Hypothalamic–Pituitary Function in Brain Death: A Review

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Abstract

The Uniform Determination of Death Act (UDDA) states that an individual is dead when "all functions of the entire brain" have ceased irreversibly. However, it has been questioned whether some functions of the hypothalamus, particularly osmoregulation, can continue after the clinical diagnosis of brain death (BD). In order to learn whether parts of the hypothalamus can continue to function after the diagnosis of BD, we performed 2 separate systematic searches of the MEDLINE database, corresponding to the functions of the posterior and anterior pituitary. No meta-analysis is possible due to nonuniformity in the clinical literature. However, some modest generalizations can reasonably be drawn from a narrative review and from anatomic considerations that explain why these findings should be expected. We found evidence suggesting the preservation of hypothalamic function, including secretion of hypophysiotropic hormones, responsiveness to anterior pituitary stimulation, and osmoregulation, in a substantial proportion of patients declared dead by neurological criteria. We discuss several possible explanations for these findings. We conclude by suggesting that additional clinical research with strict inclusion criteria is necessary and further that a more nuanced and forthright public dialogue is needed, particularly since standard diagnostic practices and the UDDA may not be entirely in accord.

Introduction

The concept of brain death (BD) is accepted nearly worldwide as equivalent to death,[1] yet a number of controversies persist, leading one scholar to name it both "well settled yet still unresolved,"[2(p1244)] and prompting the United States President's Council for Bioethics to revisit the concept in a new White Paper.[3] One issue that remains controversial is the relation of standard diagnostic tests to the statutory definition of "death" as outlined in the Uniform Determination of Death Act (UDDA), which states: "An individual who has suffered either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead,"[4(p2)] For example, the editors of *Nature* stated in a recent editorial:

> The [UDDA] seems admirably straightforward . . . In practice, unfortunately, physicians know that when they declare that someone on life support is dead, they are usually obeying the spirit, but not the letter, of this law. And many are feeling increasingly uncomfortable about it. In particular, they struggle with three of the law's phrases: 'irreversible,' 'all functions' and 'entire brain,' knowing that they cannot guarantee full compliance . . . The time has come for a serious discussion on redrafting laws that push doctors towards a form of deceit.[5(p570)]

Evidence suggests that neuroendocrine functions may be preserved in some patients after the declaration of BD.[6] However, there are no comprehensive reviews of the clinical literature on this issue. Our purpose, therefore, is to provide such a review. Specifically we want to know: how often is BD accompanied by complete hypothalamic–pituitary failure? 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. Nonetheless, since our purpose in this article is to investigate whether hypothalamic–pituitary function remains in

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some patients who are declared to be brain dead, we follow the standard usage in the clinical literature and use ''brain death'' to mean *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*. We considered the functions of the posterior and anterior pituitary separately as befitting their distinct anatomic characteristics and embryologic origins.

Hypothalamic–Pituitary Function

Magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus secrete the hormone arginine vasopressin (AVP) into the peripheral bloodstream via the posterior pituitary in response to an increase in plasma osmotic pressure or hypovolemia. The half-life of AVP is relatively short, at about 15 to 18 minutes, and as little as a 1% change in plasma osmolarity can induce a change in AVP secretion. This rapid and sensitive physiologic response is part of a negative feedback system that maintains plasma osmolarity within a narrow, roughly 3% window by controlling diuresis via the kidneys.[7] In the absence of AVP or the kidneys' ability to respond to it, diabetes insipidus (DI) develops, characterized by the excretion of large amounts of dilute urine, often accompanied by hypernatremia. The clinical condition may result from primary hypothalamic dysfunction (central DI) or from the failure of the renal collecting ducts and distal tubules to respond to AVP (nephrogenic DI).

By contrast, the hypothalamus controls the anterior pituitary indirectly by secreting hypophysiotropic hormones into the local portal circulation. The functions of the anterior pituitary hormones, their target organs, and the peripheral hormones they control are complex, diffuse, subject to multiple interconnected feedback loops, and affect metabolic functions throughout the body.

We operationalized the concept of preserved hypothalamic–posterior pituitary function as the absence of DI. In contrast to the relatively straightforward role of AVP in antidiuresis, an inference from 1 or a few physiologic variables to a conclusion regarding the preservation of hypothalamic–anterior pituitary function would be less secure. Therefore, for the functions of the anterior pituitary, the main variables of interest are direct measurements of selected hormones or responses to anterior pituitary stimulation tests. We used these concepts to target 2 literature reviews.

Methods

The MEDLINE database was accessed through PubMed in September 2013. Results were restricted to English-language articles without date restriction. For the first search, we utilized Medical Subject Headings (MeSH) terms ''brain death'' in conjunction with ''diabetes insipidus'' and with ''posterior pituitary,'' yielding 26 results and 1 result, respectively. Text words ''brain death,'' ''diabetes insipidus,'' and ''posterior pituitary'' were combined in the same pattern to reveal 105 and

18 results. Reference lists were reviewed, and we consulted organ donor management guidelines and bioethical reviews to find additional studies.

Articles were included if they reported the results of an original clinical research study that provides evidence regarding DI or quantitative measurements of AVP in BD or brain stem death (BSD), in a manner that allows discernment of how many individual patients had DI or not. In accordance with common practice, we collapse BD and BSD, the irreversible cessation of all functions of the brain stem (a legal standard for death in the United Kingdom), for the following reason. In practice, the core clinical diagnostic tests for BD and BSD are the same: brain stem areflexia, apnea, and cerebral unresponsiveness, coupled with a known, irreversible cause of coma.

For the second search, we utilized MeSH terms ''brain death'' and ''anterior pituitary,'' yielding 24 results. Text terms ''brain death'' in conjunction with ''endocrine failure,'' and with ''anterior pituitary,'' revealed 39 and 183 results, respectively. Ancillary sources, as mentioned earlier, were consulted to find additional citations. Articles were included if they reported the results of an original clinical research study that provided quantitative measurements of selected hormones (discussed subsequently) or responses to anterior pituitary stimulation tests, in BD or BSD, reported at the individual level.

