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Brain Death in Children: Incidence, Donation Rates, and the Occurrence of Central Diabetes Insipidus

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Abstract

Introduction: Brain death is currently defined as the loss of full brain function including the brainstem. The diagnosis and its subsequent management in the pediatric population are still controversial. The aim of this study was to define the demographic characteristics, clinical features and outcomes of patients with brain death and determine the incidence of brain death, donation rates and occurrence of central diabetes insipidus accompanying brain death in children.

Methods: This retrospective study was conducted at a twelve-bed tertiary-care combined medical and surgical pediatric intensive care unit of the Ondokuz Mayıs University Medical School, Samsun, Turkey. In 37 of 341 deaths (10.8%), a diagnosis of brain death was identified. The primary insult causing brain death was post-cardiorespiratory arrest in 8 (21.6%), head trauma in 8 (21.6%), and drowning in 4 (18.9%). In all patients, transcranial Doppler ultrasound was utilised as an ancillary test and test was repeated until it was consistent with brain death.

Results: In 33 (89%) patients, central diabetes insipidus was determined at or near the time brain death was confirmed. The four patients not diagnosed with CDI had acute renal failure, and renal replacement treatment was carried out. The consent rate for organ donation was 18.9%, and 16.7% of potential donors proceeded to actual donation.

Conclusion: In the current study the consent rate for organ donation is relatively low compared to the rest of the world. The prevalence of central diabetes insipidus in this pedaitric brain death population is higher than reports in the literature, and acute renal failure accounted for the lack of central diabetes insipidus in four patients with brain death. Further studies are needed to explain normouria in brain-dead patients.

Keywors: brain death, children, diabetes insipidus, cerebral blood flow, organ donation

◼ Introduction

Brain death (BD) is currently defined as the loss of full brain function including the brainstem, characterised by deep coma, apnea and lack of supraspinal reflexes. A patient determined to be BD is accepted nearly worldwide as being clinically and legally dead [1]. Although Turkey, in 1979, was one of the first countries to establish a legal framework for organ transplantation, and also has the facilities capable of performing the necessary procedures, the number of BD declarations and the consent rate for organ donation is relatively low compared to the rest of the world [2]. Children on an organ transplant waiting list, die as a consequence of the shortage of organs available to meet the demand for transplantation. Therefore, the diagnosis of BD and the care of the donor organs are vital.

Central diabetes insipidus (CDI) due to antidiuretic hormone deficiency is a well-described complication of BD in both children and adults and is characterised by polyuria, hypernatremia, and hyperosmolar dehydration [3-5]. It is not surprising that CDI develops in patients who are BD. On the contrary, it is puz-

zling that CDI does not always occur following BD. The incidence of CDI accompanying BD in adults and children varies. In a recent review of 32 studies, of the 1878 patients with BD, ranging in age from 2 months to 89 years, 925 (49%) were reported to have CDI [6]. At least some of thenormouric patients in these studies had some preserved brain function through hypothalamic osmoregulation. Although the term "brain death" is sometimes used to mean irreversible cessation of all functions of the entire brain, this implies that continued hypothalamic function in BD is a contradiction in terms.

Even with clear BD criteria in place for over three decades, diagnosis and subsequent management of the pediatric population are still controversial and cause anxiety in the medical community all over the world.

The aim of this study was to define the demographic characteristics, clinical features and outcomes of patients with BD and determine the *incidence* of CDI accompanying BD in children.

■ MATERIAL AND METHODS

Approval for the study was granted by the Ethics Committee of the Ondokuz Mayıs University. This retrospective study was conducted at 12-bed tertiary-level care combined medical and surgical pediatric intensive care unit (PICU) of the Ondokuz Mayıs University Medical School, Samsun, Turkey. The hospital information database systems were used to collect data. All deaths that occurred in PICU over a 5-yr period from 2012 to 2016were screened. The medical records of pediatric patients, (>1 month and <18 yr), who were diagnosed with BD were evaluated, and retrospective chart reviews were recorded. Data comprising demographics, major cause leading to BD, duration of BD evaluation and hospitalisation,existence of CDI, and organ donation were collected and documented retrospectively for statistical evaluation. According to Turkish law, the diagnosis of BD requires the confirmation of lack of clinical functions of the brain, as judged by apnea, brain stem areflexia, and cerebral unresponsiveness, coupled with a known, irreversible cause of coma and an ancillary test for children. Two examinations, including apnea testing, with each examination separated by an observation period, are required. An observation period of twelve hours for infants and children aged 30 days to 18 years, is needed. The final decision regarding BD must be confirmed by a commit-

tee of physicians. Relatives of patients were informed about the declaration of BD by an experienced PICU physician working in the unit. The request for organ donation was made by the organ donation coordinator of the hospital.

