MOLECULAR AUTOPsy: EVALUATION OF SUDDEN UNEXPECTED DEATH CASES IN TERMS OF “KCnQ1” GENETIC VARIATION

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Abstract

Background: Deaths occurring without a known disease and/or a known cause, deaths with non-lethal diseases are interpreted as sudden-unexpected-suspected deaths. Autopsy should always required to evaluate the cause of death. Some of the cases can be termed as negative autopsy since the cause of death cannot be determined. This is one of the main interests of the future forensics. Molecular autopsies are one of the main practices of to reduce the negative autopsy ratios. Thus, post-mortem KCNQ1 genetic variation tests are done in sudden unexpected death cases.

Material and methods: In this study 0 – 50 years old sudden-unexpected deaths autopsy cases were handled. Samples taken from cases were evaluated and “KCNQ1” genetic variation tests were done in our Department.

Results: This study included 47 cases of 42 sudden unexpected death cases (0 – 50 age group) and 5 control group. 15 cases were between 40 – 50 age group and number of cases were increasing with age. 29 of cases (% 69) were male. Evaluation of body-mass index of cases were done and normal weighted cases were the most common with 21 cases (% 50). According to death locations; 17 cases had died (% 45,9) at home. Death location records of 5 cases couldn’t be found. Pathological examinations of all cases were done. We had identified fibrosis and fatty change appearances in SA node of 9 cases (% 21,4) and AV node of 13 cases (% 30,9) especially in conduction tissue examinations. As the result of KCNQ1 genetic analysis of cases, we identified sequence variations in 1638th nucleotid of exon 13 and 1986th nucleotid of exon 16.

Conclusion: Cases with conduction system pathology and sequence variations of KCNQ1 genetic analysis shows that we are in need of these tests among routine practice to reduce negative autopsy ratios.

Key words: KCNQ1, molecular autopsy, sudden unexpected death, conduction system, negative autopsy.

Introduction

In Forensic Medicine, deaths are divided into two groups such as natural and unnatural deaths. Natural deaths usually come in the form of Sudden Unexpected Deaths (SUD). World Health Organisation (WHO) defines sudden deaths as follows; “deaths occurring within 24 hours of the onset of symptoms”. If a person without any illness died of an unexplained reason or was found dead soon or a person with a known disease died but that this disease do not have a severe clinic which can cause death; these are all evaluated as unexpected death. Autopsies are needed to understand the cause of death in these types of cases.1,2 Autopsy; is an important application in investigating the cause of death. Toxicological analyzes, chemical, microbiological, radiological and serological examinations, crime scene investigation, medical history retrieval, macroscopic examination, histological examination constitute parts of the autopsy. Despite these studies, causes of the death cannot be found in some cases and these cases are defined as negative autopsy. It is quite difficult to give a numerical ratio for negative autopsy. Studies have shown that cardiovascular system diseases are the most common causes of sudden unexpected deaths (SUD) (with country-to-country variation). The majority of sudden deaths are the result of heart diseases in the western world. Approximately 300,000 deaths occur each year in the United States, with an average of 20% of all deaths occurring as sudden cardiac deaths.3,4
Genetic diseases are very important cause of non-ischemic sudden cardiac death (SCD). Significant progress has been made in recent decades in the genetic and clinical basis of sudden cardiac death. Genetic causes of sudden cardiac deaths include; myocardial diseases such as hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia and channelopathies such as long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome and short QT syndrome. Channelopathy cases are usually sudden deaths below 35 years and there are no known health problems in the first place. Macroscopic and microscopic examinations are insufficient to diagnose. In such cases, gene analysis, namely molecular autopsy, is used. European Cardiovascular Pathology Association standards should be established in our country especially in cardiac pathologies.5,7

In a study of Madea et al., it was reported that even as a result of further studies, the cause of death is still not detected in some of the cases, the cause of death may remain undetectable in the majority of children and young adult cases, autopsy is negative in 30% of young adult sudden cardiac deaths and there are publications about the genetic causes involved in these cases. Rodriguez-Calvo et al., classified genetic causes of cardiac deaths as follows; channelopathies (long QT syndrome, catecholaminergic polymorphic ventricular tachycardias, Brugada syndrome, short QT syndrome) and myocardial diseases (hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia). Cardiac findings are of great importance for families in terms of prevention and treatment if they are detected during health screening and genetic counseling.5,8 Therefore; cases of sudden unexpected death, which were autopsied and whose causes of death were not detected despite further studies, were evaluated in terms of genetic variation of "KCNQ1".

