercise etc should be obtained
- Medical history of general health status, previous significant illnesses(chest pain, and palpitations, particularly during exercise, myocardial infarction, hypertension, respiratory, and recent infectious disease,epilepsy, asthma, etc), any surgical history are important. Previous ECG, X-rays, and other investigation reports are also valuable

Procedure for performing autopsy:

The care and attention to detail that pathologists give to sudden death autopsies varies considerably. The range of pathology in sudden death has been also summarized by Saukko and Knight.[15]

Examination of the Body:

The external examination may find clinical signs of disease, such as alcohol disease, in which patients present a raised risk of sudden death.

Moreover it is very important to perform the following procedures:

- Establish body weight and height (to correlate with heart weight and wall thickness)
- Check for recent intravenous access, intubation, ECG pads, defibrillator and electrical burns, drain sites, and traumatic lesions
- Check for implantable cardioverter defibrillator/pacemaker

While performing autopsy it is important to remember the cardiac and as well as non-cardiac causes of sudden death. Uncommon as well as common non-cardiac causes of sudden death such as (eg, subarachnoid or intracerebral hemorrhage, asthma, anaphylaxis, etc) acute hemorrhagic shock (eg, ruptured aortic aneurysm, peptic ulcer, etc) Septic shock (Waterhouse-Friderichsen syndrome).

The Standard Gross Examination of the Heart:

The size, weight, of the heart against the tables of normal weights by age, gender, and body weight.

1. The pericardium should be checked, opened, with exploration of thepericardial cavity.
2. Anatomy of the great arteries should be checked before transecting those 3 cm on top of the aortic and pulmonary valves.
3. The pulmonary veins, superior and inferior vena cava should be checkedand opened.
4. The heart valves: tricuspid, pulmonary, mitral, and aortic valves should be checked for patency to rule out any stenosis or regurgitation
5. The coronary arteries should be checked , the size, shape, position, number, and patency of the coronary ostia should be examined;
6. Make multiple transverse cuts at 3-mm intervals along the course of the main epicardial arteries and branches such as the diagonal and obtuse marginal
7. Heavily calcified coronary arteries can sometimes be opened adequately with sharp scissors. If this is not possible, they should be removed intact, decalcified, and opened transversely;
8. Coronary artery segments containing a metallic stent should be referred intact to labs with facilities for resin embedding and sub sequent processing and sectioning;
9. Coronary artery bypass grafts (saphenous

veins, internal mammary arteries, radial arteries, etc) should be carefully examined with transverse cuts. The proximal and distal anastomoses should be examined with particular care

Laboratory Test:

Progress in autopsy diagnosis of SCD depends also from the use of a rigorous protocol in order not to forget essential biologic samples for histology, toxicological, or molecular studies that are maybe required at some stage in the investigation procedure.

For histology all organs including thymus, thyroid and testes should be taken and preserved. For cytology pericardial, pleural and abdominal fluids, CSF should be taken. For Neuropathology preserve brain in formalinfor 3-4 weeks and perform histopathological and immunohistochemical tests. Pericardial fluid and vitreous humor should be taken for estimation of troponin, electrolytes and glucose estimation. For microbiological examination obtainblood, all recovered fluids and organs with septic lesions and CSF for cultures. Collect blood and heart for mutations screening according to pathology and family disease as part of molecular biology. Molecular investigations of SCD include both detection ofviral genomes in inflammatory cardiomyopathies and gene mutational analysis in both structural and non-structural genetically determined heart diseases.[16 - 18] For these purposes, 10 ML of EDTA blood and 5 g of heart and spleen tissues are either frozen and stored at -80^0C, or alternatively stored at 4^0C for up to 2 weeks. Considering the important role of ion channels and their function or malfunction in several heritable and acquired channelopathies, post-mortem mRNA expression analysis on tissue from pathologic and non-pathologic hearts could be a very useful source to investigate the expression of Na+ and K+ channels.[19]

Conclusion:

Sudden and unexpected cardiac deaths frequently represent one of the most challenging task faced by the forensic pathologist especially for the difficulties encountered in determining the precise cause of death. In detail, SCD sceneinvestigation requires a careful interrogation of witnesses, family members, and physicians of the rescue team who eventually attempted the resuscitation. Recent symptoms before death and medical history must be sought. Although most of these deaths may be ascribed to coronary atherosclerosis, there are many other potential causes of a SCD such as cardiomyopathies, which are more frequently encountered in people aged less than 35 years. 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. In fact recent advances in the field of molecular genetics have expanded our understanding of the aetiology and classification of many of the aforementioned cardiac diseases.

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