There is substantial variability in the clinical literature: the populations are not uniform in terms of age, etiology of BD, and the use of confirmatory diagnostic tests. The variables measured and study methodologies are not uniform, laboratory cutoff values are not standardized, and the key diagnostic category of DI is not uniformly applied. These limitations preclude the possibility of a systematic review with meta-analysis. Instead, we provide a compilation of all studies that meet the criteria specified earlier, in the context of a narrative review.

Results

We found a total of 32 studies that met criteria for the first search (see Table 1).[8-40] Together, the 32 studies report on 1878 patients with BD or BSD, ranging in age from 2 months to 89 years, of which 925 (49%) were reported to have DI. The 6 studies that report exclusively on adult patients collectively report that 200 (60%) of 334 had DI[23,29,31,33,35,39]; for the pediatric population, 5 studies collectively report that 145 (52%) of 279 had DI.[12,15,28,30,40]

The evidence regarding anterior pituitary function is not straightforward (see Tables 2-5). The hypophysiotropic hormones luteinizing hormone-releasing hormone (LHRH), corticotropin-releasing hormone, and growth hormone (GH)-releasing hormone (GHRH) are generally detectable in peripheral circulation.[25,27,41] The anterior pituitary hormones thyroid-stimulating hormone (TSH),[16,27,42-51] adrenocorticotropic hormone (ACTH),[27,41,51,52,54] and human GH[16,27,41,51,52,53] are also usually detectable, mostly within a normal range. Anterior pituitary responsiveness to stimulation is variable. Some studies document no response to thyrotropin-releasing hormone,[53,55] insulin-induced hypoglycemia,[41] or

Table 1. Clinical Studies Reporting on Diabetes Insipidus in Brain Death.

Publication	Age	BD, n	DI, n	DI, %
Griepp et al[8] (P)	13-52 yr	22	9	41
Jorgensen[9] (P)	us	63	23	37
Jastremski et al[10] (R)	11-89 yr	176	15	9
Jorgensen and Malchow-Moller[11] (P)[a]	12-86 yr	4	1	25
Outwater and Rockoff[12] (R)	5 mo to 16 yr	16	14	88
Pelosi et al[13] (P)	9-37 yr	21	6	29
Fiser et al[14] (R)	4 mo to 18 yr	34	13	38
Fackler et al[15] (R)	2 mo to 17 yr	45	5	11
Howlett et al[16] (P)[b]	8-67 yr	31	24	77
Kinoshita et al[18] (P)	9-54 yr	10	10	100
Hohenegger et al[19] (P)[c]	6-48 yr	11	4	36
Debelak et al[20] (R)	us	181	68	38
Nygaard et al[21] (R)	6-56 yr	114	60	53
Mackersie et al[22] (R)	us	99	38	38
Ali et al[23] (R)	Adult	43	34	79
Gramm et al[24] (P)	9-71 yr	32	25	78
Sugimoto et al[25] (P)[d]	17-61 yr	7	7	100
Rabanal et al[26] (P)	us	50	20	40
Arita et al[27] (P)	9-85 yr	18	10	56
Staworn et al[28] (R)	Peds	92	38	41
Amado et al[29] (P)	18-67 yr	18	5	28
Finfer et al[30] (R)	Peds	77	60	78
Dominguez-Roldan et al[31] (P)	Adult	59	31	53
Dosemeci et al[32] (P)	2-71 yr	94	74	79
Dominguez-Roldan et al[33] (R)	Adult	50	43	86
Kim et al[34] (R)[e]	13-49 yr	10	10	100
Salim et al[35] (R)	Adult	69	32	46
Chai et al[36] (R)[f]	17-59 yr	5	5	100
Wijdicks et al[37] (R)	2 mo to 84 yr	228	141	61
Seth et al[38] (P)	7-87 yr	55	17	31
Varelas et al[39] (R)	Adult	95	55	58
Alharfi et al[40] (R)	5-17 yr	49	28	57
Total[g]	2 mo to 89 yr	1878	925	49

Abbreviations: P, prospective study; R, retrospective study; BD, brain death; DI, diabetes insipidus; us, unstated; peds, pediatric (17 years and younger); adult, 18 years and older; AVP, arginine vasopressin.

[a]DI was serially evaluated in patients with BD at 1, 2, 4, 8, 16, 32, 64, 128, and 256 hours postresuscitation from cardiac arrest. At these times, the following incidence of DI in BD occurred: 1 of 4, 1 of 3, 2 of 4, 2 of 4, 4 of 8, 6 of 10, 6 of 11, 8 of 10, and 2 of 4. We have only included the first measurement in the compilation above.

[b]Keogh et al[17] appears to report the results of the same study.

[c]Of the 11, 4 had polyuria, but all had normal AVP levels. Exogenous vasopressin administered to 5 showed no or inadequate response, suggesting nephrogenic DI.

[d]All 7 patients had detectable levels of AVP, suggesting nephrogenic DI or iatrogenic polyuria.

[e]Of the 10 patients, 7 had a gunshot wound penetrating an area approximately 4 cm above the dorsum sella, just underneath the thalamus, crossing through the third ventricle, the body of the corpus callosum, and the cingulum. This is very close to the hypothalamus, so it seems likely that DI was caused by direct trauma to the hypothalamus.

[f]Fifteen patients were included in this sample, but only 5 underwent apnea testing, so we have only included those 5.

[g]As this is not a meta-analysis, the total only refers to the total of patients reported in this review and should not be misunderstood as implying generalizability to the population with BD as a whole.

arginine infusion,[41] whereas others document responses to each of these anterior pituitary stimuli as well as responses to LHRH and GHRH with appropriate hormonal increases.[25,27,42]

Thyroid function appears to be impaired, although the pattern of thyroid hormones (low triiodothyronine [T3] and to a lesser extent, low thyroxine [T4] with normal or high reverse T3 and normal TSH) is more consistent with euthyroid sick syndrome rather than central neuroendocrine failure[16,24,46,53,58,64] (see Tables 2-5 for further detail). Adrenal function is difficult to interpret: cortisol levels show wide

variability[16,24,27,29,46,48,58,60-62] although ACTH levels are generally preserved as mentioned earlier. Diurnal variation in cortisol appears universally lost.[16,27,44,63]

Discussion

Interpretation of Results

These data are subject to limitations, and any quantitative estimate of incidence of preserved hypothalamic function in the

Table 2. Overview of Hypothalamic–Anterior Pituitary Literature Review.