CDI has been defined as polyuria (urine output > 4mL/kg/hr for children 300mL/hr for adult-sized children ≥ 70kg) for at least two consecutive hours, hypernatremia (Serum Na > 145 mmol/L), high serum osmolality (>300 mOsm/kg) and low urine osmolality (< 300 mOsm/kg) at the time of diagnosis [7-9]. Confirmation of CDI was based on its reversal with desmopressin (DDAVP) and vasopressin infusion therapy [9,10].

The SPSS version 15.0 was used for statistical analysis. Results were analysed with descriptive statistics.

Patients (n= 341) who died in PICU between 2012 and 2016 were screened. In 37 of 341 deaths (10.8%), the diagnosis of BD had been recorded. The male to female ratio was 1.05, 19 male (51.4%) and 18 female patients (48.6%). The median age of the patients was 6 (IQR: 2-9) years. The primary insult causing brain death was post-cardiorespiratory arrest in 9 (24.3%), head trauma in 8 (21.6%), and drowning in 4 (10.8%) (Table 1).

■ RESULTS

The median duration of hospitalisation was 12 days (IQR: 9-17). The median duration of time between hos-

Table1. Demographics of the Patients Who Were Declared Brain Dead

Variable	n(%) or Median [Interquartile Range]
Number (% of deaths)	37(10.8%)
Age (yr)	6 [2,9]
Gender (male)	19(51.4%)
Primaryhospitaladmissiondiagnosis	
Post-cardiorespiratory arrest	9(24.3%)
Head trauma	8(21.6%)
Drowning	4(10.8%)
Sepsis and multiorgan dysfunction	2 (5.4%)
Status epilepticus	2(5.4%)
Brain tumour	2(5.4%)
Other etiologies	4(10.8%)
Organ donors	6(16.2%)

pitalisation and the start of BD evaluation was seven days (IQR:5-10.5), and the median duration of brain death evaluation was three days (IQR:2-7). In the current study, we first confirmed BD in patients by clinical criteria then performed a confirmatory ancillary test.

In all patients, transcranial Doppler ultrasound (TCD) was utilised as an additional test. The examination was repeated daily until BD was confirmed ultrasonographically. In four patients for whom initial TCD examination failed to establish BD, a second TCD examination was applied. After that, clinical BD that showed confirmation of TCD signs was seen in three patients. The remaining patient underwent five TCD examinations that showed confirmatory TCD signs of BD.

In 33 (89%) patients, CDI was determined to have developed at or near the time brain death was confirmed. All patients diagnosed with CDI received DDAVP and polyuria was reversed. All four patients not diagnosed with CDI had acute renal failure, and renal replacement treatment was applied. Laboratory test and admission diagnosis of these four patients are given in Table 2.

All the families were approached regarding organ donation, and consent was obtained from seven (18.9%). One had mutliorgan dysfunction syndrome, and the other six (16.2%) were medically suitable and were accepted as organ donors.From six donors, ten kidneys, five livers and two heart were transplanted successfully.Characteristics of these six donors are given in Table 3.

■ DISCUSSION

BD accounted for 10.8% of the deaths in this study. Different pediatric studies have found different rates between 11.6% and 37% [11-13]. These differences may be due to the type of ICU, e.g., trauma referral centres, local practice differences such as the emphasis on organ donation, comfort with the determination of BD, the year of study, and patient demographics.

In the current study, the primary diagnosis leading to brain death was post-cardiorespiratory arrest. Deprivation of oxygen and nutrient delivery to brain tissue is the most common underlying pathophysiology irrespective of the proximate cause leading to BD. Hypoxic-ischemic brain injury and the resulting oedema evolve, and may ultimately progress to BD after brainstem function completely disappears usually in a rostrocaudal direction, from the mesencephalon to the medulla oblongata. In most studies, the most common finding in children is reported to be traumatic brain injury [12,4,13,14]. Some studies have found a high prevalence of infectious diseases [15] and cerebrovascular accidents [11].

