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Hypothalamic function in patients diagnosed as brain-dead and its practical consequences

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Abstract. Some patients who have been diagnosed as "dead by neurologic criteria" continue to exhibit certain brain functions, most commonly, neuroendocrine functions. In this chapter, we review the pathophysiology of brain death that can lead either to neuroendocrine failure, or to preserved neuroendocrine functioning. We review the evidence on continued hypothalamic functioning in patients who have been declared "brain dead", examine potential mechanisms that would explain these findings, and discuss how these findings create additional confounds for brain death testing. We conclude by reviewing the evidence for management of hypothalamic-pituitary failure in the setting of brain death and organ transplantation.

Keywords: brain death, brainstem death, hypothalamus, pituitary, diabetes insipidus, hormone replacement therapy

Introduction

In this chapter, we review the pathophysiology of brain death and the diagnostic tests used to determine whether brain death has occurred. We focus specifically on continued hypothalamic functioning that can remain in patients who have been declared "brain dead", and discuss mechanisms that would potentially explain these findings.

In what follows, we consider "brain death" or "death by neurologic criteria" to mean, in accordance with legal statutes in the USA and most other nations, *the irreversible cessation of all functions of the entire brain* (President's Commission 1981). However, alternative formulations of "neurological death" are also used, such as the United Kingdom and Canada, which require only the irreversible cessation of the integrative functions of the brainstem, with an emphasis on the capacities for consciousness and breathing – but not the entire brain (Shemie et al. 2006; Academy of Medical Royal Colleges 2008).

At present, there is an ongoing debate in the medical and scholarly literatures, as well as in legal settings, regarding the significance of preserved hypothalamic function in the setting of brain death (Joffe 2007, 2009; Nair-Collins et al. 2016; Lewis et al. 2019; Nair-Collins and Miller 2019; Russel et al. 2019; Greer et al. 2020; Nair-Collins and Miller 2020). Our goal in this chapter is to explain the pathophysiological processes that can result in both neuroendocrine failure or preserved hypothalamic functioning, in an effort to contribute relevant scientific information to this debate. We do not specifically take any positions in this chapter regarding the validity of brain death, nor the conceptual significance of preserved neuroendocrine brain function in brain death. Finally, in an effort to preserve clarity and the use of neutral language, we choose to use the phrase "patients who have been diagnosed as brain dead" (or some

cognate), rather than, "brain dead patients", since the former is consistent with the latter but not necessarily vice versa (since a patient could be declared "brain dead" in error).

Basic Pathophysiology of Brain Death and Diagnostic Testing

At its core, brain death is a matter of fluid dynamics. Any insult or injury that causes intracranial pressure (ICP) to rise precipitously can result in severe neurological injury, including brain death. Such etiologies include but are not limited to: head trauma and subsequent intracranial bleeding and swelling; hemorrhagic or ischemic stroke; metabolic disorders that cause cerebral edema, such as fulminant liver failure or diabetic ketoacidosis; meningo-encephalitis; and cerebral anoxia or ischemia-reperfusion, usually from a period of cardiac arrest (Smith 2004; Smith and Vyas 2010; Joffe et al. 2013; Essien et al. 2017). In each instance, ICP rises to a degree and at a rate sufficient to create resistance to blood flow into the cranial vault, hence decreasing cerebral perfusion. The ischemia that results from decreasing cerebral perfusion, in turn, causes cytotoxic edema (along with other changes), which further increases ICP, causing further diminution of cerebral perfusion, in a positive feedback cycle. If ICP rises to a level greater than mean arterial pressure, this results in zero cerebral perfusion pressure and global intracranial circulatory arrest.

Brain herniation often occurs as well, where the tonsil of the cerebellum herniates downward through the foramen magnum, compressing the lower brainstem and impeding blood flow to the brain. Other areas may also herniate, such as the uncus of the medial temporal lobe, passing downwards through the tentorial notch, placing pressure on the upper brainstem (Ropper 1986; Smith 2004; Posner et al. 2007)

The process described above typically unfolds in a rostral to caudal direction, where the lowest part of the brainstem is the last to show detectable changes. This makes sense, because pyramidal neurons in cortex and the CA1 region of the hippocampus, as well as Purkinje cells of the cerebellum, are most susceptible to even short periods of ischemia, due to greater metabolic demands than other neurons, such as those in the brainstem, and greater metabolic demands than non-neuronal, glial cells throughout the brain (Bernat JL 2006; Frosch et al. 2010). As the process unfolds, brain ischemia and hypoxia causes metabolic acidosis, due to the buildup of lactic acid as a byproduct of anaerobic glycolysis, and acidosis in turn stimulates the release of inflammatory cytokines, such as IL-6 and TNFα (Barklin 2009; Essien et al. 2017). This triggers a systemic inflammatory response which itself can cause tissue damage, and the aforementioned cytokines also activate coagulation pathways (Essien et al 2017; Opdam 2019), potentially resulting in coagulopathy, thrombocytopenia, and even disseminated intravascular coagulation (Opdam 2019).

However, the host response mentioned above, triggered by cerebral acidosis, hypoxia, and adenosine triphosphate (ATP) depletion, is not entirely understood, and can trigger a range of dysregulated host responses involving inflammatory, anti-inflammatory, non-inflammatory, and other cellular signals and cascades, both locally in the brain and, so long as circulation continues, in a systemic fashion as well (Jha and Kochanek 2018; Jha et al. 2019).

Furthermore, as the hypothalamus and pituitary become ischemic, neuroendocrine function can become impaired. Magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus project axons down the pituitary stalk and into the posterior pituitary, releasing the hormones vasopressin and oxytocin into the cavernous sinus, and thence into general circulation. If this area becomes ischemic and nonfunctional, then vasopressin, also

known as anti-diuretic hormone, will not be released into general circulation and therefore will not reach the kidneys, causing massive hypo-osmotic polyuria and hypernatremia, a condition dubbed central diabetes insipidus. Dysregulation of thyroid hormones and cortisol can also occur, as results of disruption of the hypothalamic-anterior pituitary axis (Opdam 2019).

