BRAIN DEATH DIAGNOSIS IN PRIMARY POSTERIOR FOSSA LESSIONS

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ABSTRACT

Brain death (BD) concept has been increasingly widely accepted beginning since the late 1950s, but several controversies have appeared when intracranial pathology is localized to the posterior fossa. In the presence of a primary supratentorial brain lesion, a severe forebrain lesion is combined with either the subsequent gradual loss of brainstem function, due to rostrocaudal transtentorial brain herniation. In secondary brain lesions (i.e., cerebral hypoxia), the brainstem is also affected like the forebrain. However, a minority of patients with a primary infratentorial brain lesion (i.e., basilar artery thrombosis or brainstem or cerebellar bleeds) may retain cerebral blood flow and EEG activity. In this article I discuss that if a brainstem lesion does not provoke a massive increase of intracranial pressure there may be no complete cerebral circulatory arrest, explaining the preservation of EEG activity, evoked potentials, and autonomic function. I also discuss the case of Jahi McMath who was declared brain-dead, but ancillary tests, performed 9 months after initial brain insult, showed conservation of intracranial structures, EEG activity, and autonomic reactivity to “Mother Talks” stimulus, rejecting the diagnosis of BD. Jahi McMath’s MRI study demonstrated a huge lesion in the pons. Some authors have argued that in patients with primary brainstem lesions it might be possible to find a in some cases partial recover of consciousness, even fulfilling clinical BD criteria. This was the case in Jahi McMath. Further research and discussion are necessary about the use of ancillary tests in BD diagnosis in primary posterior fossa lesions.

Brain death (BD) has been increasingly worldwide accepted beginning since the late 1950s.[1-9] BD outlines medical and legal standards, and its determination is based on guidelines for children,[10] and adults,[11] that define a well-ordered set of clinical criteria assessed at the bedside, and the use or not of ancillary tests. However, quarrelsome brain-dead cases have lately raised up new debates, disputing current BD criteria by enquiring accepted medical standards.[12-17].

Three main brain-oriented formulations of death have been discussed: whole brain, brainstem death and higher brain standards.[1, 18-23] Higher brain theorists have defined human death as the "the loss of consciousness", (definition) related to the irreversible destruction of the neocortex (criterion), or “higher brain”.[24-31] I discussed that consciousness does not bear a simple one-to-one relationship with higher or lower brain structures, and therefore, the higher brain formulation is wrong, because the definition (consciousness) does not correspond directly to the criterion (neocortex).[4, 18, 24, 32]

James Bernat claimed that “the formulation of whole-brain death provides the most congruent map for our correct understanding of the concept of death”.[33] This author argued that “the irreversible cessation of the clinical functions of the brain represents death because the brain is responsible for the functioning of the organism as a whole”.[34] Hence, this author recently proposed to move from “whole brain criterion” to “brain as a whole criterion”, to fulfil the “definition of death as the cessation of the organism as a whole”.[1, 2, 20, 35]

Bernat and his colleagues’ view about the defense of the whole-brain formulation of death was cited by the United States President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral

Research as the conceptual basis of BD.[1, 22, 36] President's Commission recommended the adoption by all US states of the Uniform Determination of Death Act (UDDA).[37, 38]

According to McGee and Gardiner, [39] the legal position in the UK and several Commonwealth countries, is relatively well settled, because the historic Royal Colleges' Code of Practice provides the accepted medical standard for declaring death in the UK,[40] mainly based on the Christopher Pallis' brainstem death view. This author considered that there were practical reasons to promote this view, "a dead (i.e., irreversibly non-functioning) brainstem can be diagnosed at bedside, without resort of complicated investigations, and it predicts inevitable asystole within a short while**".** Pallis emphasized that the "capacity for consciousness" and "respiration" are the two hallmarks of life of the human being, and that brainstem death predicts an inescapable asystole. This author dismissed the use of EEG or cerebral blood flow studies as confirmatory tests in BD diagnosis. .[41-45] The physio-pathological review of consciousness generation and respiration has provided a framework for not accepting Pallis' definition of death.[19, 24, 46] Moreover, the latency between BD diagnosis and asystole can be extended by increasing life support,[47-49], and may in rare cases (i.e., pregnancy) extend to several! weeks or months, or extraordinarily even years.[48, 50, 51]

The conceptual and practical difference in BD determination between the USA and UK has been known as the "transatlantic divide".[52, 53] Wijdicks, senior author of the American Academy of Neurology (AAN) Guidelines on BD, has emphasized that "the irreversible absence of functions of the brainstem is the necessary and sufficient component of brain death, and this can be assessed

and diagnosed clinically at the bedside".[54]This is fully in concordance with the brainstem and not with the whole brain view of BD.[6, 13, 18, 55] As I have already argued, the President's Commission endorsed the adoption of the whole brain standard by all US states.

