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[UDDA Revision Series] Must Hypothalamic Neurosecretory Function Cease for Brain Death Determination? Yes: The UDDA Revision Series

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The Uniform Determination of Death Act (UDDA) states "an individual who has sustained … irreversible cessation of all functions of the entire brain, including the brainstem, is dead".[1] Therefore, an individual with preservation of any function of any part of the brain is not dead under the UDDA. There is no argument, and no evidence, that can escape this conclusion. To deny it is to deny logic itself.

Up to 50% of patients who are declared dead by neurologic criteria have some preserved hypothalamic function, as evidenced by the absence of central diabetes insipidus.[2] Therefore, some brain function continues in some patients who are declared dead by neurologic criteria. These are false positive declarations of death.

Many efforts have been made to reconcile the preservation of some brain function with the UDDA. All these efforts fail, because one cannot reconcile what is logically irreconcilable. The Table summarizes them.

One might consider hypothalamic function to be inconsequential, in the context of devastating brain injury with unresponsiveness, brainstem areflexia, and apnea. Not so. First and foremost, the truth matters. In a troubling social world characterized by lies and disinformation, professionals must hold themselves accountable to telling the truth, especially when it is inconvenient. Second, there is no medical determination more important than death. Societal ability to rely on this determination requires a justified belief that physicians are both competent and trustworthy in this practice. Declaring that an individual meets a legal standard they clearly do not meet undermines the credibility of the medical profession, as well as society's ability to rely on its determinations.

Third, organ procurement is claimed to adhere to the dead donor rule: except for living donation such as of a single kidney, organ donors are dead before organs are removed. The dead donor rule is described as "a centerpiece of the social order's commitment to respect for persons and human life",[11, p. 6] where organs will not be removed "even if the person is unconscious, extremely debilitated, or very near death".[11, p. 6] Trust in the enterprise is assured, because this is a bright line that will not be crossed. That bright line is crossed regularly. A patient with some brain function who is otherwise unresponsive, apneic, and brainstem areflexic is "unconscious, extremely debilitated, and very near death" – but not dead under the UDDA. Therefore, organs are removed from still-living patients, causing death. This is a serious violation of public trust.

Regardless of revisions to the UDDA that may come, the UDDA stands now, and it has stood for 40 years. Throughout that time, it has been repeatedly asserted that, so long as guidelines are followed, there are no cases of false positives; meanwhile, up to half have been false positives. The determination of death by neurologic criteria is routinely in error.

Table. Proposals to reconcile neuroendocrine function with the UDDA, and responses

Proposal	Response
Not every cell in the brain must die.	No one claims every cell in the brain must die.
This is posterior pituitary washout where vasopressin passively leaks from non-viable cells.[cf. 3]	Vasopressin half-life ≈ 15-18 minutes. Passive leakage insensitive to feedback likely to cause oliguria, with polyuria minutes after stores deplete. It is theoretically possible that passive leakage briefly mimics regulated secretion in some cases, but unlikely to explain 50% reported rate of DI in BD.[3]
	Direct measurements of vasopressin, Na^+, plasma and urine osmolarity and specific gravity find them within normal range for osmoregulation (in non-DI patients, when reported).[cf. 3]
Vasopressin secretion is an activity, which requires technology to assess, but is not a function, which is assessable at bedside.[4]	Osmoregulation is undoubtedly a function.
	Osmoregulation meets World Brain Death Project's definition of 'function' as "a stimulus to provoke central processing and efferent response".[4, supplement 5, p. 20]
	Flies in the face of clinical practice. For example, if correct, liver function tests do not assess liver function.
Osmoregulation is not a clinical function. Only clinical functions are relevant.[4]	UDDA makes no such distinction. All brain function must cease.
	Relies on antecedent claim that BD is a clinical diagnosis; it is not. Requires imaging and lab tests to establish severity and address confounders. Apnea test requires blood gas analysis. Ancillary tests introduce further technology.
	Osmoregulation is clinically apparent through urine output.
Osmoregulation is not a critical function. Only critical functions are relevant.[5]	UDDA makes no such distinction. All brain function must cease.
	If corneal blink reflex is a critical function, then osmoregulation is.