As the process of brain edema and cellular damage makes its way down the brainstem, a Cushing reflex often occurs, with profound bradycardia and hypertension, a result of pontine ischemia causing mixed sympathetic and vagal stimulation (Smith 2004; Nakagawa and Tang 2011; Bernat and Dalle Ave 2019). This is followed by "catecholamine storm", as large amounts of the catecholamines epinephrine and norepinephrine are released, causing severe vasoconstriction, tachycardia, hypertension, and organ damage, including myocardial injury. This "storm" occurs because, normally, parasympathetic and sympathetic responses balance each other in a reciprocal inhibitory-excitatory fashion. However, when the parasympathetic vagal and cardiomotor nuclei of the medulla become ischemic, sympathetic activation is unopposed, thus releasing massive amounts of stimulating, sympathetic hormones, which can cause severe end organ injury (Smith 2004; Bernat and Dalle Ave 2019). Finally, as the process reaches completion at the cervicomedullary junction, the upper cervical spinal cord also becomes injured (Schneider and Matakas 1971; Walker et al. 1975; Walker 1980), finally resulting in profound hypotension from loss of vasomotor tone, and the rostral-caudal progression of injury is complete.

Patients suspected of brain death will uniformly be comatose and ventilated. The cause of coma must be known, believed to be severe enough to cause irreversible loss of all brain functions, and potential confounds, such as acid-base disturbance, sedative intoxication, and hypothermia, must be ruled out. These are preconditions for brain death testing. Next, the

accepted diagnostic tests for brain death involve three cardinal features, which have stayed roughly the same since the 1960s: unresponsiveness (excepting so-called spinal reflexes); cranial nerve areflexia (of those chosen to be clinically tested); and lack of respiratory drive as determined by the apnea test. Confirmatory tests are not generally required, though are often used at the clinician's discretion, or if the apnea test cannot be completed, or in special populations, such as children and infants. The two most common types of confirmatory tests attempt to demonstrate either absent intracranial cerebral blood flow (such as 4-vessel angiography or radionuclide cerebral blood flow determination), or absent electrical activity (such as electroencephalography) (Shemie et al. 2006; Academy of Medical Royal Colleges 2008; Wijdicks et al. 2010; Nakagawa et al. 2011; Greer et al. 2020).

Hypothalamic Function in Patients Diagnosed as Brain-Dead

The hypothalamus forms the ventral part of the diencephalon, sitting beneath the thalamus, just posterior to the optic chiasm, and forms the walls and floor of the inferior part of the third ventricle (Blumenfeld 2002). It is helpful to differentiate four hypothalamic regions, moving anteriorly from the preoptic area (just in front of the optic chiasm), to the anterior, middle, and posterior regions respectively, with the mammillary bodies, the most posterior portion of the hypothalamus, themselves located just anterior to the cerebral peduncles of the midbrain. The hypothalamus is also differentiated laterally and medially by the fornix, a major limbic pathway which passes through the hypothalamus to the mammillary bodies (and elsewhere). The most medial areas of the hypothalamus, the periventricular nuclei, line the walls on either side of the third ventricle (Blumenfeld 2002).

Underneath the hypothalamus lies the pituitary fossa, which contains the pituitary gland, which itself is covered by dura (Blumenfeld 2002). The pituitary fossa is a bony structure composed of the sella turcica of the sphenoid bone inferiorly, which curves up like a saddle (hence the name, which means "Turkish saddle"), into the anterior and posterior clinoid processes anteriorly and posteriorly. Superiorly, the pituitary fossa is bounded by a piece of dura, the diaphragma sella, which contains a round hole in the middle, allowing the pituitary stalk to pass into the pituitary fossa, with continuous dura covering the pituitary gland in the pituitary fossa.

The pituitary stalk begins outside the pituitary fossa, as the infundibulum, which itself arises from the tuber cinereum, a bulge on the inferior portion of the hypothalamus; on the anterior portion of the infundibulum (outside the pituitary fossa) is a slightly elevated area known as the median eminence. The median eminence is an important area of hypothalamic communication with the anterior pituitary, to be discussed below.

The cavernous sinus bounds the pituitary fossa laterally on both sides, and there are arteries and veins traversing the bone separating the pituitary fossa from the cavernous sinus, allowing humoral signals and physiologic information from blood to pass between the hypothalamic-pituitary complex and general circulation, via the cavernous sinus, which drains through the jugular veins (Blumenfeld 2002).

The pituitary gland itself is interesting, because it is composed of two distinct glands, one, embryologically developing as a part of the brain (the posterior pituitary, or neurohypophysis), and the other not (the anterior pituitary, or adenohypophysis), though they happen to join together anatomically. The anterior pituitary develops from the roof of the pharynx, and is composed of a variety of glandular cells that secrete hormones into systemic

circulation via the cavernous sinus. The hypothalamus controls anterior pituitary function via inhibitory or excitatory factors, which are transmitted through a special, local blood system known as the hypophyseal portal system. The first capillary plexus of the portal system is located at the median eminence, and the neurons of several hypothalamic nuclei project to the median eminence, where they secrete releasing or inhibitory factors into the hypophyseal portal system, which carries the hormones a short distance paralleling the pituitary stalk and passing through the diaphragma sella, to the anterior pituitary, which then secretes hormones into the secondary capillary plexus (within the pituitary fossa), which in turn drains into the cavernous sinus and thence to systemic circulation via the jugular veins. Thus, the anterior pituitary does not embryologically develop from the brain, does not contain neurons, and is controlled indirectly by the hypothalamus, via the portal blood system (Blumenfeld 2002).

By contrast, the posterior pituitary, or neurohypophysis, develops from the floor of the developing ventricular system of the brain. It is composed of the axons of neurons from the hypothalamus itself: The cell bodies of magnocellular neurons of the hypothalamus are contained in the paraventricular and supraoptic nuclei; these neurons project axons down the infundibulum, pituitary stalk, and into the posterior pituitary, where they directly secrete hormones into their own capillary plexus, also within the pituitary fossa, and which also drains into the cavernous sinus. Thus, the posterior pituitary embryologically develops from the brain itself, is anatomically composed of the axons of neurons located in the brain, and the hypothalamic nuclei directly secrete hormones via the posterior pituitary, into systemic circulation (Blumenfeld 2002).

