Brain death in children: a retrospective review of patients at a paediatric intensive care unit

KL Hon *, TT Tse, CC Au, WS Lin, TC Leung, TC Chow, CK Li, HM Cheung, SY Qian, Alexander KC Leung

ABSTRACT

Purpose: Among patients in paediatric intensive care units (PICUs), death is sometimes inevitable despite advances in treatment. Some PICU patients may have irreversible cessation of all brain function, which is considered as brain death (BD). This study investigated demographic and clinical differences between PICU patients with BD and those with cardiopulmonary death.

Methods: All children who died in the PICU at a university-affiliated trauma centre between October 2002 and October 2018 were included in this retrospective study. Demographics and clinical characteristics were compared between patients with BD and patients with cardiopulmonary death.

Results: Of the 2784 patients admitted to the PICU during the study period, 127 died (4.6%). Of these 127 deaths, 22 (17.3%) were BD and 105 were cardiopulmonary death. Length of PICU stay was shorter for patients with cardiopulmonary death than for patients with BD (2 vs 8.5 days, P=0.0042). The most common mechanisms of injury in patients with BD were hypoxic-ischaemic injury (40.9%), central nervous system infection (18.2%), and traumatic brain injury (13.6%). The combined proportion of accident and trauma-related injury was greater in patients with BD than in patients with cardiopulmonary death (27.3% vs 3.8%, P<0.001). Organ donation was approved by the families of four of the 22 patients with BD (18.2%) and was performed successfully in three of these four patients.

Conclusions: These findings emphasise the importance of injury prevention in childhood, as well as the need for education of the public regarding acceptance of BD and support for organ donation.

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New knowledge added by this study

- This 16-year retrospective study compared demographic and clinical differences between patients with brain death and patients with cardiopulmonary death in a Hong Kong paediatric intensive care unit.
- Among 127 deaths, approximately one in five were brain death. Length of paediatric intensive care unit stay was shorter for patients with cardiopulmonary death than for patients with brain death.
- The most common mechanisms of injury in patients with brain death were hypoxic-ischaemic injury, central nervous system infection, and traumatic brain injury. The combined proportion of accident and trauma-related injury was greater in patients with brain death than in patients with cardiopulmonary death.
- Organ donation was approved by the families of four of the 22 patients with brain death (18.2%) and was performed successfully in three of these four patients.

Implications for clinical practice or policy

- Family acceptance of the diagnosis of brain death may influence the length of paediatric intensive care unit stay. Without family acceptance of the diagnosis, physicians may be compelled to continue treatment for a patient with brain death.
- Education of the general public and early dialogue between the family and the attending physician are necessary to resolve common misconceptions regarding the biological and legal statuses of patients with brain death.
- Acceptance of the diagnosis of brain death may be associated with acceptance of organ donation and withdrawal of ventilator support, which may improve organ donation rates in Hong Kong.

Introduction

Despite advances in paediatric critical care medicine, death remains inevitable in some instances, due to various aetiologies.[1,2] In paediatric critical care medicine settings, patients who would have otherwise died may be kept 'alive' by advanced cardiovascular and ventilatory support. Some patients on cardiopulmonary support may experience irreversible cessation of all brain function, which is regarded as brain death (BD).[3-6] Because BD or cardiopulmonary death is equivalent to death, there is no obligation for the physician to provide further futile treatment.[1-4,7] Nevertheless, miraculous survivals have been reported in lay media involving patients who were previously declared BD or dead, which has created a mis-informed understanding of BD.[8] In this retrospective study, all patients who underwent BD assessment over a 16-year period were evaluated to determine whether survival occurred following BD assessment; the demographics of patients diagnosed with BD were compared with those of all other patients diagnosed with cardiopulmonary death at a paediatric intensive care unit (PICU). The null hypothesis was that there would be no demographic or clinical differences between patients diagnosed with BD and those diagnosed with cardiopulmonary death.

