Preserved Hypothalamic Function Does Not Preclude Determination of Death by Neurologic Criteria

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Death by neurologic criteria was first proposed as a concept by the Harvard Ad Hoc Committee in the United States of America in 1968 following recognition that with the advent of modern intensive care medicine and the ability to artificially sustain a failing circulatory–respiratory system, there is a clinical state where all brain functions had been irreversibly lost and from which no patient would ever recover [1]. This clinical state had been described previously by Mollaret and Goulon in 1959 and termed "le coma dépassé," a state beyond coma, that is characterized by unresponsive apneic coma, poikilothermia, loss of all brainstem reflexes, and an isoelectric electroencephalogram (EEG) [2]. Clinical and pathological examination of patients in this state of irreversible coma and apnea showed that it is associated with autolysis of the brainstem [3]. The futility of continuing to provide artificial support of the circulatory–respiratory system in the presence of the permanent loss of brain function led the Harvard Ad Hoc Committee to publish its landmark paper calling for death to be confirmed using neurologic criteria as well as the established circulatory–respiratory criteria [1].

Today, there is a legal provision for determination of death by neurologic criteria in about 70% of countries worldwide, predominantly those with deceased donor transplantation programs [4]. Yet inconsistency persists between countries in the definition of, and clinical guidance for, determining death by neurologic criteria with no international consensus as to whether death by neurologic criteria requires loss of functions of the whole brain or just the brainstem (as discussed elsewhere in this book). The World Brain Death Project, a recent international consensus report, attempted to address these inconsistencies. The Project produced a series of recommendations for the minimum clinical standards for the determination of death by

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neurologic criteria in adults and children, acknowledged the importance of religious, cultural, and legal factors in making the determination, and identified future research questions [5]. The report defines death by neurologic criteria as "the complete and permanent loss of brain function as defined by an unresponsive coma with loss of capacity for consciousness, brainstem reflexes and the ability to breathe independently" [5]. This definition is a clear move away from death being based on an anatomical construct toward one based on loss of defined functions. Specifically, this definition does not require a loss of *all* functions of the entire brain and states that the "persistence of cellular level neuronal and neuroendocrine activity does not preclude the determination" and that "persistence of hormonal regulatory function does not preclude the diagnosis" [5].

In this chapter, we argue that preserved hypothalamic function is consistent with a determination of death by neurologic criteria if a functional definition of death is used, because "death entails the irreversible loss of those essential characteristics which are necessary to the existence of a living human person. Thus, the definition of death should be regarded as the irreversible loss of the capacity for consciousness, combined with irreversible loss of the capacity to breathe" [6].

1 Hypothalamic–Pituitary Function

The hypothalamus is a complex region of the brain and is important in coordinating signals between the nervous system and the endocrine system, primarily via the pituitary gland. Located below the thalamus and posterior to the optic chiasm, it forms the walls and floor of the third ventricle [7]. Lying beneath the hypothalamus is the pituitary fossa which contains the pituitary gland; they are linked via the infundibulum and the pituitary stalk. The pituitary is divided into two glands, the anterior and posterior pituitary gland, that are distinct both embryologically and functionally [8]. The anterior pituitary gland secretes hormones into the systemic circulation via the cavernous sinus. Its function is regulated by inhibitory or releasing factors originating from the hypothalamus that are transmitted to the anterior pituitary via the hypophyseal–portal system, a specialized local blood flow system that runs parallel to the pituitary stalk. In contrast, the posterior pituitary gland contains axons of neurons from the hypothalamus that secrete hormones directly into a capillary plexus that reaches the systemic circulation via the cavernous sinus [7, 8].

