Title: **Brain Death Diagnosis in Primary Posterior Fossa Lesions**

Running Title: **BD in Brainstem Lesions**

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Abstract

Background: New controversies have raised on brain death (BD) diagnosis when lesions are localized in the posterior fossa.

Objective: To discuss the particularities of diagnosis BD in patients with posterior fossa lesions.

Material and Methods. The author made a systematic review of literature on this topic.

Results and Conclusions: A supratentorial brain lesion usually produces a rostrocaudal transtentorial brain herniation, resulting in forebrain and brainstem loss of function. In secondary brain lesions [i.e., cerebral hypoxia], the brainstem is also affected like the forebrain. Nevertheless, some cases complaining posterior fossa lesions [i.e., basilar artery thrombotic infarcts, or hemorrhages of the brainstem and/or cerebellum] may retain intracranial blood flow and EEG activity. In this article I discuss that if a posterior fossa lesion does not produce an enormous increment of intracranial pressure, a complete intracranial circulatory arrest does not occur, explaining the preservation of EEG activity, evoked potentials, and autonomic function. I also address Jahi McMath, who was declared braindead, 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.

Key Message: In this article I discuss that if a posterior fossa lesion does not produce an enormous increment of intracranial pressure, a complete intracranial circulatory arrest

doesn't occur, explaining EEG preservation, as well as evoked potentials, and autonomic function.

Introduction

Brain death (BD) has been progressively wide-reaching accepted beginning since the late 1950s.[1-20] BD outlines medical and legal standards, and its determination is based on guidelines for children,[21] and adults,[22] that established an orderly set of clinical criteria assessed at the bedside, and the use or not of ancillary tests. However, argumentative braindead cases have recently raised up new disputes, arguing up-to-date BD criteria by questioning accepted medical standards.[13, 23-30]

Three standards of death on neurological grounds have been debated in the last decades: whole brain, brainstem death and higher brain.[3, 31-37] Higher brain defenders defended the concept of as the "the loss of consciousness", (definition) associated to the permanent destruction of the neocortex (criterion), or “higher brain”.[38-41] 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]”.[7, 31, 42, 43]

James Bernat claimed that “the formulation of whole-brain death provides the most congruent map for our correct understanding of the concept of death”.[44] 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”.[45] 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, 3]

The United States President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research quoted Bernat and his colleagues’ research to adopt the whole-brain formulation of death,[1, 3, 36, 46, 47] by all US states in the Uniform Determination of Death Act (UDDA). [48]

McGee and Gardiner,[49] stated that the lawful basis for death declaration in the UK and Commonwealth countries, is fairly well settled, based on the medical standards provided by the Royal Colleges' Code of Practice,[50] 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.

The brainstem standard was adopted by Common Wealth and other countries.[31] For example, India passed a law in 1994 to legalize brain-stem death.[51, 52] India supports the UK concept of brain-stem death, and hence the Transplantation of Human Organs (THO) Act was passed by Indian parliament in 1994, legalizing the brain-stem death standard in 1995.[52] Afterwards, THO rules were written which describe brain-death certification process.[52-54] The majority of the Indian states have passed this act in their assemblages, although a few states have yet include it. [53-54] Furthermore, an important document from the state of Maharashtra has recently completed the way to notify braindead cases.[19, 53, 54]

Brainstem death view defenders have not considered necessary EEG or CBF as confirmatory tests in BD determinations.[55-57] I have argued that the physio-pathological appraisal of consciousness generation and respiration provides the basis for rejecting Pallis' concept of brainstem death.[31, 39, 42] Besides, the latency for occurring an asystole after BD declaration, can be by augmented by continuous life support,[4, 25, 58, 59] and in some rare cases [i.e., pregnancy] be prolonged to weeks or months, or extremely to years.[60-62]

The conceptual and practical difference in BD determination between the USA and UK has been known as the "transatlantic divide".[8, 63] Wijdicks, who was the main author of the American Academy of Neurology (AAN) Guidelines on BD, stated 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”.[64] This is fully in concordance with the brainstem and not with the whole brain view of BD.[6-8, 10, 11, 65] As I have already argued, the President's Commission recommended to adopt the whole brain view by all US states.

