

# Autopsy in sudden cardiac deaths

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## Abstract

Sudden cardiac death is described as death that occur within the 1st hour of the onset of the symptoms or death within the 24 hours of the onset of symptoms in unwitnessed deaths. Studies conducted in our country reveal that cardiovascular originated deaths are the most frequent, with a rate of 20% of all deaths. Although sudden deaths in young people are rare, it is important to perform a detailed autopsy and other required procedures. The etiology of the sudden death is hard to determine for the forensic doctors and in 5-1% of all cases no certain cause is determined despite the macroscopic, toxicologic and histopathologic evaluations. European Society of Cardiovascular Pathology also recommends performing molecular autopsy when the certain cardiac cause cannot be determined morphological. This review aims to offer genetical consulting to the family members of the sudden cardiac death cases and clarify the etiology of death via genetical evaluation if the macroscopic, toxicologic and histopathologic examinations fail to explain the cause of the sudden cardiac death especially in children and young adults. The most important problems in our country are the lack of multidisciplinary approach and standardized management methods. In our country molecular autopsy is only considered in rare and selected cases, but if these genetical evaluations were made more applicable and accessible via interdepartmental agreements and the application of new genetical diagnosis methods, it would be possible to develop standardized methods for the case selection of molecular autopsies in the future.

**Keywords:** Molecular Autopsy; Sudden Cardiac Death; Negative Sudden Death Autopsy.

Sudden death is defined as death which occur within the 24 hours of the onset of symptoms by the WHO (1,2). Sudden cardiac death is an unexpected death due to cardiac causes which occurs within the first hour of the onset of symptoms (2,3). These descriptions are insufficient to describe the condition when death occurs in the absence of any witnesses such as during sleep. Therefore, sudden cardiac death is described as death that occur within the 1st hour of the onset of the symptoms or death within the 24 hours of the onset of symptoms in unwitnessed deaths. Sudden Arrhythmic Death Syndrome (SADS) includes cardiac originated deaths in which macroscopic and microscopic examinations of the heart are normal and toxicological autopsy result is not conclusive. In infants it is called as "Sudden Infant Death Syndrome" (SIDS) (4).

Studies conducted in our country reveal that cardiovascular originated deaths are the most frequent, with a rate of 20% of all deaths (2).

It is reported that the sudden cardiac death is the cause of 15-20% of all the natural originated deaths in the USA and the ischemic heart disease is reported to be the most common cause of the sudden cardiac deaths in the Western countries (1).

Sudden cardiac death incidences 1.4/100000/year in women, 6.68/100000/year in men, ranging between 0.46-3.7/100000/year and this rate tends to increase in older age (4,5). Sudden cardiac death is reported to be 1.3/100000/year among the 1-35 year old people and 3.2/100000/year among the 31-35 year old people in Australia and New Zealand, 2.8/100000/year in Denmark, 1.3-8.5/100000/year among the young and 1.7/100000/year among the 30-34 year old people in the USA (6,7).

The etiology of the sudden death is hard to determine for the forensic doctors and in 5-1% of all cases no certain cause is determined despite the macroscopic, toxicologic and histopathologic evaluations (2). In 3-53% of the young aged sudden cardiac death cases, no morphological abnormality could be detected during the autopsy (7). Especially in sudden cardiac deaths of the young aged people, this rate tends to be higher (2). It is called "negative autopsy" when no certain cause of death can be identified (2,7,8).

In 2/3 of all cardiac diseases the first clinical finding is sudden cardiac death (4). Although sudden deaths in young people are rare, it is important to perform a detailed autopsy and other required procedures (histopathological,

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immunopathological, and genetic evaluation) for the family and the society to understand and rationalize the death and reduce the possible anxiety about future among the family members. European Society of Cardiology recommended the postmortem genetic evaluation of the related genes, in sudden cardiac death cases when hereditary channelopathy or cardiomyopathy suspicion is present, as well as the long term follow-up of family members and starting their treatment if necessary, thus preventing the future sudden cardiac deaths (5). With autopsy and proper evaluations following the autopsy, not only would it be possible to determine the cause of death, but also it would be possible to provide the data which is crucial for the developments of the state health and the statistical analyses. It would also be possible to inform the relatives of the victim for possible future health problems (5,9). This review aims to offer genetical consulting to the family members of the sudden cardiac death cases and clarify the etiology of death via genetical evaluation if the macroscopic, toxicologic and histopathologic examinations fail to explain the cause of the sudden cardiac death especially in children and young adults. It also aims to create awareness in physicians who perform the autopsies about the importance of molecular autopsy in sudden cardiac deaths in young people. Revealing diseases which cause sudden cardiac death which is a serious public health problem, will help to develop screen tests for early detection of this diseases in individuals at risk in society.

