

Brain death: medical management in seven Brazilian pediatric intensive care units

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Abstract

Objective: To assess the incidence of brain death (BD) and its medical management and adopted protocols after its diagnosis in seven pediatric intensive care units (PICUs) located in three Brazilian regions.

Methods: A cross-sectional and multicenter study was conducted, based on the retrospective review of medical records regarding all deaths that occurred between January 2003 and December 2004 in seven Brazilian PICUs of tertiary hospitals located in Porto Alegre (two), São Paulo (two) and Salvador (three). Two pediatric intensive care residents from each hospital were previously trained and filled out a standard protocol for the investigation of demographic data, cause of death, diagnosis of BD, related protocols and subsequent medical management.

Results: A total of 525 death patients were identified and 61 (11.6%) were defined as BD. The incidence of BD was different ($p = 0.015$) across the seven PICUs, but with no difference across the three regions. Intracranial hemorrhage was the most frequent cause of BD (31.1%). In 80% of the cases the diagnosis of BD was confirmed by complementary exams (south = 100%, southeast = 68% and northeast = 72%; $p = 0.02$). The interval between the diagnosis of BD and the withdrawal of life support was different ($p < 0.01$) across the three regions, being faster ($p = 0.04$) in the south (1.8±1.9 h) than in the southeast (28.6±43.2 h) and than in the northeast (15.5±17.1 h). Only six (9.8%) children with BD were organ donors.

Conclusion: Although a Brazilian law defining the criteria for the determination of BD has been in place since 1997, we verified that it is not followed as strictly as it should be. Consequently, unnecessary life support is offered to deceased individuals, and there is a discrete involvement of PICUs in organ donation.

J Pediatr (Rio J). 2007;83(2):133-140: Brain death, organ donation, pediatric intensive care, medical ethics.

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Financial support: CNPq, protocol no. 054/2005.

Manuscript received Aug 15 2006, accepted for publication Nov 10 2006.

Suggested citation: Lago PM, Piva J, Garcia PC, Troster E, Bousso A, Sarno MO, et al. Brain death: medical management in seven Brazilian pediatric intensive care units. *J Pediatr (Rio J)*. 2007;83(2):133-140.

doi 10.2223/JPED.1594

Introduction

Before the advent of mechanical ventilation, death was defined by the loss of circulatory, respiratory or neurological function. Nowadays, owing to the improvements in cardiorespiratory support, it is possible to maintain vital functions for long time periods, even in the absence of brain activity. This perspective raises at least two major questions: to what extent should a patient be considered alive? and Is organ donation possible in individuals under perfusion and whose heart is still beating?¹

In an attempt to overcome this problem, a president's commission was established in the United States in 1981, which defined death as the irreversible cessation of circulatory and respiratory functions or irreversible loss of full brain function.^{1,2}

Brain death (BD) is currently defined as the loss of full brain function, characterized by deep coma, apnea and lack of supraspinal reflexes. Therefore, BD according to medical and ethical aspects corresponds to the death of an individual, since the brain is essential for the whole body function.^{3,4}

The diagnosis of BD is clinical. In some countries (e.g.: United States), confirmation of BD at bedside is enough.⁴ However, other countries recommend examinations that confirm the absence of electrical and metabolic functions or of cerebral flow. Electroencephalogram (EEG) is the most widely used exam in several countries. Nevertheless, this exam cannot be easily performed in the intensive care unit (ICU), due to the possible interference of artifacts with electrical activity.⁴ It has been shown that 20% of patients with BD may have some EEG activity.⁵ Cerebral ultrasound has a sensitivity of 90% and a specificity of 100%, and is performed on middle and vertebral cerebral arteries.

In Brazil, the National Medical Council (Conselho Federal de Medicina, CFM) published the diagnostic criteria for BD in 1997. The clinical criteria must be described in the declaration of BD by two experienced physicians, not necessarily neurologists, at an interval that varies according to the age of each patient. Complementary exams that confirm total absence of brain function are mandatory.⁶ This rule facilitates organ donation, and when this is not possible, it allows removing those patients considered to be dead from the life support system.

