



Research

Evaluation of Brain Death in Children in a Tertiary Pediatric Intensive Care Unit

Üçüncü Basamak Pediatrik Yoğun Bakım Ünitesindeki Çocuklarda Beyin Ölümünün Değerlendirilmesi

İD Süleyman Bayraktar¹, İD Bilge Tanyeri-Bayraktar², İD Murat Elevli³

¹University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, Istanbul, Turkey

²Bezmialem Vakıf University Faculty of Medicine, Department of Neonatology, Istanbul, Turkey

³University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic Pediatrics, Istanbul, Turkey

ABSTRACT

Objective: This study aimed to evaluate the characteristics of children who are diagnosed with brain death (BD) in a tertiary care pediatric intensive care unit (PICU) and highlight the organ donation rates.

Methods: A retrospective observational study was conducted among pediatric patients who met the criteria of BD based on the medical records in all deaths that occurred between January 2018 and May 2021. The demographic data, main BD cause, duration between admission to PICU and BD decision, length of stay, time between BD decision and cardiac arrest, presence of apnea and ancillary tests, and organ donation status were recorded.

Results: This study analyzed 642 patients who are admitted to the PICU, wherein 1.9% was diagnosed as BD. Asphyxia was the most frequent cause of BD (33.3%). The mean interval between the suspected of BD diagnosis and median of duration between BD decision and cardiac arrest were 18.58±13.77 (min: 3, max: 48) h and 36 (minimum (min): 1, maximum (max): 192) h, respectively. The mean length of stay in the PICU was 16.75±11.36 days (min: 3, max: 42). The disorders related to BD include diabetes insipidus (58.3%) and hypothermia (33.3%). Apnea test was positive in 6 (50%) of 12 children. At least one ancillary test was used in all patients. Five of 12 (41.7%) patients were not eligible for organ donation because they were refugee, and the families of the remaining 7 patients did not give permission for organ donation.

Conclusion: Organ donation can be increased if frequent family meetings are held by an experienced and trained team coordinator, including psychologists and religious authorities. This issue can be organized as a certified and standardized program throughout the country.

Keywords: Brain death, children, pediatric intensive care unit, organ donation, refugee

ÖZ

Amaç: Üçüncü basamak çocuk yoğun bakım ünitesinde (YBÜ) beyin ölümü (BÖ) tanısı alan çocukların özelliklerini değerlendirmek ve organ bağış oranlarına vurgu yapmak.

Gereç ve Yöntem: Ocak 2018-Mayıs 2021 tarihleri arasında meydana gelen tüm ölümlere ilişkin tıbbi kayıtlara dayanarak, BÖ kriterlerini karşılayan çocuk hastalarda geriye dönük gözlemsel bir çalışma yapılmıştır. Demografik veriler, BÖ'nün ana nedeni, çocuk YBÜ'ne kabul ve BÖ kararı arasındaki süre, hastanede kalış süresi, BÖ kararı ile kardiyak arrest arasındaki süre, apne testi ve yardımcı testlerin varlığı, organ bağış durumu kaydedildi.

Bulgular: Çocuk YBÜ'ye başvuran toplam 642 hastanın %1,9'u BÖ tanısı aldı. BÖ'nün en sık nedeni asfiksi idi (%33,3). BÖ şüphesi ve BÖ tanısı arasındaki sürenin ortalama değeri ve BÖ tanısından sonra kardiyak arrestin meydana gelmesi arasındaki sürenin ortanca değerleri sırasıyla 18,58±13,77 [(minimum (min): 3, maksimum (maks): 48)] saat ve 36 (min: 1, maks: 192) saat idi. Çocuk YBÜ'de ortalama kalış süresi 16,75±11,36 gün (min: 3, maks: 42) idi. BÖ'ye bağılı bozukluklar diabetes insipidus (%58,3) ve hipotermi (%33,3) idi. Oniki çocuğun 6'sında (%50) apne testi pozitif. Tüm hastalarda en az bir yardımcı test kullanıldı. On iki hastadan 5'i (%41,7) mülteci oldukları için organ bağışına uygun bulunmadı, kalan 7 hastanın aileleri ise organ bağışına izin vermedi.