#### **Sudden cardiac death causes in cardiovascular diseases**

Coronary atherosclerosis, various complications of coronary atheromatosis (e.g. ulcerated atheroma plaque, hemorrhage, coronary thrombosis), coronary occlusion or obstruction, myocardial infarction, complications of myocardial infarction (e.g. myocardial rupture, mural thrombus, pericarditis, myocardial fibrosis, cardiac aneurysm), cardiomyopathies, myocarditis, congenital abnormalities of the coronary artery, aortic valve disease, congenital heart disease can lead to sudden cardiac death (1). The most common cause of the sudden cardiac death tends to vary with age. In cases who are 40 years old or younger, the most common causes of the sudden cardiac deaths are reported to be hypertrophic cardiomyopathy (HCM), left ventricle hypertrophy, congenital heart disease, rheumatic heart disease and myocarditis, while in cases who are older than 40 years the most common cause of sudden cardiac deaths is reported to be the atherosclerotic heart disease (2,8). Studies about sudden cardiac deaths report that 80-60% of the death cause is coronary artery disease with being the most common detectable cause in cases who are 35 years or older and the end of autopsy diagnosis in 75% of all cases (8,10). Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in young adults and athletes while sudden arrhythmic death syndrome which include idiopathic left ventricle hypertrophy, arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in athletes although right ventricle displasia was reported to be the most common cause of sudden cardiac death in athletes in the North Italy (11,12). In their review, Sahin et al. reported

that the causes of sudden cardiac death were able to be determined in 70% cases who were between 0-40 years old and these included 70-65% structural heart disease, 25% coronary artery disease and 10-5% myocarditis. Among the 30% sudden cardiac death cases in whom the certain cause of death was not detectable, 60-50% of them were reported to be resulted from arrhythmogenic disorders (8). In their study which evaluated the sudden cardiac deaths of 490 cases who were aged 1-35 years old, Bagnall et al. reported that the cause of death was detectable in 60% cases which included 24% atherosclerotic disease, 16% cardiomyopathy, 7% myocarditis and in more than 50% cases a cardiac pathology was present (13). Structural cardiac abnormalities that are related to sudden cardiac deaths include congenital heart diseases, cardiomyopathies, primary cardiac rhythm and conduction disorders, channelopathies (long QT syndrome, Brugada syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), electrophysiological disorders (Wolff Parkinson White Syndrome, Long QT syndrome) while other causes include problems of the autonomic nervous system, drugs and metabolic disorders (cocaine, heroine, hypopotassemia, etc.), mechanical issues and commotio cordis (2,7,8). It is also reported that when the cause of the sudden cardiac death is undetectable with a negative autopsy, postmortem genetical evaluation or cardiologic examination of the first degree relatives provide the clinical/molecular cause of death in 1/3 of the cases (14). Bagnall et al. reported that genetical evaluation showed that in at least 27% of the sudden cardiac death cases with undetectable cause, a cardiac gene mutation was present (6).

#### **Risk factors**

Risk factors related to sudden cardiac death are the same with that of the atherosclerotic coronary artery disease and death incidence has been reported to be higher especially in the elderly and the male gender. Risk factors include hyperlipidemia, hypertension, smoking, opioid-cocaine or anabolic steroid abuse, physical inactivity, malnutrition, diabetes mellitus, glucose intolerance, left ventricle hypertrophy, central obesity, age, male gender, family history, and genetic factors (2,5).

#### **Forensic medical approach to sudden cardiac death**

Determining the cause of sudden cardiac death is important to detect the preventable causes. Although the detection and the prevention of the causes are not always easy and even possible, performing a systematical autopsy is important for the detection of the cause of sudden cardiac deaths.

