A Reason For Care in the Clinical Evaluation of Function on The Spectrum of Consciousness

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Abstract

We compare and discuss three cases including: a clearly brain-dead patient, a vegetative state/unresponsive wakefulness syndrome (VS/UWS) patient and a patient diagnosed as brain-dead (BD) demonstrating some but not all clinical features of a BD state. Two of the patients demonstrated clear presentation allowing for an effective determination of state of death or consciousness. One patient, in comparison to the other two, presented with a complete absence of brainstem reflexes, absence of spontaneous driving to breath, and required permanent mechanical ventilation. Nonetheless, preservation of intracranial structures, remaining brain function in both brainstem and cerebral hemispheres was evidenced in the third case similar to the reported VS/UWS patient. Moreover, autonomic reactivity to mother’s voice stimulation precluded the diagnosis of a BD in the latter case. This third patient was not comatose. The clinical examination demonstrated complete absence of brainstem reflexes, and no spontaneous driving to breath. This patient did not appear to be a VS/UWS, as she had not shown intermittent wakefulness with measurable sleep-wake cycles, and variably preserved cranial nerve reflexes. Therefore, the possibility of a responsive wakefulness state - minimally conscious state (MCS), or MCS emergence state was also excluded. This third patient in contradistinction to the other two demonstrates features similar to BD states, without being brain-dead, comatose, or VS/UWS or MCS states, and therefore rests somewhere on the spectrum of clinical consciousness. The importance of this paper is in that it highlights some of the difficulties in the clinical classification of states of consciousness, when the evaluation is categorized, showing that one of the patients presented rests somewhere else on the spectrum of clinical consciousness.

Keywords: Brain death (BD); persistent vegetative state, unresponsive wakefulness syndrome (PVS/UWS), minimally conscious state (MCS), EEG, magnetic resonance imaging (MRI), autonomic nervous system (ANS), heart rate variability (HRV).

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Introduction

Bernat emphasized, “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.” It is well established that neurons are irreversibly damaged after a few minutes of complete cessation of cerebral blood flow (CBF), and are globally destroyed when CBF completely ceases for about 20 to 30 minutes, leading to an irreversible total loss of brain function, and a total brain infarct.1-4

Reupertinger et al. reported a case of a 4-year-old child who was diagnosed as brain-dead and was then supported for 19 years on a ventilator. Subsequent autopsy revealed a calcified intracranial spherical structure weighing 750 g and consisting of a calcified shell containing gumous material and cystic spaces with no recognizable neural elements grossly or microscopically.5,6 Nothing similar was found in Case 3’s MRI-T1 sequences, showing preservation of intracranial structures, despite significant brain injury.

True EEG bioelectrical activity was found in Case 3 over 2 μV of amplitude, excluding an ECI. Moreover, the power spectra analysis showed predominant activity within the Delta-Theta range. Quantitative EEG analysis helped us to assess the bioelectric organization of the background activity, showing reduced but observable incipient peaks in the Alpha frequency range, and a visible Delta peak in the O1 lead. The presence of several power spectral density inter-hemispheric asymmetries is incongruent with a non-functioning cerebral cortex and a dead brain. The follow-up studies of Case 3 demonstrated evident PSD for all leads, for EEGs recorded more than one and a half years from our initial study, in September 2014. Assessing the bioelectric organization of the background EEG activity is a key point of assuring the presence of cerebral hemispheric functioning.7-9

The American Academy of Neurology (AAN), and the Task Force guidelines affirm that BD is based on a clinical diagnosis.10,11 However, the same guidelines recognize that in some circumstances, specific components of the clinical examination cannot be reliably tested or evaluated and ancillary tests should be used. In a recently published paper exploring the variability of brain death policies in the United States in relation to the AAN Guidelines, EEG was listed in 78.8 % of policies being the most frequent confirmatory test in BD diagnosis in the USA.12 In several countries in continental Europe, Central and South America, and in Asia, the demonstration of an EEG showing ECI is mandatory by law for the certification of BD.13-16

One of the main reasons whether or not to accept the use of EEG and other ancillary tests is related to the accepted neurological definition of death.17 Three main brain-oriented formulations of death have been discussed: whole brain, brainstem death and higher brain standards.17-24 The whole brain criterion refers to the irreversible cessation of all intracranial structure functions, and therefore, most defenders of this view suggest the use of EEG as a powerful diagnostic tool.17,21

