Pediatric Brain Death: Experience of a Single Center

Pediatrik Beyin Ölümü: Tek-Merkezli Çalışma

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ABSTRACT Objective: Brain death is defined as the irreversible loss of consciousness and all functions of the brain stem. The accuracy and urgency of a diagnosis of brain death in children are highly important, because of the increasing rate of organ transplantation. Our objective was to describe the features of cases where "brain death" was diagnosed in the last five years. **Material and Methods:** Demographical, clinical, electroencephalographic (EEG), Doppler ultrasonography and static single-photon emission computerized tomography (SPECT) characteristics were evaluated retrospectively in hospitalized with loss of brain stem functions and deep coma. **Results:** Twenty eight patients (8 girls/20 boys) were evaluated in this study. The median age was 72 months (10-210 months). Transcranial Doppler ultrasonography was performed in 18 (64%) patients. The cerebral catheter angiography was used in one patient. SPECT was used in eleven (40%) patients as a confirmatory test. Diabetes insipidus was present in 75% (n=21) and hypothermia was present in 50% (n=14) of the patients. **Conclusion:** We observed that serial Doppler Ultrasonography and SPECT benefited us more than other techniques in our study. Transcranial Doppler is useful and has some advantages: such as noninvasiveness, rapid application, easy bedside operation, portability, no disturbance from sedatives, repeatability and relatively low price. We conclude that diabetes insipidus may be an indicator of brain death, and an observation of diabetes insipidus should accelerate confirmatory tests and treatment immediately.

Key Words: Brain death; child; diabetes insipidus; hypothermia; transplantation

ÖZET Amaç: Beyin ölümü, solunum dâhil tüm beyin sapı işlevlerinin ve bilincin geri dönüşümsüz olarak kaybedilmesi şeklinde tanımlanmaktadır. Çocukluk çağında organ transplantasyonu yapılan olguların sayısındaki artış, beyin ölümü tanısını daha önemli hâle getirmiştir. Bu çalışmanın amacı, son beş yılda "beyin ölümü" tanısı alan olguların demografik ve klinik özelliklerini tanımlamaktır. **Gereç ve Yöntemler:** Beyin sapı fonksiyon kaybı ve derin koma nedeni ile yatışı yapılan hastaların demografik, klinik, elektroensefalografik (EEG), Doppler ultrasonografi ve "single-photon emission computerized tomography (SPECT)" görüntüleme özellikleri restrospektif olarak değerlendirildi. **Bulgular**: Çalışmaya sekizi kız,20'si erkek olmak üzere 28 hasta dâhil edildi. Ortanca yaş 72 (10-210 ay) ay idi. Transkraniyal Doppler ultrasonografi18 (%64) hastaya uygulanmıştı. Serebral kateter anjiyografi bir hastada kullanılmıştı. On bir (%40) hastaya destekleyici test olarak SPECT uygulanmıştı. Hastaların %75 (n=21)'inde diabetes insipidus, %50 (n=14)'sinde ise hipotermi saptandı. **Sonuç**: Bu çalışmada, serebral perfüzyonu göstermek için en sık transkraniyal Doppler ve SPECT'ten faydalanıldığını gördük. Transkraniyal Doppler ultrasonografinin seçilmesinin nedenlerinin de bu tekniğin yatak başında ve kolay uygulanabilir, ucuz ve tekrarlanabilir olması olduğunu düşündük. Diabetes insipidus, beyin ölümü için bir indikatör olabilir. Klinisyenlerin bu kliniği hızlı fark edip tedavi etmesi, özellikle böbreklerin korunması açısından önem taşımaktadır.

Anahtar Kelimeler: Beyin ölümü; çocuk; diabetes insipidus; hipotermi; transplantasyon

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Brain death is defined as the irreversible loss of consciousness and all functions of the brain stem.[1,2] The concept of brain death is accepted clinically, ethically and legally in our country. The accuracy and urgency of brain death diagnosis in children is increasingly important because of the increasing rate of organ donation. Therefore the determination of brain death should be made accurately and in a timely manner.