兒童腦死亡：兒科重症監護病房患者回顧

韓錦倫、謝梓芊、區卓仲、連穎琛、梁芷晴、周泰昌、李志光、張漢明、錢素雲、梁國柱

目的：儘管重症醫療的治療技術不斷進步，兒科重症監護病房（PICU）患者中還是有不可避免的死亡病例。部份PICU患者的所有腦功能可能會不可逆轉地停止，稱為腦死亡。本研究檢視PICU腦死亡患者與心肺死亡患者的人口統計學和臨床差異。

方法：這項回顧性研究納入2002年10月至2018年10月期間在一所大學附屬創傷中心內PICU死亡的兒童，並比較腦死亡患者和心肺死亡患者的人口統計學和臨床特徵。

結果：在研究期間2784名入院的重症監護病房患者中，127人死亡（4.6%），腦死亡佔22例（17.3%），心肺死亡佔105例。心肺死亡患者的PICU住院時間較腦死亡患者短（2天比8.5天，P=0.0042）。腦死亡患者的最常見損傷機制包括缺氧缺血性損傷（40.9%）、中樞神經系統感染（18.2%）和腦外傷（13.6%）。腦死亡患者中意外和創傷相關損傷的總比例高於心肺死亡患者（27.3%比3.8%，P<0.001）。22例腦死亡中有4例（18.2%）獲其家人同意捐贈器官，當中3例成功進行器官捐贈。

結論：研究結果強調預防兒童期損傷的重要性，以及對公眾教育接受腦死亡和支持器官捐贈的需求。

Methods

Study population

All children admitted to the PICU of a university-affiliated teaching hospital and trauma centre (Prince of Wales Hospital) between October 2002 and October 2018 were included in the study. The Prince of Wales Hospital provides tertiary PICU service for children, from birth to age 16 years, in the Eastern New Territories of Hong Kong. The institutional ethics committee approved this review and waived the requirement for patient consent.

Data collection

The demographics and clinical characteristics of deceased children were collected from the principal author's database (KLH), in which every PICU admission was registered; data were also collected retrospectively from the Clinical Management System of the hospital. All deaths were reviewed, including those of patients with clinical evidence of BD who underwent BD assessment. Brain death was defined as irreversible loss of all functions of the brain, including the brainstem. The presence of coma, absence of brainstem reflexes, and positive apnoea test were essential findings for diagnosis of BD. The diagnosis of BD was mainly clinical and was made in accordance with the hospital's standard protocol for paediatric patients.[4,9] Patients were classified either as BD or cardiopulmonary death.

Statistical analysis

The demographics and clinical characteristics of these two groups of patients were summarised as median (interquartile range [IQR]) or as number (percentage), and were compared using the Chi squared test, Fisher's exact test, or Mann-Whitney *U* test, as appropriate. Patient characteristics included age, sex, length of PICU stay (time from PICU admission to withdrawal of ventilator support), and diagnoses associated with PICU admissions. The GraphPad Prism 6 software (GraphPad Software, La Jolla [CA], US) and SPSS (Windows version 19.0; IBM Corp, Armonk [NY], US) were used for statistical analysis. All comparisons were two-tailed, and P values <0.05 were considered statistically significant.

Results

Patient characteristics

Of the 2784 children admitted to the PICU, 127 (4.6%) died in the PICU (Table 1). All but seven children were of Chinese ethnicity. There were 73 boys (57.5%) and 54 girls (42.5%); the median age was 3.2 years (IQR: 0.94-7.34 years). Most patients had not previously been admitted to the PICU (n=103, 81%), and most patients were aged >1 year (74.8%). Of the 127 patients who died, BD assessments were performed for 22 (17.3%) patients who had clinical evidence of BD; all 22 patients were diagnosed with BD. The remaining 105 (82.7%) patients were diagnosed with cardiopulmonary death.

