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ARAŞTIRMA / RESEARCH

Brain death diagnosis and management in the COVID-19 pandemic

COVID-19 pandemisinde beyin ölümü tanısı ve yönetimi

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Abstract

Purpose: This present study aimed to share experiences in the diagnosis and management of brain death (BD) and cadaveric donation cases, detected in a research hospital during the COVID-19 pandemic.

Materials and Methods: BD cases diagnosed between 15/03/2020-15/05/2021 in our intensive care units (ICU) were retrospectively evaluated. Patients' demographic characteristics, primary diagnoses, ICU admission time, and length of hospital stay were analyzed. Clinical suspicion, diagnosis, declaration, and donation or cardiac arrest times and supplementary tests to support the clinical judgment performed were also evaluated.

Results: 37 cases, were included in the study. Intracranial hemorrhage was the most common (54.1%) diagnosis in ICU admissions. Apnea tests could be performed only in 27 patients (73%). Cerebral CT-angiography was used as a supplementarytary test in 27 (73%) cases. Family consent for organ donation was obtained from 10 patients (27%), and 70% (n= 7) of them became donors. The time between ICU admission and BD diagnosis time was 114±92.8 (11-360) hours, the time between clinical suspicion and diagnosis was 32±15.1 (4-78) hours, the time between diagnosis and cardiac arrest of non-donors was 24±15.2 (5-72) hours, and the time between diagnosis and donation was 23±7.6 (15-35) hours.

Conclusion: Occupancy in ICUs due to COVID-19 has reduced the admission of patients who may be donors to ICUs, and there has been a decrease in the number of BD detection, family approval, and organ donation in our hospital.

Keywords:. Brain death, COVID-19, donor, organ transplantation

Öz

Amaç: Bu çalışma, COVID-19 pandemisi sırasında bir araştırma hastanesinde tespit edilen beyin ölümü (BÖ) ve kadavra bağışı vakalarının tanı ve yönetimindeki deneyimlerin paylaşılmasını amaçlamıştır.

Gereç ve Yöntem: 15/03/2020-15/05/2021 tarihleri arasında yoğun bakım ünitelerimizde (YBÜ) tanı alan BÖ olguları geriye dönük olarak değerlendirildi. Hastaların demografik özellikleri, birincil tanıları, yoğun bakıma kabul süreleri ve hastanede kalış süreleri analiz edildi. Klinik şüphe, tanı, beyan ve bağış veya kardiyak arrest süreleri ve gerçekleştirilen klinik yargıyı desteklemek için ek testler de değerlendirildi.

Bulgular: Çalışmaya yaş ortalaması 59.9 yıl olan %56.8'i erkek, %43.2'si kadın 37 olgu dahil edildi. YBÜ yatışlarında en sık (%54.1) tanı intrakraniyal kanama idi. Apne testleri sadece 27 hastada (%73) yapılabildi. 27 (%73) olguda ek test olarak cerebral BT-anjiyografi kullanıldı. 10 hastadan (%27) organ bağışı için aile onayı alındı ve bunların %70'i (n= 7) donör oldu. YBÜ'e yatışıyla BÖ tanısı arasındaki süre 114±92.8 (11-360) saat, klinik şüphe ile tanı arasındaki süre 32±15,1 (4-78) saat, donör olmayanlarda tanı ile kardiyak arrest arasındaki süre 24±15.2 (5-72) saat, tanı ile bağış arasındaki süre 23±7.6 (15-35) saatti.

Sonuç: COVID-19 nedeniyle yoğun bakım ünitelerinde doluluk, donör olabilecek hastaların YBÜ'ne kabulünü azaltmış, hastanemizde BÖ tespit, aile onayı ve organ bağışı sayılarında azalma olmuştur.

