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Brain Death and Organ Donation in Paediatric Intensive Care Unit

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Abstract

Objective: The purpose of the present study was to retrospectively analyse the brain death (BD) cases that were specified within the last 8 years in the paediatric intensive care unit of our hospital.

Methods: Archive files and computer records of 23 paediatric cases were analysed. Data on age, gender, conditions that caused BD, paediatric risk of mortality (PRISM III) scores, time between suspicion of BD and issuing of BD report, confirmatory tests used, complications that occurred following the diagnosis of BD and time to cardiac arrest development after diagnosis of BD were recorded.

Results: The average age of the patients was 6.8±5.5 years. The most frequent cause of BD was intracranial haemorrhage (30.4%). The mean time to diagnosis after BD suspicion was 5.9±6.2 days. Electroencephalography was performed in 61% of the patients in addition to the apnoea test. Radiological imaging methods were used in 39% of the patients (n=9). Of the cases, 34.7% developed hypothermia, and 4.3% developed diabetes insipidus (DI). Among them, 43.4% had both DI and hypothermia. The mean PRISM score was calculated as 22±9.2. The donation rate of the families was 17%. The mean time to cardiac arrest development after diagnosis of BD was 6.9±7.4 days in non-donor cases where medical support had been reduced.

Conclusion: Any patient with a neurologically poor prognosis in the intensive care unit should be considered to develop BD and diagnosed with BD without delay. The donation rate will increase if family interviews are done by an experienced and educated coordinator.

Keywords: Brain death, child, organ donation

Introduction

Organ failure is a major cause of morbidity and mortality in paediatric intensive care units. The most common organ failure is renal failure, followed by cardiac, hepatic and haematologic system failures. The number of patients waiting for transplantation due to organ failure is increasing in Turkey similarly worldwide. Permanent treatment of these patients is organ transplantation (1). Therefore, diagnosis of brain death (BD) and providing good donor care are becoming even more important for patients awaiting organ transplantation. BD is a clinical diagnosis and is the complete and irreversible loss of all brain functions including the brain stem. Approximately 25,000 patients are waiting for organ transplantation in Turkey according to the current data (2).

In children, the response of the brain to hypoxic damage varies as mild, moderate and severe brain injuries. Preventing secondary brain injury after primary injury is essential in treatment. Diagnosing BD is more difficult in children and takes more time. The most common causes of BD in children are trauma, anoxic encephalopathy, infections and cerebral neoplasia, respectively (3). Criteria for BD diagnosis vary between countries due to some variables,

such as the tests required for diagnosis and the number of physicians to make the diagnosis. There are a limited number of studies conducted in children regarding BD diagnosis and the subsequent process.

The demographic characteristics of paediatric BD cases diagnosed in the last 8 years in the paediatric intensive care unit of our hospital, confirmatory tests used in diagnosis, time to the development of cardiac arrest after diagnosis and families' acceptance/rejection rates of organ donation were examined in this retrospective study.

Methods

Twenty-three paediatric cases diagnosed with BD in the tertiary paediatric intensive care unit of our education and research hospital between 13.02.2009 and 18.08.2016 were retrospectively analysed. University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital Ethics Committee approved the study (Approval no.: 2016-060).

Brain death was diagnosed in accordance with the conditions outlined in the applicable law and the criteria specified in the guidelines (4-6). Age and gender of the cases were recorded, and also conditions causing BD were grouped and recorded under six headings: intracranial haemorrhage, hypoxic brain injury, intracranial infection, intracranial tumour, traumatic brain injury and intoxication. In addition, archive files and computer records were examined, and paediatric risk of mortality (PRISM III) scores, time between suspicion of BD and issuing of BD report, confirmatory tests used, and complications that occurred following diagnosis of BD were recorded. The organ donation rate of the families, the organs removed and their number was determined using data obtained from the department of organ transplant coordination. PRISM III scoring scale is used for each patient admitted to our paediatric intensive care unit based on patient data in the first 24 h. The calculated score is recorded separately for each patient. The following parameters were covered as determined by the PRISM III scoring system:

- Cardiovascular system, including systolic blood pressure and heart rate,
- Nervous system, including pupils' light reflex and level of consciousness,
- Blood tests, including arterial blood gas (pH, total CO_2, PaO_2 and $PaCO_2$), serum levels of sugar, blood urea nitrogen and creatinine, platelet and white blood cell counts, prothrombin time and partial thromboplastin time,
- Body temperature (7).