The hypothalamus is involved with multiple vital functions, including fluid homeostasis, electrolyte composition, blood pressure control, energy metabolism, reproductive behaviors,

growth and sexual development, temperature homeostasis, stress responses, circadian rhythm, and limbic functions. As a part of the limbic system, the hypothalamus participates in a complex, feedforward- and feedback-driven network involving the amygdala, hippocampus, multiple brainstem nuclei, olfactory cortex, limbic cortex, and other structures involved in the limbic system (Horn and Swanson 2013).

The hypothalamus is a critical part of the endocrine system. It controls release of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone, prolactin, luteinizing hormone, and follicle-stimulating hormone from the anterior pituitary via releasing and inhibiting hormones secreted from the median eminence, which are carried down the hypophyseal portal system to the anterior pituitary (Blumenfeld 2002). The functions of these hormones are diffuse, complex, and involve multiple feedback regulatory pathways. For our purposes here, we consider especially ACTH and TSH.

ACTH regulates hormone release from the adrenal gland, including cortisol and aldosterone, which are important in blood pressure control, electrolyte balance, and stress responses. TSH stimulates the release of thyroxine (T4) and minute amounts of triiodothyronine (T3) from the thyroid gland. Thyroid hormones, in particular, have complex and diffuse functions throughout the body, and are involved in multiple regulatory feedback loops. To simplify, thyroid hormones are important in promoting and regulating cellular metabolism throughout the body, and participate in mitochondrial production of ATP (Horn and Swanson 2013).

Finally, as mentioned above, the hypothalamus secretes vasopressin, or anti-diuretic hormone, directly through the posterior pituitary into the general circulation, in response to changes in plasma osmolality, and thereby regulates the balance of salt and water in the

extracellular fluid by controlling diuresis via the kidneys. Vasopressin binds to three different receptors: V1 receptors on vascular smooth muscle that help to control vascular tone; V2 receptors on the basolateral membrane of the distal nephron that control aquaporins in the collecting ducts and thereby fluid reabsorption; and V3 receptors in the anterior pituitary to synergize with corticotropin releasing hormone in regulating production of ACTH (Kotloff et al. 2015).

Hypothalamic-Posterior Pituitary Function in Patients Declared Brain-Dead

When hypothalamic-posterior pituitary function is lost, the result is central diabetes insipidus. Without vasopressin to bind the V2 receptors in the distal nephrons and collecting ducts of the kidney, inappropriate polyuria develops (urine output over 2.5-3 ml/kg/hr) of dilute urine (specific gravity of <1.005, and urine osmolality <200mOsm/L) with resultant hypernatremia (serum sodium >145 mmol/L) and hyperosmolality (Kotloff et al. 2015). The presence of central diabetes insipidus in patients diagnosed as brain-dead has been reported to vary anywhere from 9-90% (Lewis et al. 2019). In the largest compilation of which we are aware of original clinical studies reporting on diabetes insipidus in patients diagnosed as brain-dead, Nair-Collins et al. (2016) found that, of 1878 patients declared brain-dead, 49% were reported to have diabetes insipidus.

We updated this literature review for this chapter, following the pattern of the original review, as follows. In January 2020, we accessed the MEDLINE database through PubMed, and restricted articles from September 2013 (the date of the previous search) to January 2020. We used search terms "brain death," "diabetes insipidus," and "posterior pituitary" in various

combinations using both Medical Subject Headings (MeSH) terms, and text terms (all fields). We reviewed reference lists of articles to search for additional articles.

Studies were included if they reported the results of an original clinical study that reports the incidence of diabetes insipidus in patients diagnosed as brain-dead. Single case reports and reviews with non-original data were excluded. Both authors reviewed all articles for inclusion or exclusion, and agreed on classification in all cases. Overall, 45 articles were identified using the search strategy above, of which 5 met inclusion criteria. The majority of excluded articles were animal studies, not a brain-dead cohort, or reported on brain-death patients but for whom diabetes insipidus could not be discerned at the individual level.

The 5 additional studies (Jeong et al. 2012; Hwang et al. 2013; Essien et al. 2017; Yener et al. 2018; Ozmert et al. 2019) add 668 new patients, of whom 340 (51%) were reported to have diabetes insipidus. All told, the updated compilation includes 2546 patients diagnosed as brain-dead, of whom 1265 (50%) were reported to manifest central diabetes insipidus. See Table 1 for further detail.

It should be emphasized that this is not a meta-analysis, and the data are subject to significant limitations, including variability among the cohorts in age, etiology of injury or illness, the key diagnostic testing for central diabetes insipidus was not uniformly reported, and the majority of the studies were retrospective chart reviews. Furthermore, some of the studies are confounded by administration of exogenous vasopressin to control blood pressure (i.e., to bind to V1 receptors on vascular smooth muscle and thus treat distributive shock) for some patients, but do not report in sufficient detail to be able to remove those patients receiving vasopressin from the cohort. Essien et al. (2017), for example, clearly explained this confound: vasopressin would simultaneously treat (and thus mask) central diabetes insipidus, if present,

thereby potentially rendering the reported number with diabetes insipidus an underestimate. Nonetheless we decided to include this study, as well as Jeong et al. (2012), which similarly reported the use of vasopressin for hypotension, for the following reason. Vasopressin for blood pressure control is commonly used in the ICU, and it is likely that other studies similarly used vasopressin in this way but did not report it. Thus, at least for these two studies, and possibly others, the number of patients with diabetes insipidus may be underreported.

On the other hand, neither polyuria nor hypernatremia alone are sufficient evidence for central diabetes insipidus, and there are a number of iatrogenic and other confounding factors that can cause massive diuresis or hypernatremia, including loop diuretics, mannitol, hypertonic saline, fluid resuscitation, contrast solution for imaging, or recovery from acute kidney injury, all of which can confound the diagnosis. Most studies did not rule out these and other factors (cf. Nair-Collins et al. 2016), and thus, the number of patients with diabetes insipidus may also be over-reported in studies.