TABLE 1. Demographics and clinical characteristics of patients in the PICU with brain death and patients with cardiopulmonary death*

Variable	Total (n=127)	Brain death (n=22)	Cardiopulmonary death (n=105)	P value
Sex				
Male	73 (57.5%)	14 (63.6%)	59 (56.2%)	0.26
Female	54 (42.5%)	8 (36.4%)	46 (43.8%)	
Age (years)	3.2 (0.94-7.34)	3.7 (1.46-9.17)	3.2 (0.88-7.17)	0.44
≤1 Year	32	4	28	0.47
>1 Year	95	18	77	
PICU stay (days)	3 (1-11)	8.5 (4.75-14)	2 (1-10)	0.0042
Total diagnoses associated with deaths in PICU	n=247	n=54 (21.9%)	n=193 (78.1%)	
Trauma	14 (5.7%)	8 (14.8%)	6 (3.1%)	0.0034
Traumatic brain injury		4	1	
Submersion injury		1	1	
Falls		2	2	
Strangulation		1	0	
Foreign body aspiration		0	1	
Contusion of trunk		0	1	
Intracranial event	13 (5.3%)	6 (11.1%)	7 (3.6%)	0.041
Cerebral oedema		3	2	
Intracranial haemorrhage		3	3	
Other intracranial event†		0	2	
Respiratory diagnoses	23 (9.3%)	1 (1.9%)	22 (11.4%)	0.033
Pneumonia		1	16	
Respiratory failure		0	4	
Pleural effusion			1	
Pulmonary hypertension		0	1	
Infection	72 (29.1%)	12 (22.2%)	60 (31.1%)	0.24
Sepsis/septicaemia		4	41	
Central nervous system infection		3	1	
Respiratory infection		2	17	
Gastroenteritis		2	1	
Herpes simplex virus infection		1	0	
Haematological diagnoses	13 (5.3%)	5 (9.3%)	8 (4.1%)	0.17
Post-transplant lymphoproliferative disease		0	2	
Hemophagocytic lymphohistiocytosis		0	2	
Bleeding disorders		5	0	
Other haematological diagnoses‡		0	4	

Abbreviation: PICU = paediatric intensive care unit

* Data are shown as No. (%) or median (interquartile range), unless otherwise specified. Some patients had multiple diagnoses

† Other intracranial events: hydrocephalus (n=1), microcephaly (n=1)

‡ Other haematological diagnoses: Langerhans cell histiocytosis (n=1), beta-thalassemia major (n=1), aplastic anaemia (n=1), myelodysplastic syndrome (n=1)

§ Endocrinological diagnoses: diabetic insipidus (n=1), panhypopituitarism (n=1)

|| Other solid tumours: germ cell tumour (n=1), retroperitoneal tumour (n=1), osteosarcoma (n=1), hepatoblastoma (n=1);

¶ Other gastrointestinal diagnoses: biliary atresia (n=1), liver transplant (n=1), intestinal obstruction (n=1), Hirschsprung disease (n=1), exomphalos (n=1), ileocolic intussusception (n=1), imperforate anus (n=1), midgut volvulus (n=1), necrotising enterocolitis (n=1)

TABLE 1. (cont'd)

Variable	Total (n=127)	Brain death (n=22)	Cardiopulmonary death (n=105)	P value
Neurological diagnoses	23 (9.3%)	7 (13.0%)	16 (8.3%)	0.29
Encephalitis		5	6	
Meningitis		1	1	
Epilepsy		0	5	
Convulsion/seizure		1	2	
Spinal muscular atrophy		0	1	
Cord compression		0	1	
Endocrinological diagnoses§	2 (0.8%)	1 (1.9%)	1 (0.5%)	0.39
Oncological diagnoses	32 (13.0%)	4 (7.4%)	28 (14.5%)	0.29
Brain tumours		1	6	
Other solid tumours‖		1	3	
Leukaemias		2	16	
Lymphomas		0	3	
Cardiovascular diagnoses	34 (13.8%)	6 (11.1%)	28 (14.5%)	0.66
Cardiac/post-cardiac arrest		2	10	
Shock		3	10	
Heart failure		1	3	
Cardiomyopathy		0	2	
Arrhythmias		0	2	
Atrial septal defect		0	1	
Gastrointestinal diagnoses	17 (6.9%)	3 (5.6%)	14 (7.3%)	0.46
Gastrointestinal bleedings		0	2	
Unknown intestinal disease with hepatomegaly/hepatosplenomegaly		2	0	
Hepatitis		0	1	
Hepatic failure		1	0	
Gangrene of small bowel		0	2	
Other gastrointestinal diagnoses¶		0	9	
Nephrological diagnoses	4 (1.6%)	1 (1.9%)	3 (1.6%)	>0.99
Renal failures		1	3	