The hypothalamus plays a crucial role in maintaining normal endocrine, metabolic, and autonomic function. It incorporates complex and interconnected feedback loops to regulate the release of adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin and growth hormone from the anterior pituitary gland while secreting vasopressin and oxytocin directly into the systemic circulation via the posterior pituitary gland [7, 8]. Disorders of the hypothalamic–pituitary axis will result in distinct clinical syndromes depending on the location and extent of the underlying lesion. As the hypothalamus regulates both endocrine and autonomic function, there is usually a combination of endocrine and neurological disturbance

in hypothalamic damage including abnormalities of behavior, appetite, thermoregulation, and hormonal deficiencies. Hypothalamic dysfunction resulting in a failure of vasopressin secretion from the posterior pituitary gland in response to an increase in plasma osmolality or hypovolemia results in central diabetes insipidus. Vasopressin binds to V2 receptors in the distal nephron that control aquaporins in the collecting ducts of the kidneys, so controlling fluid reabsorption and plasma osmolality. Characterized by inappropriate polyuria, central diabetes insipidus can result in dehydration, hypernatremia, and hyperosmolality [9].

2 Hypothalamic–Pituitary Function in Death by Neurologic Criteria

It is well established that hypothalamic function can persist in patients determined dead by neurologic criteria. The clinical manifestations of central diabetes insipidus indicative of hypothalamic dysfunction are readily identified in terms of increased urine output, plasma sodium concentration, and plasma osmolality. A literature review examining hypothalamic–pituitary function in patients determined dead by neurologic criteria concluded that some of the patients who were not polyuric had maintained osmoregulation through some preservation of hypothalamic function [10]. Studies have previously suggested that the incidence of diabetes insipidus in patients who meet the conditions for death by neurologic criteria ranges from 46 to 78% [11, 12]. In a more recent literature review, only 1265 (50%) patients who met the conditions for death by neurologic criteria were found to demonstrate features of central diabetes insipidus [13]. Assessment of residual anterior pituitary function is more difficult and requires direct measurement of hormones released by the anterior pituitary or of those inhibitory or releasing factors produced in the hypothalamus that control anterior pituitary hormonal release. The same review found that there was evidence of preserved anterior pituitary hormones in the peripheral circulation, which are dependent on releasing factors produced in the hypothalamus for their secretion. This suggests the presence of residual hypothalamic–pituitary function, indicating the preservation of a degree of blood flow to the area, although this is often accompanied by peripheral endocrine insufficiency [13]. Additionally, there are reports of patients determined to be dead by neurologic criteria where physiological support has been continued and who have undergone puberty and growth which have been interpreted as further evidence of residual neuroendocrine function controlled by the hypothalamus [14].

Residual hypothalamic–pituitary function may well exist in patients determined dead by neurologic criteria and this has been recognized and accepted by authoritative institutions, yet it is not considered to invalidate the determination of death. This preserved function may be due to the vascular anatomy of the hypothalamus and pituitary gland, providing a potential sanctuary for this region from the adverse effects of raised intracranial pressure (ICP) and consequent ischemia that cause irreversible injury to the remainder of the intracranial contents [5, 10, 15].

Critics, however, have argued that this vascular supply explanation does not account for the fact that for the release of vasopressin to occur from the posterior pituitary gland, additive glutaminergic input from circumventricular (basal forebrain) areas, especially the organum vasularis of the lamina terminalis and the subfornical organ is required and the vascular supply to these areas is not protected from a rise in ICP as is hypothesized for the posterior pituitary gland [16]. Similarly, the blood supply to the hypothalamic nuclei that control the release of hormones from the anterior pituitary gland is not protected from a rise in ICP [16].

3 Death by Neurologic Criteria and Residual Hypothalamic–Pituitary Function

The persistence of residual hypothalamic–pituitary function in patients determined to be dead by neurologic criteria therefore creates a mismatch between the whole-brain criterion of death, which requires the irreversible cessation of *all* functions of the *entire* brain, and how death by neurologic criteria is actually determined in everyday clinical practice [17] where the persistence of neuroendocrine functions is considered to be consistent with determination of death by neurologic criteria. The concept of death by neurologic criteria as proposed by the Harvard Medical Committee [1] has been adopted as law in the United States following the implementation of the Uniform Determination of Death Act (UDDA) in 1981 [18]. The Harvard report required the irreversible cessation of function of the cerebral hemispheres, diencephalon, brainstem, and cerebellum, a so-called "whole-brain" formulation. The UDDA subsequently defined death as "either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem" and that "a determination of death must be made in accordance with accepted medical standards" [18].