With these caveats kept in mind, the 95% Confidence Interval for the proportion of individuals with central diabetes insipidus with a diagnosis of brain-death, calculated from the z-distribution as justified by the Central Limit Theorem, is 0.478 – 0.516, which is an extremely tight interval. The 99% Confidence Interval, calculated from the same distribution is 0.472 – 0.523. Thus, based on the clinical data available, it would appear that something in the range of half of patients declared brain-dead develop diabetes insipidus.

Hypothalamic-Anterior Pituitary Function in Patients Diagnosed as Brain-Dead

The role of the hypothalamus and anti-diuretic hormone in regulating diuresis and thus plasma osmolality is straightforward and relatively easy to discern, thus allowing justifiable inferences to the presence or absence of this brain function. By contrast, the functions of the anterior pituitary, controlled by the hypothalamus, are far more diffuse, subject to multiple feedback loops, and therefore do not lend themselves to a secure inference regarding brain function from the measurement of one or two physiologic variables.

Therefore, to provide information on hypothalamic-anterior pituitary function in patients diagnosed as brain-dead, we present direct measurements of specific hormones, including hypothalamic releasing/inhibiting hormones, anterior pituitary hormones, and other hormones regulated by the anterior pituitary. The following data is taken from Nair-Collins et al. (2016). The methodology used followed a similar pattern as described above.

Thyroid function in patients diagnosed as brain-dead is often altered, but not generally lost. Based on 12 studies (Howlett et al. 1989; Arita et al. 1993; Schrader et al. 1980; Macoviak et al. 1987; Robertson et al. 1988; Masson et al., 1990; Powner et al. 1990; Karayalin et al. 1994; Mariot et al. 1995; Goarin et al. 1996; Szostek et al. 1997; Ishikawa et al. 2009) reporting on 386 patients, TSH was commonly detectable, usually within normal limits, in peripheral circulation (see Table 2). However, TSH was low in 22% and not detectable in 16%, significant minorities of brain-dead patients. TSH is secreted from the anterior pituitary when stimulated by thyrotropin-releasing hormone (TRH), itself secreted at the median eminence, by axonal terminals whose parvocellular cell bodies are located in the paraventricular and arcuate nuclei, located respectively in the anterior (supraoptic) and middle (tuberal) region of the hypothalamus (Blumenfeld 2002; Horn and Swanson 2013). TSH, in turn, stimulates primarily T4 (as well as a

14

negligible amount of T3) from the thyroid gland, while T4, which is a prohormone, is converted into the bioactive form T3 and the inactive form reverse T3 in peripheral tissue.

In spite of the commonly preserved presence of TSH, thyroid hormone levels are altered in many patients diagnosed as brain-dead. Triiodothyronine (T3) is often low, as is, to a lesser extent, T4, combined with normal or high reverse T3 and often normal TSH (see Tables 2 and 3). This pattern is consistent with euthyroid sick syndrome, a condition in which nonthyroidal systemic illness can result or manifest in altered thyroid hormone levels, without primary hypothalamic-pituitary-thyroid dysfunction. If there were true central neuroendocrine failure then TRH, and hence TSH and the remaining cascade of thyroid hormones, would all be essentially undetectable. Euthyroid sick syndrome is common in critically ill patients, and not thought to require treatment (Meyfroidt et al. 2019). Nevertheless, the undetectable TSH, and low T4 in some patients suggests loss of the hypothalamic-pituitary-thyroid axis in at least 16% of patients with brain death.

The hypothalamo-pituitary-adrenal axis appears to be impacted, and highly variable across patients. Two studies (Kinoshita et al. 1992; Arita et al. 1993) examined corticotropin-releasing hormone (CRH), and found collectively that CRH was detectable in peripheral circulation in 17 of 24 (71%) of patients. Like TRH, CRH is secreted at the median eminence, by parvocellular neurons whose perikarya also lie in the hypothalamic paraventricular nuclei; CRH stimulates the anterior pituitary to release ACTH into systemic circulation. Five studies (Koller et al. 1990; Kinoshita et al. 1992; Arita et al. 1993; Fitzgerald et al. 1996; Ishikawa et al. 2009) collectively report that ACTH was within normal limits in 31 of 65 (48%) of patients, and detectable (not necessarily within normal limits) in 83 of 114 (73%) of patients. Finally, ten studies report cortisol levels (Hall et al. 1980; Howlett et al. 1989; Powner et al. 1990; Gramm et

al. 1992; Arita et al. 1993; Amado et al. 1995; Mariot et al. 1995; Leng et al. 1999; Lopau et al. 2000; Dimopoulou et al. 2003). These levels are highly variable, which is not unexpected in a patient population with critical illness. See Table 4 for further detail. Thus, central adrenal dysfunction may occur in at least 27-29% of patients diagnosed as brain-dead.

We were unable to determine the timing of hypothalamic-pituitary axis changes relative to the timing of brain death diagnosis, as this was rarely reported. Some of the hormonal changes described may take time to develop, particularly the changes characteristic of sick-euthyroid syndrome. Most patients diagnosed as brain dead after hypoxic ischemic brain injury have been critically ill for over 24 hours, as guidelines have suggested not making the diagnosis until at least 24 hours after the event, and until at least 24 hours after rewarming to normothermia when targeted temperature management has been used. Nevertheless, in traumatic brain injury, the diagnosis may be made even before 24 hours after the brain injury if confounding sedation and analgesia medications have not been administered, and older studies were done before targeted temperature management was used. For these reasons, we consider the estimates of hypothalamic-pituitary axis derangement to be conservative, and higher rates may be possible as duration of brain death increases. This is an area needing further research.

We did not review the incidence of all hypothalamic-pituitary functions after a diagnosis of brain death. It is worth noting that there are rare reports of "chronic brain death" where the patient had undergone puberty and proportional growth after the diagnosis of brain death (Shewmon 1998, Shewmon 2018). Given that the hypothalamus (via gonadotropin releasing hormone and growth hormone releasing hormone) and anterior pituitary (via luteinizing hormone, follicle stimulating hormone, and growth hormone) are required for pubertal development and proportional growth (Khan 2019; Wood et al. 2019), this can be considered

further evidence that at least some patients diagnosed as brain dead have remaining neuroendocrine functions.

Discussion and Implications

Why the Hypothalamus?