Address for Correspondence: Süleyman Bayraktar, University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, Istanbul, Turkey
Phone: +90 532 385 10 78 E-mail: bsuleyman@hotmail.com ORCID ID: orcid.org/0000-0002-8080-2438

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Sonuç: Psikologlar ve dini otoritelerin de dahil olduğu, deneyimli ve eğitilmiş bir koordinatör ekip tarafından, sık sık aile toplantıları yapılırsa organ bağıışı artırılabilir. Bu konu ülke genelinde sertifikalı ve standartlaştırılmış bir program olarak düzenlenebilir.

Anahtar Kelimeler: Beyin ölümü, çocuklar, çocuk yoğun bakım ünitesi, organ bağıışı, göçmen

INTRODUCTION

Brain death (BD) is a clinical diagnosis that is characterized by the complete, permanent, and irreversible loss of all brain, brainstem, and cerebellar activities (1-3). According to the Turkish Neurological Society, BD is described as "whole BD" that refers to the medical death state (4). The pathophysiologic features of BD include increased intracranial pressure, disrupted cerebral blood flow, and occluded cerebral perfusion (1,3).

The American Academy of Pediatrics, the Child Neurology Society, and the Society of Critical Care Medicine published the BD guidelines in children (5,6). Due to insufficient globally accepted definition and formal declaration guidelines, avoidance, and concerns continue in BD decisions in the pediatric intensive care units (PICU) (7). However, as access to critical care increases, more practitioners encounter this difficult clinical scenario (8). In this setting, the incidence of reported BD varies. The reported rates of BD are found in a wide range (10.8%-37%) in different pediatric studies (9-14).

Early diagnosis of BD is crucial for organ and tissue protection from cardiovascular and metabolic changes for organ donors (3,11). Turkey was one of the first countries to legally establish the guidelines of BD; however, approximately 11,932 patients are waiting for organ transplantation and 5%-13% of them are pediatric patients (15).

Today, studies that conducted diagnosis of BD and the subsequent processes in children are limited. Thus, this study aimed to analyze the characteristics of children who are diagnosed with BD and highlight the organ donation rates in the PICU.

METHODS

Study Design

This retrospective observational study was conducted among pediatric patients who met the criteria for BD between January 2018 and May 2021. The pediatric ICU at University of Health Sciences Turkey, Haseki Training and Research Hospital is a tertiary care facility that is located in a low socioeconomic and cosmopolitan place of Istanbul. While our unit has 6 beds until April 2019, it has been increased to 10 beds after this date.

BD Evaluation Policy

Declaration of BD in pediatric cases is a special issue in Turkey, as well as worldwide (16). According to the

Regulations on Organ and Tissue Transplantation Services (17) in Turkey, the process in pediatric cases is as follows: a clinical BD finding should be established to fulfill the non-reversibility criteria. At the end of the waiting period, a second examination is required to confirm the unchanged clinical BD findings and a single apnea test is sufficient for diagnosis during this process.

The waiting period is 48 h in infants up to 2 months old, 24 h between 2 months and 1 year old, 12 h in >1 year, and 24 h in anoxic BD. Therefore, experienced pediatric radiologists who can perform and evaluate tests that show cerebral blood flow can facilitate a faster BD diagnosis without waiting for re-examination of brain stem reflexes (4). The guideline on BD that was published by the Turkish Neurological Association stated that at least two confirmatory tests in the newborn group (up to 2 months) and one laboratory test in children aged >2 months are required (4).

The decision of BD was taken with the judgment of two physicians following the Turkish BD regulation (16).

Apnea Test

The apnea test objectively measures the brainstem function without the respiratory drive that support BD declaration (18). Apnea testing standards also differ among countries, both in duration (5 to 15 min) and interpretation of objective arterial blood gases (no pH guidelines for <7.4) (13,18).

The apnea test was performed by a pediatric intensivist in the PICU and was interpreted as the absence of spontaneous breathing with partial pressure of carbon dioxide (PaCO₂) of >60 mmHg (or a 20 mmHg increase in PaCO₂ over the normal PaCO₂ baseline) and the corresponding decrease in pH before buffering mechanisms can occur. Without observed respiratory efforts during the test, the apnea test demonstrates an insufficient drive to breathe, hence absence of function of the medullary respiratory centers. In the presence of hypoxia or hypotension during the testing, which makes the test invalid, the test should be stopped and the hypoxia or hypotension should be corrected (13).