The whole-brain criterion for death has been widely adopted across the United States and endorsed by many professional medical organizations worldwide. However, there is increasing scrutiny about the whole-brain criterion, the definition of death and whether the UDDA itself needs revision [19]. It is recognized that some patients who are defined as dead by neurologic criteria will retain some hypothalamic–pituitary function [15], a position that is inconsistent with a legal definition that requires the "irreversible cessation of all functions of the entire brain." Yet, it is consistent with the legal requirement for making the diagnosis in accordance with accepted medical standards. The UDDA may define death, but it makes no attempt to define accepted medical standards. This is left to the professional medical bodies, and the American Academy of Neurology (AAN), in its 1995 standard for determining death by neurologic criteria in adults [20], listed the absence of diabetes insipidus as being compatible with the determination of death, a position that was not addressed further in their 2010 update [21]. International consensus statements and accepted medical standards around the world [5, 22] agree with the AAN standard and allow the determination of death by neurologic criteria despite the presence of some neuroendocrine functions. The whole-brain criterion, therefore,

creates a dichotomy in which the legal standard is not in alignment with accepted medical standards, a so-called "legal clinical mismatch" [17]. Furthermore, currently accepted medical standards and technologies cannot categorically demonstrate irreversible loss of *all* brain and brainstem functions and can at best only approximate that legal definition.

An alternative approach to the determination of death by neurologic criteria is adopted in the United Kingdom, where the focus is on the loss of specific brain functions whether secondary to cessation of the circulation or following a devastating brain injury. There is no statutory definition of death in the United Kingdom. Instead, the legal profession has adopted and supported the definition of death, and the standards used to confirm it, as laid down by the Academy of Medical Royal Colleges in its Code of Practice for the Diagnosis and Confirmation of Death of 2008 [6, 23–26]. The Code states that "death entails the irreversible loss of those essential characteristics which are necessary to the existence of a living human person and, thus, the definition of death should be regarded as the irreversible loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe. This may be secondary to a wide range of underlying problems in the body, for example, cardiac arrest." [6]. The code also recognizes that all human death is death by neurologic criteria when it states that when determining death by circulatory–respiratory criteria "it is obviously inappropriate to initiate any intervention that has the potential to restore cerebral perfusion after death has been confirmed" [6]. This definition of death is not anatomically based, but rather focused on the loss of brain functions that are judged to be essential to the existence of a living human being. There is, therefore, no requirement that all functions be absent, only a demonstration that there has been irreversible loss of the capacity for consciousness combined with the irreversible loss of the ability to breathe. Indeed, the Code recognizes that while "the body may continue to show signs of biological activity, these have no moral relevance to the declaration of death" [6]. Thus, it is a misconception that the definition of death in the United Kingdom is primarily a brainstem formulation. Instead, it is based on the irreversible loss of those essential functions, a position that has been upheld in law, accepting that some may disagree and challenge this position [23–26].

This functional approach to the definition of death has been further developed by international collaborations seeking to achieve consensus on the scientific, biological, and medical aspects of death in a way that is hoped to supersede international differences, and which may form the basis of more consistent and globally applicable diagnostic criteria [5, 22]. The consensus collaboration with the World Health Organization convened in Montreal in 2012 defined death as occurring "when there is permanent loss of the capacity for consciousness and loss of all brainstem functions. This may result from permanent cessation of circulation and/or after catastrophic brain injury. In the context of death determination, 'permanent' refers to loss of function that cannot resume spontaneously and will not be restored through intervention" [22]. The more recent World Brain Death project also uses a functionally based definition as "the complete and permanent loss of brain function as defined by an unresponsive coma with loss of capacity for consciousness, brainstem

reflexes and the ability to breathe independently. This may result from permanent cessation of oxygenated circulation to the brain and/or after devastating brain injury" [5].

These criteria used to determine death are based on loss of specified brain functions rather than anatomically based (cardiac death, whole-brain death or brainstem death) and do not require the absence of all brain functions, acknowledging that "persistence of cellular level neuronal and neuroendocrine activity does not preclude the determination" [5]. These international definitions, and the United Kingdom's definition, offer more clarity in terminology in that there is only one criterion for death, and it is brain-based and can be confirmed using circulatory–respiratory criteria following a circulatory–respiratory arrest or using neurologic criteria following a catastrophic brain injury [27, 28]. None of these standards require the unequivocal demonstration of cessation of all functions of the entire brain. Current accepted medical standards and practice are also more consistent with this functional approach and definitions.