Factors associated with brain death and cardiopulmonary death in patients in paediatric intensive care unit

Comparison of the two groups showed that length of PICU stay was significantly longer for patients with BD (8.5 days; IQR: 4.75-14 days) than for patients with cardiopulmonary death (2 days; IQR: 1-10 days; P=0.004). The two groups shared similar demographics. The most common diagnoses associated with death in the PICU were infections (29.1% of patients), oncological diagnoses (13.0%), and cardiovascular diagnoses (13.8%) [Table 1]. Comparison of the two groups showed that trauma (P=0.003) and intracranial events (P=0.041) were more common in patients with BD, whereas respiratory diagnoses (P=0.033) were more common in patients with cardiopulmonary death. With respect to the cause of injury, the combined proportion of accident and trauma-related injury was greater in patients with BD than in patients with cardiopulmonary death (27.3% vs 3.8%, P<0.001). Among patients with BD, the most common mechanisms of brain injury were hypoxic-ischaemic injury (eg, cardiac arrest, shock, and/or respiratory failure), central nervous system infection, and traumatic brain injury (Table 2). Organ donation was approved by the families of four of the 22 patients with BD (18.2%) and was performed successfully in three of these four patients.

Brain death in patients aged <2 years

Our local guideline for BD determination does not include patients aged <2 years. Nevertheless, we found no difference in the proportion of patients aged <2 years between the BD (n=7) and cardiopulmonary death groups (n=42) [31.8% and 40%, P=0.47]. There was a non-significant trend towards greater use of ancillary tests (eg, radionuclide cerebral perfusion scan or electroencephalography) for BD determination in patients aged <2 years, compared with patients aged >2 years (85.7% and 53.3%, P=0.19). The United Kingdom guidelines recommend that ancillary tests are not required in infants from gestational age of 37 weeks to 2 months after birth.[10] None of the patients were within this age range in our study.

TABLE 2. Causative mechanisms of injury among patients in the paediatric intensive care unit with brain death*

Variables	Brain death (n=22)
Cause of injury	
Accident and trauma	6 (27.3%)†
Mechanisms of brain injury	
Traumatic brain injury	3 (13.6%)
Cardiac arrest, shock and/or respiratory failure	9 (40.9%)
Central nervous system infection	4 (18.2%)
Brain neoplasm	1 (4.5%)
Vascular condition‡	2 (9.1%)
Others§	3 (13.6%)

* Data are shown as No. (%)
† Compared with cardiopulmonary death (n=4/105, 3.8%; P<0.001)
‡ Vascular condition refers to intracranial haemorrhage (n=2)
§ Others: thrombotic thrombocytopenic purpura, liver failure, hepatic encephalopathy (n=1); suspected inborn error of metabolism, hepatomegaly, interstitial nephritis, cardiac arrest, cerebral oedema (n=1); craniosynostosis post-cranioplasty, suspected venous sinus thrombosis, cerebral oedema (n=1)

Family acceptance of the diagnosis of brain death

Family acceptance of the diagnosis of BD may have influenced the length of PICU stay in our study. Among patients with documented family acceptance of the diagnosis of BD, the time interval from BD to withdrawal of ventilator support was 0.5 days (range, 0-1.5 days; n=10). This interval was prolonged among patients with documented family resistance of the diagnosis of BD (median, 8 days; range, 5-16 days; n=5, P=0.005); three of the five patients' families eventually accepted withdrawal of ventilator support, whereas the remaining two patients remained on ventilator support and lapsed into cardiac arrest after 16 days and 66 days.