In our country, legal arrangement related to brain death is regulated by the Guide of Organ and Tissue Transplantation Services published in the official journal with the number 28191 on 01/02/2012. The clinical criteria of brain death included unresponsiveness, the absence of movement and spontaneous breathing accompanied with the absence of brainstem reflexes such as light, oculocephalic, vestibulo-ocular, corneal, palatal and tracheal reflexes. The physical examination should be evaluated twice at 12-48 hour intervals, according to age, and in our country the diagnosis should be confirmed with at least one ancillary test. Our objective was to describe the features of cases, where 'Brain Death' was diagnosed in the last five years, at the Akdeniz University Department of Pediatrics.

TABLE 1: Summary Guideline for Determining Brain Death in Turkey.

A) Preconditions of Brain Death Diagnosis as following conditions
1. Determination of the cause leading to brain injury
2. Determination of brain injury widely and irreversible
3. The body temperature should be above 32°C
4. Absence of hypotensive shock
5. Using drugs and intoxications should be excluded
6. Excluding metabolic, electrolyte imbalance and acid-base imbalance
(B) The presence of deep coma and absence of brain stem reflexes;
1. Dilated and/or fixed pupillae (4-9 mm), absence of light reflex
2. Absence of oculocephalic reflex and vestibulo-ocular reflex
4. Absence of cornea reflex,
5. Absence of palatal and tracheal reflex
5. Positive apnea test and absence of spontaneous breathing efforts
Note: If apnea testing cannot be completed, the clinicians should determine the arrest of brain arterial circulation.
(C) The recommended intervals of Physical Examination and ancillary test
1. Up to 2 months of age
a. Two examinations performed 48 hours apart+at least two ancillary tests
2. >2 months up to 1 years of age
a. Two examinations performed 24 hours apart+at least one ancillary tests
3. >1 years of age
a. Two examinations performed 12 hours apart+at least one ancillary tests
Note: If there is one ancillary test, which determines arrest of brain arterial circulation, the clinician should not wait the second physical examination.

MATERIAL AND METHODS

Demographical, clinical, electroencephalographic (EEG) and Doppler Ultrasonography characteristics of the patients, which were hospitalized in the Akdeniz University Hospital with loss of brain stem function and deep coma, between July 2007 and June 2013 has been evaluated retrospectively. The diagnosis of brain death was established with physical examination (repeated after 24 or 48 hours according to the age group), at least 1 confirmatory test and an apnea test (Table 1). The age and gender of patients, clinical features such as diabetes insipidus (DI) and hypothermia, the duration of hospitalization, and the EEG and Doppler Ultrasonography findings were also noted. DI was defined as polyuria (urine output >4 mL/kg/hr for children <70 kg, >300 mL/hr for adult-sized children ≥ 70 kg) 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.[3]

In the apnea test, the patients were supplied with 100% O_2 at 6 L/min with a cannula placed into the trachea until the superior part of the carina by endotracheal tube or tracheostomy cannula before the test. If $PaCO_2$ was 60 mmHg or higher and respiratory movements were absent, the apnea test was evaluated as positive.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

The conventional transcranial Doppler (TCD) technique was used to isolate and identify arteries using the temporal and suboccipital transcranial ultrasonic windows. A DWL EZ-Dop (DWL Elektronische Systeme GmbH, Sipplingen, Germany©) TCD device with a 2-MHz pulsed wave probe was used in all patients. The TCD criteria for cerebral circulatory arrest were: diastolic flow reversal (Oscillating flow, net zero flow) or early systolic forward flow (Systolic spikes), detected in three arteries bilaterally in the anterior circulation and the vertebra-basilar system. Transcranial Doppler Ultrasonography was performed if systolic blood pressure was between ±2 SDS according to age.[4,5] None of the subjects investigated had signs of hemodynamic failure or shock.

This study was reviewed by the local ethics committee and was exempt from requiring approval.

