Editorial

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Beyond the surface: unveiling the complexity of brain death and misdiagnoses in clinical practice

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Dear Editor,

The concept and application of brain death, also known as neurological criteria for determining death, are often portrayed as widely established and universally accepted. However, ongoing debates persist in academic and legal circles, suggesting a lack of consensus on the matter. Brain death, also known as death by neurological criteria, is defined by law in the United States and most other nations as the irreversible cessation of all brain processes[1,2]. However, in the United Kingdom and Canada, neurological death is defined as the permanent loss of integrative activities inside the brainstem, including awareness and respiration, rather than the whole brain[3]. Accurate diagnosis plays a crucial role in this context. Determining death is a distinct assessment among all medical evaluations, and it is essential to ensure that established medical protocols confirm the occurrence of death with minimal false positives. While efforts should also be made to minimize false negatives, priority should be given to avoiding false positives.

Using a patient who does not meet the legal criteria for death as a heart-beating organ donor could be seen as a violation of homicide laws. Therefore, apart from the question of whether brain death is a valid definition of human death, the issue of false positive misdiagnoses in determining brain death remains significant and urgent[4].

In this concise editorial, we amalgamate insights from many studies on brain death and death by neurologic criteria (DNC). These reviews collectively emphasize global standardization efforts, reveal protocol inconsistencies in Latin American/Caribbean nations, and navigate ethical and legal challenges. It is noteworthy that our approach involved a meticulous search for relevant articles on PubMed, Scopus, and Google Scholar, ensuring the validity and reliability of the insights contributing significantly to the ongoing discourse on standardization and ethical considerations in this pivotal medical domain.

Decoding the pathophysiology of death

When an insult or injury produces an abrupt rise in intracranial pressure (ICP), blood flow to the cranial vault is hampered. This can result in serious neurological impairment due to decreased brain perfusion, referred to as cerebral perfusion pressure (CPP). The ensuing ischaemia damage is exacerbated by cytotoxic oedema, acidosis, and dysregulated immunological responses, which elevate ICP and reduce CPP cyclically. Brain herniation may also develop, strain the brainstem, and limit blood flow even further. These processes normally advance from the front to the back of the brain, with cortical neurons being more vulnerable to even brief bouts of ischaemia due to greater metabolic needs than more ischaemia-tolerant neurons in the brainstem. The hypothalamus and pituitary gland may become ischaemic, leading to impaired neuroendocrine function. The process reaches its conclusion at the cervicomedullary junction, where the upper cervical spinal cord also sustains an injury[5,6].

Brief hypothalamus-pituitary functions and anatomy

The hypothalamus comprises magnocellular neurons located in the supraoptic and paraventricular nuclei. These neurons release vasopressin and oxytocin into the posterior pituitary, which then enters systemic circulation. The hypothalamus also controls the anterior pituitary by transmitting factors through the hypophyseal portal system. Various hypothalamic nuclei release these factors into the system, which carries them to the anterior pituitary. The anterior pituitary releases hormones into the secondary capillary plexus within the pituitary fossa. The dura covers the inferior aspect of the hypothalamus, including the diaphragma sella, which covers the entrance to the pituitary fossa. The pituitary stalk passes through a small hole in the diaphragma sella, and the dura surrounds both glands of the pituitary[7,8].

Hypothalamic-pituitary functions in brain death

Loss of hypothalamic-posterior pituitary function leads to central diabetes insipidus, characterized by excessive production of dilute urine with hypernatremia and hyperosmolality[9]. However, complications can arise in diagnosing this condition, like other clinical tests for brain death. Factors such as severe acute kidney injury or vasopressin administration can complicate the diagnosis. Studies have reported central diabetes insipidus in a significant percentage of patients diagnosed as brain-dead[5].

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The reason behind the preservation of hypothalamic-pituitary function in brain-dead patients is not fully understood. The hypothalamus maintains its functionality even in the presence of high intracranial pressure (ICP) through a specialized vascular network. The blood supply to the hypothalamus is primarily facilitated by the internal carotid artery, meningeal branches, and the inferior hypophyseal artery. These arteries take a unique path that avoids the dura mater, the tough outermost layer of the brain's protective covering. Instead, they travel outside the dura until they reach the posterior pituitary gland, where they penetrate the dura mater to supply blood to the hypothalamus. This arrangement allows the hypothalamus to receive a continuous blood supply and maintain its vital functions, such as hormone production and regulation, despite elevated intracranial pressure[7]. Although the vascular supply may offer some protection, it does not fully explain the observed phenomenon. Other brain areas with similar vascular supply show preserved function, and the involvement of magnocellular neurons and hypothalamic nuclei further complicates the explanation[10]. While anatomical variants or collateral blood supply may play a role in rare cases, they do not account for the frequent preservation of hypothalamic function after brain death diagnosis. Preserved brain function, irrespective of the vascular supply, is significant and does not invalidate the diagnosis of brain death, as certain brain functions may contradict the absence of all brain functions.