Although there is still no standardized method of evaluation in sudden cardiac death cases, there is a consensus that the evaluation should include macroscopic and microscopic autopsy, medical history and incident scene investigation findings (4). When there is no witness to death, autopsy usually start without adequate information about the incident scene investigation findings and medical history. For an ideal autopsy, an effort to obtain there informations should be made before the autopsy (2,15). These informations can be obtained by the relatives of the case or the witnesses of the sudden death. Informations especially about the age, gender,

occupation, alcohol and nicotine use, regular physical activity before/during death, time of death, duration between the onset of the symptoms and death, the place of death (home, hospital, work place, sports center, etc.), medical history, any chest pain before death, any palpitation complaint, history of hypertension, coronary artery disease, myocardial infarction, asthma, epilepsy, any recent infection or hospital application, antemortem drug use, any application to the cardiology department, previous ECG, ecocardiography, chest films or serum lipid level test results, any family history of cardiac disease or any family history of death at a young age or sudden cardiac death should be inquired. If there are any witnesses of death, information about how the incident happened should be inquired and possible CO exposure, chemical substance, drug or any other toxic exposure should be inquired regarding the incident scene investigation (2,4).

#### **Autopsy in sudden cardiac deaths**

Autopsy includes external examination, macroscopic evaluation, histopathological examinations of organs, toxicologic evaluation and in some cases immunohistochemical and microbiological evaluations as well. Medical history helps the physicians to determine any additional required procedures (4,15). Minimum standards of the routine autopsy are defined to evaluate the sudden cardiac death cases except the SIDS.

#### **External and internal examination**

Autopsy should begin with an external examination and recording of the height and weight of the case, thus allowing the evaluation the heart size later in accordance with the BMI. Detailed evaluation of congenital malformation related physical findings (e.g. arachnodactilia, scoliosis, pectus excavatum related to Marfan's) must be included in the external examination as well as the evaluation of alcohol and substance use, intoxication findings, traumatic lesions due to loss of consciousness which could also be the exact cause of the death (4,15).

Internal examination should include detailed examination of the inner spaces, the organs and the macroscopic features, the size and the weight of every organ should also be recorded. In doubt of cardiomyopathy or channelopathy especially in 30-35 years old sudden cardiac death cases, after the opening of both atriums, a transection should be made to drain the blood and after the macroscopic evaluation, the complete heart should be fixed in 10% formalin solution for further histopathologic examination (4,15).

#### **Cardiovascular system findings and sampling**

During the autopsy standard macroscopic evaluation of the cardiovascular system begins with the pericard examination. After the pericardial examination, pericardial space must be opened and any findings including pericardial adhesion, presence of any fluid or blood in the pericardial space or any pericarditis findings should be recorded and all the vessels should be checked anatomically for the presence of any congenital abnormalities. Main vessels should be cut 3 cm above the valves without any damage to the aortic and pulmonary valves. In order to preserve the sinoatrial node, the superior vena cava should be excised 2 cm above the point

where it is fused with the right atrial appendix and inferior vena cava should be excised as closely as possible to the diaphragma and the heart should be removed as a whole (2,4,15).

