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Review Article

Brain Death Determination: An Integrative Review of the Literature

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Abstract

Of all the deaths in the United States annually only 1-2% are a result of brain death. A diagnosis of brain death occurs when a physician observes a patient who has permanent cessation of cerebral and brain stem function. In the medical community, cessation of whole brain function is an acceptable medical diagnosis, however brain death determination is a complex process that also must include difficult conversations with families. In 1968, Harvard conducted studies on brain death and then published criteria defining brain death guidelines and the confirmatory tests that would be included in the guidelines. An integrative review of the evidence-based literature was conducted reviewing both brain death confirmation and secondary confirmatory testing literature. By conducting this review, the medical and bedside staff will be better equipped with the latest evidence to perform the clinical exam and confirmatory exam needed to diagnosis brain death, and then communicate this diagnosis to the family.

Keywords: Brain death confirmatory test; Brain death; Brain death exam; Coma depasse; Permanent unconsciousness

Introduction

Per the U.S. Government information on Organ and Tissue Donation and Transplantation [1] of all the deaths in the United States annually only 1-2% are diagnosed as brain deaths. Brain death (BD) is a potential diagnosis that can occur in patients who sustain a catastrophic neurological injury. Some primary neurologic diseases causing BD includes: traumatic or severe head injury, and aneurysmal subarachnoid hemorrhage. Additionally, medical and surgical primary disease diagnosis including hypoxic-ischemic brain insults and fulminant hepatic failure may result in irreversible loss of brain function. BD is diagnosed when a patient has irreversible loss of cerebral and brain stem function. Since, 1968 when Harvard defined the criteria for diagnosing BD healthcare providers have struggled with both the physical and emotional burden this diagnosis plays on the team and the patient's

family. Understanding the research that has gone into creating the guidelines and the ongoing work to confirm the guidelines are accurate can help providers better explain this irreversible loss of function to a family. Irreversible loss of brain function is not sustainable with life and through this integrative review the authors will evaluate the current evidence-based practice literature related to BD confirmation and secondary confirmatory tests. Therefore, providing the care team with a resource to utilize during this very difficult discussion [2].

Methods

An integrative review of the evidence-based literature was conducted reviewing both brain death confirmation literature and secondary confirmatory testing literature. The literature search included review of the CINAHL, PubMed, MedLine, and Cochrane Library databases. The inclusion criteria for review included peer reviewed articles written over the last 15 years including randomized control trials, observational studies, opinion and case

reports. All articles including pediatric patients were excluded (children ages 0 to 18 years of age) from the review. The articles were then graded using the Titler Iowa Model of Literature grading based on an A to D letter scale [3]. Key words used in the search included: brain death, brain death exam, brain death confirmatory test, permanent unconsciousness, coma depasse, organ donation, donation, and a combination of the words previously listed words.

Results

Twenty-four articles were included in the initial search.

After review of the abstracts, eighteen articles were included in the review (Table 1). The gap in the literature demonstrates that there are no well-designed analysis or reviews of the current state of literature related to BD determination or clinical decision making. In addition, there are no meta-analysis or other systematic reviews summarizing the evidence. Of the eleven B rated articles seven of the articles [4-9] were published within the last 10 years. The other five B rated articles [10-14] were published within the last 13 years.

Grade	Grade Criteria	Number of Grades Out of 17 Articles	Percentage of Grades Out of 17 Articles
A	Evidence from well-designed meta-analysis or other systematic reviews.	0	0%
B	Evidence from well-designed controlled trials, both randomized and nonrandomized, with results that consistently support a specific action (e.g., assessment), intervention or treatment.	11	65%
C	Evidence from observational studies (e.g., correlational descriptive studies) or controlled trials with inconsistent results.	3	18%
D	Evidence from expert opinion or multiple case reports.	3	18%

Table 1: Grading results A to D letter scale [3].

Combs, et al. [10] studied Computerized Tomography (CT) angiography as a potentially better radiologic choice for confirmation of BD. Combs, et al. [10] conducted a prospective study reviewing Computerized Tomography Angiography (CTA) as a secondary diagnostic tool for BD confirmation. The researchers compared CTA to cerebral angiography. The sensitivity confirming BD with CTA was 69.7% for 30/43 patients with 13 of the patients showing cerebral opacification and cerebral angiography to confirm BD. This study added additional support to add CTA as a potential choice as a radiological exam to confirm BD.

