ORIGINAL ARTICLE

Özgün Araştırma

Our Experience in Brain Death and Organ Donation

Beyin Ölümü ve Organ Bağışındaki Deneyimlerimiz

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Geliş Tarihi : 02 March 2023
Received
Kabul Tarihi : 12 May 2023
Accepted
E Yayın Tarihi : 01 January 2024
Online published

Bu makalede yapılacak atıf
Cite this article as

Cakin O, Goksen Gumus A, Cengiz M, Yilmaz M, Arici AG, Bilal N, Arslan U, Yuce Aktepe M, Ramazanoglu A.
Our Experience in Brain Death and Organ Donation
Akd Med J 2024;10(1): 144-149

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DOI: 10.53394/akd.1258467

ABSTRACT

Objective:

Akdeniz University Faculty of Medicine is one of the important organ transplant centers of Türkiye. This study aimed to share experiences about cerebral death rate, follow-up, donor care, and organ donation in the adult intensive care unit (ICU).

Material And Methods:

The records of patients diagnosed with brain death in the Anesthesia and Intensive Care Unit of Akdeniz University Faculty of Medicine between January 2003 and December 2016 were reviewed retrospectively. In these records, patients' demographic characteristics, admission diagnoses, intensive care coma scores, laboratory values, method and duration of evaluation tests, consultation times, and transport information are available.

Results:

In our study, 136 (66%) male and 71 (34%) female patients were included. Intracranial hemorrhage was the first line in the diagnosis of admission. This was followed by 56 (27.05%) subarachnoid hemorrhage (SAH), and 42 (20.28%) intraparenchymal hemorrhage. Among the confirmatory tests, SPECT (single-photon emission computed tomography) was the first in 70 (33.81%) patients. Spinal reflex was observed in 27 (13.04%) patients after cerebral death. Two patients (0.96%) had Lazarus sign. Sympathetic storms developed in 71 (34.29%) patients. Diabetes insipidus developed in 122 (58.93%) of the patients and all patients received medical treatment. Sixty-six (31.4%) of 207 brain death cases with detailed records donated their organs.

Conclusion:

A common diagnostic protocol is required to create an atmosphere of trust in organ transplant patients. We reiterate that more clinical research is needed in this area.

Key Words:
Brain death, Intensive care diagnosis, Organ donation

ÖZ

Amaç:
Akdeniz Üniversitesi Tıp Fakültesi Hastanesi Türkiye'nin önemli organ nakil merkezlerinden biridir. Bu çalışmada erişkin yoğun bakım ünitesinde (YBÜ) beyin ölüm oranı, izlemi, donör bakımı ve organ bağışı ile ilgili deneyimlerin paylaşılması amaçlanmıştır.

Gereç ve Yöntemler:
Akdeniz Üniversitesi Tıp Fakültesi Anestezi ve Yoğun Bakım Ünitesinde Ocak 2003-Aralık 2016 tarihleri arasında beyin ölümü tanısı alan hastaların kayıtları retrospektif olarak incelendi. Bu kayıtlarda hastaların demografik özellikleri, başvuru tanıları, yoğun bakım koma skorları, laboratuvar değerleri, değerlendirme tetkiklerinin yöntem ve süreleri, konsültasyon süreleri ve sevk bilgileri yer almaktadır.

Bulgular:
Çalışmamıza 136 (%66) erkek, 71 (%34) kadın hasta dahil edildi. Başvuru tanısında intrakraniyal kanama ilk sırada yer aldı. Bunu 56 (%27,05) subaraknoid kanama (SAK) ve 42 (%20,28) intraparankimal kanama hastası izledi. Doğrulayıcı testler arasında SPECT (tek foton emisyonlu bilgisayarlı tomografi) ilk sırada yer aldı, 70 hastada (%33,81) kullanıldı. Serebral ölüm sonrası 27 (%13.04) hastada spinal refleks gözlendi. İki hastada (%0,96) Lazarus bulgusu vardı. Yetmiş bir (%34,29) hastada sempatik fırtına gelişti. Hastaların 122'sinde (%58,93) diabetes insipidus gelişti ve tüm hastalar medikal tedavi aldı. Ayrıntılı kayıtları bulunan 207 beyin ölümü vakasının 66'sı (%31,4) organlarını bağışladı.