As a result of rapid development of DNA technology; increasingly faster and easier obtainment, working with smaller materials, increasingly accurate and reliable results, improved automated processing possibilities, the emergence of single use kits; the use of the obtained DNA evidence in the forensic science field has spread rapidly and the usage purpose has been diversified.5,10

Molecular studies should be performed in cases of genetic-related cardiac death. The definite diagnosis in these cases is the demonstration of mutant genes by DNA analysis to be performed. However, since it is a costly method in our country, it is not yet used in routine practice. In our country, especially in cases of sudden death with the label of forensic cases, the standards set by the European Cardiovascular Pathology Association should be established in evaluating cardiac pathologies in autopsies. It is important to contribute to public health by making clinical comparisons in the light of the data obtained from the autopsies. European Cardiovascular Pathology Association recommends molecular genetic testing in autopsy protocol for sudden cardiac death.5,7 Sudden deaths which have a separate importance for forensic medicine will bring with it a lot of suspicion. Special efforts may be needed to determine the cause of the actual death and to ensure that justice is fully and accurately carried out in these cases. In order to accurately assess the forensic dimension of the incident, it is very important to establish the true cause of death in cases of suspicious sudden death. Especially in the case of sudden deaths, as mentioned above, postmortem genetic studies can also prevent the possible sudden death of one of the deceased's family.

Materials and methods

There were 42 cases of sudden unexpected death that were autopsied and 5 death cases were selected as the control group from Forensic Medicine Institution Adana Group Presidency. A total of 47 cases were selected without sex discrimination. For this study, necessary permissions were taken from Ethics Committee of the University of Cukurova, Forensic Medicine Institution Education Commission and Adana Group Presidency. The age range for the study was set between 0 - 50 and blood samples of EDTA were taken to perform 'KCNQ1' genetic analysis from the cases included in the study. Blood samples until analysis were stored at -200°C in Cukurova University Faculty of Medicine Forensic Medicine Department Forensic Genetics Laboratory and genetic analysis was performed afterwards in the direction of the primers given in the table (Table 1).

In the light of the existing medical and judicial investigation documents and autopsy data of the cases in which the autopsies were carried out and included in the study in the Forensic Medicine Institution Adana Group Presidency; comparative tables were created by examining age, gender, body
mass index, death site and cardiac (myocard, coronary artery, communication system) pathologies (if present in the file).

'KCNQ1' genetic analysis was carried out at Çukurova University Faculty of Medicine Forensic Medicine Department Forensic Genetics Laboratory. The samples taken in a vacuum tube containing EDTA from the cases in which the autopsy was performed and the date, time and case number were noted were stored under appropriate conditions until the analysis was carried out. Genetic analyzes were done in the direction of the primers in the table. As a control group; 5 cases with a known cause of death were selected.

Table 1: KCNQ1 primers (F: Forward, R: Reverse)\(^{11}\)