Brainstem lesions

A critical component of this controversy in BD determination is when intracranial pathology is localized to the posterior fossa. In the presence of a primary supratentorial brain lesion, a severe forebrain lesion is combined with either the subsequent gradual loss of brainstem function due to rostrocaudal transtentorial brain herniation. In the case of a secondary brain lesion (i.e., cerebral hypoxia), the brainstem is also affected like the forebrain. However, a minority of patients, who have a primary infratentorial brain lesion (for example, in basilar artery thrombosis or large brainstem or cerebellar bleeds) may retain cerebral blood flow (CBF) and EEG activity.[52, 56-66]

Grigg and colleagues performed a single center study of 56 patients declared brain-dead by clinical criteria and reported that 20% had persistent EEG activity, suggesting that EEG is not necessary to confirm BD. However, more than a third of the patients did not undergo apnea testing, and PCO_2 thresholds for declaring BD were not described in the remaining cases. Moreover, pathologic studies performed in only two cases demonstrated ischemic necrosis of the brainstem with relative preservation of the cerebral cortex. The pathologic examination of the remaining cases was not described.[67] }

Ferbert reported a case with a hematoma over the cerebellum and the pons, who showed preserved EEG and visual evoked potentials (VEP), whereas all

brainstem clinical signs of BD were present, concluding that in infratentorial lesions, EEG should be mandatory to confirm BD.[61] Esteban et al. also reported 5 patients, fulfilling clinical BD criteria, showing long lasting EEG activity. Three of these cases presented primary posterior fossa lesions.[68]

Varela et al. recently analyzed three cases out of 161 that met inclusion criteria (1.9% of all brain deaths during this period), further adding another patient from a different hospital.[57] All four patients suffered from catastrophic posterior fossa injuries, and therefore fulfilled the UK-BD clinical criteria, including the apnea test. Those 4 patients showed preservation of supratentorial CBF, which disappeared after a period of between 2 and6 days, then allowing a diagnosis of BD, according to the whole brain criteria adopted in USA. These authors concluded that patients with primary posterior fossa catastrophic lesions who clinically seemed to be brain-dead according to USA-BD criteria would typically evolve from retaining, to losing, supratentorial blood flow. Therefore, the authors asserted that if CBF assessment is used as an ancillary test, providing an additional criterion for the declaration of BD, those patients are not different from those who become BD due to supratentorial lesions. Nonetheless, the challenge of the aforementioned cases focuses on determining when the patients were brain-dead according to the US or UK BD criteria

Wijdicks commented that in one study of patients fulfilling clinical BD criteria, 20% of 56 patients had residual EEG activity that lasted up to 168 hours. This author also noted the sensitivity as well as the specificity of EEG in BD diagnosis is 90%.[54] Nonetheless, this author emphasized there were no reports of patients who fulfilled clinical brainstem death criteria and survived, [53] but this statement is related to prognosis and not to diagnosis.[52, 55, 69]

Varela et al. concluded that patients with primary posterior fossa catastrophic lesions who clinically seemed to be brain-dead according to USA-BD criteria, would typically evolve from retaining to losing supratentorial CBF. Therefore, the authors affirmed that if CBF assessment is used as an ancillary test, those patients are not different from those who become BD due to supratentorial lesions. They also commented the theoretical possibility of lesions sparing the mesopontine tegmental reticular formation, due to isolated brainstem injury, which could lead to a total apneic locked-in syndrome, imitating brainstem death.[57, 58, 70] Walter et al. affirmed that this condition does not rule out the possibility that a patient with a primary infratentorial might still be conscious to some degree for some time.[59]

Varela et al. also emphasized that there are no reports of brain-dead patients, correctly diagnosed under either the whole brain or brainstem views, who have shown recovery of consciousness or breathing recommence. Then, they erroneously stated that persistent supratentorial CBF or EEG activity does not indicate remaining brain function.[57] This was not the case in Jahi McMath.[13, 55, 69].

Moreover, experimental studies in animals have found that near-normal EEG involving predominant alpha, beta, or theta activity is not likely to occur, if there has been substantive mesopontine tegmental reticular formation neuronal damage. Therefore, these authors remarked that ancillary tests are mandatory for diagnosing BD, to find either, electro-cortical inactivity or, preferably, cerebral circulatory arrest. Consequently, in such patients the presence of an irreversible coma has to be disbelieved, and the possibility that some degree of

consciousness remains cannot be excluded as long as there is EEG activity.[59, 71, 72]

These reports of cases with infratentorial brain lesions showing a near normal EEG, preserved supratentorial CBF, and cortical visual evoked potentials lead to stricter BD codes in European countries. These harsher BD codes consist of the mandatory demonstration of electrocortical silence (ECI) and/or cerebral circulatory arrest (on cerebral angiography, perfusion scintigraphy, or Doppler sonography) in patients with primary infratentorial lesions.[73, 74] [75-80]

Jahi McMath: A case with an enormous lesion in the posterior fossa.