Anahtar kelimeler: Beyin ölümü, COVID-19, donör, organ transplantasyonu

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INTRODUCTION

End-stage organ failure is estimated to affect more than six million people worldwide. Solid organ transplantation has changed the survival and quality of life of patients with organ dysfunction and has been life-saving for terminal patients. According to the World Health Organization data, more than 1 500 000 people worldwide live with transplanted organs[1]. In 2018, transplant systems worldwide could not meet the high demand despite providing kidney, heart, lung, liver, or other solid organs to nearly 150,000 patients[2]. Due to the difficulties in obtaining organs from living donors, organ donation from cadavers has come to the fore. Therefore, the importance of brain death (BD) diagnosis, donor care, and organ donation have increased. BD is a complete and irreversible loss of cerebral function, characterized by apnea and the absence of brainstem reflexes[3]. The diagnosis of BD is made clinically by demonstrating the presence of irreversible coma, areflexia, and apnea. Radiologic imaging methods which assist clinical diagnosis and show the absence of cerebral perfusion are applied in most patients.

The apnea test is a critical component in the clinical determination of BD. The apnea test is used to evaluate the loss of function of medullary chemoreceptors during the determination of BD[4]. A positive apnea test has no respiratory response to hypercarbia, defined as PaCO2 >60 mmHg or an increase of >20 mmHg from baseline. Although there is no international consensus on the apnea test procedure, the most frequently chosen method is the "traditional apneic oxygenation" technique which requires the patient to be disconnected from the ventilator before observing spontaneous breathing. However, there is a high risk of aerosol formation in this method, in which the oxygen insufflation technique is used, and the risk can be reduced by clamping the endotracheal tube in this technique[5]. Aerosol generation and the risk of viral transmission during apnea test can also be reduced but not eliminated when continuous positive airway pressure delivered through a ventilator is used as a means of apneic oxygenation[6].

The coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, which started in China in December 2019 and spread rapidly to other countries, was accepted as a pandemic by the World Health Organization on March 11, 2020. Due to this rapidly progressing disease during the global pandemic period, serious changes and transformations have been experienced in the health system in Turkey and the rest of the world[7]. The capacities of hospital critical care facilities have been increased significantly due to the increasing number of COVID-19 patients by shifting most of the workforce and technical support to the fight against the pandemic to avoid disruptions in the healthcare system. In order to provide the most appropriate care to COVID-19 patients with respiratory distress, most of these patients are treated in intensive care units (ICU). The restricted number of available ICU beds and reallocating the health care professionals, working at brain death, organ donation, and transplantation teams, to wards and ICUs during the pandemic, affect the general donation activities and ultimately lead to a decrease in the number of organ transplants[8].

Although many contributions have been made to the literature on COVID-19 during the pandemic process, studies on BD are limited. The aim of our study is to share our experience in the analysis and management process of BD cases detected in the early stages of the pandemic in our hospital, which ranked first in Turkey in organ donation in 2019.

MATERIALS AND METHODS

Sample

This single-center, retrospective study was conducted at Health Sciences University Bursa Yuksek Ihtisas Training and Education Hospital. After the Health Sciences University Bursa Yuksek Ihtisas Training and Education Hospital Ethics Committee approval (2011-KAEK-25, 2021/06-01), the medical data of adult and pediatric cases diagnosed with BD in our hospital between 15/03/2020 and 15/05/2021 during the COVID-19 pandemic were retrospectively analyzed. All BD cases in the examined period were examined, no case was excluded. Medical data were obtained from patient archive files and the hospital information system. Considering the confidentiality of patient information in BD cases, patient data kept by organ transplant coordinators and submitted to the National Coordination Center were analyzed.

Demographic characteristics of the cases, diagnoses, COVID-19 real-time polymerase chain reaction (RT-PCR) results, brain death detection time, additional tests performed, organ donation rate, donor ratio, type and number of transplanted organs, and the time elapsed until a cardiac arrest was recorded in patients who were not donors and were diagnosed with BD.