The mismatch between a legal definition of death and accepted medical standards also exists when death is defined as the "irreversible cessation of circulatory and respiratory functions" since, in everyday clinical practice, death is routinely determined using circulatory–respiratory criteria at the point of their permanent cessation. This is the point beyond which the circulation will not return spontaneously and will not be restarted through intervention because a decision has been made not to attempt to do so [29]. However, it is understood that it may still be possible to restore circulatory–respiratory functions through intervention at this point. Also, irreversible cessation of circulatory and respiratory functions is dependent on which technologies are used and/or available to restore these functions. This mismatch does not exist when using a unifying brain-based definition of death. The point of permanent loss of circulatory–respiratory functions is predictive of the irreversible loss of brain function as long as no intervention with the potential to restore brain perfusion is undertaken after the circulatory–respiratory confirmation of death [27, 30]. This point of permanence is reached within 5 min of continuous circulatory–respiratory arrest [31], a point not always compatible with a definition based on irreversible loss of circulatory–respiratory functions. However, it remains the most widely accepted medical standard used in everyday clinical practice when determining death using circulatory–respiratory criteria [32].

Dying is a process, and death is a defined point along that process. Where we choose to place that line between life and death is a decision with significant individual, social, legal, medical, and cultural implications. It determines who is recognized as a person with constitutional and legal rights, who deserves legal entitlements and benefits, and when last wills and testaments become effective [33]. A determination of death also removes any unrealistic expectations the family may have about outcome, giving them a definitive determination of death rather than a prognosis, and allowing them to begin to grieve. The use of neurologic criteria to identify the line between life and death is well established in legal and medical practice. The law and ethics generally defer to medical expertise regarding the standards to determine death by neurologic criteria. This is probably the most reasonable way to manage

the process of dying: when consensus professional guidance is followed, there are no false-positive determinations of death [33]. If the whole-brain legal criterion for death were to be strictly adhered to, then 50% of patients with preserved neuroendocrine function who otherwise meet the conditions for death by neurologic criteria could not be declared dead. On the other hand, 100% of patients who meet the accepted medical standards for the determination of death by neurologic criteria will never regain consciousness or breathe independently again, irrespective of whether neuroendocrine function is present or not.

4 The Whole-Brain Criterion vs. the Brainstem Criterion

Some may conclude that the persistence of hypothalamic–pituitary function in patients who have been determined dead by neurologic criteria is consistent with a brainstem criterion for death, but is not consistent with the whole-brain criterion since the hypothalamus is not part of the brainstem. Despite this, and other, apparent differences in the "transatlantic divide" between the two criteria for determining death by neurologic criteria, it is increasingly recognized that in practice the difference is largely one of semantics and the accepted medical standards used to make the determination are largely the same [34, 35]. Irrespective of whether a jurisdiction follows a whole-brain or a brainstem criterion and irrespective of the underlying pathology, both criteria rely on a similar three-stage approach to determine death:

1. Establishing a cause for the clinical state;
2. Excluding reversible causes or confounding factors that could be contributing to the clinical state; and
3. Undertaking a series of clinical tests to confirm the absence of brainstem reflexes and the ability to breathe.

These minimum clinical criteria confirm the permanent loss of the capacity for consciousness and the ability to breathe independently and allow death by neurologic criteria to be confidently determined. The criteria do not, however, demonstrate the "irreversible cessation of all functions of the entire brain." That is practically impossible using currently accepted medical standards and technologies, a situation that perpetuates the legal, ethical, and practical difficulties created by the mismatch between the legal whole-brain requirement for death and the current accepted medical standards used to determine death by neurologic criteria [17]. Potentially, this mismatch not only increases legal challenges to a determination of death by neurologic criteria but may also expose clinicians to accusations of operating outside the law when they follow accepted medical practice in determining death by neurologic criteria. More importantly, it risks undermining public confidence in the determination of death. The adoption of a functional-based definition of death that is based on accepted medical standards will provide greater clarity for both clinicians and the court. Ongoing research on all aspects of accepted medical standards including the clinical examination, modern imaging technologies, and

new diagnostic modalities will allow further refinements to the determination. This will maintain confidence and certainty in the determination of death by neurologic criteria, provide stronger evidence of irreversibility and reduce concerns around safety.

