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[UDDA Revision Series] Must Hypothalamic Neurosecretory Function Cease for Brain Death Determination? No: The UDDA Revision Series

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The Uniform Determination of Death Act of 1980 [1], which provides the statute of death in the United States, states:

1. [Determination of Death]. An individual who has sustained 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. A determination of death must be made in accordance with accepted medical standards.

Most of the attention has been placed on the word "entire". The reason is that in other countries, such as the United Kingdom, the entire brain criterion is not required and instead the brainstem criterion is deemed adequate [2]. In the United States the word "entire" has also generated debates, with a small minority arguing that when used to the letter, up to half of brain dead (BD) patients are erroneously diagnosed as dead and, in fact, when heart-beating organ donation follows, these mistakenly diagnosed dead patients may be considered homicide victims [3]. I will try to refute this proposition.

The rationale behind this serious accusation is that not all BD patients lose pituitary activity. The reason for any residual pituitary activity may be traced to anatomical variances that theoretically could allow some perfusion of these basal brain structures [4, 5]. For example, central diabetes insipidus (DI) was encountered in 65% of 266 BD patients included in a recent large single-center study [6]. In review articles, 50-60% of adult and 52% of pediatric BD patients were diagnosed with DI [3, 7]. The authors of these review articles speculate that hypothalamic and pituitary *function* was still present. This argument is problematic for many reasons: First, not every study used rigorous diagnostic criteria for central DI. Polyuria is an easily noticed feature, but not pathognomonic in patients treated with diuretics, such as mannitol. Rising serum sodium is also not indicative of DI when these patients receive osmotic agents that have an uplifting effect on sodium. If hypotension occurs and vasopressin infusion is used, this external hormone will not allow DI to clinically manifest and may be confused with inherent hormone production. Similarly, if the peripheral organ (the kidney) has decreased function due to an acute or chronic process, clinical signs of DI will not be observed. Although this association has not been rigorously assessed but in a small sample of pediatric patients [8], in the aforementioned study [6], those patients who did not develop DI had statistically significant higher BUN and creatinine levels (implying kidney dysfunction) than those who did (*Varelas, unpublished data*). Therefore

it is possible that a higher percentage of posterior pituitary or hypothalamic loss of function could be present due to "masking" effect on DI.

Similarly to vasopressin, other hypothalamic hormones may or may not be reduced in BD patients, but because they do not lead to an obvious clinical sign (such as polyuria), they are nor regularly measured nor reported [3]. Although, there is paucity of autopsy data on pathological injury of hypothalamus/pituitary in BD patients, the few studies that exist are revealing. In the NINCDS Collaborative "non-intervention" study, 226 out of 459 patients who died had brain autopsies. Although the thalamus/hypothalamus was one of the areas examined, the pituitary gland was not. The diencephalon had damage in 85% of the cases, but the hypothalamic and periventricular regions contained normal cells amongst necrotic areas [9-11]. In another study of 60 BD patients, the central part of the anterior pituitary lobe showed autolysis, but the marginal part was spared if the autopsy was done in BD patients of less than 10 days [12]. Similarly, 28 patients with structural injuries were diagnosed BD by clinical criteria and with negative intracranial blood flow and were maintained on ventilatory support until cardiac arrest ensued [5]. Duration of post-BD diagnosis period played a role on the pathological findings of the 12 autopsied patients. Extensive necrosis of the brain including the hypothalamus was observed only in patients maintained for longer than 3 days. The hypothalamus was completely necrotic in cases with brain death duration of > 17 hours. More revealing was the fact that ACTH and TSH positive substances were clearly recognized in the necrotic cells, implying that these hormones may be maintained even in dead cells. The posterior pituitary showed little or no change in 11/12 autopsies. Of great importance, however, was the observation that intrinsic ADH secretion decreased sharply with the occurrence of BD, implying cessation of supra-optic and paraventricular nuclei function, but plasma levels were detectable and ADH positive cellular granules were observed long-time after BD, indicating "leak" of ADH to the periphery and thus masking of clinical DI. This would *mimic osmoregulation*, as even the detractors of entire brain function loss, eventually admit [7]. Lastly, for other hypothalamic hormones such as GRF and LH-RH that are detected in the serum long after the hypothalamus becomes completely necrotic and without having any correlation with levels of LH, FSH or HGH, an extracerebral source is the likely explanation [5].