	If anything is a critical function, then maintaining extracellular milieu is.
Inferior hypophyseal artery is extradural and supplies blood to posterior pituitary, likely explaining absence of DI.[cf. 2]	UDDA makes no distinction according to blood supply. If any brain function is preserved, the UDDA is not met.
	Inadequate explanation: Osmoreceptive perikarya located in diencephalon outside pituitary fossa are supplied by intradural superior hypophyseal and hypothalamic arteries. Secondary osmoreceptors in circumventricular areas also do not receive protected blood supply.[6]
"Brain death" is a clinical syndrome defined by unresponsiveness, cranial nerve areflexia, and apnea.[7]	This describes the core features of accepted diagnostic tests, not the physiologic criterion or legal standard that the tests allege to identify.
"Determination of death must be made in accordance with accepted medical standards" (UDDA): The precise medical standards are deferred to the medical profession.	"Accepted medical standards" explicitly refers to diagnostic tests,[1, p.78] not the physiologic criterion or legal standard that is tested for; the latter is not deferred to medicine.
Perhaps the hypothalamus is not part of the brain.[8]	The hypothalamus is part of the brain.
Perhaps UDDA authors did not mean to include hypothalamic function; "hypothalamus" is not included in report.[9]	"All functions of the entire brain" means all functions of the entire brain.
Neuroendocrine function is explicitly described as consistent with BD by American Academy of Neurology and World Brain Death Project.[4,10]	Preservation of any function of any part of the brain is inconsistent with irreversible cessation of all functions of the entire brain. To deny this is to deny logic itself.

DI = central diabetes insipidus; BD = brain death as defined by the UDDA; UDDA = Uniform Determination of Death Act

References

1. 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, D.C.: U.S. Government Printing Office; 1981.
2. Nair-Collins M, Joffe AR. Hypothalamic function in patients diagnosed as brain dead and its practical consequences. In: *Handbook of clinical neurology vol. 182 (3rd series). The human hypothalamus: neuropsychiatric disorders*. D. Swaab, Buijs RM, Kreier F, Lucassen PJ, Salehi A. eds. Amsterdam: Elsevier; 2021.
3. Nair-Collins M, Northrup J, Olcese J. Hypothalamic-pituitary function in brain death: A review. *J Intensive Care Med.* 2016;31:41-50.
4. Greer DM, Shemie SD, Torrance S, et al. Determination of brain death/death by neurologic criteria. The World Brain Death Project. *JAMA.* 2020;324(11):1078-1097.
5. Bernat JL. The whole-brain concept of death remains optimum public policy. *J Law Med Ethics.* 2006;34(1):35-43.
6. Nair-Collins M, Joffe AR. Frequent preservation of neurologic function in brain death and brainstem death entails false-positive misdiagnosis and cerebral perfusion. *AJOB Neurosci* 2021. Online ahead of print. doi: 10.1080/21507740.2021.1973148
7. Wijdicks EF. The case against confirmatory tests for determining brain death in adults. *Neurology.* 2010**;**75(1):77-83.
8. Lewis A, Bonnie RJ, Pope T. It's time to revise the Uniform Determination of Death Act. *Ann Intern Med* 2020;172(2):143-144.

9. Lewis A, Bonnie RJ, Pope T, et al. Determination of death by neurologic criteria in the United States: the case for revising the Uniform Determination of Death Act. *J Law Med Ethics* 2019;47;S4:9-24.
10. Russell JA, Epstein LG, Greer DM, et al. AAN position statement. Brain death, the determination of brain death, and member guidance for brain death accommodation requests. *Neurology* 2019;92:1-5.
11. Robertson JA. The dead donor rule. *Hastings Cent Rep* 1999;29(6):6-14.

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