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Original Review Article

Molecular Autopsy in Sudden Unexpected Death: A Review

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Abstract

Introduction: The term "molecular autopsy" refers to a technique in forensic medicine that focuses on the use of genetic diagnostic in post-mortem samples in the absence of a definitive diagnosis, therefore classifying the death as sudden unexplained death (SUD). In addition to traditional autopsy, these post-mortem molecular investigations have the ability to identify genetic changes that may have contributed to the disease that resulted in the SUD. **Challenges**: There are multiple reasons for implementation of this procedure, comprising of economic causes or the legal restrictions involved with the sample collection, The storage time and the number of genes analysed, as well as the ethical implications of inheritable results attained after a molecular necropsy. **Medicolegal issues**: Post-mortem examinations within the country are performed as per the minimal prescribed standards, there is void in uniformity of the procedures followed in multiple countries thereby creating hindrance to appropriate rendition in clinical practice. A negative autopsy in the cases of sudden death creates a room of suspicion or dissatisfaction in the minds of the relatives of the deceased about the death of the deceased. In such case molecular autopsy can be considered as critical approach to uncover the pathogenic inheritable condition. **Conclusion:** Ascertaining of the cause of death of the deceased permits to satisfy the family members of deceased to exclude suspicion. It also aids the treating doctors to detect promptly the occurrence in the condition in the relatives of the deceased and performing the preventive measures of causing genetic abnormalities.

1. Introduction

Sudden cardiac death (SCD) is defined as a natural unexpected death without an obvious non-cardiac cause arising within 1 hour of onset of symptom, while in unwitnessed settings the natural unexpected death occurs within 24 hours of last being observed in normal health.[1] Adult sudden fatalities are primarily brought on by terminal ventricular arrhythmias and atherosclerotic coronary artery disease.[2] Aortic dissection, myocarditis, hypertrophic cardiomyopathy, congenital coronary artery anomali-

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es, such as the left coronary artery's anomalous origin from the right sinus of Valsalva, and congenital coronary artery anomalies can all be used to explain many sudden deaths in young people.[3] Although there were no aberrant autopsy results, children who had previously been healthy account for roughly half of all abrupt fatalities. These fatalities are written off as cases of SUDS (sudden unexplained death syndrome).[4] Because potentially fatal arrhythmogenic illnesses including long QT syndrome (LQTS), Brugada syndrome, and Wolf-Parkinson-White syndrome leave no evidence at autopsy examination, forensic pathologists could only surmise that a fatal arrhythmia might be at the core of SUDS in the past. Molecular autopsy can be of immense help in such cases.[5]

The term "molecular autopsy" refers to a technique in forensic medicine that focuses on the use of genetic diagnostic in post-mortem samples in the absence of a definitive diagnosis, therefore classifying the death as sudden unexplained death (SUD).[3] In addition to traditional autopsy, these post-mortem molecular investigations have the ability to identify genetic changes that may have contributed to the disease that resulted in the SUD. Nearly 5% of all performed autopsies result in a comprehensive forensic autopsy of a deceased individual being non-conclusive (also known as a negative autopsy). [4] The incidence of sudden cardiac death is 40–100 per 100,000 person-years worldwide, accounting for 15–20% of all deaths.[6] After a thorough autopsy examination, almost 30% of SCD cases in young people still have an undetermined cause of death. [7, 8]

When an inherited arrhythmogenic Syndrome (IAS) is suspected, an underutilised tool from the current forensic field i.e. genetic testing is used. There is possibility that the family members are carrying pathogenic genetic modifications because most illnesses are inherited in nature, increasing the likelihood that they may develop the same malignant arrhythmogenic entity. Considering all available information, identifying the genetic change is essential for diagnosis, assisting in determining the most likely reason for an untimely death, as well as for preventing arrhythmogenic events in the families of the deceased. Early detection of genetic carriers who are at risk permits the implementation of preventive, personalised therapy. [9] Genetic analysis can now be done more quickly and affordably due to next-generation sequencing (NGS) technologies. In nearly 20% of instances, notably in the young population. [8,10–16]A clear pathogenic genetic change is found during a molecular autopsy utilising next-generation sequencing (NGS).