RESULTS

In this study, 28 patients (8 girls/20 boys) were evaluated. The median age was 72 months (10-210 months). Two patients were under one year of age. The duration of hospital stay was 2-22 (median=6) days. The underlying illnesses of the patients were as follows: car or motorcycle accident (43%) (n=12), tumor in central nervous system (11%) (n=3), drowning (10%) (n=3), trauma (4%) (n=2), cerebral palsy (4%) (n=1), upper airway tract infection (4%) (n=1), syncope (4%) (n=1), foreign body aspiration (4%) (n=1), gunshot wound (4%) (n=1), aspiration (4%) (n=1), meningitis (4%) (n=1), and postoperative complication (4%) (n=1). The reason for brain death was evaluated as follows: asphyxia (46%) (n=13), hemorrhage in the central nervous system (36%) (n=10), increase in intracranial pressure (IICP) (11%) (n=3), and acute hydrocephalus (7%) (n=2). DI existed in 75% (n=21), and hypothermia existed in 50% (n=14) of the patients. The apnea test was positive in 90% (n=25) of the patients. The test was interrupted or not used in three patients because of acute desaturation and hemodynamic deterioration. At least one confirmatory test was used in the patients, when the clinical examination was compatible with brain death. Transcranial Doppler Ultrasonography was performed in 18 (64%) of patients. Cerebral circulatory arrest was observed in 13 of the 18 patients in the first examination. Although cerebral blood flow was observed in the first examination in two patients, cerebral circulatory arrest was observed during the second examination. In these 2 patients, the second TCD Ultrasonography's were evaluated on the fifth and eighth days after the first. The circulatory arrest was proved with cerebral catheter angiography was used in one patient, who had blood flow on Doppler Ultrasonography and 2-5 microvolt activity on an EEG. The EEG was evaluated in four patients, and two of them had cerebral activity amplitudes under 2 microvolts. Flat activity could not be obtained in the other two patients. Therefore, TCD Ultrasonography was used to determine circulatory arrest in these patients. Static single photon emission computerized tomography (SPECT) was used in eleven (40%) patients as a confirmatory test. The donation rate was 46% (n=13). The most commonly transplanted organs were: kidneys (92%) (12/13), liver (84%) (11/13), cornea (23%) (3/13), heart (8%) (1/13), and pancreas (8%) (1/13) in our study (Table 2, Figure 1).

DISCUSSION

The criteria for brain death included unresponsiveness, an absence of movement and spontaneous breathing and an absence of the light, oculocephalic, vestibulo-ocular, corneal, palatal and tracheal brainstem reflexes. Before examination; intoxication, hypothermia, usage of sedative analgesics and neuromuscular blocking agents should be excluded, as these may cause this clinical picture. It should be kept in mind that high cervical cord injury, fulminant Guillain-Barre' Syndrome, organophosphate intoxication, baclofen and lidocaine toxicity, and delayed vecuronium clearance have also been reported as clinical mimics of brain death.[6-12] The clinical evaluation should be performed twice at an interval of 12-24 hours depending on the age of the patient. In our patients, the clinical evaluations were performed twice, 24 hours apart, and all brainstem reflexes were absent in all patients. In our study, twenty-eight patients fulfilled the diagnostic criteria of brain death. We were able to the perform apnea test in twenty-five patients and all of them were positive. The test was interrupted or not used in three patients because of acute desaturation and hemodynamic deteriora-

TABLE 2: The demographic and clinical features of patients.