The criteria for BD are accepted by most western countries, but some physicians from the Latin American community are still reluctant to remove ventilatory support from patients whose heart is still beating. This difficulty increases the conflict between the medical staff and family members, especially when personal or religious values are involved. Some cultures and religious groups do not accept death if vital functions have not ceased. In these cases, the removal of life support causes discomfort, since the individual

is apparently alive because his/her body is being kept through an artificial support system.^{6,7}

In Brazil, the declaration of BD to organ donation teams is mandatory.⁸ If donation is not possible, the physician must withdraw life support. Withdrawal of inotropic agents and of mechanical ventilation is legally supported and should be done by the intensivist after the family is contacted.⁵

Even with well-defined criteria for over 2 decades, the diagnosis of BD and its subsequent management are still controversial and cause anxiety in the medical community all over the world.^{6,7,9} Few studies have been published on BD in children.¹⁰⁻¹² We believe that, in Brazil, just as in other countries, medical management regarding BD is not uniform, with regional discrepancies. The aim of this study is to assess the reality of BD in Brazilian pediatric intensive care units (PICU), its incidence, adherence to the protocol established by the CFM and the management used in the PICUs of three Brazilian regions.

Methods

An observational, cross-sectional and retrospective study was carried out in seven PICUs with all children who died between 2003 and 2004 and who had been diagnosed with BD in their medical records. Seven PICUs were selected for this study:

- a) two in the Southern region - Hospital São Lucas, affiliated with Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS) and Hospital de Clínicas de Porto Alegre (HCPA), affiliated with Universidade Federal do Rio Grande do Sul (UFRGS);
- b) two in the Southeastern region – Hospital das Clínicas de São Paulo and Hospital Universitário, both affiliated with Universidade de São Paulo (USP);
- c) three in the Northeastern region – Hospital São Rafael, Hospital da Criança and Hospital Ernesto Simões Filho.

These seven PICUs operate in a similar fashion, with professors or coordinators who visit them every day, in addition to hired physicians and residents in pediatrics and/or intensive therapy that care for the patients during the day and night. The management of each patient is defined by the whole medical staff in daily meetings. All PICUs assessed perform extremely complex procedures. The Southern and Southeastern region hospitals carry out organ transplants.

Both patients and their medical records were identified by active search, by reviewing all admission and discharge data of each PICU between January 1, 2003 and December 31, 2004. The medical records were then carefully reviewed in search of patients who had the diagnosis of BD established according to their daily outcome, prior to their death. Two physicians from each PICU were selected and trained for data collection. They filled out a protocol with objective answers

using the data obtained from the patients' medical records. If any questions arose, they were discussed over the phone or via Internet.

From the selected medical records, the following information was obtained:

- a) demographic and general data about each patient;
- b) data about the death (number of multiple organ failures in the last 48 h of life, date and time of death);
- c) data related to BD (date and time of BD diagnosis, complementary exams for the diagnosis, necessity for complete cardiopulmonary resuscitation, dose of vaso-pressor drugs at 48 h, 24 h and at the time of death, as well as mechanical ventilation parameters at 48 h, 24 h and at the time of death);
- d) organ donation.

Based on the admission and death data obtained from each PICU in the last years, we estimated that each unit had approximately 400 admissions a year with a mortality rate of 10%, amounting to nearly 560 deaths in 2 years. Based on studies carried out in PICUs in southern Brazil and in Argentina,¹⁰⁻¹² the BD rate for this group is estimated at 10%. Therefore, we expected to obtain approximately 56 cases of BD in these seven PICUs.

The continuous variables were expressed as mean and standard deviation, and those without normal distribution were expressed as median and interquartile range (IQR 25-75%). Student's *t* test and ANOVA with Bonferroni's *post hoc* test, in case of differences between three or more groups, were used to compare normally-distributed continuous

variables. The Kruskal-Wallis and Mann-Whitney tests were used to compare variables without normal distribution. The *post hoc* analysis of data with asymmetric distribution was made using rank ANOVA for asymmetric data and using Tukey's *post hoc* test. The categorical variables were expressed as percentage and compared by the chi-square test and by Fisher's exact test, followed by the Finner-Bonferroni's p-value adjustment. All the data were loaded into an Excel (Microsoft) spreadsheet and analyzed by SPSS 11.0.

The present study was approved by the Research Ethics Committees of the seven hospitals that participated in the study.

Results

In the seven PICUs analyzed, there were 525 deaths in 2003 and 2004, 152 of which occurred in two PICUs in the southern region, 143 in two PICUs in the southeastern region and 230 in three PICUs in the northeastern region.