Bernat’s and his colleagues’ views about the defence of the whole-brain formulation of death,25-28 was cited by the United States President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research as the conceptual basis of BD.29 The President’s Commission recommended the adoption by all US states of the Uniform Determination of Death Act.30

Wijdicks stated that, “the irreversible absence of functions of the brainstem is the necessary and sufficient component of brain death”31. This point of view is fully related to the brainstem death standard, and not to the whole brain criterion.32 Christopher Pallis articulated the brainstem death view, denying the use EEG as confirmatory test in BD diagnosis.32

Material And Methods
Case Presentations

A patient diagnosed as brain-dead (BD) is reported who actually demonstrated clinical features of a BD state, nonetheless, preservation of intracranial structures, remaining brain function in both brainstem and cerebral hemispheres was evidenced. To discuss this unusual case, we also describe here two other cases: brain-dead, and vegetative state/unresponsive wakefulness syndrome (VS/UWS) patients. Cases 1 and 2, were paired in age and gender with Case 3. We will focus our portrayal of Case 3, and Cases 1 and 2 will be partially described, mainly for comparison with Case 3.

Clinical Findings

Case 1. A 13-year-old suffered a near-drowning incident being submerged for at least 10 minutes in a swimming pool. CPR was initiated at the scene by the lifesaver, and a rescue ambulance arrived within approximately 5 minutes. The patient was intubated and mechanically ventilated. Heartbeat was recovered in approximately 15 minutes after the initial immersion. Upon arrival at the hospital, the patient was admitted to the ICU. The patient was comatose, had a Glasgow Coma Scale score of 3 points, and neurological examination demonstrated a complete loss of brainstem reflexes (corneal, oculo-cerebral, oculo-vestibular, gag and cough). An EEG showed electrocerebral inactivity (ECI). Forty-eight hours later, she was clinically diagnosed as brain-dead (additional confirmed by apnoea testing), and a second EEG showed again an ECI pattern.

Case 2. We studied a 14-year-old after a near drowning incident left the patient in a VS/UWS for one year before the study. Diagnostic criteria for (VS/UWS) included: eye movements with lack of fixation, lack of evidence of awareness of self or environment, lack of interaction with others, and lack of comprehension or expression of language. Stimuli often resulted in massive stretching or
startle reactions, without proper habituation, showing sometimes massive flexing responses. Occasionally grimacing occurred after stimulation. Nonetheless, external stimuli did not evoke purposeful or sustained and reproducible voluntary behavioral responses.

**Case 3.** A 13-year-old, female patient suffered post-surgery cardio-respiratory arrest, and was subsequently declared brain-dead. At her family’s request, she remained under life support. Nine months afterwards she was assessed clinically, by magnetic resonance imaging (MRI), EEG, and heart rate variability (HRV) studies, in addition to clinical examination by an attending licensed neurological practitioner. We herein describe the findings of the patient studied nine months after the trauma.

The patient was supine on a bed, with her eyes closed, demonstrating an apparent absence of awareness of self and 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 apnoea test beyond the original performed nine months prior. Although the data was unavailable to these authors, one of the two original attending neurologists did certify an apnoic state.

**Ancillary Tests**

As the relative of Case 3 did not give permission to perform additional apnoea testing, we proceeded to apply ancillary tests, according to the recommendations of the Task Force on Brain Death in Children. Ancillary tests beyond the original performed nine months prior. Although the data was unavailable to these authors, one of the two original attending neurologists did certify an apnoic state.

**Magnetic Resonance Imaging**

All three patients’ brains were studied by magnetic resonance imaging (MRI). MRI data were collected on a 1.5T GE MR system (Signa HDxt, GE Healthcare, Milwaukee, USA). The MRI examination consisted of a 3D whole-head MPRAGE volume, a turbo fluid-attenuated inversion recovery (FLAIR) in the transverse plane, T2 turbo spin-echo sequences (T2-TSE) in the axial, coronal and sagittal planes. 3D surface reconstructions and image processing were performed off-line by methodology more fully described elsewhere.

**EEG Recording**

EEG was recorded in all three cases using Mitsar amplifiers (Mitsar EEG System, Mitsar-EEG-10/70-201, St. Petersburg), in two experimental conditions: during 30 minutes without any stimulus (“Basal record”), and during 10 minutes, when the patients’ mothers spoke to the patients employing familiar and day-to-day expressions (“Mother Talks”), more fully described elsewhere.