Ancillary Tests

Uncompleted clinical examination or the apnea test, concerns about the validity of clinical findings, and desire to shorten the observation period between examinations are the indications of using ancillary tests (19). Ancillary tests assess for brain function [electroencephalogram (EEG)] or cerebral blood flow (radionuclide imaging, angiography,

etc.) in the BD diagnosis (18). The term “ancillary” is preferred to “confirmatory,” nevertheless, they can assist the clinician in BD diagnosis. Generally, ancillary tests are mandatory in BD diagnosis in some countries (10). Ancillary tests that are used in our hospital were EEG, computed tomography angiography (CTA), and transcranial Doppler sonography (TDS).

Declaration of BD to the Family

As soon as the diagnosis is made, BD declaration should be announced to the family and the organ transplant coordinator should be notified. These procedures were applied for all cases in the present study. According to the relevant law, BD was firstly declared to parents by the PICU team. After that, the hospital’s local organ transplant coordinator interviews the families for organ donation.

Ethical Approval and Data Selection

The Local Ethical Board of University of Health Sciences Turkey, Haseki Training and Research Hospital approved the study (approval no: 61-2021 date: 14.07.2021).

The medical records of patients were accessed using the hospital database. The following demographics were recorded: age at diagnosis, sex, main BD cause, and duration between admission to PICU and BD decision, length of stay, interval between BD decision and cardiac arrest, and organ donation status.

The main cause to BD was grouped into the following categories: Multiple trauma, central nervous system (CNS) infection, hypoxia/asphyxia (status epilepticus, following cardiopulmonary arrest, sudden death, etc.), stroke, and CNS tumor.

Alterations accompanying to BD were analyzed, such as diabetes insipidus, hypothermia, hyperglycemia, coagulopathy, and hemodynamic instability.

Diabetes insipidus: Polyuria (urine output of >4 mL/kg/h for children and 300 mL/h for children >70 kg), urine density of <1.005 , high serum osmolality (>300 mOsm/kg) and low urine osmolality (<300 mOsm/kg) at the time of diagnosis, and hypernatremia with Na of >145 mEq/dL.

Hypothermia: Core temperature of $<35^{\circ}\text{C}$

Hyperglycemia: Blood glucose of >180 mg/dL

Coagulopathy: Prothrombin time of $<60\%$

Hemodynamic dysfunction: Mean blood pressure of <2 standard deviations (SD) from the 50th percentile for the age and/or inotrope or vasopressor requirements or increased dosage

All patients were eligible for organ donation; however, five of them were refugees.

Statistical Analysis

The results were analyzed using the Statistical Package for the Social Sciences statistical software program (version 18.0, SPSS Inc. IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as frequency and percentage values for categorical variables and mean \pm SD (min, max) for continuous variables. If the measured outcome distribution based is abnormal, values were expressed as median and interquartile range.

RESULTS

Totally, 642 patients were followed up in the PICU, where 50 (7.8%) died. Of the 50, 12 (24.0%) were diagnosed with BD. Of all PICU admissions, 1.9% were diagnosed with BD. The demographic and clinical findings were presented in Table 1. The mean age of patients was 6.7 ± 3.8 years [minimum (min): 4 months, maksimum (maks): 11.5 years]. Of the children, 58.3% (n=7) were girls. The causes of BD were listed as asphyxia in 4 (33.3%), CNS tumor in 3 (25.0%), CNS infections in 3 (25.0%), and trauma in 2 (16.7%) patients. The suspected of BD to BD diagnosis and the median duration of cardiac arrest after diagnosis were 18.58 ± 13.77 (min: 3, max: 48) h and 36 (min: 1, max: 192) h, respectively. The mean length of stay in the PICU was 16.75 ± 11.36 days (min: 3, max: 42). The disorders related to BD include diabetes insipidus (58.3%) and hypothermia (33.3%). Apnea test was positive in 6 (50%) of 12 children. During apnea test one patient had pneumothorax. Eight (66.7%) children were followed with EEG, which revealed isoelectrical activity. Ten (83.3%) children had CTA and only 2 (16.7%) patients had TDS. Both the ancillary tests were compatible with BD. All cases were suitable for organ donation. Since 5 patients are refugees, they were accepted as unsuitable for organ donation. The families refused organ transplantation in 7 patients. The main reasons for the rejection of organ donation were religious beliefs in 5 (71.4%) families and the inability to accept the beating of the heart as dead in 2 (28.6%) families.