Epicardial examination should follow this procedure: Atrial spaces, interatrial septum, mitral and tricuspid valves should be evaluated after the atrial dissection followed by the ventricular spaces, chorda tendinea and the papillary muscles, aortic and pulmonary valves via a continuous dissection along the route of the bloodflow. Presence of atrial or ventricular septal defects, the presence, number and localization of the ostia of the coronary arteries should be checked. Size of the heart, measurements of the left and the right ventricle walls at the midventricular level, the septum and the circumference of the valves should be made. Via the dissection of epicardial coronary arteries at every 2-3 mm, the position of the main arteries should be checked for any abnormalities or pathologies, arterial walls should be checked for any lesions that could have played a role in the sudden cardiac death, such as thrombi or atherosclerotic plaque formation and in the presence of any positive findings coronary arteries should be sampled. Although the long term prognosis has been reported to be good in the myocardial bridging cases, in some rare cases death due to ventricular tachyarrhythmia and sudden cardiac death have been reported. Therefore all the epicardial coronary arteries should be checked for myocardial bridging especially the left anterior descending artery. Coronary arteries containing stent and bypass grafts should be examined via transections and histopathological sampling should be made. Examination of the ventricular spaces and cardiac walls should be completed via transverse dissections at every 1 cm, up to the apex or following the transverse dissection at the midventricular level. The weighing of the heart must be performed after the drainage of the intracardiac blood and basic measurements of the heart should be made. After the macroscopic examination, standard histopathological sampling should be performed. Standard myocardial sampling should include the anterior, lateral and posterior walls of both ventricles and the anterior, posterior and the middle parts of the septum. Any regions containing lesions should also be sampled. Samples should be fixed in 10% formalin solution. H&E, connective tissue dyes and Congo Red dye can also be used for the evaluation, if necessary immunohistochemical dyeing methods can be used (2,4,15,16).

In the absence of any certain cardiac etiologies, if the relation of death with physical exercise and the macroscopic evaluation lead to any suspicion of the conductive system pathology, conductive system sampling can be performed (4,15).

If the suspicion of mitochondrial cardiomyopathies or other rare cardiomyopathies are present, 1 mm myocard tissue should be fixed in 2.5% glutaraldehyde solution for further electron microscopic evaluation (15).

In case of inflammatory cardiomyopathy or hereditary cardiac disease suspicion, 5-10 ml blood sample should be taken into an EDTA tube, and/or 5 grams fresh myocard, liver and

spleen tissues should be frozen at -80 degrees Celsius and no formalin solution should be added till the DNA isolation (7,8,15,17). Recent studies showed that DNA isolation is possible from the parafine blocks as well (18).

In sudden cardiac death cases histopathological sampling of other organs should be made. Cocaine and opioid use have been reported to cause coronary artery vasoconstriction, high dosage fendimetrazine and/or phenylpropranolamine or bupropion use as anorectic have been reported to cause septal and ventricular hypertrophy of medium severity, non-ischemic scar tissue formation in the myocardium and inflammatory findings compatible with toxic myocarditis, also synthetic cannabinoid use has been reported to cause atrial fibrillation and myocardial infarction. For this reason, sampling for toxicologic evaluation should be made and the samples should be kept in adequate conditions (2-4,15,19-21). Although blood drawn from the femoral vein is the most suitable material for the toxicologic sampling, vitreous fluid, Urine, Stomach Contents, Cerebrospinal Fluid, Liver And Kidney Samples Can Also Be Used.

#### **Postmortem findings of coronary artery disease as being the most common cause of sudden cardiac death**

During the examination of the coronary arteries, obstructive atheroma plaque frequency and severity should be evaluated since any atheroma plaque which obstructs more than 75% of the coronary artery might be the cause of the sudden cardiac death. Trombus presence in coronary arteries should be checked, myocardial infarction findings and scar tissues should be evaluated. Trombi detection and/or myocardial infarction prove that the coronary artery disease is the primary cause of death (15,16).

#### **Genetical causes of sudden cardiac deaths and molecular autopsy**

Postmortem genetical studies are called as "molecular autopsy" (22). Structural heart diseases such as hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia, left ventricle noncompaction and arrhythmogenic heart diseases are the common etiologies of sudden cardiac deaths in cases who are younger than 40 years (23). European Society of Cardiovascular Pathology also recommends performing molecular autopsy when the certain cardiac cause cannot be determined morphologically (16). Studies report that molecular autopsy can detect the cardiac cause of death in 50-20% of the adult sudden cardiac deaths and 35-25% of the sudden arrhythmogenic deaths while in 50-30% of the arrhythmogenic right ventricular dysplasia cases there is a genetic abnormality (24-28). In a small number of cases even the molecular autopsy cannot determine the cause (8,29).