| Exon | Primers | PCR fragment length |
|------|---------|---------------------|
| 1    | F:CTCGCCTTCGCTGCAGCTC  
R:GCGCGGGGCTAGGAACCTACC  
F:CGCCCGGCCCCCCACAGTTCG  
R:CAGAGCTCCCCACACCCAGG | 334 |
| 2    | F:ATGGGCCAGAGGCGCGATGGCTGAC  
R:ATCCAGCCATGCCCTCAGATGC | 165 |
| 3    | F: TCCTTAGGGACCTCCATCTG  
R:GCTGTTCTAGGCTGTTCTCTT | 343 |
| 4    | F:CTCTTCCCTGGGGCTGCTGC  
R:TGGGGAGAGCTTGTGGCACG  
F:TCAGCCCTCCTCCCTCAG | 170 |
| 5    | F:TCAGCCCCACACCATCCTCCCTC  
R:CTGGGGCCCTACCTCTTACC | 154 |
| 6    | F:TCCTTGGGACAGGACACTGTGTGTG  
R:GTCTTCTGCCACACTCTCAAGCC | 238 |
| 7    | F:TGGCTGACACACTGTCCCTCT  
R:CACCAGGACCACAGCCCTCCAAC | 195 |
| 8    | F:GTCTTGGAGATGTGGTCTTGGA  
R:AAAGTGGACCAATGTGAGACG | 191 |
| 9    | F: TGGCTCAGAGGTGCAGGACG  
R:GACACCGGCTGTACCAAGCCAA | 280 |
| 10   | F:GCCTGAGGGACAGGTGTCCAC  
R:CAACTGCCTGAGGGTTCTCTT | 216 |
| 11   | F:CTGTCACCTACATCTCCTCCTT  
R:TGGATCAGCGCTCCCTCCAG | 195 |
| 12   | F:TGGCCACTCAACAATCCTCCT  
R:GCCTTGGACACCTCCACTA | 222 |
| 13   | F:CACTGCGCTCAGGTAGGACC  
R:GTGAGAGAAGGGGCTGTTT | 304 |
| 14   | F: TCTGAATCTAGGGAGAGAC  
R:AGTGAACCGCAGGCCCCTAG | 293 |
| 15   | F:GGGCTGGATGGGCTGTTTTA  
R:GCAGGAGCTCAGCCCTACA | 186 |
| 16   | F: GCTCTTCTCCTGGGGCCCTTT  
R: CAGCATGCACTTGAGAC | 470 |
Results

Forty-seven autopsy cases were included, including 42 cases with sudden-unexpected deaths and 5 cases as control group. Causes of death in the control group were as follows; hanging, drowning, traffic accidents, firearm injuries and sharp object injury.

In our study, the age range was determined as 0 - 50 and the samples were collected in this context. The youngest case was 7 months old and the oldest case was 49 years old. Age ranges were organized in decades. The sudden-unexpected death was mostly observed in the age range of 41 - 50 (5th decade) (Table 2).

Table 2: Distribution of Cases According to Age

| Age   | n   |
|-------|-----|
| 0-10  | 4 (% 9,5) |
| 11-20 | 7 (% 16,6) |
| 21-30 | 8 (% 19,0) |
| 31-40 | 8 (% 19,0) |
| 41.50 | 15 (% 35,7) |

Twenty-nine of the cases (69%) were male and 13 (31%) were female. The mean age was 32 for male cases and 34 for female cases.

Evaluation of body-mass index of cases were done with World Health Organization Body-Mass index Classification. Normal weighted cases were the most common with 21 cases (% 50). Obesity-risk evaluation couldn’t be done because our cases were not chosen randomly among all cases. All cases were distributed according to death locations. 17 cases had died (% 45,9) at home. Death location records of 5 cases couldn’t be found. Pathological examinations of all cases were done (Myocardium-Coronary Artery and Cardiac Conduction System). Hematoxylin eosin staining method used during pathological examinations. We had identified fibrosis and fatty change appearances in SA node of 9 cases (% 21,4) and AV node of 13 cases (% 30,9) especially in conduction tissue examinations. Randomly selected 5 cardiac pathologic findings are seen in table 3.

Table 3: Cardiac pathology features of the control group

| Sr. No | Coronary artery | Myocard |
|--------|-----------------|---------|
| 1      | Normal          | Normal  |
| 2      | Lumen is mildly constrictive in atheromatous plaques | Mildly perivascular and interstitial fibrosis |
| 3      | Lumen is mildly constrictive in atheromatous plaques | Normal |
| 4      | Lumen is moderately constrictive in atheromatous plaques | Minimal scarce areas |
| 5      | Normal          | Interstitial severe congestion in myocardial tissue |

KCNQ1 Gene Sequence Analysis Results

Sequence variations

In the KCNQ1 gene sequence analysis with 42 samples, two different polymorphisms were found in exon 13 and exon 16, which do not cause amino acid changes. As a result of the G = A polymorphism at nucleotide 1638 of exon 13; TCG codon is transformed into TC A codon. Serine aminoacid can be produced with both codons. This variation was detected at 1, 5, 11, 13, 19, 24, 26 and 37 numbered samples. One of the 8 samples, in which polymorphism was detected in exon 13, was homozygous (AA) and the others were heterozygous (GA). Another polymorphism that does not lead to amino acid changes is the C=T substitution at nucleotide position 1986 in exon 16. The TAC codon at this point translates into the TAT codon, but there is no problem in product synthesis since both codons form the tyrosine amino acid. This polymorphic variation identified in 2 out of 42 samples was found to be heterozygous. The sequence variations identified in the KCNQ1 gene are shown in Table 4 and Figure 1-2.