Statistical analysis

Descriptive statistics were expressed as frequency and percentage values for categorical variables and mean±SD (min, max) for continuous variables.

Results

Twenty-three paediatric cases diagnosed with BD in the paediatric intensive care unit of our hospital between 13.02.2009 and 18.08.2016 were identified. The average age of the patients was 6.8±5.5 (min: 7 months, max: 17 years) years. The diagnoses leading to BD were examined in six groups, and the most frequent cause of BD was determined to be intracranial haemorrhage (30.4%, n=7). The mean time to diagnosis after BD suspicion was 5.9±6.2 days (Table 1). Apnoea test was performed in all cases except for one case where it could not be completed due to cardiac arrest. Electroencephalography (EEG) was performed in 61% of the patients (n=14) in addition to the apnoea test. Radiological imaging methods, computerised tomographic angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA), were used in 39% of the patients (n=9). Of the cases, 34.7% (n=8) developed hypothermia, and 4.3% (n=1) developed diabetes insipidus (DI). Among them, 43.4% (n=10) had both DI and hypothermia, whereas 17.3% (n=4) did not develop any complications (Table 2). PRISM scores ranged between min: 8 and max: 41, and the mean PRISM score was 22±9.2. The donation rate of the families was 17% (n=4), and only three cases were donors according to the department of organ transplant coordination data. In two cases, both kidneys and liver were used, and in the other case, two kidneys and pancreas were used.

One case was not found eligible as a donor in the transplant unit. The mean time to cardiac arrest development after diagnosis of BD was 6.9±7.4 days in non-donor cases where medical support had been reduced.

Discussion

When we examine the statistical results regarding the number of BDs occurring in our country, the number is increasing annually. The most important reason for this is that the records on this subject have been kept more regularly in the last decade. There are reports in the literature about the statistical results related to the diagnosis of BD in different hospitals, but data related to child patients are rarely seen especially in our country. In the present study, we reviewed the patients who were monitored in the paediatric intensive care unit who were done the apnoea test by our department and their follow-ups after the apnoea test retrospectively.

Brain death often occurs following acute brain injury. The cause of BD in children is mainly associated with traumatic

Table 1. Demographic characteristics of the patients	
Variables	**(n=23)**
Age (years), mean±SD (min, max)	6.8±5.5 (min: 0.6, max: 17)
Gender	
Male, n (%)	12 (52)
Female, n (%)	11 (48)
Diagnosis, n (%)	
Intracranial haemorrhage	7 (30.4)
Hypoxic brain damage	6 (26)
Intracranial infection	4 (17.3)
Intracranial tumour	3 (13)
Traumatic brain injury	2 (8.6)
Intoxication	1 (4.3)
Confirmatory tests	
EEG	14 (61)
EEG+CT angiography/ MR angiography	8 (34.7)
EEG+DSA	1 (4.3)
Duration of diagnosis of brain death (days), mean±SD (min, max)	5.9±6.2 (min: 1, max: 26)
PRISM III score, mean±SD (min, max)	22±9.2 (min: 8, max: 41)
Complications, n (%)	
No	4 (17.3)
Hypothermia	8 (34.7)
Diabetes insipidus	1 (4.3)
Hypothermia+diabetes insipidus	10 (43.4)
Parental approval, n (%)	
Yes	4 (17.3)
No	19 (82.7)
Organ donation, n (%)	3 (13)
Duration of survival after diagnosis of BD (days), mean±SD (min, max)	6.9±7.4 (min: 0.2, max: 25)
Age-related waiting period, n	
Children between 2 months and 1 year old, (neurological examination after 24 h/patient numbers; 1, 12, 15, 23)	4
Children >1 year, (neurological examination after 12 h)	19