Variables	# of Studies	Findings/Comments
Selected hypophysiotropic hormones	3	LHRH det 10/10 pts[25]; CRH and GHRH det 5/5 and 4/5[41]; GHRH det 13/23, CRH det 12/19, LHRH det 21/22, and 1 or more of GHRH, CRH, or LHRH det 23/23[27]
Selected anterior pituitary hormones	5-12	TSH[16,27,42-51]: wnl 272/347 (78%); det 325/386 (84%) GH[16,27,41,51,52,53]: wnl 37/60 (62%); det 102/109 (94%) ACTH[27,41,51,52,54]: wnl 31/65 (48%); det 83/114 (73%)
Anterior pituitary stimulation tests	6	0/36 and 0/7 responded to TRH with ↑TSH[53,55] 0/5 responded to insulin-induced hypoglycemia or arginine with ↑GH[41] 15/23 responded to 1 or more of TRH, LHRH, or insulin[27] 2/7 and 4/5 responded to arginine and GRH with ↑GH[27] 1/1 and 1/1 responded to TRH and LHRH[42] 1/2 responded to insulin[42] 4/5 responded to TRH[25]
T4 (total and free)	6-7	T4[16,43,44,50,56,57]: Wnl or ↑ 80/129 (62%) fT4[45-50,58]: wnl or ↑ 194/299 (65%)
T3 (total, free, and reverse)	6-9	T3[16,43,44,50,56,57]: wnl 27/129 (21%) fT3[44-50,56,57,59]: wnl or ↑ 57/133 (17%) rT3[16,45-48,50,58]: wnl or ↑ 152/169 (90%) Thyroid hormone patterns (including TSH) most consistent with euthyroid sick syndrome rather than central neuroendocrine failure.
Cortisol	8	Highly variable.[16,24,27,29,46,48,58,60-62] Diurnal variation apparently lost in every case.[16,27,45,63]

Abbreviations: LHRH, luteinizing hormone-releasing hormone; CRH, corticotropin-releasing hormone; GHRH, growth hormone-releasing hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; GH, growth hormone; ACTH, adrenocorticotropin hormone; T4, thyroxine; fT4, free T4; T3, triiodothyronine; fT3, free T3; rT3, reverse T3; wnl, within normal limits; det, detectable; ↑, high.

Table 3. Anterior Pituitary Stimulation Tests.

Publication	Age	BD, n	Variables	Findings
Schrader et al[42] (P)	16-56 yr	6	IH-t, LHRH-t, TRH-t	IH-t + in 1/2; LHRH-t + in 1/1; TRH-t + in 1/1
Koller et al[53] (P)	16-64 yr	36	TRH-t	+ in 0/36
Imberti et al[55] (P)	19-62 yr	7	TRH-t	+ in 0/7
Sugimoto et al[25] (P)	Adult	5	TRH-t	+ in 4/5
Kinoshita et al[41] (P)	17-50 yr	10	IH-t, AI-t	IH-t + in 0/5, AI-t + in 0/5
Arita et al[27] (P)	9-85 yr	39	TRH-t, LHRH-t, IH-t, AI-t, GHRH-t	15/23 + to 1 or more of TRH-t, LHRH-t, or IH-t; 2/4 + in add'l LHRH-t 7 d post-BD; AI-t + 2/7; GHRH-t + 4/5

Abbreviations: P, prospective study; R, retrospective study; BD, brain death; adult, 18 years and older; IH-t, insulin-induced hypoglycemia test; LHRH-t, luteinizing hormone-releasing hormone test; TRH-t, thyrotropin-releasing hormone test; +, positive response; AI-t, arginine infusion test; GHRH-t, growth hormone-releasing hormone test; add'l, additional; yr, years; d, days.

population with BD in general should be taken as having unknown confidence. However, this does not imply that no conclusions can be drawn.

The magnocellular neurons of the hypothalamus are osmoreceptors, directly responsive to the osmotic pressure of their extracellular environment. Although osmotically induced depolarizations increase the likelihood that an action potential will fire, they are not typically large enough to induce the cell to reach its threshold voltage.[65] Normal osmoregulation requires excitatory glutamatergic input from circumventricular areas, particularly the organum vasculosum of the lamina terminalis, creating an additive effect that allows the membrane potential to reach spike threshold, generating an action potential down the axon and hence inducing the secretion of AVP into the bloodstream.[65]

The half-life of AVP is about 15 to 18 minutes, which allows for a rapid physiologic response to osmotic changes. As little as a 1% change in plasma osmolarity induces a change in AVP release, and small changes in AVP concentration in plasma (normal range between approximately 0.5 and 5-6 pg/mL) result in changes throughout the full range of urine osmolarity and urine volume.[7] Thus, the osmoregulation system is sensitive and rapid, with small changes in plasma osmolarity resulting in rapid changes in AVP secretion from the hypothalamic–pituitary complex at a rate and level sufficient for minute-to-minute changes in urine osmolarity and volume. In the absence of AVP, the distal tubules and collecting ducts of the kidney's nephrons are nearly impermeable to water, which prevents the reabsorption of water back into the bloodstream, resulting in the production and release of large quantities of dilute urine. The simplest explanation for the observation of normuria in patients with BD is that the hypothalamic osmoregulation system continues to function, in at least some patients.

Table 4. Hypothalamo–Pituitary–Thyroid Axis.