DISCUSSION

This retrospective study found the rate of BD as 24.0% among patients who died in the PICU, and suitable donors were found for organ donation; however, no family consent could be obtained.

Bonetto et al. (10) reported the overall mortality as 7.45% and BD as 19.14%. Kirschen et al. (9) declared the rate of

Table 1. Demographic and clinical features of children diagnosed with BD

Patient no	Age (year)	Sex	Cause of BD	Length of stay (d)	Time to diagnosis of BD (h)	Time of cardiac arrest after BD (h)	Apnea test	Ancillary tests	Complications	Suitability for organ donation	Organ donation
1	11.5	M	Traumatic brain injury	42	28	36	Positive	EEG	Hypothermia, diabetes insipidus	Suitable	None
2	10.5	M	Optic glioma	27	6	12	Inconclusive	EEG, CTA	-	Suitable	None
3	10	F	Encephalitis	28	8	168	Positive	EEG, CTA	Hypothermia	Suitable	None
4	7.5	F	Pons glioma	4	6	36	Positive	CTA	-	Suitable	None
5	7.5	F	Asphyxia, epilepsy	3	3	1	Inconclusive	CTA	Hypothermia, diabetes insipidus, pneumothorax	Suitable	None (Syrian)
6	11	F	Traumatic brain injury	10	16	192	Positive	EEG	Diabetes insipidus	Suitable	None
7	6	M	Menengitis (Tbc)	23	11	11	Positive	EEG, CTA, TDS	Hypothermia, diabetes insipidus	Suitable	None (Georgian)
8	8	M	Encephalitis	13	48	32	Inconclusive	CTA	-	Suitable	None (Syrian)
9	2.5	F	Atypical rhabdoid tumor	17	12	48	Inconclusive	EEG, CTA	Diabetes insipidus	Suitable	None
10	0.4	F	Asphyxia, post arrest	14	35	48	Inconclusive	EEG, CTA	Hypothermia, diabetes insipidus	Suitable	None
11	3.5	M	Asphyxia, post arrest	11	26	26	Inconclusive	CTA, TDS	Diabetes insipidus	Suitable	None (Syrian)
12	2.5	F	Asphyxia, post arrest	9	24	44	Inconclusive	EEG, CTA	Hypothermia	Suitable	None (Iraqi)

BD: Brain death; M: Male; F: Female; EEG: Electroencephalogram; CTA: Computed tomography angiography; TDS: Transcranial Doppler sonography

BD as 20.7%. The crude rate of BD was 1.1% in the PICU from our country (20). Sucu et al. (1) noticed the mortality as 10.2% and the BD as 17% of these patients. Yener et al. (11) mentioned 10.8% of deaths as BD. Our BD percentage was found to be similar to the previous studies.

A study conducted in children revealed the average age as 6.8 ± 5.5 years (21). Kirschen et al. (9) reported that the age of patients in this group was between 2 and 12 years. The mean age of children in our study was consistent with the study of Özmert et al. (21).

The major disease that causes BD varied in studies. The most common causes of BD include hypoxic-ischemic injury, shock, and/or respiratory arrest, and traumatic brain injury (9,12,22). Some studies have classified the common

diseases of BD according to the age of children. Multiple trauma was found as the main cause at median 7 years old (10), whereas traumatic brain injury was the leading cause of BD in children over 1 year old in developed countries, and no clear data is reported on this subject in our country (1). Trauma and intracranial hemorrhage were found as the highest rate in patients who are diagnosed with BD in some studies (2,6,21). A study conducted in our country revealed that traumatic brain injury was the leading cause in 70% of patients (20). Thus, Sucu et al. (1) stated that traumatic brain injury was a cause at a rate of 7%. Contrarily, Yener et al. (11) found post-cardiorespiratory arrest as a common cause of BD. Our study found that the most common reason was asphyxia (33.3%) and the diagnosis of patients at admission

varied in a large spectrum.