Table 4: Sequence variations identified in the KCNQ1 gene (n: number of samples)

| Gene | Exon | Nucleotides | Aminoacid | %/(n:42) |
|------|------|-------------|-----------|----------|
| KCNQ1| Exon 13 | G □ A | Ser546Ser | 10.7 |
|      | Exon 16 | C □ T | Tyr662Tyr | 2.4 |
Discussion

The genetic basis of cardiac diseases is based on the mutation of genes involved in the coding of structural heart proteins. Due to the quantitative and functional problems inherent in the protein structure and function of this genetic basis, wide spectrum of cardiovascular diseases occur. Sudden cardiac death occurs with many entities that are defined as the end result of genetic features coexisting with environmental factors. Gene mutations are found in the basis of congenital cardiac diseases as well as many acquired cardiovascular diseases such as cardiomyopathy and atherosclerosis. Entities causing sudden cardiac death, can be inherited autosomal dominantly, autosomal recessively, by X chromosome or mitochondrial. Missense mutations, which are point mutations in genes responsible for the coding of cardiac proteins, do not alter protein levels, but may at least modulate protein structure, leading to functional disorders. Nonsense mutations cause translation to stop at the stop codon. Mutations in both the intron and exon regions cause splicing errors. Various diseases can arise due to the occurrence of such mutations at different levels and localizations.\textsuperscript{12,13}

Long QT syndrome is a disease characterized by genetic heritability, mutations in the potassium or sodium channel genes that are characterized by prolonged QT interval, and can cause sudden cardiac death. The polymorphism or mutation found on the basis of genetics may not be the cause of death itself, but is a predisposing factor in situations such as physical stress, medication. Other causes of death should be excluded and the diagnosis should be clarified in this way before mutation can be accepted as the rational cause of death. Syncope associated with ventricular tachycardia, usually of the \textit{torsades de pointes} type, is a common symptom. When rhythm disturbance is degenerated in ventricular fibrillation, SCD is observed. According to international LQTS records, SCD occurs in 4\% of patients. No signs of LQTS are seen in 50\% of mutation carriers. In a study of Garson et al., with 287 pediatric patient who had LQTS, it was reported that 8\% of the patients died at the end of the 5-year follow-up period. Children with long QT syndrome have a higher likelihood of SCD compared with adults and recurrent syncope is more common in adults.\textsuperscript{14,15}

Until recently 7 different LQTS genes encoding the ion channels (or subunits) (LQT1-3,5-7) and binding proteins (LQT4) and located on chromosomes 3, 4, 7, 11, 17 and 21 were defined in the long QT syndrome but now there are ten congenital long QT syndromes. While the seven is autosomal dominant and two are autosomal recessive, the inheritance type of one is not yet known. Mutations are most common in the KCNQ1 gene.\textsuperscript{5}

Considering symptomatic patients as the result of analysis of more than 780 LQT gene carrier, the first cardiac event occurred in 50\% of patients until the age of 12 and in 90\% until the age of 40. Multivariate analyzes defined congenital deafness, syncope story, female gender, documented \textit{torsades de pointes} type tachycardia / ventricular fibrillation, age at first symptom and affected gene as independent risk factors for SCD. QT duration is related with syncope and SCD independent of these.\textsuperscript{16,17}
Within the framework of mutation analysis, gene regions related to poor disease progression have rarely been shown. In a study, more frequent and earlier, more severe events have been detected in patients with HERG mutations (LQT2) in the pore region of the potassium channel, namely IKr when compared with patients who had mutations at other gene regions. In another study, a mutation in the C-terminal region of the KCNQ1 gene (LQT1) was shown to be associated with a more mild illness course, and an increase in the prevalence of the symptomatic gene carrier was detected when these mutations were in the transmembranous region of the channel.