Publication	Age	BD, n	Variables	Findings
Schrader et al[42] (P)[a]	16-56 yr	6	TSH	TSH wnl or ↑ 4/6
Gifford et al[56] (R)	7-54 yr	22	T4, T3	T4 wnl 10/22, det 22/22; T3 wnl 0/22, det 10/22
Macoviak et al[43] (P)	15-36 yr	22	TSH, T4, T3	TSH wnl 17/22; T4 wnl 17/22; T3 wnl 6/22
Novitzky et al[59] (P)	16-40 yr	21	fT3	fT3 wnl 1/21, det 21/21
Robertson et al[44] (P)	Adult	13	TSH, T4, T3, fT3	TSH wnl 13/13; T4 wnl 10/13; T3 wnl 3/13; fT3 wnl 1/13
Montero et al[57] (P)	us	21	T4, T3	T4 wnl or ↑ 14/21, det 21/21; T3 wnl 3/21, det 21/21
Howlett et al[16] (P)	8-67 yr	31	TSH, T4, T3, rT3	TSH wnl or ↑ 24/31; T4 wnl 18/31; T3 wnl or ↑ 6/31; rT3 wnl or ↑ 29/29 (15/29 wnl and 14/29 ↑)
Robertson et al[58] (P)	Adult	36	fT4, fT3, rT3	fT4 wnl or ↑ 30/36; fT3 wnl or ↑ 3/36; rT3 wnl 34/36
Masson et al[45] (P)	14-48 yr	20	TSH, fT4, fT3, rT3	TSH wnl 15/20; fT4 wnl 7/20, fT3 wnl 4/20; rT3 wnl or ↑ 18/18 (3/18 wnl and 15/18 ↑)
Powner et al[46] (P)	19-60 yr	16	TSH, fT4, fT3, rT3	TSH wnl 8/16; fT4 wnl or ↑ 15/16 (12/16 wnl and 3/16 ↑); fT3 wnl 1/16; rT3 wnl or ↑ 15/16 (11/16 wnl and 4/16 ↑)
Arita et al[27] (P)	9-85 yr	39	TSH	TSH det 39/39
Karayalcin et al[47] (P)	11-60 yr	50	TSH, fT4, fT3, rT3	TSH wnl or ↑ 36/50, (35/50 wnl, 1/50 ↑), det 50/50; fT4 wnl or ↑ 20/50 (19/50 wnl, 1/50 ↑); fT3 wnl 18/50; rT3 wnl or ↑ 48/50 (44/50 wnl, 4/50 ↑)
Mariot et al[48] (P)	us	120	TSH, fT4, fT3	TSH wnl 99/120, fT4 wnl 75/120; fT3 wnl 15/120
Goarin et al[49] (P)	15-55 yr	37	TSH, fT4, fT3	TSH wnl 35/37, fT4 wnl or ↑ 37/37; fT3 wnl 6/37
Szostek et al[50] (P)	17-55 yr	20	TSH, T4, fT4, T3, fT3, rT3	TSH wnl or ↑ 13/20 (11/20 wnl and 2 ↑); T4 wnl or ↑ 11/20; fT4 wnl or ↑ 10/20; T3 wnl or ↑ 9/20; fT3 wnl or ↑ 8/20; rT3 wnl or ↑ 8/20; both T3 and T4 positively correlated with TSH
Ishikawa et al[51] (P)[b]	39-70 yr	12	TSH	TSH wnl 8/12

Abbreviations: P, prospective study; R, retrospective study; BD, brain death; us, unstated; adult, 18 years and older; TSH, thyroid-stimulating hormone; T4, thyroxine; fT4, free T4; T3, triiodothyronine; fT3, free T3; rT3, reverse T3; wnl, within normal limits; det, detectable; ↑, high; ↓, low; yr, years.
[a]"Serum TSH was within normal range . . . in the majority of the patients but was slightly elevated in case 5."[42(p241)] We have transcribed this statement into our compilation as the lowest number of cases possible such that the majority was within the normal range (ie, 4 of 6).
[b]Hormones were measured at autopsy, 4 to 25 days post-BD. All patients were autopsied within 12 hours of cardiac arrest. Blood was taken from the right cardiac chamber.

It is possible that an extracranial tumor could secrete AVP into the bloodstream; however, this would not be subject to inhibitory feedback, therefore, the patient would likely be oliguric or anuric. More importantly, this is an unusual circumstance and would not explain the common finding of the absence of DI in about half of the patients reported previously. Another possibility is that AVP passively leaks from the axonal terminals of nonviable hypothalamic cells whose perikarya have been destroyed (ie, posterior pituitary washout). This source of AVP is also not subject to feedback so the patient would more likely exhibit anuria or oliguria, followed by polyuria minutes after the AVP stores are depleted. However, depending on the rate at which AVP passively leaks, it seems plausible that passive leakage of AVP could mimic osmoregulation at least while AVP stores last and so this may account for some of the cases of lack of apparent DI.

A third possibility is that glomerular filtration rate (GFR) is significantly decreased. This would result in the diminution of the amount of fluid delivered to the distal tubule and hence would limit renal water excretion and prevent polyuria.[66] Theoretically, this phenomenon may occur even in the absence of AVP; therefore, the absence of polyuria does not necessarily imply function of the hypothalamic osmoregulation system. Although this is a possibility, it cannot account for all of the cases of lack of DI in patients with BD. Fiser et al,[14] for example, report no significant difference in creatinine levels between patients with BD with DI (n = 13) and patients with

BD without DI (n = 21), suggesting that decreased GFR cannot account for the absence of DI in these patients. Finfer et al[30] reported mean maximum creatinine level of 1.02 ± 0.7 mg/dL in their sample. In the 17 patients without DI (of 77 with BD in total), decreased GFR cannot account for the absence of polyuria. Furthermore, several studies directly measured plasma AVP, finding AVP within the normal range for osmoregulation in some patients with BD.[19,24,25,27]

For example, 1 study followed a rigorous protocol, correlating plasma AVP with plasma osmolarity.[27] Using standardized criteria for DI,[67] these authors found that 10 of the 18 patients in their sample had DI, 1 had the syndrome of inappropriate antidiuretic hormone, and the remaining 7 (39%) of the 18 demonstrated normal plasma osmolarity and normal AVP. It should be noted that it is unlikely that passive leakage, not subject to any feedback, would account for the normal plasma osmolarity, given the negative feedback needed to maintain a delicate balance of plasma osmolarity within a narrow, roughly 3% window.[7]

Furthermore, anatomical considerations suggest 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.[68] Pathology studies support this explanation. Walker and colleagues[69]

Table 5. Hypothalamo–Pituitary–Adrenal Axis and GH.