Early recognition of BD in hospital follow-up is important in evaluating the patients for organ donation (23). The mean time to diagnosis after BD suspicion was 5.9 ± 6.2 days in a study by Özmert et al. (21), whereas another study mentioned 3 days (24). Karasu et al. (25) reported that these periods were 6.8 days in patients aged 18 years. Additionally, Altınsoy et al. (26) compared two different time periods and found that duration of BD diagnosis shortened over the years. In previous studies, the time of BD diagnosis was not found to be different in children compared with adults. Our study revealed that the time of diagnosis was 18.58 hours, which was shorter than the reported studies because of not waiting for the second examination.

The studies also reported the interval from BD diagnosis to cardiac death, which revealed 6.8 days in patients younger than 18 years of age and 2.5 days in patients aged 18 years and older (25) since the time for cardiac death lasts longer than expected because physicians tend to continue life support both for cultural reasons, while getting the decision of BD from the families and change their minds for organ donation idea (27). The mean time to develop cardiac arrest after the diagnosis of BD was 6.9 ± 7.4 days in non-donor cases whose medical support had been reduced (21). The duration of cardiac arrest after diagnosis was similar in both children (3.63 ± 4.93 days) and adults (2.17 ± 2.31 days) (26). Our study revealed that the median interval between BD and cardiac arrest was 36 h.

The most common alterations reported in studies include hypothermia, diabetes insipidus, and hemodynamic dysfunction (10,11,21). Antidiuretic hormone deficiency occurs in 65%-90% of patients with BD due to neurohypophysis damage (20). Bonetto et al. (10) also found hemodynamic dysfunction (63.2%) and diabetes insipidus (46.6%) in their study. A careful organ preservation treatment protocol in intensive care is the first step in successful organ transplantation. Therefore, knowing and addressing the mechanisms of complications is important (21). In our patients, hypothermia and diabetes insipidus were obtained in accordance with the literature.

Apnea test is mandatory in BD diagnosis in Turkey; however, Sucu et al. (1) found positive apnea test in 36% of patients. Our study applied the apnea test to all of patients, but was terminated due to complications (hypoxia, hypotension, etc.) in 50%. Positive apnea test was found higher in our study than the study of Sucu et al. (1). The reasons behind low apnea testing in some countries are as follows: 1. It is invasive and risky 2. Obtaining consent form from the guardians is difficult (7). Our country does not mandate

taking a consent form for an apnea testing. During the apnea test, serious complications (cardiac arrest, hypotension, hypoxemia, and pneumothorax) may occur (28,29). One patient had pneumothorax during the apnea test.

The clinical evaluation is prioritized over the ancillary tests according to the pediatric BD guidelines that was revised in 2011, but a variety of ancillary tests are currently used in clinical practice (10,19,29). Studies showed that healthcare professionals used more ancillary tests in pediatric patients than in adults (19). The idea behind this behavior may be an attempt to objectively demonstrate the absence of cerebral blood flow or electrical brain function, rather than findings that appear subjective on clinical examination (19). BD declaration using ancillary methods is mandatory in Argentina (10). The consequences of adopting a health policy in the mandatory ancillary methods are based on the ethical and cultural conditions specific to each country. A study conducted in our country revealed that 76.2% of patients needed ancillary tests, the most common was CTA (22.4%) and mentioned that the need for ancillary tests declined throughout the years because of awareness and clinical experience of involved physicians (27). Özmert et al. (21) reported that EEG was performed in 61% of patients in addition to the apnea test. They used radiological imaging methods in 39% of patients (21). Another study by Altınsoy et al. (26) used DSA to support the diagnosis of BD and mentioned that DSA was the gold standard in BD diagnosis and might contribute to shortening the diagnosis period (26). Karasu et al. (25) showed that 30.4% of BD cases needed ancillary tests for diagnosis. In our study, the ratio of the ancillary tests performed seemed higher than the other studies to convince the families in BD decision. In our hospital region, the educational level of population is low, thus they rely on sophisticated diagnostic tools. They have no idea about BD. The term BD is a traumatic diagnosis for families who face it for the first time in their lives. BD is often confused with the diagnosis of vegetative life. Socio-cultural structure, religious beliefs, influence of family elders, and being a refugee are the factors effecting family reactions. Efforts should be made to improve the society's understanding of BD and to improve physician practices in determining BD (19). However, the diagnosis and process of BD is difficult in pediatric patients, especially in patients with hemodynamic disorders, thus physicians may act more cautiously.