Some patients who are declared to be dead by neurological criteria retain some viable neural tissue and brain function (indicating some intracranial circulation), that is, hypothalamic neuroendocrine function. It is to be noted that the American Academy of Neurology acknowledged the preservation of this particular brain function, but declared that preservation of neuroendocrine function is consistent with the diagnosis of brain death (Russell et al. 2019). Similarly, multiple international professional societies, known as "The World Brain Death Project", also acknowledged the possibility of preserved neurohormonal function, and stated, "It is recommended that persistence of hormonal regulatory functions does not preclude the diagnosis of [brain death]" (Greer et al. 2020). This is an area of ongoing debate in medical and scholarly literatures (Bernat and Dalle Ave 2019, Nair-Collins and Miller 2019, and Nair-Collins and Miller 2020). For the purpose of this chapter we do not comment on this debate, instead focusing on explaining why this may occur, along with practical consequences of its occurrence.

Noting that some patients declared brain-dead retain some brain function, an interesting question arises: Why the hypothalamus? The absence of central diabetes insipidus is a brain function that may be preserved in a patient diagnosed as brain-dead, and if the clinical data reported above are reasonably reliable, it would appear that this brain function is preserved in about half of patients diagnosed as brain-dead. Thus, hypothalamic circulation and perfusion

pressure are not zero; so, why don't we commonly observe other brain areas with retained function? For example, why do the tested cranial nerve reflexes show lack of response?

One common answer is that the posterior pituitary and hypothalamus have a somewhat unique blood supply (Leclercq and Grisoli 1983). The meningeohypophyseal trunk of the internal carotid gives rise to the inferior hypophyseal artery, which pierces the bony sella turcica from the cavernous sinus to supply blood to the inferior portion of the posterior pituitary, which itself is wrapped in dura. Importantly, the dura mater, more than the cranium itself, is the inelastic container within which ICP rises. This is an important detail, because the internal carotid, meningeohypophyseal trunk, and inferior hypophyseal artery take a pathway that remains outside the dura, until the inferior hypophyseal artery finally pierces the dura to reach the posterior pituitary (Blumenfeld 2002).

Theoretically, this anatomic location, outside the dura for much of its course, provides some protection against raised ICP. If this is the case, the artery is protected from raised ICP until shortly before it reaches its target. This protection could result in greater driving force pushing the blood and hence higher local perfusion pressure than elsewhere, where the force created by the cardiovascular system must push blood against raised intracranial pressure for a longer distance.

While this mechanism plausibly plays some role in the explanation for why some functions of the hypothalamus are commonly observed in patients diagnosed as brain-dead, it is not the entire explanation. First, although the inferior portion of the posterior pituitary may receive a protected blood supply, the posterior pituitary is composed of the axons of cell bodies that are located in several hypothalamic nuclei, outside the pituitary fossa in the diencephalon, whose blood supply is no more nor less protected from increased ICP than any other area of the

18

brain (apart from the inferior portion of the posterior pituitary). Clearly these cell bodies require ongoing blood supply in order to continue functioning.

Second, some magnocellular neurons are osmoreceptors, directly responsive to their immediate osmotic environment via mechanosensitive ion channels, with stretch receptors responsive to minute changes in cell size due to changes in osmotic pressure and the resultant shift of water across the cell membrane, resulting in a voltage-independent inward cationic current, thus depolarizing the cell (Leng et al. 1999). However, the depolarization resulting from their immediate osmotic changes is not typically large enough to trigger an action potential down the axon, and thence to release vasopressin stored in vesicles. Instead, normal osmoregulation requires additive, glutamatergic input from circumventricular (forebrain) organs, particularly the organum vasculosum of the lamina terminalis to the supraoptic nucleus (Leng et al. 1999). Lesions to the organum vasculosum of the lamina terminalis result in the near complete absence of any drinking behavior in response to hyperosmolarity, natriuretic deficits leading to hypernatremia. and a major deficit in osmoregulatory vasopressin release (Leng et al 1999).

In other words, normal osmoregulation is a function of more than the magnocellular neurons of the hypothalamus: it requires additional, additive, stimulating input from circumventricular organs as well. These circumventricular areas are also supplied by arteries that are not protected in the same way as hypothesized for the posterior pituitary. Thus, preserved, normal hypothalamic osmoregulation is a clear sign of some hypothalamic function, but also strongly suggests preserved blood flow, viability and function of the organum vasculosum of the lamina terminalis.

Third, preserved secretion of anterior pituitary hormones entails preservation of hypothalamic nuclei that control the anterior pituitary. While the majority of these nuclei secrete

releasing or inhibiting factors at the median eminence, that is where the axons terminate, not where they originate. Instead, the cell bodies for these axons also lie in hypothalamic nuclei; and again, the blood supply to this area is not protected from ICP in the way that the inferior hypophyseal artery is hypothesized to be protected.

The answer as to 'why the hypothalamus' is most likely the following. Anatomical studies of patients declared brain-dead demonstrate lack of complete pathological destruction of the brain. While there is wide variability in the findings, it is common to report areas of intact neural tissue, particularly in the study by Wijdicks and Pfeifer (Walker et al. 1975; Schroder 1983; Wijdicks and Pfeifer 2008). Therefore, the fact of preserved hypothalamic function demonstrates that intracranial circulation is not completely arrested in all cases, and this is supported by anatomic studies which do not find ischemic changes in all areas of the brain. It is likely that the involved areas had low flow, but enough to preserve hypothalamic-pituitary and lamina terminalis tissue viability and function.

Confounding Conditions in the Diagnosis of Brain Death

A prerequisite to brain death testing, according to standard guidelines, is to rule out confounders, such as sedative intoxication, hypothermia, or acid-base disturbance. However, there are additional confounds introduced above that are rarely taken into account, but if present, confound the diagnosis of brain death using current tests. In this context, a confound is a condition that interferes with the ability to determine any one of the brain function tests used to assess whether the criteria of brain death have been met.