Patients	Gender	Age (Month)	Primary Disease	The Reason of Brain Death	The Duration of Hospitalization (Day)	DI	Hypotermia	Apnea Test	1. TCD	2. TCD	Angiography	EEG	SPECT	Prognosis	Transplante organs
1	Female	48	Upper Airway Infection	Asphyxia	4	+	+	Positive	Circulatory arrest		-	-	-	Ex	
2	Female	168	Down Syndrome and Trauma	IICP	11	+	-	Positive	Positive Circulation		Circulatory Arrest	2-5 mcVolt	-	Donor	Kidneys
3	Male	60	Glioblastoma Multiforme	IICP	16	+	+	Positive	Circulatory arrest		-	-	-	Donor	Liver
4	Male	120	Drowning	Asphyxia	7	-	+	Positive	Circulatory arrest		-	< 2 mcVolt	-	Reject	
5	Male	18	Cerebral Palsy	Asphyxia	12	+	+	Positive	Positive Circuliaion	Circulatory arrest	-	-	-	Donor	Kidneys, liver
6	Male	120	Car Accident	IICP	3	+	+	Positive	Circulatory arrest		-	< 2 mcVolt	-	Donor	Kidneys
7	Male	24	Car Accident	Subarachnoid hemorrhage	6	+	+	Positive	Circulatory arrest		-	-	-	Reject	
8	Male	144	Car Accident	Subarachnoid hemorrhage	2	+	+	Positive	Circulatory arrest		-	-	-	Reject	
9	Male	140	Gunshot Wounds	Asphyxia	4	+	+	Positive	None		-	-	+	Donor	Kidneys, liver
10	Male	210	Car Accident	Subarachnoid hemorrhage	8	+	+	Positive	None		-	-	-	Reject	
11	Male	204	Drowning	Asphyxia	7	+	-	Positive	Positive Circulation	Circulatory arrest	-	2-5 mcVolt	-	Reject	
12	Male	48	Drowning	Asphyxia	5	+	+	Positive	Circulatory arrest		-	-	-	Reject	
13	Male	10	Foreign Body Aspiration	Asphyxia	8	-	+	Positive	None		-	-	+	Reject	
14	Male	24	Car Accident	Asphyxia	11	-	-	Positive	Reduced Circulation		-	-	+	Reject	
15	Female	18	Accident	Subarachnoid hemorrhage	5	-	-	Positive	Circulatory arrest		-	-	-	Reject	
16	Female	198	Car Accident	Subarachnoid hemorrhage	2	-	-	Positive	None		-	-	-	Donor	Heart, Kidneys, liver, Cornea
17	Female	33	Posterior fossa tm	Acute Hydrocephaly	5	+	-	Positive	Circulatory arrest		-	-	-	Reject	
18	Male	76	Car Accident	Asphyxia	6	+	+	Positive	Circulatory arrest		-	-	-	Reject	
19	Male	14	Car Accident	Hypoxia	4	+	-	Positive	Circulatory arrest		-	-	-	Reject	
20	Male	92	Syncope	Hemorraghe in Brainstem	4	+	+	Positive	Circulatory arrest		-	-	-	Donor	Kidneys, liver, cornea
21	Female	74	Menengitis	Acute Hydrocephaly	10	-	+	Positive	None		-	-	+	Reject	
22	Male	72	Car Accident	Subdural Hematoma	8	+	-	None	None		-	-	+	Donor	Kidneys, liver
23	Male	210	Motorcycle Accident	Subarachnoid hemorrhage	8	+	-	Positive	None		-	-	+	Donor	Kidneys, liver
24	Male	204	Trauma	Subarachnoid hemorrhage	4	+	-	Positive	None		-	-	+	Donor	Kidneys, liver, cornea, pancreas
25	Male	58	Car Accident	Subarachnoid hemorrhage	6	+	-	Positive	Positive Circulation		-	-	+	Donor	Kidneys, liver
26	Female	204	Suprasellar Tumor	Asphyxia	22	+	-	Positive	None		-	-	+	Ex	
27	Female	48	Aspiration	Asphyxia	5	+	-	None	Circulatory arrest		-	-	+	Donor	Kidneys, liver
28	Male	10	Postoperative Complication	Asphyxia	9	-	-	None	None		-	-	+	Donor	Kidneys, liver

DI: Diabetes insipidus; TCD: Trancranial Doppler; EEG: Electroencephalogram; SPECT: Single photon emission computerized tomography; IICP: Increase in intracranial pressure.