Jahi McMath underwent pharyngeal surgery for obstructive sleep apnea, but she suffered a massive hemorrhage inside her respiratory ways, leading to a cardiorespiratory arrest. Although CPR allowed return of spontaneous circulation, a significant hypoxic encephalopathy resulted from the event. She was declared brain-dead. After a legal litigation, the family and the hospital reached an unusual agreement for her body to be released to her mother, with continuation of the ventilator and intravenous fluids, and Jahi McMath was moved to the New Jersey State, where relatives can decide to accept a cardio-respiratory or a neurological standard of death.[14, 16, 17, 81]

In September 2014, I was invited to travel to New Jersey, as an expert advisor, giving me the opportunity of evaluating ancillary tests prescribed by a US licensed neurologist. The results of these studies have been recently published in the Journal of Functional Neurology, Ergonomics, and Rehabilitation (FNRE).

Summarizing my findings in Jahi McMath, after 9 months of her intial diagnosis [13, 55, 69]

- Clinical examination. The patient was supine on a bed, with her eyes closed, and demonstrated no signs of awareness of self and/or environment. Neurological examination demonstrated a complete loss of brainstem reflexes (corneal, oculo-cephalic, oculo-vestibular, gag and cough). The patient was unable to trigger a ventilator and the patient's relatives did not give permission to perform an additional apnea test, beyond the original performed nine months prior. The Coma Recovery Scale -Revised - CRS-R total score was: 3 (reproducible movement to command).
- Her MRI showed preservation of intracranial structures, in spite of the presence of enormous abnormalities, documented 9 months after a cardiac arrest: preservation of cortical and brainstem gross anatomy, with non-expected relative slight atrophy, and a huge lesion in the brainstem: posterior regions of the pons, lateralized to the left side.
- EEG bioelectrical activity was found in this case over 2 μV of amplitude Moreover, the power spectral analysis showed generalized predominant activity within the delta–theta range.
- All heart rate variability (HRV) bands were preserved in this patient. Autonomic reactivity, assessed by HRV, to "Mother Talks" stimulation demonstrated preservation of function at different levels of the autonomic system.

This striking finding of the preservation of intracranial structures both in the brainstem and cerebral hemispheres was observed nine months after initial cardiac arrest. It has been extensively described that brain-dead patients have a complete absence of CBF.[18, 82-85]. The fact that the patient had preserved intracranial structures indicated that her cerebral perfusion was not totally absent.[55]

Bernat recently emphasized that “the most confident way to demonstrate that the global loss of clinical brain functions is irreversible is to show the complete absence of intracranial blood flow.”[86] Neurons are irreversibly damaged after a few minutes of complete cessation of CBF, and are globally destroyed when blood flow completely ceases in about 20-30 minutes, with normal body temperature. Hence, if CBF has stopped for more than 30 minutes, this proves brain damage irreversibility in BD. The rationale is that absence of the cerebral circulation for this period of time causes a total brain infarct.[35, 66, 87-90] Dalle Ave and Bernat recently propose that “to uphold the standard of clinical certainty, we advocate proving the whole-brain criterion of death by showing the absence of intracranial blood flow”.[88]

Therefore, the first argument against that the diagnosis of BD in Jahi McMath, 9 months after the initial diagnosis, was the preservation of intracranial structures.[13, 55] The preservation of EEG activity, is in concordance with other cases I have preciously discussed of main lesions in the posterior fossa. This also might explain why some functions of the central autonomic nervous system were preserved. [55]

As previously noted, the MRI of Jahi McMath demonstrated a huge lesion in the pons. Hence, a number of reasons might explain the intermittent conscious

responses in this patient. These include the relative intactness of the upper brainstem, paramedian thalamus and cortex, as well as the partial sparing of the mesopontine tegmental reticular formation. She probably might also had preserved its connections to the temporo-parieto-occipital associative cortices, and/or its ventral pathway to the cortico-cortical projection systems, and parts of the associative cerebral cortices. These findings might explain the intermittent conscious responses in this patient. [13, 55, 63]

Therefore, Jahi McMath was not brain-dead, or in an unresponsive wakefulness state (UWS), previously termed persistent vegetative state (PVS), or in a minimally conscious state (MCS), or in a locked-in syndrome (LIS). I concluded that Jahi represented a new state of disorder of consciousness, non-previously described, that I have termed: “responsive unawake syndrome” (RUS).[63]

Final remarks

It is evident that the presence of primary posterior fossa lesions enforces the needs of “aligning the criterion and tests for brain death”. If a brainstem lesion does not provoke a massive increase of intracranial pressure there may be no complete cerebral circulatory arrest, explaining preservation of EEG activity, evoked potentials, and autonomic function in those cases. .[52, 56-66]

Some authors have argued then that patients with primary brainstem lesions it might be possible to find a in some cases partial recover of consciousness, even fulfilling clinical BD criteria.[59] This was the case in Jahi McMath. [13, 63]

Further research and discussion are necessary about the use of ancillary tests in BD diagnosis in primary posterior fossa lesions.

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