Sonuç:
Organ nakli hastalarında güven ortamı oluşturmak için ortak bir tanı protokolü gereklidir. Bu alanda daha fazla klinik araştırmaya ihtiyaç olduğunu yineliyoruz.

Anahtar Kelimeler:
Beyin ölümü, Yoğun bakım tanıları, Organ nakli

INTRODUCTION and PURPOSE
"Brain death" is the permanent, irreversible loss of all functions of the brain, brain stem, and cerebellum, which are the part of the central nervous system that remains inside the skull (1, 2). The first publication on brain death was made in 1959 at the Paris Claude Bernard Hospital. Mollaret and Goulon described a new type of coma they encountered in 23 cases. These patients lived on mechanical ventilator support and were characterized by complete loss of consciousness, loss of all brainstem reflexes, absence of spontaneous breathing, and isoelectric electroencephalography (EEG). They named this "le coma de passe" (beyond coma) and separated cardiorespiratory functions from brainstem functions (3). In the same year, Wertheimer et al. saw that the patients did not have respiration after the ventilator connections were disconnected, and they called it "death of the nervous system" and suggested that the ventilators could be stopped (4). The work of the Harvard Medical School Interim Board at the Massachusetts hospital was published in 1968. In this article, brain death was defined as the irreversible loss of all brain activities, including the brain stem, thus making the first official definition of brain death (5). Then, in 1981, the 'President's commission report containing the brain death guide allowed the standardization of the 'Death Act' (6).

Although it is widely believed that the concept of brain death has evolved to benefit organ transplants with the increase in successful organ transplants in the 1960s, however, when the historical process is examined, it is seen that both cases have different foundations and developments. While brain death is accompanied by developments in intensive care treatment and technologies; surgical techniques and immunosuppressive treatments come to the fore in the development of organ transplantation (7). Despite the advances in transplantation, one of the most important problems in organ transplantation today is the limited number of adequate donor resources and the inability to meet the increasing number of end-stage organ failure patients. Especially in developing countries, the number of cadaveric organs has not yet been increased at the desired level, and therefore the necessary organs are still being sought from living donors (8).

This study aimed to share experiences about cerebral death rate, follow-up, donor care, and organ donation in the adult intensive care unit (ICU).

MATERIAL and METHODS
The records of patients diagnosed with brain death in the Anesthesia and Intensive Care Unit of Akdeniz University Faculty of Medicine between January 2003 and December 2016 were reviewed retrospectively. Patient data were obtained from the data processing system of our hospital and the Anesthesia Intensive Care observation forms. Detailed brain death detection reports are kept by the intensive care unit and archived in a separate place within the hospital. In these records, patients' demographic characteristics, admission diagnoses, intensive care coma scores, laboratory values, method and duration of evaluation tests, consultation times, and transport information are available. Patients who were hospitalized in the ICU and met the criteria for brain death as per the laws of the Republic of Türkiye were included in the study. Patients who did not have a brain death diagnosis in the file scan, who had brain stem death, and whose tests could not be defined were excluded from the study. This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Akdeniz Medical Faculty Ethical Committee, Akdeniz University. Ethics committee number is 676 and date is 15.11.2017.

In all cases, the prerequisites for the diagnosis of brain death were met. The diagnosis of the disease or process with the potential to cause cerebral death was definite in all patients. Structural cerebral damage was observed in the irreversible process, and there was no treatment for the damage caused. Blood pressure was normal for the age group with or without vasopressor support, systolic blood pressure was ≥100mmHg, and the central temperature was ≥36 °C above 18 years of age.

There was no electrolyte imbalance or metabolic disorder that would affect the process. The patients were not under the influence of drugs that would affect the level of consciousness, and in the cases of drug exposure, the drug level was measured; in the cases where the drug level could not be measured, it was monitored five times its half-life.

Clinical brain death was diagnosed per the national guidelines, requiring irreversible coma, absence of brainstem reflexes, and a positive apnea test in a normothermic, feverless patient.

Coma was confirmed in all patients. The absence of brain stem reflexes was demonstrated, and an apnea test was performed. It was ensured that the pH and PaCO2 values of the arterial blood gas sample taken before the test were within normal limits, and the PO2 value was ≥200 mmHg. For the apnea test to be interpreted as positive (consistent with brain death), it was accepted that the patient did not have any breathing effort despite having a PaCO2 ≥60 mmHg at the end of the test and an increase of ≥20 mmHg compared to the baseline value.