Table 5: 'KCNQ1' mutations / sequence variations detected in studies

| Gene    | Area     | Nucleotide Change | Aminoacid Change |
|---------|----------|-------------------|------------------|
| KCNQ1   | Intron 3 | 604 + 34A> C     |                  |
| KCNQ1   | Exon 8   | 1110G>A          | A370A            |
| KCNQ1   | Exon 11  | 1455C>T          | F485F            |
| KCNQ1   | Exon 16  | 1860C>T          | H620H            |
| KCNQ1   | Exon 16  | 1944C>T          | V648V            |
| KCNQ1   | Exon 16  | 1986C>T          | Y662Y            |
| KCNQ1   | Exon 13  | G>A              | Ser546Ser        |
| KCNQ1   | Intron 12| A>T              | IVS12-7 A>T      |
| KCNQ1   | Intron 12| T>C              | IVS12+14 T>C     |
| KCNQ1   | Intron 12| T>C              | IVS12+35 T>C     |
| KCNQ1   | Intron 14| T>C              | IVS 14+43 T>C    |
| KCNQ1   | Intron 16| G>A              | IVS16+5 G>A      |
| KCNQ1   | Intron 16| G>A              | IVS16+11 G>A     |
| KCNQ1   | Intron 16| G>A              | IVS16+18 G>A     |

Table 6: 'KCNQ1' polymorphisms detected in the studies

| Gene    | Area     | Nucleotide Change | Aminoacid Change |
|---------|----------|-------------------|------------------|
| KCNQ1   | Intron 11| 1514 + 18C>T     |                  |
| KCNQ1   | Exon 2   | 435C>T           | I145I            |
| KCNQ1   | Exon 10  | 1343C>G          | P448R            |
| KCNQ1   | Intron 12| 1590+31A>T       |                  |
| KCNQ1   | Exon 13  | 1638G>A          | S546S            |
| KCNQ1   | Exon 16  | 1927G>A          | G643S            |
| KCNQ1   | Intron 13| 1685+36G>A       |                  |
In our study, as detailed in the findings section, sequence variations were detected at 13th exon 1638th nucleotide position and 16th exon 1986th nucleotide position as a result of our KCNQ1 genetic analysis. As a result of the G = A polymorphism at nucleotide 1638 of exon 13; TCG codon is transformed into TCA codon. Serine amino acid can be produced with both codons. Another polymorphism that does not lead to amino acid changes is the C=T substitution at nucleotide position 1986 in exon 16. The TAC codon at this point translates into the TAT codon, but there is no problem in product synthesis since both codons form the tyrosine amino acid. Except for cases with sequence variations within our study, cases consistent with literature such as acute coronary thrombosis, giant cell myocarditis, and hypertrophic cardiomyopathy have been encountered. No sequence variation was observed in these cases. When the cases with sequence variation were compared with histo-pathological findings; morphological pathologies seen in publications are seen. Sequence variations detected in our study have been interpreted as mutations in many studies and in others it is defined as polymorphism (Table 5-6). However, in order to be able to make a realistic interpretation about the mutation, we believe that larger patient series should be used and that richer primers should be used. The results of our study and other mentioned studies, shows that autopsy should not be terminated before making molecular analysis in cases with negative autopsy, especially in cases with sudden unexpected death. It is thought that molecular studies should be performed even in cases where the cause of death can be said.

In sudden cardiac deaths, measures against preventable causes should be taken and health screening should be done. Detailed and definitive cardiac findings, health screening and genetic counseling will be important for families in terms of prevention and treatment at risk. In order to develop these strategies, the incidences of incidence, causes and sudden death must be well known, and this is often achieved through judicial investigations.

Conclusion

Our work is a pioneer in our country and it has to be expanded and replicated more broadly (in terms of budget and number of genes). Sequence variations detected in our study have been accepted as mutations in many studies. However, in order to be able to make a realistic interpretation about the mutation, we believe that larger series should be used and that richer primers should be used. Locus studies should be performed in larger series and with multiple parameters, sequence variations and mutation presence must be investigated. We believe that the profile of genetic pathologies should be uncovered in sudden death cases in our country, primarily within our region. Although molecular autopsy practices are not among the routine autopsy applications because of high cost, DNA sequence analysis is needed to identify mutations. First, sequence analysis should be performed on a large number of samples to determine mutations and frequency. After this initial step, rapid screening methods such as real-time PCR or SNaPShot multiplex PCR allow to detect mutations with faster, more practical methods without sequence analysis.

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