While preserved hypothalamic-pituitary function is common among patients declared to be "brain-dead", the loss of hypothalamic-pituitary function itself can confound brain death testing. Specifically, adrenal dysfunction and failure can cause coma, seizures, and, in infants, apnea (Cortet et al. 2017; Patti et al. 2018). Thyroid dysfunction and failure can cause coma, hypoventilation with poor response to carbon dioxide, and seizures (Massumi and Winacker 1964; Domm and Vassalo 1973; Zwillich et al. 1975; Ishii 2017). Therefore, even in the absence of seizures, loss of hypothalamic-pituitary brain function is itself a confounder to the diagnosis of brain death, because it can mimic apnea and coma, which may be assumed to be of brainstem origin, when they are not. Future brain death guidelines should consider the approach to ruling out this confounding factor, considering that central thyroid and adrenal failure may occur in up to 16% and 29% of patients diagnosed with brain death.

Management of the Patient Diagnosed as "Brain-Dead"

There are many narrative reviews on the management of patients diagnosed as brain-dead (Gupta and Dhanani 2016; Maciel and Greer 2016; Chamorro-Jambrina et al. 2017; Meyfroidt et al. 2019; Opdam 2019). There are also systematic reviews (D'Aragon et al. 2017; Buchanan and Mehta 2018), and guidelines on this management (Kotloff et al 2015; Canadian Blood Services 2019). These publications give guidance on all acute clinical management of patients with brain death, with an emphasis on maintaining organ functions to optimize organ donation rates. It is beyond the scope of this chapter to discuss all of this management, and here we focus on what has been called Hormonal Replacement Therapy (HRT) aimed to replace hypothalamic-pituitary axis hormonal deficiencies.

When hypothalamic-posterior pituitary function is lost, indicated by central diabetes insipidus (see above for manifestations of this), treatment with antidiuretic hormone replacement is indicated to prevent dehydration, hypovolemia, hemodynamic instability, and hypernatremia from the hypo-osmotic polyuria. This can be done using desmopressin (1-deamino-8-D-arginine vasopressin, or DDAVP), a vasopressin analogue with much greater affinity for V2 renal receptors than for V1 vascular smooth muscle receptors. Usually, a dose of 1-4 mcg IV is used initially, typically followed by 1-2 mcg IV q6h titrated to maintain urine output <3-4 ml/kg/hr (Kotloff et al. 2015). In pediatrics, the dose for DDAVP is 0.25-1 mcg IV q6h for the same target urine output (Gupta and Dhanani 2016). If the dosing is adequate, intravenous fluids can be administered as insensible losses (20% maintenance fluids as dextrose 5% in 0.9% sodium chloride) plus urine output (as normal saline (NS)); if the serum sodium is dropping at a rate more than 10 mmol/L/day, and urine sodium is measured to be much lower than that of NS (i.e., <<154 mmol/L), urine replacement fluid may need to be changed to 0.45% sodium chloride with close following of serum sodium measured every 4-6 hours initially.

Another option to replace antidiuretic hormone is to use vasopressin, which has affinity for all three receptors, and thus can treat diabetes insipidus and also improve vasodilatory shock from vasopressin deficiency at the vascular smooth muscle V1 receptor (Gupta and Dhanani 2016; Maciel and Greer 2016; Chamorro-Jambrina et al. 2017; Meyfroidt et al. 2019; Opdam 2019). In the presence of hypotension from vasodilatory shock, vasopressin is considered as a first-line vasoactive agent, and given by intravenous infusion (Kotloff et al. 2015; Canadian Blood Services 2019). The dosing of vasopressin suggested in the literature can be confusing, given variously in units/min, units/hour, milliunits/hour, milliunits/kg/minute (mU/kg/min), etc., and clinicians need to pay close attention to these details when prescribing vasopressin to avoid

dosing errors. We suggest the dose used is best given as 0.3 to 0.7 mU/kg/min, with the maximum being an absolute dose of 40 mU/min (which is 2.4 U/hr) IV, titrated to effect on blood pressure and urine output of ~100 ml/hour in adults and 2-3 ml/kg/hour in children. Oral DDAVP is used in the setting of chronic vasopressin deficiency from loss of hypothalamic-posterior pituitary function; however, this is not a reliable treatment in the acute setting, and will not be discussed more here.

More controversial is whether to treat for hypothalamic-anterior pituitary loss of function. As reviewed above, central thyroid deficiency may occur in 16-22% of patients with brain death, and central adrenal deficiency in at least 27-29% of patients with brain death. Studies and reviews focus on whether replacing thyroid and adrenal hormones improve outcomes of number of organs donated and post-organ-transplant organ function, and not on efficacy for long-term maintenance. Most narrative reviews suggest replacement of thyroid and corticosteroid hormones based on retrospective observational studies and expert opinion; however, the evidence from randomized controlled trials is not supportive of this practice (Meyfroidt et al. 2019; Opdam 2019). There are no studies of the efficacy of HRT in pediatric patients.

Thyroid hormone replacement has had no effect on the number of organs donated (based on findings from 5 of 6 observational studies), on heart donation rates (based on 4 of 6 observational studies and 4 of 4 randomized controlled trials), or on heart function (based on 3 of 3 randomized controlled trials; Buchanan and Mehta 2018; Canadian Blood Services 2019). Nevertheless, the Society of Critical Care Medicine guideline still suggests that thyroid replacement be "considered" for hemodynamically unstable donors or for potential heart donors with "left ventricular ejection fraction <45%" (Kotloff et al. 2015). If used, T4 can be given as 20 mcg IV bolus followed by 10 mcg/hr IV, or, if available, T3 can be given as 4 mcg IV bolus

followed by 3 mcg/hr IV infusion (Kotloff et al. 2015). In pediatrics, the dosing of T4 is initial bolus of 1-5 mcg/kg IV followed by 0.8-1.4 mcg/kg/hr IV infusion. These ranges are based on age: for age ranges of 0-6 months, 6-12 months, 1-5 years, 6-12 years, 13-16 years, and >16 years, the loading dose is 5, 4, 3, 2.5, 1.5, and 0.8 mcg/kg IV respectively, followed by the infusion dose of 1.4, 1.3, 1.2, 1.0, 0.8, and 0.8 mcg/kg/hr IV respectively. T3 dosing in pediatrics is 0.05-0.2 mcg/kg/hr IV infusion, with the higher dose used in younger patients (Kotloff et al. 2015; Gupta and Dhanani 2016). Again, for chronic thyroid deficiency oral dosing is used, and this is beyond the scope of this review.