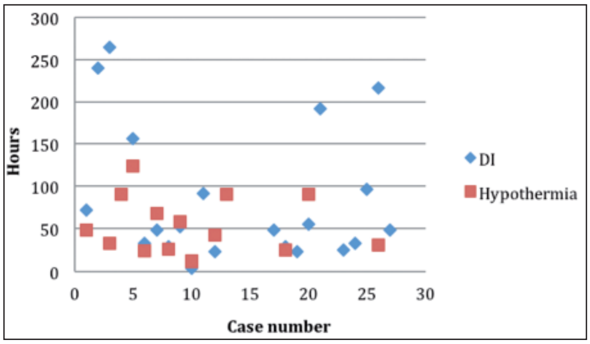

FIGURE 1: The value of detection time of diabetes insipidus and Hypothermia of patients.

tion. Static SPECT was used in these three patients as a confirmatory test.

Supportive tests are necessary if certain parts of the neurological examination or the apnea test cannot be reliably performed, or their validity is drawn into question. Officially, the recommended tests are conventional angiography, EEG, TCD, Tc99 HMPAO SPECT scan and a bilateral absence of the N20-P22 response to median nerve stimulation (SSEP).[2]

The electrical activity in the EEG should be under 2 microvolts for 30 min in order to confirm brain death.[13,14] Even if it seems reliable and useful, there are several disadvantages in clinical practice. EEG may be inadequate for detecting brain activity in the lower brainstem. The activity may be flat in patients with preserved subcortical function, and EMG artifacts are one of the major problems.[15-17] Furthermore, 3.6% of patients fulfilling clinical criteria for brain death had EEG activity for up to 168 h in a series of 56 patients.[18] Given these results, the electrophysiological evaluation is not useful as a recommended test in childhood. Electroencephalography was performed in four of our cases diagnosed as brain death. We could not perform the EEG to the remaining twenty-four patients due to the lack of a portable EEG in our clinic. Only two of them had electrical activity <2 microvolts. Additional tests were needed in two patients due to a lack of flat activity.

Transcranial Doppler Evaluation has advantages such as noninvasiveness, rapid application, portability and relatively low price. Its specificity and sensitivity has been reported to be 91-100% and false positive results have rarely been reported. Transcranial Doppler Ultrasonography should be performed if systolic blood pressure is between ±2 standard deviations according to age.[19-23] The evaluation of intracranial circulation was made in 18 of the 28 patients. Circulatory arrest was observed in 15 of 28 patients in the first or second examination. Three of the 18 patients had evidence of cerebral circulation. The most useful finding for diagnosis was the presence of blood flow in the early period, and the disappearance of acceleration in follow-up scans. Since brain death is characterized by an intracranial circulatory arrest, conventional TCD Ultrasonography appears to be the most promising method with easily application at the bedside. There were three patients in our study in which arterial flow was determined in the cerebrum. The underlying conditions of brain death in these patients were asphyxia, subarachnoid hemorrhage and increased intracranial pressure syndrome. All of these patients had positive apnea tests when we performed TCD. If the criterion of brain death is defined as circulatory arrest, then these three patients were still alive, even though they had clinical signs of brain death. On the other hand, we observed that two patients had a circulatory arrest in the second evaluation (on fifth and eighth days after the first) of cerebral blood flow. It has been shown that total circulatory arrest was confirmed within 2 hours of clinical diagnosis in adults.[24] The clinicians should define the timing of TCD to confirm brain death, or should reevaluate if the clinical findings suggest brain death. Further studies are needed about the timing of TCD, especially in childhood.