In a recent meta-analysis of 32 studies, concerning 1878 patients with BD, ranging in age from 2 months to 89 years, 925 (49%) were reported to have CDI [6]. The five studies that have published exclusively on pediatric patients, collectively indicated that 145 (52%) of 279 patients had CDI [3,4,9,16,17]. The data of the current study suggest that the prevalence of CDI in our pediatric BD population is higher (89%) than other reports

Table 2. Laboratory Tests and Diagnosis of Patients Without CDI

	Age	BUN (mg/dL)	Creatinin (mg/dL)	Diagnosis
Patient 1	5 months	46,6	2,7	Post-CRA
Patient 2	1 years	98	2,5	Head trauma
Patient 3	8 years	178	6,5	Post-CRA
Patient 4	9 years	111	7,3	Head trauma

CRA:Cardiorespiratory arrest

Table 3. Characteristics of Donors

	Age	Diagnosis	Transplanted organs
Donor 1	5 months	Post-CRA	Liver
Donor 2	3.5 years	Drowning	Liver,2 kidney
Donor 3	5 years	Head trauma	2 kidney
Donor 4	6 years	Post-CRA	Heart,2 kidney
Donor 5	17 years	Acute hydrocephalus	Heart,liver,2 kidney
Donor 6	2 years	Head trauma	Heart,2 kidney

CRA:Cardiorespiratory arrest

in literature. The four patients not diagnosed with CDI had acute renal failure, and renal replacement treatment was undertaken. Acute renal failure results in the diminution of the amount of fluid delivered to the distal tubule and hence would limit renal water excretion and prevent polyuria. Theoretically, this phenomenon may occur even in the absence of AVP, and CDI was not diagnosed in these patients. Excluding the patients with acute renal failure, in the current study population, CDI prevalence was 100%.

Brain functions may continue in many BD brains[18]. For example, electroencephalographic (EEG) activity has been documented in more than 20% of brain death patients [19], cerebral blow has been recorded in more than 5% of brain death patients [20], and it has been stated that CDI does not occur in more than half of brain death patients [6]. The most straightforward explanation for the observation of normouria in patients with BD is that the hypothalamic osmoregulation system continues to function, in at least some patients. The various findings consistent with the preservation of hypothalamic control of the anterior pituitary corroborate this by suggesting preserved blood flow to the area, and suggest some hypothalamic–anterior pituitary function as well, albeit often in the presence of peripheral endocrine insufficiency[6]. Furthermore, anatomical considerations indicate that preserved hypothalamic osmoregulation may be expected in BD. The inferior hypophyseal arteries branch off the extradural segments of the internal carotids and thus are protected from increased intracranial pressure, and these arteries supply the posterior pituitary, the hypophysial stalk, and parts of the hypothalamus including the median eminence [21].

The diagnosis of BD is clinical. In some countries, e.g., United States, confirmation of BD at the bedside is sufficient [1]. However, other countries recommend examinations that confirm the absence of electrical and metabolic functions or of cerebral flow. EEG is the most widely used examination in several countries. Nevertheless, this examination cannot be easily performed in an intensive care unit, due to the possible interference of artefacts with electrical activity [1]. TCD has been validated as an ancillary test for brain death with specificity of 98% to 100% and sensitivity ranging from 88% to 99%, and it is performed on middle and vertebral cerebral arteries [22,23]. In Turkey, the law requires an additional testing, together with an apnea test for diagnosis of BD in children. In our clinic, a TCD, as an additional test, was conducted on all patients with a clinical diagnosis of BD. This TCD test was repeated until it was consistent with BD. Studies in literature, which have researched the frequency of CDI accompanying BD, give no information related to how BD was diagnosed and which additional tests were applied. That the rate of CDI in cases diagnosed with BD was higher in the current study compared to reports in the literature may be explained by the fact that brain blood circulation may not be shown in all patientswith TCD.

In the current study, the consent rate for organ donation was 18.9%, and the organs of 16.2% of potential donors proceeded to actual donation. In a Canadian study, the consent rate was 64%[12]. Tsai et al., (2005) reported a consent rate of 63%, although the organs of only 41% of potential donors proceeded to actual donation[24], while in the Canadian study, organs of 47% of donated were used [12]. In the current study, the major reason for a patient not being an organ donor candidate was the family's refusal, and this was the case in 30 (81%) of the patients. In some studies, religion, primary language and place of residence have all been highly correlated with ethnic background, and affect the consent rate [25,26].

Donation rates may increase with carefully planned public educational broadcasting campaigns. We believe that the more information given to a family regarding the medical condition of their child, the better prepared the family members will be to having a conversation about organ donation.

In conclusion, the persistence of cerebral blood flow after BD can be considered to result in normouria in at least some patients. Further studies are required to explain the normouria in BD patients.

■ CONFLICT OF INTEREST

None to declare.

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