Replacement of corticosteroids has had possible benefit on treating hypotension (based on 2 of 4 observational studies reporting increased donor blood pressure; however, this was not confirmed in meta-analysis of 3 randomized controlled trials), no clear benefit on number of organs donated (based on 5 observational studies and 2 randomized controlled trials), and no effect on post-organ-transplant organ function in recipients (based on 9 randomized controlled trials) (D'Aragon et al. 2017; Canadian Blood Services 2019). In spite of these findings, for unclear reasons the guideline from the Society of Critical Care Medicine states that administration of corticosteroids "reduces the potential deleterious effects of the inflammatory cascade on donor organ function," and therefore recommends using methylprednisolone 15 mg/kg (up to 1g) IV daily, or 250 mg IV bolus followed by 100 mg/hr infusion (Kotloff et al. 2015). In pediatrics, the dose is 20-30 mg/kg IV daily (up to maximum of 1g IV daily) (Kotloff et al. 2015; Gupta and Dhanani 2016). Some reviews suggest an alternative is to use hydrocortisone 1mg/kg/dose q6h, up to 50 mg IV q6h (Canadian Blood Services 2019; Opdam 2019). In the setting of chronic adrenal insufficiency oral corticosteroids are used, and the dosing is beyond the scope of this review.

It is important to emphasize that these reviews and guidelines only address the acute short-term (i.e., at most days) management of the hypothalamic-pituitary axis in brain-dead patients. No study we are aware of addresses whether treatment of thyroid and/or adrenal failure can change results of apnea testing. No study we are aware of addresses cases of 'chronic-brain-death' where testing for, and treatment of central thyroid and/or adrenal failure may be used to support homeostasis. The testing and treatment of these deficiencies in the chronic setting are beyond the scope of this chapter.

Conclusion

Some hypothalamic-pituitary and basal forebrain brain functions continue in some patients diagnosed with brain death. Most commonly, this brain function manifests in the form of hypothalamic osmoregulation and the attendant absence of central diabetes insipidus in about half of brain dead patients. In addition, central thyroid and adrenal failure do not occur in about three-quarters of brain dead patients. To quote two prominent authors on the concept and praxis of brain death, "even when the brain death tests are performed and interpreted correctly, inevitably, cases will occur in which some brain functions persist" (Bernat and Dalle Ave 2019). In cases where these hypothalamic-pituitary functions are lost, this has implications for management, including consideration of untreated central thyroid or adrenal failure as confounding factors to the clinical examination for brain death, and consideration of treatment for central thyroid or adrenal failure and diabetes insipidus to improve outcomes, both for donated organs if that is the patient's or family's wish, or for treatment of the patient in those relatively rare cases where treatment continues after the diagnosis of brain death.

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Tables

Table 1. Central Diabetes Insipidus in Patients Diagnosed as Brain-Dead

Publication	Age	BD (n)	DI (n)	DI (%)	Publication	Age	BD (n)	DI (n)	DI (%)
Griepp et al. (1971) (P)	13 - 52y	22	9	41	Staworn et al. (1994) (R)	peds	92	38	41
Jorgensen (1973) (P)	u.s.	63	23	37	Amado et al. (1995) (P)	18-67 y	18	5	28
Jastremski et al. (1978) (R)	11 - 89y	176	15	9	Finfer et al. (1996) (R)	peds	77	60	78
Jorgensen and Malchow-Moller (1981) (P)[a]	12-86y	4	1	25	Dominguez-Roldan et al. (2002) (P)	adult	59	31	53
Outwater and Rockoff (1984) (R)	5m - 16y	16	14	88	Dosmeci et al. (2004) (P)	2-71 yrs	94	74	79
Pelosi et al. (1986) (P)	9 - 37y	21	6	29	Dominguez-Roldan et al. (2005) (R)	adult	50	43	86
Fiser et al. (1987) (R)	4m - 18y	34	13	38	Kim et al. (2005) (R)[e]	13-49y	10	10	100
Fackler, Troncoso, and Gioia (1988) (R)	2m - 17y	45	5	11	Salim et al. (2006) (R)	adult	69	32	46
Howlett et al. (1989) (P)[b]	8 - 67y	31	24	77	Chai, Tu, and Huang (2008) (R)[f]	17-59 y	5	5	100
Kinoshita et al. (1990) (P)	9 - 54y	10	10	100	Wijdicks et al. (2008) (R)	2 m-84 y	228	141	61
Hohenegger et al. (1990) (P)[c]	6 - 48y	11	4	36	Seth et al. (2009) (P)	7-87 yrs	55	17	31
Debelak, Pollak, and Reckard (1990) (R)	u.s.	181	68	38	Varelas et al. (2011) (R)	adult	95	55	58
Nygaard, Townsend, and Diamond (1990) (R)	6 - 56y	114	60	53	Jeong et al. (2012) (R)	adult	123	42	34
Mackersie, Bronsther, and Shackford (1991) (R)	u.s.	99	38	38	Alharfi et al. (2013) (R)	5-17y	49	28	57
Ali, Wood, and Gelb (1992) (R)	adult	43	34	79	Hwang et al. (2013) (R)	adult	112	67	62
Gramm et al. (1992) (P)	9 - 71y	32	25	78	Essien et al. (2017) (R)	>14y	373	187	50
Sugimoto et al. (1992) (P) [d]	17-61 y	7	7	100	Yener et al (2018) (R)	1m – 18y	37	33	89
Rabanal et al. (1993) (P)	u.s.	50	20	40	Ozmert et al. (2019) (R)	peds	23	11	48
Arita et al. (1993) (P)	9-85 y	18	10	56	**Total:**	**1m – 89y**	**2546**	**1265**	**50**

Modified from Nair-Collins et al. (2016), Table 1.

Abbreviations: P = prospective study; R = retrospective study; BD = brain death or brainstem death; DI = central diabetes

insipidus; y = year; m = month; u.s. = unstated; peds = pediatric (17 years and younger); adult = 18 years and older.