In the field of pediatrics, the need for solid organ donations has increased worldwide, 1.5%-2% patients were in the waiting list of developed countries (21). Organ donation rate was found in 43.8 people per million in Spain (30). A

retrospective adult study in Qatar reported the rate of family rejection as 93%. This result was attributed to various factors, such as religious beliefs, culture, population dynamics (high number of immigrants), and ignorance of the importance of organ donation (31). Another study included 268 patients with a family approval rate of 78.4% and the organ donation approval rate rose with the increased frequency of meetings held by an organ transplantation coordinator with the family after BD declaration (32). Organ transplant centers and physicians in our country are adequately equipped; however, the number of organ donations is insufficient. The trained physicians, standardization of BD protocols, use of a checklist, and frequent meetings with families using precise, consistent, and clear language are important to ensure the integrity of BD determination and organ donation (9,32). Battal et al. (24) found the rate of organ donation as 29.03% in their study, whereas other studies reported 17%-34.2% (21,25,27). The rate of organ donation is still less than expected, and many patients are on transplant waiting lists (27). A study conducted in PICU revealed that no donor was issued like our study (1). Previous studies stated that the most serious problem regarding organ donation in Turkey was the death of patients without BD diagnosis and the lack of organ transplant coordinators (2). Recently, the use of international guidelines and the organization of the intensive care team enabled early BD diagnosis, but the organ donation rate is still low. When interviewed with the families of organ donors, Kiraklı et al. (33) reported that 36% of them seemed previously positive, and 64% attributed this to the influence of the coordinator. Altinsoy et al. (26) revealed that the rate of organ donation was 37.87% before 2014 and 21.15% after 2014. They commented that this difference may be due not only to be social characteristics of the guardian of patients but also to the communication skills of the employees in the organ donation coordination unit (26). Therefore, organ transplant coordinators, who will receive family approval, should be trained and experienced. Family interviews that are conducted by an experienced and trained transplant coordinator should emphasize that BD is a real death and organ donation is important. Religious, cultural, and legal reasons and the lack of adequate infrastructure and resources are the main reasons behind the continuation of life-saving and life-improving treatment and rejection of organ donation. Some physicians reported that it is commonly requested to continue organ support because of the belief that a patient who is declared BD can regain neurological function or a lack of acceptance that a person can be dead if the heart was still beating (9). Another obstacle to organ donation in our study was being a refugee. According to the organ transplant regulation, the

inability to receive organ donations from refugees reduces the rate of organ transplants, as seen in our study.

Study Limitations

The study was conducted in a retrospective design. The results are from a single center of 10-bed PICU, thus the size of the study may be too small.

CONCLUSION

Families should be informed that BD is considered a definite death and that organ donation is important. In this respect, the importance of informing the public, regularly through the media, and social media was emphasized. Having a psychologist who is experienced as an organ donation coordinator and can properly communicate with families will increase the rate of organ donation. The donation rate is believed to increase if family meetings are frequently held by an experienced and trained coordinator team including religious authorities. This issue can be organized as a certified and standardized program throughout the country. Shortly, organ donation rates can be increased by designing the regulations about refugees becoming organ donors.

ETHICS

Ethics Committee Approval: The Local Ethical Board of University of Health Sciences Turkey, Haseki Training and Research Hospital approved the study (approval no: 61-2021 date: 14.07.2021).

Informed Consent: This study is retrospective.

Authorship Contributions

Surgical and Medical Practices: S.B., M.E., Concept: S.B., B.T.B., Design: S.B., B.T.B., Data Collection or Processing: S.B., Analysis or Interpretation: S.B., B.T.B., M.E., Literature Search: S.B., B.T.B., Writing: S.B., B.T.B., M.E.

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