The waiting time was 48 hours in infants younger than two months, 24 hours in children older than two months and younger than one year, 12 hours in children over one year old, and in adults, while it was 24 hours in cases of cardiopulmonary resuscitation or similar hypoxic ischemic acute cerebral injury. Except for the apnea test, other examinations were repeated in the patients who were included in the waiting period.

A second neurological examination was not expected for confirmatory tests. The clinical diagnosis of brain death was confirmed by the law dated 02.01.2014 by the "Brain Death Physicians Board" consisting of a neurology or neurosurgery specialist and an anesthesiologist or intensive care specialist and was finalized with the signatures of at least two physicians. After the diagnosis, the patient's relatives were informed of the death by the patient's doctor, and then the organ transplant coordination for brain death and organ donation was reported. The primary doctor of patient did not participate in the organ donation interviews.

Statistical Analysis

The data of our study were loaded into the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA) version 18.0 program. Parametric data are presented as mean SD (minimum-maximum) and categorical data as frequency (%).

RESULTS

It was determined that there were 411 patients diagnosed with brain death in the ICU between January 2003 and December 2016. Two hundred and four patients who did not have a registration form during the file scan, two patients who had a brain stem death, and 18 patients whose tests could not be completed after clinical suspicion were excluded from the study. A total of 207 patients' files were reviewed retrospectively. Demographic characteristics and hospitalization diagnoses of the patients are given in Table I.

Table I. Demographic data

Gender	
Female	71 (34%)
Male	136 (66%)
Age, years*	37.77 (2-78)
Hospitalization Diagnoses	
Intracranial hemorrhage	
Intraparenchymal bleeding	42 (20.28%)
SAH**	56 (27.05%)
Intracranial mass	16 (7.72%)
Multiple injuries due to trauma	59 (28.50%)
Infarct	7 (3.38%)
Post CPR***	7 (3.38%)
Central nervous system infection	7 (3.38%)
Drowning	4 (1.93%)
Intoxication	4 (1.93%)
Other	5 (2.41%)

Gender and the number of patients were expressed as (%), and the age was expressed as mean(min-max).

*Data are presented as mean SD (minimum-maximum) and frequency (%)

**SAH: Subarachnoid hemorrhage

***CPR: Cardiopulmonary resuscitation

In our study, there were 136 (66%) male and 71 (34%) female patients, and the mean age was 37.77±SD. Intracranial hemorrhage was the first line in the diagnosis of admission. Of these, 56 (27.05%) were subarachnoid hemorrhage (SAH), and 42 (20.28%) were intraparenchymal hemorrhage. Multiple injuries due to trauma were seen in 59 (28.50%) patients, followed by infarction, post-CPR, and central nervous system infections with 7 (3.38%) people each. Drowning was seen in 4 (1.93%), intoxications were in 4 (1.93%), and 5 (2.41%) were seen in other causes (sarcoidosis, renal transplant rejection, rectus sheath hematoma, lymphoma).

While GCS was 6.69 in the admission of the patients to the emergency department, it was observed that it decreased to 4.65±SD in the time until ICU. Neurological examination was performed on all patients at the time of diagnosis. The apnea test was performed in all patients who met adequate conditions before the apnea test, but the test could not be completed in 14 (6.7%) patients. Among the confirmatory tests, SPECT (single-photon emission computerized tomography) was used in 70 (33.81%) patients, TCD (Transcranial Doppler Ultrasonography) was used in 57 (27.53%) patients, more than one diagnostic method, EEG (Electroencephalography) + TCD, EEG + SPECT, TCD + SPECT was used in 74 (35.74%) patients, cerebral angiography was performed in 6 (2.89%) patients (Table II).

Table II. Confirmatory Tests Used in the Diagnosis of Cerebral Death

	n	%
SPECT	70	33.81
TCD	57	27.53
Angiography	6	2.89
Multiple Test	74	35.74
SPECT: Scintigraphy TCD: Transcranial Doppler Ultrasonography		

Spinal reflex was observed in 27 (13.04%) patients after cerebral death. Two patients (0.96%) had Lazarus sign. Sympathetic storms developed in 71 (34.29%) patients, and 14 (19.71%) of these patients underwent medical intervention. Diabetes insipidus developed in 122 (58.93%) of the patients, and all patients were treated medically. Inotrope was needed in 147 (71,04%) patients whose hemodynamic stabilization deteriorated during the follow-ups. Noradrenaline was started in 64 (43.53%) of these patients (Table III).