However, the majority of SCD cases still have a negative or inconclusive genetic diagnosis, primarily because uncommon variations found in known genes related with IAS are still categorised as having an unclear role or as having unknown significance. Despite this, the most recent clinical guidelines advise molecular autopsy in SUD cases with a highly suspected IAS cause of death. [9, 17, 18]

2. Conditions involving risk of sudden death in cardiac diseases with normal heart

In the majority of affluent nations, cardiovascular illnesses are responsible for nearly 90% of all cases of sudden death.[19] It has both coronary and non-coronary causes, with coronary factors being the predominant cause in most instances. Embolization, dissecting aneurysms, arteritis, and congenital anomalies are only a few of the non-atherosclerotic causes. Non-coronary causes include congenital heart defects, hypertensive heart conditions, illnesses of the heart valves, myocarditis, and other conditions.[19]Postmortem genetic testing becomes essential to determine the cause of death in genetic cardiac illnesses, such as channelopathies and cardiomyopathies, which are evaluated if the first forensic investigation cannot determine the cause of death.[20] LQTS, SQTS, CPVT, and BrS are all considered to be channelopathies. Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, arrhythmogenic cardiomyopathy (ACM), restrictive cardiomyopathy, and specific and undefined cardiomyopathy are all included in the cardiomyopathy group. [21, 22]

Channelopathies are diseases brought on by genetic changes to the proteins or genes that code for the cardiac ion channels. No abnormality of heart structural anatomy is detected in cardiac channelopathies, but sudden mortality results from electrical anomalies including ventricular fibrillation or polymorphic ventricular tachycardia.[23, 24] About 10–25% of adult SUD and up to a third of SUD in babies and adolescents are caused by cardiovascular channelopathies. [22]

Long QT syndrome (LQTS): The term "LQTS" refers to a hereditary ion channel issue and excludes acquired causes of QT prolonging include heart conditions, medications, hypokalemia, and stroke, which are referred to as "acquired LQTS." This

syndrome is characterized by prolonged repolarization. The heart-rate-corrected QT interval (QTc) of greater than or equal to 480 ms can be used to diagnose it, as can the Schwartz criteria, which comprise the clinical history, family history, and 12-lead ECG. [24,25]

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is more common in males and children between the ages of 4 and 12 years old. It is caused by exercise, especially swimming and manifest as syncope or cardiac arrest. It is less frequent than LQTS, but it is more severe because the postmortem CPVT results in cases of sudden arrhythmic death syndrome (SADS) are almost as often as LQTS. RYR2 and CASQ2 mutations are the most often found harmful mutations. In the resting ECG, CPVT has no abnormalities.[24,25] Hypertrophic cardiomyopathy (HCM) is one of the most prevalent autosomal dominant hereditary diseases among cardiomyopathies. It is a significant contributor to SCD in kids and athletes. It can be recognized by the asymmetrical hypertrophy of the ventricular septum, thickening of the ventricular wall, increased heart weight, and narrowed ventricular cavity. Both familial and sporadic pathogenic mutations have been linked to HCM. The third most frequent cause of SCD, accounting for 5.9–6.2% of all SCDs, is hereditary cardiomyopathy. [26]

Numerous epileptic diseases have underlying genetic abnormalities that enhance the incidence of SUDEP, such as familial focal epilepsy linked to the DEPDC5 gene[27], Dravet syndrome with a genetic variant in SCN1A, early infantile encephalopathy with a genetic variant in SCN8A, and early infantile encephalopathy. The importance of genetic analysis in SUDEP and the potential preventative measure for high-risk living relatives is highlighted by knowledge of these underlying genetics. [28] Metabolic disorders: SUDI is a term used to refer to all sudden unexpected deaths that occur between the ages of birth and up to 12 months, including occurrences of SIDS. [29]

3. Samples for genetic testing

Postmortem genetic testing for SIDS refers to cases where the cause of death can't be determined after an in-depth autopsy .[30] Blood is currently considered the optimal specimen for molecular genetics studies.[31] Currently, there are several technical platforms for genetic analysis, and each platform has its own specific protocols. Therefore, samples must meet the specific specifications of each system before an NGS study can be performed. It is recommended to retain at least 5 – 10 ml of blood and store it in Ethylene, Diamine Tetra Acid (EDTA) tube. Collection of blood less than 48 hours after the death is the best time to avoid progressive DNA degradation, which would prevent a proper NGS.