Conventional 4-vessel angiography is another technique used to assess intracranial circulation. It has limitations, such as nephrotoxicity, difficulty in transporting the patient to the radiology unit and a long duration of performing the technique. This technique was used and cerebral circulatory arrest observed in one of our patients, who had blood flow in Doppler Ultrasonography and 2-5 microvolt cerebral bioelectric activity on an EEG.[25]

The most accurate information indicating brain death is obtained by showing the absence of brain blood flow. The lack of intracranial radionuclide activity on static SPECT images, creating a so-called ''hollow skull'' appearance, is indicative of brain death. The nasal area lights up due to well capillary circulation and is the so-called ''hot nose sign''. The rates of residual flow were reported to vary widely from 3 to 40%. The most commonly encountered problem with SPECT studies that they may be negative early on in the setting of brain death, and thus possibly delay the diagnosis.[26-29] We also used SPECT in 11 (39%) patients as a confirmation test of brain death.

In our cohort, brain death mostly occurred after asphyxia (46%), and hemorrhage in the central nervous system (36%). The most common underlying mechanism of injury was car or motorcycle accidents (43%). In a published report, it has been shown that the most frequent cause of brain death in children is traumatic brain injury (30%) caused by child abuse and motor vehicle accidents. The other causes are central nervous system infection (16%), asphyxia (14%) drowning (9%) and sudden infant death (5%).[30] Our results therefore matched those found in previous literature.

The loss of neuroendocrine function, such as in DI, must be treated to increase the success of organ donation.[31] The underlying pathophysiologic mechanism of central DI is likely to be a failure of the hypothalamic-hypophyseal tract that decreases the production of antidiuretic hormone. In experimental animal studies, a significant decrease in hypophyseal hormone production was observed 15 minutes after brain death. The rate of DI was 75% (n=21) in our study, and most of them (16 patients) occurred in the last 4 days before the diagnosis of brain death. Similar to our results, Dosemeci et al showed that the rate of DI was 78.7% in adults.[32] It has been shown that high serum sodium concentrations and increased plasma osmolality in brain dead kidney and liver donors adversely affect long-term graft function.[33] In another study, it has been published that hypernatremia may be independent marker of the severity of brain injury and an independent prognostic indicator of death.[34] The dose of desmopressin should be determined according to the patient's hourly urine output and the serum sodium level should be decreased and controlled until the diagnosis of brain death was confirmed. Given these results, if the clinician considers brain death and observes DI they should accelerate the confirmatory tests and treat hypernatremia immediately with desmopressin to protect the organs.

Hypothermia occurs in about 50% of children who are comatose after critical brain injury.[31] Dosemeci et al showed that the hypothermia rate was 48.9%.[32] The beneficial and neuroprotective effects of hypothermia were previously demonstrated in hypoxic ischemic and traumatic brain injury and cardiopulmonary arrest in childhood.[35-37] Hypothermia was present in fourteen patients (50%) in our study and was mostly observed in the 90 hours period before the diagnosis of brain death.

The donation rate was 46% (n=13) in our study. The transplanted organs were kidneys (92%), liver (85%), cornea (23%), heart (8%), and pancreas (8%) respectively. Dosemeci et al reported that the donation rate was 53.2% (pediatric and adult together) in their intensive care unit.[32] Parental consent rates for donation were found by Tsai et al. and Webster et al. to be 63% and 69%, respectively, in North American brain-dead children.[38-39] Brierley found a 58% parental consent rate in brain-dead children in the United Kingdom (2006-2007).[40] The reasons for the low rate of organ donation are a lack of adequate diagnostic criteria, as well as cultural and religious factors.

CONCLUSION

We observed that serial Doppler Ultrasonography and SPECT were more advantageous than other techniques for the diagnosis of brain death in our study. TCD is useful due to its noninvasiveness, rapid application, ease of use, bedside operation and portability, lack of disturbance from sedatives, repeatability and relatively low price. We conclude that DI may be an indicator of brain death; and if clinicians observe DI, confirmatory tests should be performed and DI should be treated immediately.