Brainstem lesions

The presence of a primary lesion localized to the posterior fossa sets a main controversial debate on BD determination. A primary supratentorial brain lesion usually provokes a rostrocaudal transtentorial brain herniation syndrome, resulting on brain function impairment in both cerebral hemispheres and the brainstem. When a secondary brain lesion [i.e., cerebral hypoxia] is present, the brainstem is also affected like the forebrain. Nevertheless, some patients, who have a primary infratentorial brain lesion [for example, in basilar artery thrombosis or large brainstem or cerebellar bleeds], without a significant increment of intracranial pressure, may retain CBF and EEG activity. [7, 8, 10, 65-71]

Grigg et al. studied 56 patients fulfilling BD clinical criteria, and 20% preserved EEG activity, suggesting that EEG is not required as ancillary test to confirm BD. Nonetheless, apnea test was not performed in one-third or more of the cases, and these authors did not describe which PCO_2 thresholds they took in account for confirming BD in the remaining patients. Pathologic studies were realized in only two cases which demonstrated ischemic

brainstem lesions, relatively sparing the cerebral cortex. The pathologic examination of the rest of the cases was not described.[72]

Ferbert reported preservation of EEG and visual evoked potentials [VEP] in a patient with a hematoma in the cerebellum and the pons, who fulfilled brainstem clinical BD criteria. Hence, this author stated that EEG should be mandatory for BD diagnosis in the presence of posterior fossa lesions.[73] Esteban et al. also reported 5 patients, fulfilling clinical BD criteria, who showed long long-lasting EEG activity. Three of those patients had primary posterior fossa lesions.[74]

From a series of 161 braindead cases, Varela et al. studied three cases (represented 1.9%), and added another patient from a different hospital.[68] These four patients presented posterior fossa injuries, and therefore fulfilled the UK-BD clinical criteria, including the apnea test. All four patients suffered from catastrophic posterior fossa injuries, and therefore fulfilled UK-BD criteria, including the apnea test. These 4 patients showed preservation of supratentorial CBF, which vanished after a period of between 2 and 6 days, then permitting BD diagnosis, according to the US accepted standard of whole brain criteria. These authors concluded that in patients complaining primary posterior fossa catastrophic lesions, fulfilling USA-BD clinical criteria, would characteristically progress from conserving, to losing supratentorial CBF. Therefore, the authors stated that if CBF assessment is used as a confirmatory test, those patients are not dissimilar from those braindead patients with supratentorial lesions. Nonetheless, the challenge of the aforementioned cases focuses on determining when the patients were braindead according to the US or UK-BD criteria.

In fact, the main difference in applying “whole brain” or “brainstem” standards BD criteria, is precisely when a primary posterior fossa lesion is present.[65] Dattatray-Dhanwate precisely described the causes and pathophysiology of brain-[stem] death in a

paper entitled "Brainstem death: A comprehensive review in Indian perspective". This author emphasized that "traumatic injury to the head [e.g. road accident], subarachnoid hemorrhage and ischemic stroke are the most common causes of brain-death", among others like intracerebral hemorrhage, hypoxic-ischemic encephalopathy, etc. Hence, Dattatray-Dhanwate comprehensively described the way how increased ICP lessens cerebral perfusion pressure and CBF, and provokes transtentorial herniation and coning at foramen magnum occur. [19] Nonetheless, this author does not describe when primary posterior fossa lesions don't produce a significant increment of ICP and CBF, with subsequent preservation of CBF and EEG.[65]

Wijdicks commented about a study of 56 cases fulfilling clinical BD criteria, that 20% retained EEG activity, lasting up to 168 hours. This author also stated that the EEG sensitivity and specificity in BD determination is about 90%.[75] This author remarked there is not one patient fulfilling brainstem death criteria who has survived,[63] but this statement is related to prognosis and not to diagnosis.[31]

Varela et al. commented that in the case of isolated brainstem lesions, sparing the mesopontine tegmental reticular formation, this condition would theoretically lead to a fully apneic locked-in syndrome, which imitates brainstem death.[67, 69] Walter et al. affirmed that hence, a patient with a primary posterior fossa injury could retain some degree of consciousness, lasting some time.[71]