Tests

Turkish Neurological Society guidelines and the criteria of the Ministry of Health were followed in the diagnosis process of BD. The diagnosis of BD was made by doctors in our hospital according to "brain death diagnostic criteria"[9,10]. According to the regulations in force in our country, patients were evaluated for BD by two specialist physicians (1- Anesthesiology and Reanimation or Intensive Care Minor specialist, 2- Brain and Nerve Surgery or Neurology specialist).

Apnea test and neurological tests are performed in all patients with prerequisites for the diagnosis of BD. Apnea test is administered by Anesthesiology and Reanimation or Intensive Care Minor specialist, while neurological tests are administered by Brain and Nerve Surgery or Neurology specialist. In cases where apnea test cannot be performed, radiological imaging method is used to evaluate cerebral blood circulation. Computed tomography (CT) cerebral angiography is often preferred. Demographic characteristics of cases, diagnoses, COVID-19 real-time polymerase chain reaction (RT-PCR) results, brain death detection time, additional tests performed, organ donation rate, donor ratio, type and number of transplanted organs, and time. Non-donor and BD diagnosed The time elapsed until cardiac arrest was recorded in patients was examined.

During the pandemic process RT-PCR tests were required for every potential donor with a Glasgow Coma Scale score of 6 or lower, in line with the recommendations of the Scientific Advisory Board in our country, and it had been suggested to investigate travel and contact history and COVID-19 symptoms[11]. In line with the recommendations, the cases accepted as potential donors were screened for COVID-19. In addition, RT-PCR tests were performed twice on intratracheal aspirate samples, at least 24 hours apart, before the transplant coordinators presented the cases to the National Coordination Center, taking into account the incubation period of SARS-CoV-2. In order to exclude COVID-19, potential donors were screened by lung computed tomography, and cases were evaluated by physicians in radiology, infectious diseases, clinical microbiology and pulmonology.

After BD is determined, the interview with the family for organ donation is done by the organ transplant coordinators of our hospital. Coordinators present patient data to the National Coordination Center and prepare legal documents after family interviews.

Statistical analysis

Statistical analysis was done using Statistical Package for the Social Sciences 21 (SPSS, Armonk, New York, IL, USA) software. The Shapiro-Wilk test were used to determine the conformity of variables to the normal distribution. Numerical variables with normal distribution are expressed as mean±standard deviation, and those without normal distribution as median (minimum-maximum [min-max]). Categorical variables are presented as frequency and percentages.

RESULTS

Between 15/03/2020-15/05/2021, 37 cases diagnosed with BD were detected in the ICUs of our hospital. 26 (70.3%) in Anesthesiology and Reanimation ICUs, 7 (18.9%) in COVID-19 ICUs, 2 (5.4%) stroke ICU, 1 (2.7%) in cardiovascular surgery ICU, 1 (2.7%) in pediatric ICU. The mean age was 59.9 (9-83). Demographic data of the cases are presented in Table 1. It was found that the patients were admitted to the ICUs most frequently from the emergency department (94.6%), and the most common diagnosis was intracranial bleeding (54.1%) (Table 1). RT-PCR (+) was found in 7 cases (18.9%). The apnea test was performed successfully in 43.2% of the cases, the apnea test could not be completed in 29.8%, and the apnea test was not applied in 27% of the cases because hemodynamics was not stable. Neurological tests were completed in all cases. An imaging method was used to support the diagnosis in 73% (n=27) of the cases. The preferred imaging method was computed tomography-angiography (CT-angiography). In a 9-year-old patient, a clinical diagnosis of BD was made by an apnea test and neurological tests, and radiological imaging could not be performed due to the patient's general condition. In only 1 of the cases with RT-PCR (+) at admission, radiological imaging could not be performed due to medical problems, and a clinical diagnosis of BD was made. Apnea test was not performed in the other 6 cases with RT-PCR (+), and the diagnosis of BD was made after radiological imaging and neurological tests were completed.