REFERENCES

1. Fackler J, Goldstein B. Pediatric brain death. Crit Care Med 2011;39(9):2197-8.
2. Nakagawa TA, Ashwal S, Mathur M, Mysore MR, Bruce D, Conway EE Jr, et al; Society of Critical Care Medicine; Section on Critical Care and Section on Neurology of the American Academy of Pediatrics; Child Neurology Society. Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations. Crit Care Med 2011;39(9):2139-55.
3. Alharfi IM, Stewart TC, Foster J, Morrison GC, Fraser DD. Central diabetes insipidus in pediatric severe traumatic brain injury. Pediatr Crit Care Med 2013;14(2):203-9.
4. Ducrocq X, Hassler W, Moritake K, Newell DW, von Reutern GM, Shiogai T, et al. Consensus opinion on diagnosis of cerebral circulatory arrest using Doppler-sonography: Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology. J Neurol Sci 1998; 159(2):145-50.
5. Ünal A, Dora B. [Transcranial Doppler ultrasonography as a confirmative diagnostic test in brain death]. Turkish Journal of Cerebrovascular Diseases 2012;18(3):49-58.
6. Waters CE, French G, Burt M. Difficulty in brainstem death testing in the presence of high spinal cord injury. Br J Anaesth 2004; 92(5):760-4.
7. Friedman Y, Lee L, Wherrett JR, Ashby P, Carpenter S. Simulation of brain death from fulminant de-efferentation. Can J Neurol Sci 2003;30(4):397-404.
8. Kainuma M, Miyake T, Kanno T. Extremely prolonged vecuronium clearance in a brain death case. Anesthesiology 2001;95(4):1023-4.
9. Ostermann ME, Young B, Sibbald WJ, Nicolle MW. Coma mimicking brain death following baclofen overdose. Intensive Care Med 2000; 26(8):1144-6.
10. Peter JV, Prabhakar AT, Pichamuthu K. Inlaws, insecticide--and a mimic of brain death. Lancet 2008;371(9612):622.
11. Richard IH, LaPointe M, Wax P, Risher W. Non-barbiturate, drug-induced reversible loss of brainstem reflexes. Neurology 1998;51(2): 639-40.
12. Rivas S, Douds GL, Ostdahl RH, Harbaugh KS. Fulminant Guillain-Barré syndrome after closed head injury: a potentially reversible cause of an ominous examination. Case report. J Neurosurg 2008;108(3):595-600.
13. Okuyaz C, Birbicer H, Doruk N, Atici A. Bispectral index monitoring in confirmation of brain death in children. J Child Neurol 2006; 21(9):799-801.
14. Guideline three: minimum technical standards for EEG recording in suspected cerebral death. American Electroencephalographic Society. J Clin Neurophysiol 1994;11(1):10-3.
15. Sethi NK, Sethi PK, Torgovnick J, Arsura E, Schaul N, Labar D. EMG artifact in brain death electroencephalogram, is it a cry of "medullary death"? Clin Neurol Neurosurg 2008;110(7): 729-31.
16. Welschehold S, Boor S, Reuland K, Thömke F, Kerz T, Reuland A, et al. Technical aids in the diagnosis of brain death: a comparison of SEP, AEP, EEG, TCD and CT angiography. Dtsch Arztebl Int 2012;109(39):624-30.
17. Hori G, Cao J. Selecting EEG components using time series analysis in brain death diagnosis. Cogn Neurodyn 2011;5(4):311-9.
18. Grigg MM, Kelly MA, Celesia GG, Ghobrial MW, Ross ER. Electroencephalographic activity after brain death. Arch Neurol 1987; 44(9):948-54.
19. de Freitas GR, André C. Sensitivity of transcranial Doppler for confirming brain death: a prospective study of 270 cases. Acta Neurol Scand 2006;113(6):426-32.
20. Kuo JR, Chen CF, Chio CC, Chang CH, Wang CC, Yang CM, et al. Time dependent validity in the diagnosis of brain death using transcranial Doppler sonography. J Neurol Neurosurg Psychiatry 2006;77(5):646-9.