In the ESC Guideline For Management of Patients With Ventricular Arrhythmias and The Prevention Of Sudden Cardiac Death, autopsy is recommended for the differentiation of the arrhythmic and non-arrhythmic sudden death causes (Class I Recommendations). Toxicological examinations of blood and other body fluids in addition to the standart autopsy were also recommended in the guideline and for the first time postmortem genetic evaluation of arrhythmias and sudden

cardiac death cases was mentioned as postmortem genetical evaluation making the diagnosis of channelopathies which are responsible for 25-15% of the sudden cardiac deaths, possible (30). Although postmortem genetical analysis is recommended in all sudden cardiac death cases with a suspicion of channelopathy or cardiomyopathy in the ESC Guidelines, in many European countries genetical analysis is only performed if any clinical phenotype is present in the victim's family members (4,5,7).

In addition to some genetical analysis techniques not being frequently used, in some of the sudden cardiac death cases even autopsy is not performed if no legal obligation is present, in our country (30). This makes it hard to diagnose genetical diseases which are reported to cause sudden cardiac death even during and after the autopsy. For this reason, especially in young sudden cardiac death cases autopsy must be performed and forensic doctors should collect the adequate samples for further molecular autopsy if any possibility of a genetical etiology is present (7,8,30).

ESC recommends DNA sampling for molecular autopsy from all cases (30). Forensic pathologists and forensic science specialists should work together in a multidisiplinary manner in sudden cardiac death cases and after consulting a cardiologist and genetic consultant, it must be concluded whether genetical consulting should be recommended to the family members of the victim (31). In determining the families who are at risk of genetical cardiac problems, the role and importance of forensic science specialists and forensic pathologists are crucial (32). In the current clinical practice in our country, if any suspicion of channelopathy or cardiomyopathy is present, the heart is sampled as a whole in 30-35 years old cases, conduction system pathologies and molecular evaluation is also performed to determine the cause of the sudden cardiac death.

Mutation search via scanning of suspected genes responsible for cardiac channelopathy or cardiomyopathy in sudden cardiac death cases is recommended (9,22). DNA isolation from the adequate samples and scanning of (with methods such as Sanger DNA Sequence Analysis or Next Generation Sequencing) gene mutations which are reported to be linked to arrhythmogenic heart diseases is performed (4). If no mutation is detected, full exome sequencing can be performed (6,8). Identified mutations can be scanned with gene probes that contain several mutant genes and separate probe sets for channelopathies and cardiomyopathies are also available. In the 2011 Guideline of the European Heart Rhythm Association, use of these panels in autopsies of the young sudden death cases whether this unavaible adequate sampling and storage of this tissue and organs are recommended for further analysis (7).

Since 95% of the cardiac diseases have autosomal dominant inheritance pattern, detection of these diseases via molecular autopsy would mean that with 50% possibility the first degree relatives of the victim would have the same alleles (33,34). Genetical consulting can be recommended to the living relatives of the victim. Considering that next generation sequencing techniques allow scanning hundreds of genes

at the same time, it would not be hard to suggest that not only the arrhythmogenic heart diseases but also many other hereditary heart diseases could be detected with genetical analysis in the near future (8).

Standardized and adequate histopathological evaluations and if necessary additional histochemical and molecular genetic evaluations are recommended (16). Genetical analysis results should be evaluated in a multidisciplinary management along with the history of the victim and the victim's family and the autopsy findings (4,32). To determine in which of the natural death cases molecular autopsy should be performed standardized methods must be developed (8).

Although it is not clear who is to afford the high expenses of the molecular autopsy, since molecular autopsy could prevent the future sudden cardiac deaths and thus lessen the need of autopsy in time, expenses are not an unsolvable problem. Currently, genetical analysis in alive residents are afforded by the Turkish Social Security System while autopsies are afforded by the Turkish Ministry of Justice. It was suggested that if both departments agreed upon it, the autopsy expenses could be paid by the Turkish Ministry of Justice and the collected samples could either be directly given to the victim's family members or send for the genetical evaluation and the expenses would be paid by the Turkish Social Security System, if any genetical cardiac disease suspicion was present (35).

Sudden cardiac deaths are extremely tragic and important events both for the population and the relatives of the victim since they represent the sudden cardiac death risk. Autopsy should be performed in all of the sudden cardiac death cases. Although autopsy provides the certain cause of death in most of the cases, in 5-1% of the cases the macroscopic, toxicologic and histopathological evaluations fail to identify the cause. This unidentification rate is even higher in young sudden cardiac death cases. Regarding the hereditary cardiac diseases, macroscopic autopsy findings are important to determine whether a molecular autopsy is required, thus both macroscopic and histopathologic examinations should be carried out carefully and completely in accordance with the standardized methods and the whole heart sampling should be performed and forensic pathologists should be consulted when necessary.