In 61 of 525 deaths (11.6%), the diagnosis of BD was identified in the medical records. The incidence of BD in these seven PICUs ranged from 4.5 to 24.2% ($p = 0.015$) (Table 1). However, when we grouped and compared the deaths per region (Table 2), we did not find any difference in the incidence of BD across the three regions (7.4, 15.3 and 12.6%; $p = 0.052$). According to Table 2, the general characteristics (sex, age and number of organ failures) of this group with diagnosis of BD did not differ across the three regions.

Table 1 - Distribution of deaths and the respective incidence of brain death in seven pediatric intensive care units*

Hospital	No. of deaths	Deaths < 24 h	BD, n (%)	Deaths due to other causes
1	67	4	6 (8.9)	57
2	85	6	15 (17.6)	64
3	110	9	14 (12.7)	87
4	33	1	8 (24.2)	24
5	101	4	6 (5.9)	91
6	67	8	3 (4.5)	56
7	62	4	9 (14.5)	49
Total	525	36	61 (11.6)*	428

BD = brain death. * $p = 0.015$ (Fisher's exact test).

The length of stay in the PICU prior to death varied considerably and significantly across the seven hospitals (2 to 455 days, $p = 0.041$). However, this difference was not observed when the medians for PICU stay were compared across the three regions (2 to 5 days, $p = 0.12$).

In 80.3% of cases, the clinical diagnosis of BD was confirmed by brain flow tests (ultrasound or scintigraphy) and/or EEG. The southern region was the one that best complied with the recommendations for definition of BD in

Brazil (confirmation through complementary exams), where 100% of patients with BD underwent confirmatory tests, comparatively to 68% in the southeastern region and to 72% in the northeastern region ($p = 0.02$).

Cerebrovascular accident was the most frequent cause (31.1%) of BD, followed by post-cardiorespiratory arrest and meningoencephalitis (Table 3).

Out of 61 patients diagnosed with BD, only six (9.8%) were organ donors (four patients in the southern region and

Table 2 - Demographic characteristics of deaths resulting from brain death in seven pediatric intensive care units in three Brazilian regions

	South n = 167 (2 PICUs)	Southeast n = 143 (2 PICUs)	Northeast n = 230 (3 PICUs)	p
Brain death: n (%)	21 (12.6)	22 (15.3)	18 (7.4)	0.052
Age (months)				
Mean \pm SD	62.6 \pm 58.8	60.3 \pm 55.8	81.6 \pm 58.6	0.48
Median IQR 25-75%	46 (9-115)	39.5 (11-97)	73.5 (28-135.7)	0.34
Male sex (%)	13 (59)	10 (45)	7 (39)	0.32
L in the PICU (days)				
Mean \pm SD	6.7 \pm 7.1	27.2 \pm 95.7	5.5 \pm 6.5	0.48
Median IQR 25-75%	2 (5-7)	5 (3.2-8.7)	3 (2-5.7)	0.12
More than 3 organ failures (%)	11 (52)	10 (45)	14 (77)	0.10

IQR = interquartile range; L = length of hospital stay; n = number of deaths; PICU = pediatric intensive care unit; SD = standard deviation.

Table 3 - Causes of brain death in seven pediatric intensive care units in three Brazilian regions

	PCRA	CVA	Mgtis/Enc	HT and ICH	Tumor	Snake	Total
South	3	5	7	4	2	0	21
Southeast	7	7	2	5	1	0	22
Northeast	1	7	4	4	1	1	18
Donors	3	1	0	2	0	0	6

CVA = cerebrovascular accident; HT = head trauma; ICH = intracranial hypertension; Mgtis/Enc = meningitis and/or encephalitis; PCRA = post-cardiorespiratory arrest; Snake = snakebite.

two in the southeastern region, $p = 0.13$). Post-cardiorespiratory arrest was the most frequent cause of BD in organ donors (three cases). Of 13 deaths due to head trauma and/or intracranial hypertension, situation that favors organ donation, there were only two donations (Table 3). When we compared organ donors and non-donors, we did not find any significant difference in age ($p = 0.56$) or in the length of stay in the PICU ($p = 0.24$).