The Sugimoto et al., study is remarkable for another reason. It introduces the time concept for these pathological changes and shows that as time passes, even initially preserved areas in the

pituitary lose cellular integrity and become necrotized. More recent pathological studies may not have found these alterations, including the 'respirator brain", because of the rapid advance to organ harvesting or withdrawal from support, which has shortened the time from BD to autopsy. For example, in a more recent study of 41 BD patients, all had cardiac arrest after BD declaration within 36 hours, with 29% in <12 hours. The pituitary gland showed moderate to severe neuronal loss in 45% of the 16 pituitaries examined [13].

One may then ask the following question: even in the rare patients with hypothalamic neurosecretory activity, how relevant is this? Are these brain dead patients not dead, i.e patients who can "survive"? In the discussion regarding the Construction of the Statute (pages 75-79), the President's Commission focused on the definition of 'individual", "functions" and "dead" leaving out any meaningful discussion on the key word "irreversible" [14]. Moreover, the Commission makes an important distinction between functions and activities, clarifying that electrical or metabolic *activities* at an individual cell level (for example hormones) or even groups of cells, *can still be present* for a period of time, but unless organized and directed, they are considered " irrelevant in judging whether the organism, as opposed to its components, is "dead."

Irreversible cessation of a vital function means that, once it ceases, it cannot be restored with available technology because doing so is impossible [15]. Another way of saying this is that irreversibility is loss of brain function that cannot resume spontaneously and cannot be resumed through technological intervention. Key here is the understanding that although the function can be replaced by technology (ex. blood circulation by artificial heart, breathing by ventilator etc), the *organ function cannot be restored by the organism* (no circulation without a heart, no breathing without an alive medulla oblongata). Consciousness or brainstem reflexes cannot be restored spontaneously or with interventions in BD patients with severe, diffuse cellular-level injury and no intracranial circulation. But most importantly, these patients *cannot spontaneously restore cardiorespiratory function*. This loss of the lower medullary function, as clinically noticed by the cardiocirculatory collapse and the apnea testing in patients who have additional diffuse injury to the rest of the brain, are in deep coma and with loss of all the other brainstem reflexes, cannot be restored either by the patient or by our current technology (no artificial brain or transplanted brain are available) *and is irreversible*. And this despite allowing years to pass, as

in those rare BD patients chronically maintained on ventilators [16]. This is a completely different situation than traumatic upper cervical spine injury with inability to breathe, where consciousness, brainstem reflexes and supratentorial connectivity are preserved. In the former, no hypothalamic/pituitary action can counteract the profound loss of integrative function of the rest of the brain. When these BD patients (who are not organ donors) are disconnected from technological support, their blood pressure plummets, the pulse disappears and the heart stops beating within minutes. These patients reach the same endpoint and look exactly alike to those who lose cardiorespiratory function after cardiac arrest. No breathing means no heart beat and no circulation, exactly like no heart beat means no circulation and no breathing. All these despite any potential hypothalamic/pituitary secretions. BD patients are dead the same way that everybody became dead since the dawn of man, before ventilators and ICUs were invented…

In conclusion, residual hypothalamic neurosecretory function is highly unlikely (as compared to activity, which may be present in a small percentage of BD cases). Requirement for cessation of this activity does not add to the declaration of BD and is irrelevant, since these patients with irreversible cessation of all other functions of the brain cannot survive, similarly to patients without cardiopulmonary function. These cardiopulmonary dead patients may also have hypothalamic- pituitary activity for a period of few minutes until their cells become irreversibly damaged, but nobody has ever confirmed such activity in a pulseless, non-breathing dead patient, because this is irrelevant to their death.

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