Discussion

Brain death demographics and survival

Over this 16-year period, BD assessment was only performed in 22 (17.3%) patients who had clinical signs of BD; all 22 patients were confirmed to have BD. Notably, patients with BD had longer length of PICU stay and a greater combined proportion of accident and trauma-related injury, while patients with cardiopulmonary death had a greater frequency of respiratory diagnoses. In the present study, the percentage of patients with BD in the PICU was comparable to the numbers of patients with BD in two large reports (one from the US and the other from Canada; Table 3).[5,6] Accident and trauma-

TABLE 3. Comparison of three databases describing brain death in patients in the PICU*

	Hong Kong (present study)	United States[5]	Canada[6]
Diagnosis of brain death among PICU deaths	22 (17%)	3170 (21%)	135 (15%)
No. of participating centres	1	145	4
Male sex	14 (63.6%)	1861 (58.7%)	72 (53%)
Age (years)	3.7 (1.46-9.17)	<2 (33.5%) 2-12 (44.2%) ≥13 (22.3%)	
Mechanisms of injury			
Traumatic brain injury	3 (13.6%)	634 (20%)	58 (44%)
Cardiac arrest, shock and/or respiratory failure	9 (40.9%)	2071 (65.3%)	25 (19%)
Central nervous system infection	4 (18.2%)	104 (3.3%)	13 (10%)
Cause of injury			
Accident and trauma	6 (27.3%)	1285 (40.5%)	NS
PICU stay (days)	8.5 (4.75-14)	2.5 (1.6-4.2)	1.3 (NS)

Abbreviations: NS = not specified; PICU = paediatric intensive care unit
* Data are shown as No. (%) or median (interquartile range), unless otherwise specified

related injury led to one in four diagnoses of BD in our study, whereas the proportions of accident and trauma-related injury, as well as traumatic brain injury, were higher in the US and Canada.

Brain death and evaluation

Guidelines for BD assessment vary in terms of the numbers of examinations, numbers and types of physicians, time intervals between examinations, and use of ancillary tests.[11,12] In general, if BD is suspected, two physicians (neither of whom would be involved in organ harvesting from the patient) should perform two sets of brainstem examinations, at least 6 hours apart to ensure sufficient observation time. A single apnoea test should also be performed. If the results of these tests are positive, the patient can then be declared legally and clinically BD.[1-4] Before these examinations, conditions that may confound the clinical diagnosis of BD should be excluded.[1-4,11,12] Absence of the pupillary reflex to direct and consensual light, as well as the absence of corneal, cough, and gag reflexes, support the clinical diagnosis of BD. The calorie test can aid in determining the integrity of the oculovestibular reflex. A positive result consists of the absence of eye deviation when ice water is irrigated into an external auditory canal. The apnoea test is performed after the second examination of brainstem reflexes; only a single apnoea test is needed. Before the apnoea test is performed, the physician must confirm that the patient is not hypothermic, is euvolemic, and has normal arterial pressure of carbon dioxide and pressure of oxygen levels. The patient should then be connected to a pulse oximeter and the ventilator should be disconnected. Concurrently, 100% O_2 is delivered into the trachea at 6 L/min. A patient with BD may exhibit systolic blood pressure <90 mm Hg, significant oxygen desaturation, or cardiac arrhythmia. If respiratory movements are absent and the arterial pressure of carbon dioxide is ≥60 mm Hg, the apnoea test result is considered positive. If the patient is very unstable and an apnoea test might not be tolerated, or if the results of the apnoea test are inconclusive, physicians may opt for other neuro-diagnostic options (eg, four-vessel cerebral angiography, radionuclide cerebral perfusion scan, and/or electroencephalography). A lack of blood perfusion to the brain and lack of electrical activity would support a diagnosis of BD.