Publication	Age yr, years	BD, n	Variables	Findings
Schrader et al[42] (P)	16-56 yr	6	GH	GH wnl or ↑ 5/6
Howlett et al[16] (P)	8-67 yr	31	GH, cort	GH wnl 10/31, det 27/31; cort wnl 5/21, det 20/21
Robertson et al[58] (P)	Adult	36	Cort	Cort wnl 27/30
Powner et al[46] (P)	19-60 yr	16	Cort	Cort wnl or ↑ 10/11
Kinoshita et al[41] (P)	17-50 yr	10	GHRH, GH, CRH, ACTH, cort	All hormones det in all patients, except GHRH det 4/5
Arita et al[27] (P)	9-85 yr	39	GHRH, GH, CRH, ACTH, cort, LHRH	GHRH det 13/23; CRH det 12/19; LHRH det 21/22; 1 or more of GHRH, CRH, or LHRH det in every case; GH det 38/39; ACTH det 33/39; mean concentration all hormones wnl except GH was ↑. Cortisol wnl 23/30
Mariot et al[48] (P)	us	120	Cort	Cort wnl 101/120
Fitzgerald et al[54] (P)	25-61 yr	11	GH, ACTH, cort	GH wnl 11/11; ACTH wnl 9/11, det 10/11; cort wnl 10/11
Dimopoulou et al[60] (P)	Adult	17	Cort	Cort wnl 5/17[a]
Ishikawa et al[51] (P)[b]	39-70 yr	12	GH	GH wnl or ↑ 11/12
Nicolas-Robin et al[52] (P)	Adult	42	ACTH	ACTH wnl 17/42, det 25/42

Abbreviations: P, prospective study; R, retrospective study; BD, brain death; us, unstated; adult, 18 years or above; LHRH, luteinizing hormone-releasing hormone; GHRH, growth hormone-releasing hormone; GH, growth hormone; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropin hormone; cort, cortisol; wnl, within normal limits; det, detectable; ↑, high; yr, years.
[a]"Within normal limits" is here considered to be above 10 μg/dL. Although this is high, it is considered normal in the context of acute stressful illness.
[b]Hormones were measured at autopsy, 4 to 25 days post-BD. All patients were autopsied within 12 hours of cardiac arrest. Blood was taken from the right cardiac chamber.

reported finding some intact regions of the hypothalamus with relatively well-preserved neurons, intermingled with neurons with lytic changes, in patients with coma dépassé (a diagnostic precursor to BD: all patients were comatose, apneic, and with isoelectric encephalograms). In a more recent pathology study of 41 patients with BD,[70] moderate to severe ischemic changes in brain stem and higher brain structures were found in only about 34% to 68% of patients (with variability in different brain areas). Of these 41 patients, 16 of the pituitary glands were examined, with 55% of those showing mild or absent ischemic changes.

Polyuria alone is not sufficient evidence of dysfunctional hypothalamic control of plasma osmolarity, yet the majority of studies did not rule out confounding factors nor corroborate urine output with laboratory values. There are a number of iatrogenic reasons for polyuria, including diuretics or fluid resuscitation. To illustrate, Fiser and colleagues[14] report that 26 of the 34 patients were polyuric, yet only 13 had DI while the remaining 13 did not have hypernatremia, serum hyperosmolarity, or urine hyposmolarity. Polyuria was determined to be due to the administration of furosemide, mannitol, or contrast solution for computed tomography. In 2 studies,[12,26] DI was found to spontaneously resolve in some patients without administration of exogenous vasopressin, suggesting reperfusion or a decrease in edema, or both, to the hypothalamic–pituitary complex after an initial insult that rendered the area temporarily nonfunctional.

Regarding anterior pituitary function, measurement of hypophysiotropic hormones in peripheral circulation is not entirely reliable due to pulsatility of the hormones and the minute amounts secreted. However, finding preserved anterior pituitary hormones, which depend on hypophysiotropic hormones for their secretion, corroborates the finding of preserved hypophysiotropic hormones. Responsiveness to stimulation suggests viability of the anterior pituitary as well as preserved blood flow. Thyroid and adrenal functions, while impaired, are not absent. If there were central neuroendocrine failure, the pattern of thyroid hormones would be very different, with significant hypothyroidism as well as undetectable TSH. These data suggest variable preservation of some areas of the hypothalamus and anterior pituitary. Furthermore, they serve as corroborating evidence for the preservation of hypothalamic osmoregulation, by suggesting preservation of circulation to the pituitary and parts of the hypothalamus.

Although the data have limitations, we believe the following modest conclusions are justified. At least some of the patients in these studies who were normuric had some preserved brain function through hypothalamic osmoregulation. The various findings consistent with 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 although often in the presence of peripheral endocrine insufficiency. Anatomical considerations explain why these findings are to be expected, and pathology studies corroborate this explanation. It is to be emphasized that this is not a meta-analysis and no specific incidence estimates are offered for the general population of patients with BD.

General Discussion

The results of this review suggest that some basal parts of the brain can continue to function in a nontrivial proportion of patients who are declared dead on the basis of neurological

criteria. Given that the UDDA and all state laws based on it describe the statutory definition of "death" as "irreversible cessation of all functions of the entire brain," it follows that any patient who retains neuroendocrine regulation does not, strictly speaking, meet the statutory standard for death by neurologic criteria in the United States (nor any other nation with similar "whole-brain death" laws). Therefore, we make 2 suggestions.

First, further clinical research is needed, with well-designed studies (including stricter inclusion criteria) aimed at ascertaining the nature and incidence of preserved brain function in patients who meet standard diagnostic tests for BD. In addition to neuroendocrine function, electrophysiology studies suggest that the integrity of a variety of neural pathways may be preserved as manifested by evoked potentials as well as organized cortical activity.[6] It is to be emphasized that the triad of unresponsiveness, brain stem areflexia, and apnea are *tests*—they do not define the nosological category of BD itself. Legally in the United States, BD is the irreversible cessation of all functions of the entire brain; hence, if a patient satisfies clinical tests while maintaining, for example, hypothalamic osmoregulation, then that is a false positive.