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

[b] Keogh et al. (1988) appears to report the results of the same study; therefore duplicate results are not included

[c] Four of 11 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] 7/10 patients suffered a gunshot wound penetrating an area approximately 4cm 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've only included those 5.

Table 2. Overview of Hypothalamo-Pituitary-Thyroid Axis

Variables	Findings	References
Thyroid-stimulating hormone (TSH)	TSH: wnl 272/347 (78%); det. 325/386 (84%)	Schrader et al. 1980[a]; Macoviak et al. 1987; Robertson et al. 1988; Howlett et al. 1989; Masson et al., 1990; Powner et al. 1990; Arita et al. 1993; Karayalin et al. 1994; Mariot et al. 1995; Goarin et al. 1996; Szostek et al. 1997; Ishikawa et al. 2009[b]
Total T4	T4: wnl or ↑ 80/129 (62%)	Gifford et al. 1986; Macoviak et al. 1987; Montero et al. 1988; Robertson et al. 1988; Howlett et al. 1989; Szostek et al. 1997
Free T4	fT4: wnl or ↑ 194/299 (65%)	Robertson et al. 1989; Masson et al. 1990; Powner et al. 1990; Karayalin et al. 1994; Mariot et al. 1995; Goarin et al. 1996; Szostek et al. 1997
Total T3	T3: wnl 27/129 (21%)	Gifford et al. 1986; Macoviak et al. 1987; Montero et al. 1988; Robertson et al. 1988; Howlett et al. 1989; Szostek et al. 1997
Free T3	fT3: wnl or ↑ 57/133 (17%)	Novitzky et al. 1987; Montero et al. 1988; Robertson et al. 1988; Robertson et al. 1989; Masson et al. 1990; Powner et al. 1990; Karayalin et al. 1994; Mariot et al. 1995; Goarin et al. 1996; Szostek et al. 1997
Reverse T3	rT3: wnl or ↑ 152/169 (90%)	Howlett et al. 1989; Robertson et al. 1989; Masson et al. 1990; Powner et al. 1990; Karayalin et al. 1994; Mariot et al. 1995; Szostek et al. 1997

Modified from Nair-Collins et al. (2016), Table 2

Abbreviations: 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.

[a] "Serum TSH was within normal range … in the majority of the patients, but was slightly elevated in case 5". (p. 241) We've transcribed this statement into our compilation as the lowest number of cases possible such that the majority was within the normal range (i.e., 4/6).

[b] Hormones were measured at autopsy, 4-25 days post-BD. All patients were autopsied within 12 hours of cardiac arrest. Blood was taken from the right cardiac chamber.

Table 3. Hypothalamo-Pituitary-Thyroid Axis: Findings Summarized by Study

Publication	Age	BD (n)	Variables	Findings and Comments
Schrader et al. (1980) (P)[a]	16-56 y	6	TSH	TSH wnl or ↑ 4/6
Gifford et al. (1986) (R)	7-54 y	22	T4, T3	T4 wnl 10/22, det. 22/22; T3 wnl 0/22, det. 10/22
Macoviak et al. (1987) (P)	15-36 y	22	TSH, T4, T3	TSH wnl 17/22; T4 wnl 17/22; T3 wnl 6/22
Novitzky, Cooper, and Reichart (1987) (P)	16-40 y	21	fT3	fT3 wnl 1/21, det. 21/21
Robertson, Hramiak, and Gelb (1988) (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. (1988) (P)	u.s.	21	T4, T3	T4 wnl or ↑ 14/21, det. 21/21; T3 wnl 3/21, det. 21/21
Howlett et al. (1989) (P)	8-67 y	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, Hramiak, and Gelb (1989) (P)	adult	36	fT4, fT3, rT3	fT4 wnl or ↑ 30/36; fT3 wnl or ↑ 3/36; rT3 wnl 34/36
Masson et al. (1990) (P)	14-48 y	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. (1990) (P)	19-60 y	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. (1993) (P)	9-85 y	39	TSH	TSH det. 39/39
Karayalin, Umana, and Harrison (1994) (P)	11-60 y	50	TSH, fT4, fT3, rT3	TSH wnl or ↑ 36/50, det. 50/50 (35/50 wnl, 1/50 ↑); 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. (1995) (P)	u.s.	120	TSH, fT4, fT3	TSH wnl 99/120, fT4 wnl 75/120; fT3 wnl 15/120
Goarin et al. (1996) (P)	15-55 y	37	TSH, fT4, fT3	TSH wnl 35/37, fT4 wnl or ↑ 37/37; fT3 wnl 6/37
Szostek et al. (1997) (P)	17-55 y	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. (2009) (P)[b]	39-70 y	12	TSH	TSH wnl 8/12

Reproduced from Nair-Collins et al. (2016), Table 4

Abbreviations: P = prospective study; R = retrospective study; BD = brain death or brainstem death; y = years; u.s. = 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.

[a] "Serum TSH was within normal range … in the majority of the patients, but was slightly elevated in case 5". (p. 241) We've transcribed this statement into our compilation as the lowest number of cases possible such that the majority was within the normal range (i.e., 4/6).

[b] Hormones were measured at autopsy, 4-25 days post-BD. All patients were autopsied within 12 hours of cardiac arrest. Blood was taken from the right cardiac chamber.

Table 4. Hypothalamo-Pituitary-Adrenal Axis

Variables	Findings/comments	References
Corticotropin-releasing hormone (CRH)	CRH det. in 17/24 (71%)	Kinoshita et al. 1992; Arita et al. 1993
Adrenocorticotropic hormone (ACTH)	ACTH: wnl 31/65 (48%); det. 83/114 (73%)	Koller et al. 1990; Kinoshita et al. 1992; Arita et al. 1993; Fitzgerald et al. 1996; Ishikawa et al. 2009
Cortisol	Highly variable.	Hall et al. 1980; Howlett et al. 1989; Powner et al. 1990; Gramm et al. 1992; Arita et al. 1993; Amado et al. 1995; Mariot et al. 1995; Leng et al. 1999; Lopau et al. 2000; Dimopoulou et al. 2003

Modified from Nair-Collins et al. (2016), Table 2

Abbreviations: wnl = within normal limits; det. = detectable.