Regarding the evaluation of sudden cardiac deaths, the correct differential diagnosis via adequate sampling and correct use of methods, would help recognize diseases which are hard to be diagnosed. The most important problems in our country are the lack of multidisciplinary approach and standardized management methods. For this reason a standard protocol including detailed autopsy, incident scene investigation, personal and family medical history should be developed and put into the clinical practice. In our country molecular autopsy is only considered in rare and selected cases, but if these genetical evaluations were made more applicable and accessible via interdepartmental agreements and the application of new genetical diagnosis methods, it would be possible to develop standardized methods for the case selection of molecular autopsies in the future.

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## REFERENCES

- Saukko P, Knight B. The pathology of sudden death. In: Knight's Forensic Pathology 4th edition. New York: CRC Press; 2016. p. 515-37.
- Gulmen MK, Meral D. Ani kardiyak ölümler. In: Koc S, Can M, eds. Birinci Basamakta Adli Tıp 2nd edition. İstanbul: İstanbul Tabip Odası 2011. p. 107-16.
- Lucena J, Bianco M, Jurado C, Rico A, Salguero M, Vasquez R, et al. Cocaine-related sudden death: a prospective investigation in south-west Spain. *Eur Hear J* 2010;31(3):318-29.
- Basso C, Aguilera B, Banner J, Cohle S, d'Amati G, de Gouveia RH, et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. *Virchows Arc* 2017;471(6):691-705.
- Kautzner J, Osmancik P, Taborsky M. Summary of the 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Prepared by the Czech Society of Cardiology. *Cor et Vasa* 2016;58:29-80.
- Bagnall RD, Das KJ, Duflo J, Semsarian C. Exome analysis-based molecular autopsy in cases of sudden unexplained death in the young. *Hear Rhythm* 2014;11(4):655-62.
- Boczek NJ, Tester DJ, Ackerman MJ. The molecular autopsy: An indispensable step following sudden cardiac death in the young? *Herzschrittmacherther Elektrophysiol* 2012;23(3):1-13.
- Sahin Y, Fedakar R, Gok E, Sen A, Akdeniz C, Tuzcu V, et al. Ani Kardiyak Ölümünde Moleküler Otopsinin Önemi. *J Forensic Med* 2016;30(2):162-9.
- Campuzano O, Sarguella-Brugada G, Brugada R, Brugada J. Genetics of channelopathies associated with sudden cardiac death. *Glob Cardiol Sci Pract* 2015;2015(3):39
- Arzamendi D, Benito B, Tizon-Marcos H, Flores J, Tanguay J, Ly H, et al. Increase in sudden death from coronary artery disease in young adults. *Am Heart J* 2011;161(3):574-80.
- Finocchiaro G, Papadakis M, Robertus J, Dhutia H, Steriotis AK, Tome M, et al. Etiology of sudden death in sports. Insights From a United Kingdom Regional Registry. *J Am Coll Cardiol* 2016;67(18):2108-15.
- Yucel AS, Catikkas F, Gumusdag H. Sporda kardiovasküler sebepli ani ölümler. *Uluslararası Hakemli Ortopedi Travmatoloji ve Spor Hekimliği Dergisi* 2014;1(1).
- Bagnall RD, Weintraub RG, Ingles J, Duflo J, Yeates L, Lam L, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med* 2016;374(25):2441-52.
- Tester DJ, Ackerman MJ. The molecular autopsy-should the evaluation continue after the funeral? *Pediatr Cardiol* 2012;33(3):461-70.
- Akcay A. Makroskopiden genlere; ani kalp ölümü. *J Foren Med* 2016;2(1):44-56.
- Pakis I. Adli otopsilere histopatolojik inceleme. *J Foren Med* 2016;2(1):57-63.
- Basso C, Calabrese F, Angelini A, Carturan E, Thiene G. Classification and histological, immunohistochemical and molecular diagnosis of inflammatory myocardial disease. *Heart Fail Rev* 2013;18(6):673-81.
- Bagnall RD, Ingles J, Yeates L, Berkovic SF, Semsarian C. Exome sequencing-based molecular autopsy of formalin-fixed paraffin-embedded tissue after sudden death. *Genet Med* 2017;19(10):1127-33.
- Efe TH, Felekoglu MA, Cimen T, Dogan M. Atrial fibrillation following synthetic cannabinoid abuse. *Turk Kardiyol Dern Ars* 2017;45(4):362-4.
- Parlakpınar H, Celbis O, Ozhan O, Petekkaya S, Samdancı E, Ermis N, et al. Cardiovascular effects of JWH-018 from