EEG: electroencephalography; CT: computerised tomographic; DSA: digital subtraction angiography; MR: magnetic resonance; SD: standard deviation

brain injury (8-12). In our study, the highest incidence of BD was observed after intracranial haemorrhage (non-traumatic) (30.4%), followed by hypoxic brain injury and intracranial in-

fection. In the present study, traumatic brain injury was diagnosed in 2 (8.6%) patients. In a similar study with two centres, the most common causes of BD were intracranial haemorrhage (non-traumatic) in one centre and traumatic brain injury in the other centre (13). In another retrospective study, the main aetiology was intracranial haemorrhage (45.3%), followed by ischaemic injury (17%) and traumatic brain injury (15.1%) (14). There is another hospital in the vicinity of our hospital, which handles paediatric trauma cases and is a trauma centre, and this centre is the first resort for child trauma patients. We attribute the low rate of traumatic brain injury in our study due to this fact. As a result, all these pathologies cause severe cerebral damage resulting in decreased cerebral perfusion and transtentorial herniation in response to cerebral oedema formation and increased intracranial pressure.

Ashwal et al. (9) stated that the declaration of BD in many paediatric patients who developed coma due to severe and acute central nervous system injury occurs within the first 2 days of hospitalisation. In a two-centre study, Gunduz et al. (13) found that the times to BD diagnosis are 6.7 days in the first centre and 1.7 days in the second, which admitted trauma patients. In another study evaluating BD in children, this period was 6.6 days (15). In our study, the mean time from BD suspicion to final diagnosis was 5.9±6.2 days, which was consistent with the literature.

The finalisation of BD diagnosis and management in the subsequent period vary according to the medical and legal regulations in different countries. Clinical evaluation must be verified by more than one physician in many countries and also in Turkey. Until recently, approval of a neurologist, neurosurgeon, cardiologist and anaesthesiologist was required for the declaration of BD as enforced by a law that was in force at the time. With the amendment in 2014, approval of two physicians, one neurologist or neurosurgeon and one anaesthesiologist and reanimation specialist or intensive care specialist, is sufficient for the diagnosis of BD (5). BD declaration was performed in our hospital in accordance with these laws. In many paediatric patients in coma due to severe and acute central nervous system damage, BD diagnosis is made by consecutive neurological examinations made every 12 h, confirmatory radiological tests for cerebral blood flow (DSA, CTA, MRA, transcranial Doppler ultrasonography (USG) and brain scintigraphy) or by one of the electrophysiological tests with less diagnostic value (EEG and evoked potentials) and apnoea tests. It is necessary to demonstrate irreversible failure of the brain cortex, brain stem and reticular activating system by clinical and radiological/electrophysiological tests (confirmatory tests) in order to diagnose BD. Since paediatric intensive care patients are haemodynamically unsuitable for transport, performing supporting tests is time consuming. These tests are difficult to perform due to hypotension, hypo-