Varela et al. also stated that there are no reports of braindead patients, properly diagnosed under either the whole brain or brainstem views, who have shown consciousness recovery or breathing recommence. Then, they erroneously stated that persistent supratentorial CBF or EEG activity does not indicate remaining brain function.[68] This was not the case in Jahi McMath.[65, 76]

Moreover, experimental studies in animals with important mesopontine tegmental reticular formation neuronal damage, quasi normal EEG with major alpha, beta, or theta activity is not certain to occur. Therefore, these authors remarked that confirmatory tests should be mandatory for diagnosing BD, to find no EEG activity, or even better no CBF. Therefore, in this condition BD diagnosis has to be doubted, and as long as EEG activity is present, and it cannot be excluded that patients might be at least partially conscious.[71, 77, 78] Arguing about brain-stem death formulation, Bernat point out the possibility of a "profound locked-in syndrome" in which awareness might be retained in the absence of brain-stem activity.[44]

These reports of near normal EEG, preserved supratentorial CBF, and cortical visual evoked potentials in cases with posterior fossa injury, lead to harsher BD codes in Europe. These tougher BD codes require mandatory demonstration of electrocortical silence, one or both absent CBF [assessed by cerebral angiography, perfusion scintigraphy, or Doppler sonography], when a primary posterior fossa lesions is present. [79-86]

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

Jahi McMath suffered a immense hemorrhage inside her respiratory ways, as a surgical complication, leading to a cardiorespiratory arrest. CPR permitted to recover spontaneous circulation, but an extensive hypoxic encephalopathy was caused by the event. She was declared braindead. After a legal litigation, her body was released to her mother, allowing to continue mechanical ventilation and intravenous fluids. Then, Jahi McMath was moved to the New Jersey State, where relatives can decide to accept a cardio-respiratory or a neurological standard of death.[24-26, 30, 65, 87]

In September 2014, I was invited to travel to New Jersey, as an expert advisor, to evaluate ancillary tests prescribed by a US licensed neurologist.

Summarizing my findings in Jahi McMath, after 9 months of her intial diagnosis.[65, 76]

- Clinical examination. The patient was supine on a bed, with her eyes closed, and demonstrated "no signs of awareness of self and/or environment".[27] 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 activity over 2 μV of amplitude was clearly recorded. Moreover, delta–theta range predominant activity was found.
- Heart rate variability (HRV) methodology showed preservation of all bands. "Mother Talks" stimulation demonstrated autonomic reactivity.

Preservation of intracranial structures was demonstrated nine months after initial insult. It has been widely described that braindead patients have a complete absence of CBF.[31, 88-92] As this patient had preserved intracranial structures, it is possible to remark that her CBF was not completely absent. [31]

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."[93] After a few minutes of complete intracranial circulatory arrest, neurons are irreversibly injured, and are widely damaged in about 20-30 minutes, when CBF fully stops, with normal body temperature. Therefore, a total absence of CBF for more than 30 minutes demonstrates irreversible brain damage in BD. The justification is that a full intracranial circulatory arrest during this time causes a total brain infarct.[93-96] Dalle Ave and Bernat proposed 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".[97]

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.[65, 76] The preservation of EEG activity, is in concordance with other cases that I have previously referred of main lesions in the posterior fossa. This also might explain why some functions of the central autonomic nervous system were preserved. [76]

The MRI of Jahi McMath showed a huge lesion in the pons. Hence, a number of reasons might explain the intermittent conscious responses in this patient: relative integrity of the upper part of the 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. .[7, 65, 76]

Therefore, Jahi McMath was not braindead, 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).[7]

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". [7] When a brainstem lesion does not provoke an important increment of intracranial pressure there may be not a full absence of CBF, explaining preservation of EEG activity, evoked potentials, and autonomic function in those cases.[65-67, 69, 73, 98, 99]

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. [71] This was the case in Jahi McMath.[65, 76] Further research and discussion are necessary about the use or not of confirmatory tests in BD diagnosis, in the presence of primary posterior fossa lesions.

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