Quesnel, et al. [13] did a prospective operational study over a twelve-month period aimed to determine the accuracy of using CTA instead of Electroencephalogram (EEG) as the confirmatory test done once clinical BD has been determined. The results of the study determined that the sensitivity of an EEG test was 100% (all cases were confirmed) were as CTA had sensitivity of 52.4% (11 of the 21 patients showed no cerebral perfusion). The study concluded that CTA could not be recommended as a means of BD confirmation. Therefore, the healthcare team should continue to utilize EEGs as their confirmatory test after a clinical diagnosis of BD has occurred [13].

Escudero, et al. [5] aimed their study to assess the use of CTA and Computerized Tomography Perfusion (CTP) in determining

cerebral circulatory arrest as occurs in BD as a confirmatory test that could be used after a clinical exam has been completed and BD is diagnosed. In 24 of the 27 patients enrolled in the study the CTP did not detect cerebral blood flow, and the CTA images demonstrated an absence of anterior and posterior intracranial circulation (89% sensitivity). With such a high sensitivity and a safety margin of 100% this study demonstrated that obtaining a CTP and CTA can be a technique capable of being a confirmatory test for BD once the clinical exam is completed.

Also, in 2009 Frampas, et al. [6] published a prospective multicenter study to validate the sensitivity of a simplified 4-point CTA versus the normal 7-point CTA that is currently used within France to confirm the diagnosis of BD. The simplified 4-point CTA was used to review the opacification of the cortical segments of the Middle Cerebral Arteries (MCAs) and Internal Cerebral Veins (ICVs). The 4-point CTA started at C1-C2 level to determine opacification of the cortical segments. Results of the study demonstrated that the sensitivity of a 4-point CTA was 85.6% versus the normal 7-point CTA which showed segments further up in the brain demonstrated an opacification sensitivity of 62.8%. The absence of flow in the ICV in the 4-point CTA seems to be the most sensitive at 98.1% and appears to be the earliest confirmatory sign of BD. Finally, the specificity of the 4-point CTA is 100%

making it a highly sensitive test to confirm BD in patients needing a confirmatory test post clinical exam [6].

Berenguer, et al. [4] came along several years later and conducted a prospective nonrandomized trial comparing whether CTA radiologic exam is an equivalent confirmatory test for BD as a Nuclear Medicine Perfusion Test (NMPT) test. The study found a strong positive correlation ($r = 0.66$) between the use of CTA providing similar results when used to determine BD as when a NMPT is done to confirm BD. This study found that CTA maybe the new norm as a confirmatory test because it is quicker (30 minutes) then NMPT (one hour) which can help to bring more timely closure to families waiting for news of their loved one.

A retrospective study was also published in 2010 by Savard, et al. [7] out of Canada hypothesizing that some patients might demonstrate evidence of intracranial arterial opacification, but none would show intracranial capillary or venous drainage. Savard, et al. [7] reviewed all Selective Four Vessels Angiography (S4VA) ancillary tests performed to determine BD. Thirty-two patients in total were included in the review and of the thirty-two patients nine of the patients S4VA ancillary study showed some proximal opacification of intracranial arteries, as opposed to the thirty-two patients whose scans showed absence of cerebral capillary or deep venous drainage opacification, therefore this portion of the study's results are comparable with intracranial circulatory arrest and therefore can be used as a confirmatory test for BD. A limited number of prospective randomized and nonrandomized studies have been conducted and published related to the actual clinical exam conducted by the healthcare team to determine BD. Within the B rated articles reviewed several studies discussed different aspects of the clinical exam including both pre and during the execution of the exam.

BD exams are done more often by neurointensivist and neurosurgeons over a twelve-year period and found to follow the AAN guidelines for exam and apnea test more accurately as demonstrated in a retrospective analysis conducted by Wijdicks, et al. [9]. The first part of the study looked at the procedure used during the apnea portion of the clinical exam. The apnea test includes insertion of an endotracheal suction catheter providing 6 to 10 liters of oxygen during the 5 to 10-minute period the patient spends off the ventilator. The study found that using this technic that one in ten patients in the study were unable to complete the apnea test and needed a confirmatory test to determine BD. The study also showed by a neurointensivist or neurosurgeon performing the BD exam it was done within twenty-four hours of ictus in 30% of the patients and 62% were done within three days of ictus. The final finding from this study that can help the healthcare team when providing ICU care is that acute polyuria signaled the moment of BD in 61% of the patients and therefore, needed to be treated with vasopressin.