Still, tubes can be retained during first 48 hrs after collection even If no cold temperature is available for storage at room temperature. If the sample needs to be stored more than 2 days for DNA profiling, it's recommended to store tubes at 4*C (2 – 4 weeks). [32] Preservation at -20*C is an option available if DNA analysis will be performed after more than 2 – 4 weeks in order to preserve DNA integrity.[33] But storage of EDTA tube at freezing temperature to be avoided as there is possibility of damage to DNA structure. Similarly, 5 g of heart, liver, muscle or spleen tissue can also be preserved considering the fact that that testing to be done immediately. If the timing of the analysis is delayed, then the tissue can be placed in liquid nitrogen for one minute and then freezed at -20 to -80 * C till the DNA extraction is being done. Defrosting of the tissue is needed before DNA extraction of such tissue so as to prevent breaking of DNA sequence.

In routine protocols performing necropsy, formalin fixed paraffin embedded tissue samples are stored. But it is not recommended as the DNA extracted is highly variable in these tissues and quality or quantity of the DNA extracted is less for carrying out NGS study. [34]There is destruction of DNA during the process of paraffin embedding ultimately causes faults in the sequences. In spite of this there are studies where DNA can be extracted from FFPE tissues that is well suited for DNA sequencing. [35 – 38]

4. Recommendations

The main considerations affiliated to molecular necropsy were all cases of SCD in those under 40 times of age, the collection and acceptable storehouse of samples for the study, communication with the family, and a multidisciplinary approach that includes genetic counselling.

A comprehensive forensic necropsy should include a protocol for the collection and storehouse of tissue suitable for molecular autopsy. In depth familial history is essential to ascertain the cause of death in cases of SUD. If genetic testing is not possible then genetic testing of first-degree relatives needs to be done.[33]

5. Challenges for molecular necropsy

Eventually, despite the fact that molecular necropsy is extensively recommended, it isn't included in forensic protocols in many countries across the globe. There are multiple reasons for implementation of this procedure, comprising of economic causes or the legal restrictions involved with the sample collection, the storage time and the number of genes analysed, as well as the ethical implication of inheritable results attained after a molecular necropsy. Also due to the progressive number of rare variants which lead to obstruse role after a molecular necropsy, ultimately leading to large number of SUD cases remains unsettled. Hence it very essential to develop guidelines concentrated on variant interpretation in forensic Medicine.[39]

6. Medico-legal issues

Despite recommended in current guidelines, performing molecular necropsy generally depends on the authorization given by the competent public authorities.[40] Even if this authorization is granted, consent for the analysis isn't generally needed.[41] But, in certain countries and under specific conditions, consent of relatives can be still asked for authorization to preserve any tissue from the dead body. When an IAS is suspected, postmortem genetic testing should be considered be of public health significance, since these diseases are transmitted in a autosomal dominant fashion.[42] First degree relative, who are directly exposed to this threat, should be precisely counselled, thereby balancing health drawbacks.[43] It is advisable to provide information to the person who providing consent regarding reason and procedure of carrying out genetic study as well as the benefits for family members, and especially newborns.[31, 41]

In our country, foundation of multidisciplinary referral units at various levels in the postmortem opinion of SCD cases and treatment of their cousins with an implicit IAS is extensively recognised in spite of not ultimately enforced.[44] Currently there are great variations present in avoidance of SCD at level of judiciary and healthcare due to variation in the recognition of forensic skills as well as variances in the forensic organizations within the country.[45] In addition, even though post-mortem examinations with in the country are performed as per the minimal prescribed standards, there is void in uniformity of the procedures followed in multiple countries thereby creating hindrance to appropriate rendition in clinical practice.

7. Conclusion

A negative autopsy in the cases of sudden death creates a room of suspicion or dissatisfaction in the minds of the relatives of the deceased about the death of the deceased. In such case molecular autopsy can be considered as critical approach to uncover the pathogenic inheritable condition. Ascertaining of the cause of death of the deceased permits to satisfy the family members of deceased to exclude suspicion. It also aids the treating doctors to detect promptly the occurrence in the condition in the relatives of the deceased and performing the preventive measures of causing genetic abnormalities.

In these cases, the transition into clinical practice should be done with caution, and a close multidisciplinary collaboration including fore nsic experts, pathologists, cardiologists, pediatric cardiologists, and specialized geneticists is pivotal.

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