The time between diagnosis of BD and withdrawal of life support was different across the seven PICUs, ranging from 1 to 193 h ($p = 0.01$). This difference was observed again when we grouped and compared the three regions. We noted that the average time for withdrawal of life support after the diagnosis of BD was significantly ($p = 0.041$) lower in the southern region (1.8 ± 1.9 h) than in the southeastern and northeastern regions (28.6 ± 43.2 h and 15.5 ± 17.1 h, respectively). In the southern region, no patient with BD was kept for over 24 h on the life support system, differently ($p = 0.002$) from the northeastern and southeastern regions, where ventilatory support was kept for more than 24 h in 17 patients ($\sim 40\%$ of BD in these regions), but none of them was an organ donor. In 13 (21%) patients, we found an increase in the use of inotropic agents after the diagnosis of BD, and in this case, only six patients were organ donors. In 28 patients, respiratory frequency of the ventilatory support was maintained or increased after the diagnosis, with differences across the three regions ($p < 0.001$) (Table 4).

Discussion

From the scientific and ethical point of view, BD certainly corresponds to the death of an individual. In the United States, the criteria that define BD were published in 1981,¹ whereas in Brazil, these criteria were legally adopted in 1997.⁶ The necessity to establish criteria that define BD and to legalize them aims to encourage and standardize organ donation, and allow for the removal of life support from nondonor patients in irreversible coma.⁵ The concept of BD should convey the idea of what being alive or dead means, not being directly related to organ donation.¹²

By analyzing the diagnosis of BD and the medical management subsequently adopted in seven PICUs in three different Brazilian regions, we note that this issue is not sufficiently clear among Brazilian pediatric intensivists, with regional variations and without uniform actions. Therefore, in this study, we may point out that:

- a) the incidence of BD varied considerably across hospitals;
- b) although the Brazilian law is clear as to the necessity of complementary exams for the diagnosis of BD, such exams were not carried out in 20% of the cases diagnosed as BD;

c) the time for removal of life support after the diagnosis of BD was extremely long. In the southeastern and northeastern regions, over 40% of children diagnosed with BD were kept for over 24 h on ventilatory support;

d) organ donation rates were not significant.

The incidence of BD in adult ICUs in Europe and in the United States amounts to approximately 12%,¹³ which is similar to the one described in studies undertaken in PICUs of Brazil, Argentina and United States.^{10,11,14} In this study, the overall incidence of BD (11.6%) was similar to the one described in the literature. However, when the hospitals were analyzed separately, there was a remarkable difference, which ranged from 4.5% in one hospital in the northeastern region to 24.5% in a PICU in the southeastern region, in Brazil. This difference can be related to the characteristics of inpatients, or be related to the difficulty in establishing the diagnosis of BD due to medical or technical problems in some of these Brazilian hospitals.^{13,15}

The clinical confirmation of BD requires deep coma with absence of supraspinal activity and apnea secondary to an irreversible process of known etiology.¹⁵ In Brazil, as well as in several European, Asian, Central American and South American countries, the diagnosis of BD requires confirmatory tests, showing absence of electrical and metabolic brain activity or of blood perfusion. This situation differs from that of the United States, for instance, where complementary exams are optional, and where only clinical examination at bedside is enough. In Canada, EEG is not considered to be a confirmatory test and, in Switzerland, brain angiography is mandatory for all patients with clinical diagnosis of BD.^{3,4}

The statement of BD, according to the resolution of CFM in 1997, establishes that confirmatory tests should be performed in donor and in nondonor patients, so that life support can be withdrawn.⁶ In this study, we observed that 20% of patients diagnosed with BD described in the medical records were not submitted to confirmatory tests. This may be the result of the poor infrastructure for such exams in some hospitals. On the other hand, another hypothesis is the bias of the medical staff in not wanting to cease life support in this situation and, in such case, the exams would not be necessary.

After confirmation of BD, the withdrawal of life support is an ethical duty of the medical staff, since maintaining life support in these cases is not beneficial, in addition to causing suffering to the family and unnecessary expenses.

In order to avoid conflicts, the medical staff may choose to keep life support until cardiac arrest occurs "spontaneously," with a do-not-resuscitate order. After BD, even if all life support is maintained, cardiac arrest occurs in approximately 1 week.¹ However, there have been some cases in which

Table 4 - Medical management after the diagnosis of brain death in seven pediatric intensive care units in three Brazilian regions

	South n = 21 (2 PICUs)	Southeast n = 22 (2 PICUs)	Northeast n = 18 (3 PICUs)	p
Time for withdrawal of life support (h)	1.8±1.9*	28.6±43.2	15.5±17.1	0.041
Median (minimum-maximum)	1 (1-9)†	20 (1-193)	4.5 (1-49)	0.002
Withdrawal of MV (%)	20 (95)‡	4 (18)	3 (17)	< 0.001
Increase in the dose of inotropics (%)	3 (14)	3 (14)	7 (39)	0.135
Increase or maintenance of MV parameters after diagnosis (%)	0‡	16 (76)	12 (67)	< 0.001
Maintenance of support for over 24 h after diagnosis (%)	0‡	9 (41)	8 (44)	0.001
Donors (%)	4 (19)	2 (9)	0	0.13

MV = mechanical ventilation; PICU = pediatric intensive care unit.