- synthetic cannabinoids. *Medicine Science Int Med J* 2016;5(4):1049-54.
21. Leone O, Agostini V, Foà A, Cerbelli B, Rosaria C, Aromatario M, et al. Cardiac pathologic findings in three unusual cases of sudden cardiac death related to anorexiants drugs. *Human Pathology* 2017;69:101-9.
  22. Semsarian C, Ingles J, Wilde AA. Sudden cardiac death in the young: The molecular autopsy and a practical approach to surviving relatives. *Eur Hear J* 2015;36(21):1290-6.
  23. Pilmer CM, Kirsh JA, Hildebrandt D, Krahn AD, Gow RM. Sudden cardiac death in children and adolescents between 1 and 19 years of age. *Heart Rhythm* 2014;11(2):239-45.
  24. Skinner JR, Crawford J, Smith W, Aitken A, Heaven D, Evans C, et al. Prospective, population-based long QT molecular autopsy study of postmortem negative sudden death in 1 to 40 year olds. *Heart Rhythm* 2011;8(3):412-9.
  25. Tester DJ, Medeiros-Domingo A, Will ML, Haglund CM, Ackerman MJ. Cardiac channel molecular autopsy: insights from 173 consecutive cases of autopsy-negative sudden unexplained death referred for postmortem genetic testing. *Mayo Clin Proc* 2012;87(6):524-34.
  26. Chung HYG, Vyas M, Jacoby D, West B. Arrhythmogenic right ventricular cardiomyopathy (ARVC) in a young female athlete at 36 weeks gestation: a case report. *Pathol Res Pract* 2017;213(10):1302-5.
  27. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. *J Am Coll Cardiol* 2007;49(2):240-6.
  28. Hendrix A, Borleffs CJ, Vlink A, Doevendans PA, Wilde AA, van Langen IM, et al. Cardiogenetic screening of first-degree relatives after sudden cardiac death in the young: a population-based approach. *Europace* 2011;13(5):716-22.
  29. Madea B, Saukko P, Oliva A, Musshoff F. *Molecular Pathology in Forensic Medicine-Introduction*. *Forensic Sci Int* 2010;203(1-3):3-14.
  30. Deniz A, Demir M. 2015 Avrupa Kardiyoloji Derneği ventrikül aritmisi olan hastaların yönetimi ve ani kardiyak ölümün önlenmesi kılavuzu. *Türk Kardiyol Dern Ars* 2016;44(1):9-14.
  31. Semsarian C, Hamilton RM. Key role of the molecular autopsy in sudden unexpected death. *Heart Rhythm* 2012;9(1):145-50.
  32. Wilhelm M, Bolliger SA, Bartsch C, Fokstuen S, Grant C, Martos V, et al. Sudden cardiac death in forensic medicine – Swiss recommendations for a multidisciplinary approach. *Swiss Med Wkly* 2015;145:14129.
  33. Wilde AA, Behr ER. Genetic testing for inherited cardiac disease. *Nat Rev Cardiol* 2013;10(10):571-83.
  34. Cerrone M, Priori SG. Genetics of sudden death: focus on inherited channelopathies. *Eur Heart J* 2011;32(17):2109-18.
  35. Fedakar R, Gok E, Cetin S, Baduroglu E, Saka NE, Aslanhan N. Medicolegal aspect of the young sudden cardiac deaths: A case report. *Uludag Med J* 2012;38(3):201-5.