Many organizations struggle with single verse double BD exams. Varela, et al. [8] looked at the equivalence of a dual brain death exam to a single exam. A retrospective chart review was done after the hospital policy changed from needing a dual exam meaning a total of two clinical exams done several hours apart to a single exam. The review found no difference in lab work on the patients, no difference in consent rate, or organ recovery/transplantation. One difference found was that 35% of the patients fell in the dual exam category were on a higher dose of vasopressors upon start of the second exam. One suggestion that organizations may want to pull from this study and consider for their organization was the researchers did find a higher consent rate for donation when the exam was performed by an intensivist who could explain things to the family while the process was going on [8].

Freitas and Andre [11] conducted a study looking further at the clinical exam and the characteristics of reflexes when a patient is clinically determined BD. The purpose of their study was to characterize the plantar reflex in BD patients by eliciting the planter reflex through applying tactile stimulation to the lateral plantar surface and transverse arch. The findings of the study determined that 55% of the patients retained their plantar reflex, but none of the patients demonstrated a Babinski sign. So if the Babinski sign exists in what is perceived to be a BD patient this should signal a red flag to the clinical team to get a confirmatory test if the clinical exam diagnosed the patient BD or the team may want to wait to conduct the exam once the patient has lost their Babinski reflex [11].

A year later, Levesque, et al. [12] conducted a study to prospective compare three methods of providing oxygenation during the final step of the clinical exam the apnea test. During the apnea test it is important to provide the patient with continues oxygen through their Endotracheal Tube (ET). This study looked at three options: oxygen catheter, T-piece, and Continuous Positive Airway Pressure (CPAP). No difference was found in the partial pressure of carbon dioxide (PaCO_2) compared to baseline when the 3 apnea techniques were used. The PaCO_2 rose above 60 mm HG at the end of the ten-minute period each time. Once additional finding was that CPAP technique maintained arterial oxygen saturation higher during the ten-minute period [12].

Vivien, et al. [14] aim of their study was to evaluate the accuracy of transcutaneously measured carbon dioxide tension (PtCO_2) monitoring as a real time estimate of PaCO_2 during the apnea test and whether it can be an accurate predictor of when the 60 mmHG is reached enabling a shorter duration for the apnea test. The finding of this study determined that PtCO_2 monitoring during a BD exams apnea test could shorten the duration of the test to determine that the patients CO_2 had risen above the threshold of 60 mmHg. By the use of a PtCO_2 monitor that apnea test length could be shortened and provide more accurate timing of the PaCO_2 drawl

and decrease the occurrence of complications such as hypoxemia or hypotension during the apnea test.

Of the lower graded research studies that fall within the 3 C rated articles [15-17] all fell under the survey/questionnaire/empirical data research related to BD exams, and were all published within the last 11 years. All the articles demonstrate an understanding of the problems facing BD exams and the perceptions surrounding them by healthcare providers. The problem with perception is it becomes reality and often taints the view of the healthcare provider and team. The following studies will help institutions to think about the heightened emotions and often ethical concerns around a diagnosis of BD when the institution is updating the clinical guidelines and policy around performing a BD exam.

Chen, et al. [15] designed an empirical analysis of statistical methods for quantitative EEG analysis. The findings of the study demonstrated that by utilizing bedside EEG analysis the recording provided to the physician can prove to be a valuable cueing tool to the ongoing activities/signals being fired or lack of fire within the brain. The study presented a process to reduce interference in the signal by introducing a smaller number of electrodes to provide an EEG examination procedure for the physician to review at the bedside. Chen, et al. [15] study demonstrated a need for further research to provide a stronger in-depth analysis of signal capture from the EEG machine while in use at the bedside in an ICU.

The next group of articles used a questionnaire format to review responses of physicians understanding of what a BD exam means based on experience and comfort of performing the exam on a patient who meets the criteria for the exam to be performed. Chin, et al. [16] emailed a questionnaire to 111 clinicians asking them questions related to knowledge of BD and organ procurement legislation, technical performance of exam, and their current view of BD. The response rate was 32.4% (36/111 clinicians) and demonstrated a need to have a well written detailed protocol for how to do a BD exam for both inexperienced, as well as, experienced clinicians can follow. Because only 19% of the respondents were confident in their technical ability to perform the exam correctly with the apnea and cold caloric tests being prone to the biggest error and variation in practice between clinicians [16].