Table III. Complications Observed in Brain Death Patients

	n	%
Spinal Reflex	27	13.04
Lazarus sign	2	0.96
Sympathetic Storm	71	34.29
Diabetes insipidus	122	58.93
Hemodynamic instability	147	71.04
Need for Vasoactive Agent	64	43.53

Between 2003 and 2016, 139 (33.8%) of 411 patients in total became organ donors, and 66 (31.4%) of 207 brain death cases with detailed records donated their organs.

DISCUSSION and CONCLUSION

Brain death is the complete and irreversible loss of brain and brain stem activity. It is very important that the history, examination, and neuroimaging of the brain injury be consistent with the irreversible catastrophic damage to the brain (9).

When brain death diagnosed patients were examined regarding gender, it was seen that the male gender was prominent in the literature. In the study of Karasu et al, the rate of male gender was 62%, while in the study of Battal et al., it was 72% (10,11). In our study, the male gender was more common with a ratio of 66% (136) which was consistent with the literature. Aneurysmatic subarachnoid hemorrhages, traumatic brain injury, and intracranial hemorrhages are the leading causes of brain death. While intracranial bleeding was 59.5% and cerebrovascular events were 11% in Karasu et al. study, in the study of Yorick J et al. , this rate was approximately 80-90% (10,12). In our research, the three most common causes were intracerebral hemorrhage (49.52%), traumatic cerebral injury (28.57%), and intracranial mass (7.24%).

The definition of brain death is controversial. There are no clear and generalized protocols for the definite brain death diagnosis. These tests should be reliable, specific, sensitive, and valid (13). In the initial evaluation, the apnea test is important in addition to the neurological examination. Apnea testing is an important part of the brain death diagnosis and is the most error-prone and controversial part of the examination. The patient must be hemodynamically stable before and during the apnea test; if not, the apnea test should be discontinued and an ancillary test should be performed instead (14). Although there is universal consensus that apnea testing is a requirement for the clinical determination of brain death in adults, prospective studies on its safety are lacking (15). In our study, the test was terminated in 14 (6.7%) patients due to hemodynamic instability during the apnea test. Pneumothorax occurred in two patients. Tracheal oxygen was given to these patients. The studies reported that limiting the flow rate to no more than 6-8 L/min minimizes the risk of pneumothorax in cases where the O2 catheter method is used (16). In the study of Goudreau et al.(17), the complication rate during the apnea test was 28%; they reported that cardiac complications occurred in approximately one out of every four patients, and complications doubled if the necessary support was not provided before the test. In the study conducted by Saposnik et al., it was reported that two-thirds of the patients developed apnea test-related complications, 12% of these patients developed hypotension, 63% acidosis, and 23% hypoxemia, and four patients experienced major complications (18). In the study of Ali Daneshmand et al., this rate was <2% (19). In our study, the rate of termination of the test due to complications related to the apnea test was 6.7%. The differences between studies are considered to be the differences in determining complications (19). We think that the differences between the studies and our study are due to the different termination criteria. While complications were evaluated in the first two studies, in our study termination of the test was accepted as a criterion.

Supportive tests used to confirm brain death aim to confirm the loss of bioelectric activity in the brain or the cessation of cerebral circulation (20). In our study, the diagnosis was made by SPECT in 70 (32.8%) patients, TCD in 57 (26.7%) patients, angiography in 6 (2.89%) patients, and multiple diagnostic methods were used in 74 (35.74%) patients. In more than one diagnostic method group, some patients underwent EEG and did not obtain satisfactory results in TCD; in this case, additional methods were used. In the study by Karasu et al., radiological imaging methods were used to support the diagnosis in 30.4% (23 patients) of the cases diagnosed with brain death (10). The 99mTc -HMPAO SPECT method that we used in our study is a common and reliable method that requires facilities.