Table 1. Demographic and pre-hospitalization data of the patients in the intensive care unit

	n (number)	% (percent)
Female	16	43.24
Male	21	56.76
Admission to the ICU from the emergency room	35	94.59
Admission to ICU from other services	2	5.41
RT-PCR (+)	7	18.92
RT-PCR (-)	30	81.08
Intracranial hemorrhage	20	54.05
Occlusive CVD	5	13.51
Traumatic SAH	5	13.51
Post CPR*	5	13.51
COVID-19 pneumonia	1	2.71
Cardiac injury	1	2.71

RT-PCR: Real-time polymerase chain reaction, CVD: Cerebrovascular disease, SAH: Subarachnoid hemorrhage, CPR: Cardiopulmonary Resuscitation, ICU: Intensive care unit * Cardiopulmonary resuscitation after multi-trauma without head trauma

The time between ICU admission and BD diagnosis time was 114±92.8 (11-360) hours, and the time between clinical suspicion and diagnosis was 32±15.1 (4-78) hours. In cases diagnosed with BD, BD declaration time after diagnosis was 81.1±69.7 (15-360) minutes. In non-donor cases, the time elapsed between the diagnosis of BD and cardiac arrest was 24±15.2 (5-72) hours. In donor cases, the time between BD diagnosis and donation was 23±7.6 (15-35) hours. In the 9-year-old case, the time between the diagnosis of BD and cardiac arrest was 11 hours. Despite the development of BD, seven patients with COVID-19 RT-PCR (+) were not considered donors.

Since 2 of 37 patients diagnosed with BD were foreign nationals, family interviews were not conducted. Family consent was obtained for organ donation in 28.6% (n=10) of 35 cases whose families were interviewed. Although donor care was provided among the organ donation cases, only 7 (70%) cases could be donors. 3 (30%) patients who donated organs were not accepted as donors by the National Coordination Center for medical reasons. A case diagnosed with BD had individual organ donation, and this case became a donor upon obtaining family consent. The organs used in the donation of the donor cases are presented in Table 2. Only one kidney was used for transplantation due to pathology in the other kidney. The donor rate in cases with BD was 18.9%.

Table 2. Organs used in donation

Number of cases (n)	Organs used in donation			
	Kidney	Liver	Cornea	Heart
3	+	+	+	-
1	+	+	-	+
1	+	-	-	-
2	+	+	-	-
Total (n)	13	6	6	1

DISCUSSION

In our study, cases with BD in our hospital during the 14-month COVID-19 pandemic cross-sectional period were examined. 37 BD cases were detected, and 7 cases could not be donors due to COVID-19 RT-PCR (+). The total number of donations is 10, but only 7 cases became donors. The donor rate in cases with BD was 18.9%.

After the successful first organ transplantation from a cadaver by Dr. James Hardy in 1963, the interest in diagnosing BD and organ transplantation from a cadaver increased[12]. Although legal and scientific regulations have been made on the diagnosis of BD and organ transplantation over the years, organ transplantation continues to be an important problem globally and in our country. The number of cadaveric organ donations is insufficient worldwide and in our country. Loss of potential donors without

being diagd, families are not allowed to donate organs, families' refusal to donate, improper donor care, and disruptions in organ transplant coordination may cause cadaveric organ scarcity. The number of patients waiting for organs is constantly increasing, and the mortality rate of patients awaiting transplantation increases with the prolongation of this process[13].