Table 2. Causes of brain death

Patient no.	Age (years)	Gender	Diagnosis	Confirmatory tests	Duration of diagnosis of brain death (days)	Survival after diagnosis (days)	Complications	Apnoea test
Patient 1	0.9	F	Traumatic brain injury, intracranial bleeding, falling high	EEG, CT angiography	3	Donor	DI, hypothermia	Yes*
Patient 2	13	F	Hypoxic brain damage, relapse pre-B ALL	EEG, CT angiography	3	0.2	DI, hypothermia	Yes
Patient 3	3.5	F	Hypoxic brain damage, I-cell disease	EEG, CT angiography	9	6	DI, hypothermia	Yes
Patient 4	2	F	Intracranial infection, necrotising encephalitis	EEG, CT angiography	26	25	DI, hypothermia	Yes
Patient 5	11	M	Intracranial tumour	EEG	13	Donor	Hypothermia	Yes
Patient 6	9	M	Intracranial infection, autoimmune encephalitis	EEG	2		DI, hypothermia	Yes
Patient 7	12	F	Hypoxic brain damage, CP MMR	EEG	2	3	Hypothermia	Yes
Patient 8	14	M	Intracranial bleeding, op. meningomyelocele	EEG	3	4	Hypothermia	Yes
Patient 9	2.5	F	Hypoxic brain damage, afebrile convulsion	EEG, DSA	4	2	DI	Yes
Patient 10	15	M	Hypoxic brain damage, SSPE	EEG	5		Ø	Yes
Patient 11	17	M	Intracranial infection	EEG	11	9	DI, hypothermia	Yes
Patient 12	1	M	Intracranial bleeding	EEG	20		DI, hypothermia	Yes
Patient 13	3	F	Intoxication, hydrogen peroxide intoxication	EEG	5		DI, hypothermia	Yes
Patient 14	7	F	Intracranial tumour, medulloblastoma	EEG	3		Ø	Yes
Patient 15	0.7	M	Hypoxic brain damage, afebrile convulsion	EEG, MR angiography	3	3	Hypothermia	Yes
Patient 16	5.5	M	Traumatic brain injury, intracranial bleeding, road accident	EEG	3	16	DI, hypothermia	Yes
Patient 17	11	F	Intracranial infection	EEG	2		Hypothermia	Yes
Patient 18	2.5	F	Intracranial bleeding	EEG, MR angiography	1	2	Hypothermia	Yes
Patient 19	4.5	F	Intracranial bleeding, aneurysm rupture	EEG	1		Ø	Yes
Patient 20	8	F	Intracranial bleeding	EEG, MR angiography	5		Hypothermia	Yes
Patient 21	6	F	Intracranial tumour, pons ganglioglioma	EEG	1		Ø	Yes
Patient 22	11	M	Intracranial bleeding	EEG, MR angiography	6	6	DI, hypothermia	Yes
Patient 23	0.6	M	Intracranial bleeding	EEG	5	Donor	Hypothermia	Yes

*Apnoea test was performed in all cases except for one case where it could not be completed due to cardiac arrest. The diagnosis of this patient was made using computerised tomographic angiography as a confirmatory test. DI: diabetes insipidus; M: male; F: female; EEG: electroencephalography; MR: magnetic resonance; CT: computerised tomographic; DSA: digital subtraction angiography

thermia, electrolyte imbalance, high-dose inotropic and fluid treatments and extracorporeal membrane oxygenation treatment. In our study, apnoea test was performed in all suspected BD cases, but the test could not be completed in one patient due to cardiac arrest during the test. The diagnosis of this patient was made using CTA as a confirmatory test. There was no problem with transfer in our patients. EEG was the most frequently used confirmatory test (61%). Radiological imaging methods were used in 39% of the patients. In previous studies, EEG was the most commonly used confirmatory test, followed by MR/CT angiography, DSA and Doppler USG (13, 16).

Declaration of BD in paediatric cases is a special case in Turkey as well as the rest of the world. According to the Regulations on Organ and Tissue Transplantation Services in Turkey, the process in paediatric cases is as follows: once the presence of clinical findings of BD is established, in order to fulfil the non-reversibility criteria, these findings do not change at the end of the waiting period. The waiting period is 48 h in infants up to 2 months old, 24 h in children between 2 months and 1 year old, 12 h in children >1 year and adults and 24 h in anoxic BDs. At the end of the waiting period, a second examination is required to confirm that the clinical findings of BD have not changed. Declaration can be made without a waiting period if a confirmatory test is performed after the initial neurological examination and shows that there is no cerebral circulation. During this process, a single apnoea test is sufficient for diagnosis (17). The diagnosis guide on BD 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 >2 months are required. The Turkish Neurological Association guideline regards laboratory tests and supporting tests as synonyms and suggests that confirmatory tests should be conducted on all cases (18). Therefore, having experienced paediatric radiologists who can perform and evaluate tests showing cerebral blood flow in hospitals with paediatric intensive care units can facilitate a faster diagnosis of BD without waiting for re-examination of brain stem reflexes. After this stage, BD declaration must be communicated to the family as soon as the diagnosis is made, and the department of organ transplant coordination should be notified. We have followed these procedures for all cases in the present study.