In a significant majority of potential organ donors, the pituitary gland is compressed during brain herniation, potentially developing central diabetes insipidus. These patients have high hourly urine output. The development of hypernatremia and hypotension may be observed (21). Treatment of diabetes

insipidus is necessary to prevent hypovolemia and hypernatremia, which if left untreated can harm organ outcomes, particularly liver and kidney transplant outcomes. (22). In our study, the rate of diabetes insipidus was 57.2%, and all patients were treated with desmopressin. When we look at the literature, there are studies with a wide range of results. Diabetes insipidus was found in 925 (49%) of 1878 patients diagnosed with brain death, and this rate was 78% in another series of 78 patients (23,24). Desmopressin, a synthetic vasopressin analog lacking vasopressor property, was recommended as first-line treatment for diabetes insipidus in 23 guidelines (23/27; 85.2%) with or without combined vasopressin infusion (25). In a retrospective analysis of 10,431 donors, the use of AVP (Arginine vasopressin) was associated with an increased organ healing rate. This rate is 50.5% in those who take AVP and 35.6% in those who do not (20).

In our cohort, inotropic therapy was utilized in 147 (71.04%) cases whose hemodynamic stabilization deteriorated during follow-up. Noradrenaline was administered in 64 (43.53%) of these patients, and dopamine was started in 58 patients. In a series of 247 cases by Schnuelle P et al., dopamine was observed to be particularly protective in renal transplantation (26). Dopamine use is not recommended due to the rare occurrence of vasoconstriction in the use of low-dose dopamine for management in multi-organ donors and the lack of sufficient evidence for the beneficial effects of dopamine. Indeed, its use has been gradually replaced by norepinephrine in most countries worldwide (27).

An organ donor who had brain death usually has a functioning spinal cord and therefore, the donor may present unregulated sympathetic and motor spinal reflexes in response to stimulation. Various studies have reported that the frequency of spinal reflexes in patients with cerebral death was between 30% and 70%. Ivan examined 52 patients with brain death who had deep tendon reflexes (35%), plantar flexor responses (35%), and abdominal reflexes (40%) (28). Another study showed the presence of deep tendon reflexes in the upper extremity in 31 and the lower extremity in 24 of 63 patients with brain death. Withdrawal response was observed in the lower extremities in 50 patients, and arm and forearm pronation in response to extension and cutaneous stimulation in 21 patients (29). Saposnik et al. reported this response as 39% in their study and most frequently observed myoclonus and similar movements in the fingers (30). In our cohort, spinal reflex was observed after brain death in 27 (12.6%) of the cases. Lazarus sign developed in two patients, sympathetic storm developed in 71 (33.3%) patients and medical intervention was performed in 14 patients. None of these patients died and developed acute organ dysfunction.

Our study has some limitations. First, the study was planned as a retrospective file review. Secondly, the data used in the study are only detailed observation forms belonging to our clinic, so the current transplant rates data do not fully reflect the actual rates. It is thought that the number of brain death and transplant percentages will be higher, especially considering the inaccessible files.

The biggest problem in managing brain death is the lack of a valid accepted worldwide protocol and the differences in the diagnosis of brain death. Recognition of brain death is a clinical condition that requires training and attention. It is very important to think about the diagnosis, to perform the tests leading to the diagnosis correctly, to make the necessary preparations before the tests, to apply the accepted algorithms carefully, and especially in cases who can be donors. The clinical situation expected during the follow-up should be well-known and correct, and timely intervention should be made. We think effective communication and working with the transplant unit will affect organ donation after the diagnosis of brain death. All these needs should be considered in a broad framework. Apart from medical approaches, the public's view of the subject should be discussed in detail as social and religious influences, and multiple approaches should be exhibited.

We reiterate that more clinical research is needed in this area. A common diagnosis protocol is required to establish an environment of trust. Successful management of trained and experienced teams will correct the results of public relations that do not allow for medically clear, legal complexity established by considering the dynamics of society.

Ethics Committee Approval:

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Akdeniz Medical Faculty Ethical Committee, Akdeniz University. Ethics committee number is 676 and date is 15.11.2017.

Informed Consent:

Our study was conducted retrospectively by scanning the files, and it was not necessary to obtain informed consent from the patients.

Author Contributions:

Concept – Ö.Ç.; Design – M.Y. ; Supervision – M.Y.A ; Resources – A.G.A. ; Materials – N.B. ; Data Collection and/or Processing – A.G.G. ; Analysis and/ or Interpretation – Ö.Ç. ; Literature Search – A.R. ; Writing Manuscript – Ö.Ç. ; Critical Review – M.C., Ü.A.

Conflict of Interest:

The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Presented Congress:

Our study was presented at the 18th Congress of the European Society for Organ Transplantation, 24-27 September 2017, Barcelona, Spain.

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