Then in 2012, Joff, et al. [17] emailed out a questionnaire asking 500 neurologists 3 sets of questions. A total of 218 surveys were returned to provide a response rate of 44%. Of the 218 returned 192 or 40.3% were included in the data analysis and results. The first set of questions related to whether the neurologist accepted the concept of BD as a stand-alone reason that was equivalent to death, and results demonstrated that only 52 (27%) of the neurologist felt this way. The second set of questions referred to which objective test results/pathology would not be compatible with BD. The majority of the respondent's answered they were unaware of their patients' results at time of BD diagnosis. The

third set of questions asked about wave form and length of time a patient had to be hooked up to an EEG machine before declaring the patient BD. Of the 192-neurologist included in the results of the study 90 (47%) of the neurologist only declared BD when the EEG demonstrated isoelectric activity for twelve hours. The final set of questions focused on how the respondents felt about BD and their comfort level diagnosing BD. Of the 192 neurologist in the survey results 104 (54%) of them responded that BD is a state of permanent unconsciousness and equal to cardiac death [17].

The final set of articles reviewed focused on case review and expert opinion. Three of the articles [2,18-20] were published within the last 10 years, and demonstrate the evolution of BD within the medical community. The first of two case studies were reported by Burns and Login [18], reviewing two critical lessons that clinicians need to learn: 1. the need for a rigorous understanding of the how to diagnosis BD and 2. the distinction between grave prognosis and BD. The case study taught both the role of how other medical conditions can play a key part in the diagnosis of BD even when the three cardinal neurologic conditions exist (coma, absence of brainstem reflexes, apnea). And the role family decision to withdrawal care before all confirmatory tests are complete can be an expectable decision with the appropriate decision makers present and participating in the discussion of prognosis [18]. The second of two case studies were reported by Drakowski [2] in *Seminars in Neurology*. Drakowski [2] case study reviewed three case studies of patients admitted to an ICU that meet the criteria of BD to determine if the physicians performing the exam followed the criteria. Drakowski was looking at post dissemination of the Harvard criteria in 1968 studies were done defining BD guidelines and the confirmatory tests that would be included in the guidelines. This process was again revisited in January 2007 by the American Academy of Neurology which reaffirmed the practice parameters for determining BD via neurologic and physical exam [2].

Machado, et al. [20] wrote an expert opinion article around the concept that BD owes its evolution and development to the advancement of intensive care techniques. But, before that in 1959 two publications came about characterizing death of the nervous system and the term coma depasse was introduced. Finally, the article that changed how physicians approached BD was in 1968 when the Harvard Committee Report was published providing a paradigm for defining BD by neurologic criteria.

Discussion

Many gaps still exist related to BD both the clinical exam and a strong recommendation for confirmatory test when the patient is unable to complete the clinical exam or if there is a question among the care team related to the clinical diagnosis. In the literature, there are a moderate number of research articles discussing BD the results section of this paper outlined the literature search

results that are currently published. One gap is that there are little evidence referencing studies on the actual clinical exam performed when a physician suspects a patient has progressed to BD, except for the actual apnea exam which is the final step in the clinical exam sequence. A second gap quickly identified was the sample size for the studies; they were small with often a recommendation for further research with a larger sample size and use of a multi hospital site design. Review of the literature also revealed that retrospective chart review could prove limiting because there is perceived bias built into the review along with many times missing documentation of necessary lab results, vital sign numbers, and essential clinical exam information

The literature search indicates an ongoing need to study and review current BD policies and protocols specifically related to secondary confirmatory tests once a clinical exam is completed. Research needs to focus on strengthening the clinical expertise of those conducting the exam and building a team approach where all players involved in the exam understand their role and perform it with accuracy every time.

Practice Implications

Critical care bedside nurses and Advanced Practice Nurse practitioners provide care to non-survivable head injury patients in a critical care unit, these patients often progress to BD.

The evidence presented provides the care team with valuable information needed to capitalize on providing a strong evidence-based protocol for pronouncement of BD in a patient who has suffered permanent cessation of cerebral and brain stem function.

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