Second, a forthright public dialogue is needed, which better takes into account the complexities of this topic. This should include frank discussion of the biomedical science underlying BD and its diagnosis, including the possibility of minimal brain function in some patients declared "dead by neurologic criteria." If, as it would appear, diagnostic practices and the UDDA are not entirely in accord, then there should be an open public conversation. Whether those laws that "push doctors toward a form of deceit" need to be redrafted, as the editors of *Nature* suggested,[5] or whether more stringent diagnostic practices should be used is a question with important medical, ethical, social, and legal components and therefore should be publicly vetted.

For example, the diagnosis of BD has important legal and ethical implications for organ transplantation, since brain dead organ donors remain the primary source of transplantable organs. One well-accepted legal and ethical principle is known as the "dead donor rule," which states that organ donors must be dead before vital organs are procured.[3] However, the results of this review suggest the possibility that some patients who are declared dead may maintain some minimal brain function and therefore, at least in a strict sense, do not meet legal standards for death by neurologic criteria. Were such patients to become organ donors, adherence to the dead donor rule could be called into question. The ethical issues related to BD and organ donation are complex, however, and cannot be adequately addressed in this context (see Nair-Collins for a review of the philosophical and ethical literature on this topic).[71] It should suffice to point out that there are clear ethical, legal, and social implications of the diagnosis of BD, which reach beyond rather technical concerns regarding AVP secretion and osmoregulation; and therefore, an informed public dialogue is needed.

One might reply that "BD is a clinical diagnosis," and only those functions that are clinically ascertainable are relevant to the determination of death.[72,73] But this is a nonsequitur. The UDDA is clear and straightforward: an individual that has any brain function cannot be said to satisfy the UDDA's definition of irreversible cessation of all functions of the entire brain, regardless of whether the preserved function is clinically observable or not. Furthermore, normuria is a clinically observable sign of brain function just as much as pupillary constriction or spontaneous inspiration.

One might also point to the immediately following phrase in the UDDA: "A determination of death must be made in accordance with accepted medical standards." Since brain stem areflexia, apnea, and cerebral unresponsiveness constitute long-accepted medical standards upon which to diagnose BD, perhaps it follows that the use of such diagnostic standards is in accordance with the UDDA. However, "accepted medical standards" refers to the *tests* to be used to identify those patients who have irreversibly lost all functions of the entire brain, and this was made explicit by the authors of the UDDA.[4(pp78-79)] Although it is accepted practice to not test for certain brain functions (particularly neurohormonal functions), this does not show that doing so is consistent with the UDDA in either letter or spirit, since both the UDDA and the President's Commission's report upon which it is based are explicit in insisting that *all* brain functions must be lost.

Finally, we have not discussed in any depth the diagnostic tests that were used in these studies. Given that there is variability in diagnostic practices,[1,74] perhaps it is simply the case that many of the patients reported in these studies were misdiagnosed and that, with stricter diagnostic criteria, no patient with neuroendocrine function would be classified as brain dead. This response is also a nonsequitur, since the question of misdiagnosis is precisely the point. We wished to address, in light of continued controversy over BD and its diagnosis, whether some patients who are in fact declared to be dead by neurologic criteria nonetheless maintain some brain function. The results of our review suggest an affirmative answer, and potentially almost half of the patients reported in the cited studies should be classified, in a strict sense, as false positives. It therefore follows that diagnostic practices—variable they may be—might not be entirely in accord with legal standards such as the UDDA (note 1). Whether to alter diagnostic practices, for example by insisting on direct tests of hypothalamic function (a practice that is not routinely used anywhere, to our knowledge), or whether to redraft the laws is a question that should be addressed explicitly.

We conclude by reiterating that further clinical research is needed in this area. Furthermore, a serious and forthright public dialogue is in order, which takes into account the medical, ethical, and legal complexity and nuance of these issues.

Acknowledgments

Note

1. For thoroughness, the absence of diabetes insipidus (DI) cannot be simply attributed to variable diagnostic practices: 18 of the studies[8-10,12,14,15,18,19,21,24,25,27,29,32,35,38-40] cited in the first review explicitly listed diagnostic criteria that are in accord with standard consensus guidelines, such as the American Academy of Neurology's guidelines for diagnosing brain death[75] and most used additional confirmatory tests such as electroencephalography or angiography, in addition to standard clinical criteria. Collectively those studies report that 539 (58%) of the 928 patients did not have DI. Therefore, the appearance of preserved hypothalamic function cannot be dismissed as a result of diagnostic variability or imprecision in the cited studies.

References

1. Wijdicks EFM. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology*. 2002;58(1):20-25.

2. Capron AM. Brain death—well settled yet still unresolved. *N Engl J Med*. 2001;344(16):1244-1246.

3. The President's Council on Bioethics. Controversies in the determination of death: a white paper by the President's Council on Bioethics. Washington, DC: The President's Council on Bioethics, 2008.

4. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Biobehavioral Research. *Defining Death: A Report on the Medical, Legal and Ethical Issues in the Determination of Death*. Washington, DC: President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Biobehavioral Research; 1981.

5. Delimiting death. *Nature*. 2009;461(7264):570.

6. Halevy A, Brody B. Brain death: reconciling definitions, criteria, and tests. *Ann Intern Med*. 1993;119(6):519-525.

7. Robinson A, Verbalis J. *Posterior pituitary. Williams Textbook of Endocrinology*, 10th ed. Philadelphia: WB Saunders; 2003: 281-329.

8. Griepp RB, Stinson EB, Clark DA, Dong E Jr, Shumway NE. The cardiac donor. *Surg Gynecol Obstet*. 1971;133(5):792-798.

9. Jorgensen EO. Spinal man after brain death. The unilateral extension-pronation reflex of the upper limb as an indication of brain death. *Acta Neurochir (Wien)*. 1973;28(4):259-273.

10. Jastremski M, Powner D, Snyder J, Smith J, Grenvik A. Problems in brain death determination. *Forensic Sci*. 1978;11(3): 201-212.

11. Jorgensen EO, Malchow-Moller A. Natural history of global and critical brain ischaemia. Part II: EEG and neurological signs in patients remaining unconscious after cardiopulmonary resuscitation. *Resuscitation*. 1981;9(2):155-174.