Ischaemic penumbra

The assumption that CPP reaches zero in all brain-dead patients is just an assumption, not a proven fact. The concept of intracranial circulatory arrest as a fail-safe mechanism leading to the loss of all brain functions is based on a continuous decrease in CPP proportional to increased ICP[11]. However, CPP does not abruptly drop to zero but gradually decreases, resulting in periods of low flow that may be insufficient to support neural tissue function but are not below the threshold for brain necrosis/apoptosis[12].

The ischaemic penumbra is an important topic in stroke pathogenesis. It refers to parts of the brain that are ischaemic (don't have enough blood flow) but haven't yet infarcted (died from tissue death). These areas have insufficient blood supply to maintain normal function, but they still contain viable brain tissue that, given enough time, may recover. The ischaemic penumbra, which surrounds acutely infarcted brain tissue, is important in stroke therapy. It is feasible to rescue live tissue and restore clinical functions by restoring blood flow above the penumbra threshold using therapies such as fibrinolytic or clot-retrievers. The principle also applies to fragile "watershed" locations between main routes. Understanding the ischaemic penumbra aids in the development of stroke therapy options that aim to protect and perhaps restore brain tissue[13].

Well-documented cases exist where brain function persisted or returned despite no detected blood flow, including hypothalamic-pituitary functions and other neurological functions[14]. Relying solely on neuroimaging as a gold standard for demonstrating zero blood flow requires validation, as current clinical tests are consistent with preserved brain function. Several reviews have reported the presence of brain perfusion in a significant percentage of patients diagnosed as brain-dead[15]. Therefore, the assumption of complete intracranial circulatory arrest in brain-dead patients lacks substantiation from existing evidence.

Jahi McMath gained attention for surviving nearly 5 years after being declared brain-dead[16]. Another case involved a boy with meningitis who lived for an additional 20 years on ventilation at home[17]. Pregnant women diagnosed as brain-dead have successfully delivered healthy babies in several reported cases. A recent instance involved a pregnant woman supported for over 30 weeks, delivering a baby via spontaneous vaginal delivery, following which the mother's organs were donated according to her wishes[18]. The baby was discharged from the hospital and is progressing well.

Analyzing the findings: a discussion of key observations

The clinical diagnosis of "brainstem death" uses the same tests as "whole-brain death" to determine the irreversible cessation of brain functions. However, cases of "brainstem death" have shown evidence of hypothalamic-pituitary function, suggesting the presence of brain blood flow below the detection threshold but above the viability threshold. This suggests the possibility of viable brainstem tissue, contradicting the assumption that brainstem function has irreversibly ceased. Some documented cases have demonstrated signs of brainstem function in patients initially diagnosed as brain dead, including "brainstem death." Primary brainstem injury can cause brain death while preserving the viability and function of certain brainstem areas. Brainstem neurons are known to be resistant to hypoxia-ischaemia, further supporting the idea of preserved brainstem function in some cases of brain death[19].

It is scientifically established that the hypothalamus is part of the brain, and there is no reasonable debate about this fact. Even if one were to entertain the false notion that the hypothalamus is not considered part of the brain, it is important to note that the circumventricular areas, which are undeniably part of the brain, play a crucial role in normal osmoregulation. Normal osmoregulation relies on input from these circumventricular areas, regardless of the debate surrounding the inclusion of the hypothalamus[20]. Therefore, the claim that the hypothalamus is not part of the brain does not support the argument that osmoregulation can persist in the absence of all brain functions, as required for brain death diagnosis.

The assertion that neuroendocrine function can be preserved in brain death is logically contradictory. A neuroendocrine function is a form of brain function, and the presence of any brain function contradicts the claim of irreversible loss of all brain functions. Therefore, it is clear that the statement "some X is present" cannot coexist with the statement "no X is present." There is no room for debate on this matter.

Conclusions

In conclusion, brain death, often perceived as a straightforward and well-established concept, proves to be complex upon closer examination. One of the primary concerns is the diagnostic's dependability and credibility. Numerous individuals who have been incorrectly labelled as brain-dead or brainstem-dead show continuous brain function, most notably in the setting of hypothalamic osmoregulation and the lack of central diabetes insipidus. This commonly seen brain function, suggesting the vitality and perfusion of neural tissue, might just be a fortuitous finding,

given the clinical absence of diabetes insipidus. The extent of viable brain tissue left in individual individuals is uncertain. These findings cast doubt not just on the generally used "whole-brain standard," but also on the "brainstem standard." The occurrence of false positive brain death misdiagnoses is a serious concern in clinical practice.

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A.F. did the conceptualization. R.S., U.A.A.M. and T.K.F.A. conducted the literature and drafting of the manuscript. M.A.S. and A.F. performed the editing and supervision. All authors have read and agreed to the final version of the manuscript.

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