The first diagnosis of BD was made in our hospital in 2007. BD cases had been donors 27 of 79 between 2007 and 2014, 44 of 151 cases between 2014 and 2018, and 23 of 66 BD cases in 2019 in our hospital[14-16]. Raising awareness among healthcare professionals working in ICUs through training on BD diagnosis, donor care, and organ donation and working in teams with organ transplant coordinators have increased the number of donor cases in our hospital over the years. During the pandemic, crucial changes in the health systems have been made in our country and worldwide. With the pandemic process, BD detection, donor care, donation, and organ transplantation practices have been adversely affected by the configurations in health systems. Because of the increase in the number of COVID-19 patients hospitalized in ICUs, the number of patients who could be potential donors has been limited in General ICUs. During the pandemic period, there has been a significant decrease in the number of BD detection, family consent, and organ donation in Turkey. In Turkey, there were 2309 and 1385 BD diagnoses, 619 and 263 organ donations, and 2504 and 1050 accepted organs in 2019 and 2020, respectively [16]. When data in 2019 is compared with data in 2020, it is seen that 40% in the BD detection, 57.5% in a family consent for donation, and 57.8% in the number of donor organs decreased. When the number of BD cases in the 14-month pandemic period we examined in our study is compared with 2019, it is seen that there is an average decrease of 43.9%. This situation is similar to the rate in Turkey in general.

The gender of patients diagnosed with BD varies by country. For example, in the study conducted by Aghighi et al. from Iran, it was stated that the rate of BD diagnosis in men was two times that of women, while Han et al. reported that more women were diagnosed with BD in South Korea[17,18].

In studies conducted in our country, it is seen that the majority of cases diagnosed with BD are male [14,15,19]. In our study, similar to the results of other studies, it was found that the majority (56.8%) of the cases diagnosed with BD were male. The mean age of patients diagnosed with BD varies in the literature, and it is reported to be common in patients aged 40-50 years[14,20]. In our study, the mean age of patients diagnosed with BD was 59.9 years, and this result was similar to the results of other studies conducted in our country[15,19].

The most common hospital admission diagnoses that lead patients to the BD process are hemorrhagic or occlusive cranial events [14,20,21]. While it was stated in one study that the most common causes of BD were hemorrhagic and ischemic cranial events, another study reported that intracerebral hemorrhage, traumatic brain injury, subarachnoid hemorrhage, and stroke were the most common causes of BD[21,22]. In our study, hospitalization diagnoses of BD cases were found to be 67.5% cranial hemorrhagic events and 13.5% occlusive cerebrovascular disease, similar to the diagnoses in the literature. In the literature, it is seen that BD is diagnosed in the first week after admission to the ICU[14,15,19,20]. However, in a study conducted during the pandemic process, it was reported that this period was four days on average[23]. Similarly, in our study, this period was found to be approximately five days (114 hours) on average.

The main clinical findings of brain death are coma, absence of brain stem reflexes, and apnea[24]. A clinical diagnosis of BD is made by performing an apnea test and a detailed neurological examination. Apnea test should be performed using complete personal protective equipment (PPE) in the team unless the diagnosis of COVID-19 is definitively excluded[25]. There are two handicaps to performing an apnea test in patients with COVID-19. When the ventilator system is disconnected, aerosols are formed, increasing the risk of transmitting viral particles. Another is that many patients with acute respiratory failure due to COVID-19 need high positive end-expiratory pressure (PEEP) to maintain adequate alveolar uptake and oxygen exchange. When the ventilator is disconnected, hypoxia and hypotension may occur due to the closure of the alveoli as well as a collapsed lung. In the literature, studies show the feasibility of the apnea test in cases with COVID-19, and articles state that by skipping the apnea test, supportive tests can be used to diagnose BD by directly documenting cerebral circulatory arrest[25,26]. While apnea test was performed in only one of the COVID-19 cases, and the apnea test could not be completed in the other 6 cases due to the development of hypoxemia or was not performed

due to hemodynamic instability. The oxygen insufflation technique was preferred in the apnea test applied in a case with COVID-19. PPE use, aerosol, and contact isolation methods were applied during the apnea test.