12. Outwater KM, Rockoff MA. Diabetes insipidus accompanying brain death in children. *Neurology*. 1984;34(9):1243-1246.

13. Pelosi G, Zanghi F, Agnes S, Magalini SC. Maintenance of unstable kidney donors. *Eur J Anaesthesiol*. 1986;3(3): 209-217.

14. Fiser DH, Jimenez JF, Wrape V, Woody R. Diabetes insipidus in children with brain death. *Crit Care Med*. 1987;15(6): 551-553.

15. Fackler JC, Troncoso JC, Gioia FR. Age-specific characteristics of brain death in children. *Am J Dis Child*. 1988;142(9): 999-1003.

16. Howlett TA, Keogh AM, Perry L, Touzel R, Rees LH. Anterior and posterior pituitary function in brain-stem-dead donors. A possible role for hormonal replacement therapy. *Transplantation*. 1989;47(5):828-834.

17. Keogh AM, Howlett TA, Perry L, Rees LH. Pituitary function in brain-stem dead organ donors: a prospective survey. *Transplant Proc*. 1988;20(5):729-730.

18. Kinoshita Y, Yahata K, Yoshioka T, Onishi S, Sugimoto T. Long-term renal preservation after brain death maintained with vasopressin and epinephrine. *Transpl Int*. 1990;3(1):15-18.

19. Hohenegger M, Vermes M, Mauritz W, Redl G, Sporn P, Eiselsberg P. Serum vasopressin (AVP) levels in polyuric brain-dead organ donors. *Eur Arch Psychiatry Neurol Sci*. 1990;239(4): 267-269.

20. Debelak L, Pollak R, Reckard C. Arginine vasopressin versus desmopressin for the treatment of diabetes insipidus in the brain dead organ donor. *Transplant Proc*. 1990;22(2):351-352.

21. Nygaard CE, Townsend RN, Diamond DL. Organ donor management and organ outcome: a 6-year review from a Level I trauma center. *J Trauma*. 1990;30(6):728-732.

22. Mackersie RC, Bronsther OL, Shackford SR. Organ procurement in patients with fatal head injuries. The fate of the potential donor. *Ann Surg*. 1991;213(2):143-150.

23. Ali MJ, Wood G, Gelb AW. Organ donor problems and their management. A four year review of a Canadian transplant center. *Can J Anaesth*. 1992;39:A125.

24. Gramm HJ, Meinhold H, Bickel U, et al. Acute endocrine failure after brain death? *Transplantation*. 1992;54(5):851-857.

25. Sugimoto T, Sakano T, Kinoshita Y, Masui M, Yoshioka T. Morphological and functional alterations of the hypothalamic–pituitary system in brain death with long-term bodily living. *Acta Neurochir (Wien)*. 1992;115(1-2):31-36.

26. Rabanal JM, Teja JL, Quesada A, Cotorruelo J. Does diabetes insipidus in brain dead organ donors protect acute tubular necrosis in renal grafts? *Transplant Proc*. 1993;25(6):3143.

27. Arita K, Uozumi T, Oki S, Kurisu K, Ohtani M, Mikami T. The function of the hypothalamo–pituitary axis in brain dead patients. *Acta Neurochir (Wien)*. 1993;123(1-2):64-75.

28. Staworn D, Lewison L, Marks J, Turner G, Levin D. Brain death in pediatric intensive care unit patients: incidence, primary diagnosis, and the clinical occurrence of Turner's triad. *Crit Care Med*. 1994;22(8):1301-1305.

29. Amado JA, Lopez-Espadas F, Vazquez-Barquero A, et al. Blood levels of cytokines in brain-dead patients: relationship with circulating hormones and acute-phase reactants. *Metabolism*. 1995; 44(6):812-816.

30. Finfer S, Bohn D, Colpitts D, Cox P, Fleming F, Barker G. Intensive care management of paediatric organ donors and its effect on post-transplant organ function. *Intensive Care Med*. 1996;22(12): 1424-1432.

31. Dominguez-Roldan JM, Garcia-Alfaro C, Diaz-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):13-14.

32. Dosemeci L, Yilmaz M, Cengiz M, Dora B, Ramazanoglu A. Brain death and donor management in the intensive care unit: experiences over the last 3 years. *Transplant Proc*. 2004;36(1):20-21.

33. Dominguez-Roldan JM, Jimenez-Gonzalez PI, Garcia-Alfaro C, Hernandez-Hazanas F, Fernandez-Hinojosa E, Bellido-Sanchez R. Electrolytic disorders, hypersmolar states, and lactic acidosis in brain-dead patients. *Transplant Proc*. 2005;37(5):1987-1989.

34. Kim KA, Wang MY, McNatt SA, Pinsky G, Liu CY, Giannotta SL, Apuzzo MLJ. Vector analysis correlating bullet trajectory to outcome after civilian through-and-through gunshot wound to the head: using imaging cues to predict fatal outcome. *Neurosurgery*. 2005;57(4):737-747.

35. Salim A, Martin M, Brown C, Belzberg H, Rhee P, Demetriades D. Complications of brain death: frequency and impact on organ retrieval. *Am Surg*. 2006;72(5):377-381.

36. Chai CL, Tu YK, Huang SJ. Can cerebral hypoperfusion after sympathetic storm be used to diagnose brain death? A retrospective survey in traumatic brain injury patients. *J Trauma*. 2008; 64(3):688-697.

37. Wijdicks EF, Rabinstein AA, Manno EM, Atkinson JD. Pronouncing brain death: contemporary practice and safety of the apnea test. *Neurology*. 2008;71(16):1240-1244.

38. Seth AK, Nambiar P, Joshi A, et al. First prospective study on brain stem death and attitudes toward organ donation in India. *Liver Transpl*. 2009;15(11):1443-1447.

39. Varelas PN, Rehman M, Abdelhak T, et al. Single brain death examination is equivalent to dual brain death examinations. *Neurocrit Care*. 2011;15(3):547-553.

40. 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):203-209.

41. Kinoshita Y, Go K, Yoshioka T, Sugimoto T. Absence of response to hypothalamic stimulation test in brain death. *Neurol Med Chir (Tokyo)*. 1992;32(3):153-156.

42. Schrader H, Krogness K, Aakvaag A, Sortland O, Purvis K. Changes of pituitary hormones in brain death. *Acta Neurochir (Wien)*. 1980;52(3-4):239-248.