21. Dosemeci L, Dora B, Yilmaz M, Cengiz M, Balkan S, Ramazanoglu A. Utility of transcranial doppler ultrasonography for confirmatory diagnosis of brain death: two sides of the coin. Transplantation 2004;77(1):71-5.
22. Ashwal S. Clinical diagnosis and confirmatory tests of brain death in children. In: Wijdicks EFM, ed. Brain Death. 1st ed. New York, NY: Lippincott Williams & Wilkins; 2001. p.91-114.
23. Monteiro LM, Bollen CW, van Huffelen AC, Ackerstaff RG, Jansen NJ, van Vught AJ. Transcranial Doppler ultrasonography to confirm brain death: a meta-analysis. Intensive Care Med 2006;32(12):1937-44.
24. Lovrencic-Huzjan A, Vukovic V, Gopcevic A, Vucic M, Kriksic V, Demarin V. Transcranial Doppler in brain death confirmation in clinical practice. Ultraschall Med 2011;32(1):62-6.
25. Quesnel C, Fulgencio JP, Adrie C, Marro B, Payen L, Lembert N, et al. Limitations of computed tomographic angiography in the diagnosis of brain death]. Intensive Care Med 2007;33(12):2129-35.
26. Newberg A, Alavi A, van Rhijn S, Cotter A, Reilly P. Radiologic diagnosis of brain death. JAMA 2002;288(17):2121-2.
27. Harding JW, Chatterton BE. Outcomes of patients referred for confirmation of brain death by 99mTc-exametazime scintigraphy. Intensive Care Med 2003;29(4):539-43.
28. Kraft O, Samlík J, Chmelová J. The diagnosis of brain death--own experience. Nucl Med Rev Cent East Eur 2006;9(2):132-7.
29. Munari M, Zucchetta P, Carollo C, Gallo F, De Nardin M, Marzola MC, et al. Confirmatory tests in the diagnosis of brain death: comparison between SPECT and contrast angiography. Crit Care Med 2005;33(9):2068-73.
30. Ashwal S, Serna-Fonseca T. Brain death in infants and children. Crit Care Nurse 2006; 26(2):117-24, 126-8.
31. Domínguez-Roldan JM, Garcia-Alfaro C, Díaz-Parejo P, Murillo-Cabezas F, Barrera-Chacon JM, Caldera-Gonzalez A. Risk factors associated with diabetes insipidus in brain dead patients. Transplant Proc 2002;34(1):13-4.
32. Döşemeci L, Yilmaz M, Cengiz M, Dora B, Ramazanoğlu A. Brain death and donor management in the intensive care unit: experiences over the last 3 years. Transplant Proc 2004; 36(1):20-1.
33. Kwiatkowska E, Bober J, Ciechanowski K, Kędzierska K, Gołmbiewska E. Increased serum sodium values in brain-dead donor's influences its long-term kidney function. Transplant Proc 2013;45(1):51-6.
34. Maggiore U, Picetti E, Antonucci E, Parenti E, Regolisti G, Mergoni M, et al. The relation between the incidence of hypernatremia and mortality in patients with severe traumatic brain injury. Crit Care 2009;13(4):R110.
35. Shankaran S. Therapeutic hypothermia for neonatal encephalopathy. Curr Treat Options Neurol 2012;14(6):608-19.
36. Erb JL, Hravnak M, Rittenberger JC. Therapeutic hypothermia after cardiac arrest. Am J Nurs 2012;112(7):38-44.
37. Georgiou AP, Manara AR. Role of therapeutic hypothermia in improving outcome after traumatic brain injury: a systematic review. Br J Anaesth 2013;110(3):357-67.
38. Tsai E, Shemie SD, Cox PN, Furst S, McCarthy L, Hebert D. Organ donation in children: role of the pediatric intensive care unit. Pediatr Crit Care Med 2000;1(2):156-60.
39. Webster P, Markham L. Pediatric organ donation: anational survey examining consent rates and characteristics of donor hospitals. Pediatr Crit Care Med 2009;10(4):500-4.
40. Brierley J. Paediatric organ donation in the UK. Arch Dis Child 2010;95(2):83-8.