Implications for management of patients with brain death in the paediatric intensive care unit

The length of PICU stay was longer for patients with BD than for patients with cardiopulmonary death; this differed from the trends observed in the US and Canada (Table 3).[5,6] As noted in the Results, family acceptance of the diagnosis of BD may have influenced the length of PICU stay in our study. Unfortunately, not all stakeholders understand or accept the implications of a diagnosis of BD. In our experience, the reasons for the family's resistance might be two-fold. First, it might be emotionally difficult to accept the death of a loved one, when the child is apparently 'breathing' and appears physically 'well' when ventilatory support is provided. Second, the family might have confused persistent vegetative state with BD[3,4]; notably, patients with persistent vegetative state have intact brainstem function, while patients with BD have an irreversible loss of brainstem function. In such instances of confusion, families may wish to wait for the patient's 'miraculous revival'.[1,13-16] While the acknowledgement of BD as biological death may be counterintuitive to the public, there is a need to emphasise and accept that BD is legal death.[17] Thus, public education is necessary to resolve common misconceptions regarding the biological and legal statuses of patients with BD.[18] Notably, among university students in Hong Kong, improved knowledge has been shown to promote acceptance of the withdrawal of ventilator support following BD.[19] From a physician's perspective, withdrawal of ventilator support for patients with BD should not be regarded as withdrawal of life support; in addition, continued use of ventilator support that allows a patient to lapse into cardiac arrest is not a suitable option. Prolonged and unnecessary treatment in the PICU prevents other critically ill patients from using the PICU service; it also constitutes ineffective use of scarce medical resources. Abuse of PICU beds is undesirable because medical resources in the public sector are extremely competitive and limited.[20] Further studies regarding physician counselling skills and family acceptance of the diagnosis of BD may improve resource utilisation.

Medical professionals should closely monitor aetiologies that can lead to BD and consider discussions with affected patients' families at an early stage of medical treatment. These early discussions would allow more time for families to comprehend the implications of a BD assessment and potential positive test results. In a previous study, we found that prolonged length of PICU stay was associated with a Do-Not-Attempt-Resuscitation order, which was placed in nearly half of our PICU deaths; this finding implied that patients' families often need considerable time to accept the end-of-life decision when futility of medical treatment becomes evident.[1] Family acceptance of the diagnosis of BD is critical for successful management of such situations. If family acceptance is not achieved, physicians may become involved in a conflict with the family, which results in an ethical dilemma regarding the need to continue treatment for a patient with BD. For example, one patient in the present study remained in the PICU for 66 days due to this difficult situation.

Communication to identify common values and establish options based on objective criteria may resolve potential disputes and allow physicians and families to reach agreements before, during, and after BD assessment.[21]

Implications for organ donation

A practical aspect of BD assessment involves its implications for the organ donation process. Four of 22 patients' families opted for organ donation; notably, all four families also accepted the diagnosis of BD. Successful donations of liver or kidneys were made from three patients. Acceptance of the diagnosis of BD may be associated with acceptance of organ donation and withdrawal of ventilator support.[19] Support for organ donation, which was initiated by the organ transplant coordinator, had avoided potential instances of conflict. Acceptance of the diagnosis of BD could be a factor, in combination with other cultural and religious beliefs, for the lower organ donation rate than that observed in Western countries.[12]

Conclusions

In this study, one in five PICU deaths were BD. Acute hypoxic-ischaemic injury was the most common mechanism of brain injury; moreover, accident and trauma-related injuries were the cause of injury in one quarter of patients with BD. Diagnosis of BD was associated with significantly longer PICU stay. Notably, the organ donation rate was suboptimal. These findings emphasise the importance of injury prevention in childhood, as well as the need for education of the public regarding acceptance of BD and support for organ donation.

Author contributions

Concept or design: KL Hon.
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All authors have full access to the data, contribute to the study, approve the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, KL Hon was not involved in the peer review process. Other authors have no conflicts of interest to disclose.

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Ethics approval

The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee approved this review (CREC Ref. No. 2016.116).

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