43. Macoviak JA, McDougall IR, Bayer MF, Brown M, Tazelaar H, Stinson EB. Significance of thyroid dysfunction in human cardiac allograft procurement. *Transplantation*. 1987;43(6):824-826.

44. Robertson KM, Hramiak IM, Gelb AW. Thyroid function and haemodynamic stability after brain death. *Can J Anaesth*. 1988; 35:S102.

45. Masson F, Thicoipe M, Latapie MJ, Maurette P. Thyroid function in brain-dead donors. *Transpl Int*. 1990;3(4):226-233.

46. Powner DJ, Hendrich A, Lagler RG, Ng RH, Madden RL. Hormonal changes in brain dead patients. *Crit Care Med*. 1990;18(7): 702-708.

47. Karayalcin K, Umana JP, Harrison JD. Donor thyroid function does not affect outcome in orthotopic liver transplantation. *Transplantation*. 1994;57(5):669-672.

48. Mariot J, Sadoune LO, Jacob F, et al. Hormone levels, hemodynamics, and metabolism in brain dead organ donors. *Transplant Proc*. 1995;27(1):793-794.

49. Goarin JP, Cohen S, Riou B, et al. The effects of triiodothyronine on hemodynamic status and cardiac function in potential heart donors. *Anesth Analg*. 1996;83(1):41-47.

50. Szostek M, Gaciong Z, Danielelewicz R, et al. Influence of thyroid function in brain stem death donors on kidney allograft function. *Transplant Proc*. 1997;29(8):3354-3356.

51. Ishikawa T, Michiue T, Quan L, et al. Morphological and functional alterations in the adenohypophysis in cases of brain death. *Leg Med (Tokyo)*. 2009;11(suppl 1):S234-237.

52. Nicolas-Robin A, Barouk JD, Darnal E, Riou B, Langeron O. Free cortisol and accuracy of total cortisol measurements in the diagnosis of adrenal insufficiency in brain-dead patients. *Anesthesiology*. 2011;115(3):568-574.

53. Koller J, Wieser C, Gottardis M, et al. Thyroid hormones and their impact on the hemodynamic and metabolic stability of organ donors and on kidney graft function after transplantation. *Transplant Proc*. 1990;22(2):355-357.

54. Fitzgerald RD, Dechtyar I, Templ E, Pernerstorfer T, Hackl W, Lackner FX. Endocrine stress reaction to surgery in brain-dead organ donors. *Transpl Int*. 1996;9(2):102-108.

55. Imberti R, Filisetti P, Preseglio I, Mapelli A, Spriano P. Confirmation of brain death utilizing thyrotropin-releasing hormone stimulation test. *Neurosurgery*. 1990;27(1):167.

56. Gifford RR, Weaver AS, Burg JE, Romano PJ, Demers LM, Pennock JL. Thyroid hormone levels in heart and kidney cadaver donors. *J Heart Transplant*. 1986;5(3):249-253.

57. Montero JA, Mallol J, Alvarez F, Benito P, Concha M, Blanco A. Biochemical hypothyroidism and myocardial damage in organ donors: are they related? *Transplant Proc*. 1988;20(5):746.

58. Robertson KM, Hramiak IM, Gelb AW. Endocrine changes and haemodynamic stability after brain death. *Transplant Proc*. 1989;21(1 pt 2):1197-1198.

59. Novitzky D, Cooper DK, Reichart B. Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. *Transplantation*. 1987;43(6):852-854.

60. Dimopoulou I, Tsagarakis S, Anthi A, et al. High prevalence of decreased cortisol reserve in brain-dead potential organ donors. *Crit Care Med*. 2003;31(4):1113-1117.

61. Taniguchi S, Kitamura S, Kawachi K, Doi Y, Aoyama N. Effects of hormonal supplements on the maintenance of cardiac function in potential donor patients after cerebral death. *Eur J Cardiothorac Surg*. 1992;6(2):96-101.

62. Lopau K, Mark J, Schramm L, Heidbreder E, Wanner C. Hormonal changes in brain death and immune activation in the donor. *Transpl Int*. 2000;13(suppl 1):S282-S285.

63. Hall GM, Mashiter K, Lumley J, Robson JG. Hypothalamic–pituitary function in the brain-dead patient. *Lancet*. 1980;2(8206):1259.

64. Garcia-Fages LC, Cabrer C, Valero R, Manyalich M. Hemodynamic and metabolic effects of substitutive triodothyronine therapy in organ donors. *Transplant Proc*. 1993;25(6):3038-3039.

65. Leng G, Brown CH, Russell JA. Physiological pathways regulating the activity of magnocellular neurosecretory cells. *Prog Neurobiol*. 1999;57(6):625-655.

66. Taal MW. *Brenner & Rector's the Kidney*. Philadelphia, PA: Elsevier/Saunders; 2012.

67. Robertson GL. The regulation of vasopressin function in health and disease. *Recent Prog Horm Res*. 1976;33:333-385.

68. Leclercq TA, Grisoli F. Arterial blood supply of the normal human pituitary gland. An anatomical study. *J Neurosurg*. 1983;58(5):678-681.

69. Walker AE, Diamond EL, Moseley J. The neuropathological findings in irreversible coma. A critique of the "respirator brain". *J Neuropathol Exp Neurol*. 1975;34(4):295-323.

70. Wijdicks EF, Pfeifer EA. Neuropathology of brain death in the modern transplant era. *Neurology*. 2008;70(15):1234-1237.

71. Nair-Collins M. Brain death, paternalism, and the language of "death". *Kennedy Inst Ethics J*. 2013;23(1):53-104.

72. Bernat JL. A defense of the whole-brain concept of death. *Hastings Cent Rep*. 1998;28(2):14-23.

73. Wijdicks EF. The case against confirmatory tests for determining brain death in adults. *Neurology*. 2010;75(1):77-83.

74. Greer DM, Varelas PN, Haque S, Wijdicks EF. Variability of brain death determination guidelines in leading US neurologic institutions. *Neurology*. 2008;70(4):284-289.

75. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. Evidence-based guideline update: determining brain death in adults: report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 2010;74(23):1911-1918.