In cases where an apnea test or detailed neurological examination can not be performed, supportive tests documenting cerebral circulatory arrest are applied. Radiological imaging (MR-angiography, CT-angiography, and perfusion SPECT) is safely preferred as a supported application in the diagnosis of BD[22]. CT-angiography was preferred only as a supportive method. In our study, CT-angiography was used in the clinical diagnosis in 73% of the cases. CT-angiography was performed in 6 of 7 BD cases with COVID-19 using PPE, contact, and aerosol isolation methods during transport.

The diagnosis of BD begins with the determination of clinical criteria and is completed with the documentation of cerebral-circulatory arrest [11]. Diagnosis and declaration processes may differ worldwide[24]. In the literature, it is seen that the diagnosis time of BD is usually within 24-48 hours[18,21,27]. In a single-center study from Turkey, the time to diagnose BD during the pandemic was reported to be 29 hours[23]. In our study, the time to diagnose BD was approximately 32 hours. With the concerted work of the ICU team and organ transplant coordinators, it was seen that the BD diagnosis process of the cases in our hospital was not affected much by the pandemic conditions.

Before the pandemic, the patients' families in ICUs received face-to-face information from their physicians about their patients, because of the restrictions during the pandemic (eg, the ban of visitors to the ICUs, ban of quarantined family members from family visits), clinicians have started to communicate with patients' relatives by phone. It is difficult for the clinician to tell the patient's devastating brain damage to the family over the phone and share the risk of developing BD with the patient's family. Open and effective communication is imperative, as family acceptance of brain death depends on how they understand it. The New York State Department of Health has created new safety protocols that prohibit hospital visits due to the highly contagious COVID-19 and mandated that all patient information, including BD, be given over the phone[28]. In our country, BD information was given to families face-to-face by the patient's clinicians in line with the COVID-19 precautions. After the announcement, organ transplant coordinators continue face-to-face family meetings, giving information about organ donation and answering their questions.

In March 2020, multiple national and international organizations published recommendations regarding the possibility of accidental transplantation from a donor with COVID-19 and severe problems in immunocompromised recipients[29,30]. In the official letter of the Ministry, dated 27.04.2020 and numbered 44773052-149 on COVID-19 Precautions in Organ and Stem Cell Transplantation, it was stated that cadaver donors with a definitive diagnosis could not be donors with COVID-19 if there is a cadaver donor for solid organ transplantation. Although organ transplantation is not possible in cases of COVID-19, only BD detection and notification could be made in our country [31]. In our hospital, all necessary tests were performed on COVID-19 patients with suspected BD, and their families were informed if BD was detected. Despite all the difficulties brought by the pandemic, BD follow-up and examinations were not missed in our hospital. COVID-19 contact history and symptoms, thorax CT findings, and RT-PCR results of the patients who donated organs were re-evaluated. As recommended, organ donation cases were evaluated by infectious diseases, clinical microbiology, and chest disease physicians [11,30]. In our study, PPE, aerosolization, and isolation measures were meticulously applied in the donation of the cases whose family consent was obtained and who were documented as not having COVID-19.

In our study, cases with BD in our hospital during the cross-sectional period of the 14-month COVID-19 pandemic were examined. Similar studies conducted in our hospital and other centers give 12-month results. Our study does not cover exactly the same time period as other studies. The results of our study were compared with the 12-month results in other studies.

In conclusion, during the pandemic there has been a significant decrease in the number of BD detection, family consent, and organ donation in Turkey, likewise all over the world. It is a fact that the pandemic has reduced the likelihood of potential donors being admitted to intensive care units. The need for additional tests in cases where the possibility of being a donor arises, the late results of the tests, and consultations with other branches also complicate the donor management. These conditions

may have adversely affected the general donation activities and may have caused a decrease in the number of cadaveric organ transplantations. The number of patients in the order of organ transplantation is increasing day by day, but the number of organs provided is insufficient compared to the current need. We believe that determining the reasons for the low number of cadaveric donors during the COVID-19 pandemic compared with the previous years and restructuring the training for the national organ donation system will significantly contribute to donor procurement.

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