In both formulations for death by neurologic criteria, most cases result from infratentorial (brainstem) manifestations of a catastrophic supratentorial (whole brain) event such as an intracerebral hemorrhage, traumatic brain injury, subarachnoid hemorrhage, or hypoxic–ischemic brain injury [36]. It is only in 2–9% of cases that the cause is an isolated posterior fossa lesion or one limited to structures supplied by the posterior cerebral circulation [37, 38]. The few patients with an isolated brainstem lesion who are determined to be dead by neurologic criteria may have persistent supratentorial blood flow initially that is then lost with time [37], meaning that although they initially met only the brainstem criterion, they eventually also met the whole-brain criterion.

The requirement to undertake ancillary investigations is mandatory in some jurisdictions, but not in others [39]. While not mandatory, ancillary investigations assessing electrophysiology or brain blood flow are often undertaken in circumstances where aspects of the clinical testing cannot be performed, when the effects of confounding factors cannot be confidently excluded, or when there is uncertainty about the significance of possible spinally mediated movements [5]. Some have also suggested that ancillary tests should be mandatory when the underlying diagnosis is an isolated posterior fossa lesion due to a hypothetical possibility of sparing of the meso-pontine tegmental reticular formation with the potential for a total apneic, locked-in syndrome mimicking death [40]. This requires, however, knowledge of the boundaries and exact position of the reticular formation and implausible ellipsoid lesions sparing all brainstem nuclei and tracts, none of which are known or seen.

For all these reasons the considerations about persistent neuroendocrine function in the context of determination of death by neurologic criteria are the same irrespective of whether the whole-brain or brainstem criterion is followed, and whether ancillary tests are used or not. If more functional definitions of death consistent with acceptable medical standards are adopted [5, 6, 22], the important consideration is not whether there is any residual neuroendocrine function, but if loss of that function could be a confounding factor contributing to the coma or apnea. Severe metabolic derangement, hypothermia, Addisonian crisis, and myxedema coma can all confound the determination of death by neurologic criteria and can all be caused by hypothalamic dysfunction. The absence of poikilothermia and central diabetes insipidus when hypothalamic–pituitary function persists may therefore be regarded merely as an internal mechanism to control the body temperature and serum sodium at levels that allow neurologic testing. Similarly, the continued secretion of thyrotropin and corticotropin-releasing hormones allows more confident exclusion of either an Addisonian crisis or myxedema coma as contributing to the current clinical state. For those patients where central adrenal or thyroid function was not demonstrable (if tested for), it is biologically implausible to consider that following a sudden and obvious catastrophic intracranial injury in a person who had previously not

demonstrated any signs or symptoms of a hyposecretory disorder, the clinical state would be explained by the absence of adrenal or thyroid function in the hours or short days following the event. The presence of residual hypothalamic–pituitary function is not incompatible with a determination of death by neurologic criteria and may even increase confidence in excluding confounding factors that are known to exist as a result of complete failure of the hypothalamic–pituitary axis.

5 Conclusion

There is increasing acknowledgment within academic circles that there is a mismatch between the legal criteria for whole-brain death and the way that death by neurologic criteria is determined using accepted medical standards. The preservation of some degree of neuroendocrine function, indicative of some hypothalamic function, is common in patients who fulfil the conditions for death by neurologic criteria. Whether this mismatch precludes a determination of death appears to be dependent as much on the definition of death, particularly in a legal statute, as it is on the concept of death itself. While making the determination in the presence of retained neuroendocrine function is consistent with internationally accepted medical standards, it may be difficult to reconcile with a whole-brain criterion for death. However, patients who are confirmed dead by neurologic criteria do not ever regain consciousness or breathe again, irrespective of whether neuroendocrine function is present or not.

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