As a result of irreversible loss of brain functions, central regulatory mechanisms are disrupted. Hypothalamic pituitary adrenocortical regulation ceases. Antidiuretic hormone deficiency occurs in 65%-90% of the patients with BD due to neurohypophysis damage (19, 20). Owing to the resulting polyuria, subsequent hypovolaemia and hypernatraemia are seen, and hypokalaemia can develop. Evident hypothermia is inevitable as the primary thermoregulation centre is affected by hypothalamus injury, and vasoplegia-induced body heat loss occurs. Hypothermia causes myocardial contractility to decrease and makes the heart more prone to arrhythmias (21). In our study, hypothermia (<36°C) was observed in 78.2% of the cases after BD declaration, and DI was observed in 47.8% of the cases. Bonetto et al. (16) also found similar complication rates in their study. A careful organ conservation treatment protocol in intensive care is the first step in a successful organ transplant. For this reason, it is important to know the mechanisms of complications and to address them.

The mean PRISM III score of the cases in our study was 22. This value is higher than the mean intensive care PRISM III values in the literature (22, 23). Early recognition of BD in patients with high PRISM III scores may accelerate the diagnosis of BD.

The time to cardiac arrest development in non-donor cases with continued life support was 6.9±7.4 days in our study. Karasu et al. (24) reported that these periods are 6.8 days for patients <18 years old and 2.5 days for those >18 years old. In a study in which the length of life in cases with final BD diagnosis and continued respiratory and circulatory support was defined as "somatic survival" (>18 years old), this period was approximately 4 days (14). In a study conducted on 40 BD patients in Kuwait, the average survival time was found to be 6 days.

Out of the 23 cases in our study, only 4 (17.3%) families agreed to organ donation. This ratio was found to be 25% in a similar study (13). In a retrospective study on BD in Qatar (>18 years old), the reported family rejection rate was 93%. This result was attributed to various factors, such as religious beliefs, culture, dynamics of the population (high number of immigrants) and lack of awareness on the importance of organ donation (14). In a study on factors affecting organ donation, researchers found that the organ donation rates are 66.7% in cases <20 years old and 52.6% in cases >20 years old. Although not statistically significant, as the education level of the relatives of the patients increased, the donation rate also increased, and approval of the families was facilitated when the initial meeting on organ donation was conducted by the coordinator (25). In another study including 268 patients with a family approval rate of 78.4%, organ donation approval rate increased with the increased frequency of meetings held by an organ transplantation coordinator with the family after BD declaration (26). As can be seen, the family approval rates for organ donation vary greatly in different health centres. The rate of organ donation was low in our study. Nevertheless, this can be increased by self-devoted proactive efforts of organ transplant coordinators, as they meet regularly with patient's relatives from the beginning of the process and provide detailed and satisfactory information. Family factors that

could affect organ donation rates were not examined in our study, which may be regarded as a limitation of our study. We believe that further studies should be conducted in this regard.

The limitations of our study are the fact that the study cannot be planned prospectively, it cannot be known whether the organs of three donors function normally in the recipient or not and it cannot be determined if the families who refuse organ donation changed their views over the years or not. However, owing to ethical reasons, the present study was planned retrospectively, and no retrospective interview could be done with the families to obtain this information.

Conclusion

Any patient in the intensive care unit with definite primary damage and a poor prognosis from a neurological point of view should be suspected of BD and be diagnosed without delay. Diagnosis and donor care is a team effort. Having an experienced radiologist while performing confirmatory tests is important in faster diagnosis. Early diagnosis and good donor care are of great importance, especially for paediatric patients waiting for transplants. The organ transplantation rates from a cadaver are still far below the targets in Turkey. In this regard, intensive care doctors, nurses and organ transplant coordinators should be trained at regular intervals to raise awareness. We believe that the donation rate will increase if family meetings are held by an experienced and educated coordinator.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (Approval no.: 2016-060).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

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