* ANOVA followed by Bonferroni's *post hoc* test.

† Rank ANOVA for asymmetric data and Tukey's *post hoc* test.

‡ Fisher's exact test followed by Finner-Bonferroni's p-value adjustment.

these patients generated costs and took up ICU beds for nearly 2 months.¹ The question in this case is about who benefits from the delayed withdrawal of life support from an individual who is already dead. The avoidance of a "possible conflict" does not seem a plausible explanation from the ethical point of view.⁷

Several studies have shown the difficulty pediatric intensivists have in discontinuing therapy in patients with BD.^{6,12} In this study, the time for withdrawal of life support after the diagnosis of BD differed across the three regions and, in some of them, it was extremely long (more than 24 h). In the southeastern and northeastern regions, over 40% of children were kept on ventilatory support for more than 1 day. Maintenance of life support after confirmation of BD probably results from the lack of information about the concept of BD or from unfounded legal fears.

The CFM admits that physicians have the power to cease life support after confirmation of BD, even if the family refuses it, respecting cultural and religious beliefs.⁵ Moreover, in response to the specific request made by PUCRS,¹⁶ the CFM reaffirms the diagnosis of BD after the clinical criteria are met and complementary exams are performed, and advocates the removal, by physicians, of devices and support that maintain respiratory and

cardiocirculatory functions, even in those patients that are not eligible for organ donation.

Although the criteria for BD have been well defined for more than 2 decades, there is still some controversy over this concept. In a recent study, Joffe et al. demonstrated that of 54 pediatric intensivists interviewed in 15 Canadian PICUs, 48% incorrectly regarded loss of consciousness as diagnosis of BD. In addition, 34% of interviewees did not feel comfortable switching off the respirator in patients with BD when the family did not authorize the withdrawal of life support.⁶ This behavior suggests that physicians make a distinction between BD and death.

In a study carried out in 16 Argentine PICUs, Althabe also showed the difficulty of pediatric intensivists in accepting BD as death of the patient. This was observed in 52 cases of BD, in which ventilatory support was maintained in 100% and inotropic therapy in 82% of the cases.¹² Therefore, there is much that remains to be clarified, discussed and demystified, both in the medical and lay communities.

In regard to organ donation, in this study, we noted a low incidence of donor patients - only six (9.8%), which shows the lack of involvement of medical teams in organ donation initiatives. This lack of commitment of the medical staff analyzed is worrying, since the southern and southeastern

regions are the major centers for organ transplants in Brazil. Furthermore, patients with BD secondary to head trauma were not donors in any of the hospitals analyzed, which seems to be incoherent, since head trauma is considered one of the major injuries that lead to donation.¹⁷⁻¹⁹ Morris, for instance, described 40 pediatric patients with head trauma and BD, among whom over 50% were organ donors, but the main reason for nondonation was the refusal of the family to do so.²⁰ In the analyzed patients, we could not check whether some families were asked about organ donation or whether there was no interest in reporting the death to the organ harvest teams.

This study, as most retrospective studies on end-of-life care, has some limitations in terms of methodology. Since this study is based on data from medical records, it is not possible to rule out collection biases. In an attempt to minimize this risk, we developed a protocol with closed and objective questions. Even though we considered these possible methodological biases, we noted that the data obtained are similar to those of other studies on BD carried out in other countries.^{6,9,19}

Death-related issues are still taboo in our setting. For this reason, the discussion about data related to BD involving both children and adults and the subsequent management can be the initial step towards an in-depth discussion about ethical and moral aspects regarding end-of-life care, such as death with dignity, responsibility, and correct resource allocation for the management of terminal patients, larger diffusion of transplantation programs, physician-patient-family relationship based on trust and honesty, and demystification of fantasies. In this study, the difficulty in establishing the diagnosis of BD and its subsequent management highlights the importance of an urgent change in behavior regarding the end-of-life care of these patients.

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