Nineteen monopolar derivations of the International 10/20 System were recorded (FP1, FP2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz) using linked earlobes as a reference. A Low-cut filter was set at 0.5 Hz, high-cut at 70 Hz, and a notch-filter at 60 Hz. The sampling frequency was 500 Hz. The impedance of all derivations was required to be below 5 KΩ. The EEG recording was performed in accordance with the standards of the American Electroencephalographic Society to detect (ECI). ECG artefact removal from the EEG was performed using an algorithm that was developed by a coauthor. This algorithm included the combination of independent principal component analysis and linear regression techniques. No analogic and/or digital filters were applied to the EEG raw data.

The original EEG was converted to a sampling frequency of 200 Hz, and the power spectral density (PSD) was estimated for 65-seconds of continuous bioelectric brain activity from each lead, using the method more fully described elsewhere.

The same methodology for all cases was used for the follow-up EEGs recorded on April 23, 2016, and May 14, 2016 for Case 3.

**Electrocardiogram (ECG) Recording**

For all three cases, ECG was simultaneously recorded with the EEG employing disposable electrodes placed on the chest in positions CM2 and V5, using a sampling frequency of 500 Hz, in two experimental conditions: “Basal record” and “Mother Talks conditions, as described more fully elsewhere.” Filters were set for a band spectrum of 0.5-70 Hz.

**Ecg Processing And Heart Rate Variability Calculation**

Time and frequency domain indices of heart rate variability (HRV) were calculated from 5 minutes of R-R ECG tachograms, free of artefacts, in both experimental conditions using methods described elsewhere.

The R-R sequences were also submitted to an empirical mode decomposition method (CEEMDAN) to obtain the valid intrinsic mode functions (IMFs). Instantaneous values of frequency and spectral amplitude were calculated every 0.25 seconds during 256 seconds, with the Hilbert transform. Those results were graphically depicted for visual analysis for all three cases.

Figure 1A shows a T1 MRI sagittal slice where the lesion is present at the pons, extending to the medulla (Case 3). Figures 1B and 1C demonstrate 3D surface reconstructions of the right hemisphere plotted over sagittal and axial slices where the circumvolutions are more accurately represented. We can observe preservation of the brainstem structures, with the above-described lesion at the level of the pons, extending to the medulla (Case 3).
**Figure 1.** Figure 1 all referring to Case 3 shows (A) a T1 MRI sagittal slice; meanwhile (B) and (C) illustrate 3D surface reconstructions of the right hemisphere plotted over sagittal and axial slices. Circumvolutions or cortical ribbons, belonging to the medial right hemisphere, are clearly present. Significant damage with volume loss is present in the corpus callosum. A lesion is present at the pons, extending to the medulla.

**Figure 2.** Figure 2 relates to Case 3 and shows 65 seconds of EEG contaminated with ECG (Upper panel). In the lower panel, the same EEG record after ECG artefact removal is shown. Records show a disorganized EEG background, with a prevalence of a diffuse Delta-Theta activity. EEG amplitude was clearly over 2 μV of amplitude, excluding a pattern of electro-cerebral inactivity.
Figure 3 demonstrates 65 seconds of EEG recorded from 19 standard channel leads, contaminated with ECG (upper panel) in Case 3. In the Fp2 and Fz leads there is an incipient, but observable, peak in the Alpha band. In the O1 lead, a visible Delta peak is also present. Several power spectral density inter-hemispheric asymmetries are found for homologous EEG leads.

Figure 4 shows the HRV power spectral density spectrum for Case 3. Spectral frequencies within the VLF, LF, MF, and HF bands are clearly present (upper panel). The bottom panel shows the values of power spectral density expressed as normalized (%) values. Normalized values show a predominance of the HF band.

Figure 2 demonstrates 65 seconds of EEG recorded from 19 standard channel leads, contaminated with ECG (upper panel) in Case 3. In the lower panel, the same EEG record for Case 3 is shown after ECG artefact removal. Records demonstrate a disorganised EEG background, with a prevalence of diffuse Delta-Theta activity. Although records were characterised by a low-voltage output, EEG amplitude was clearly over 2 μV, excluding a pattern of electro-cerebral inactivity.

Figure 3 shows the power spectral density obtained for 65 seconds of artefact-free continuous EEG in Case 3. EEG activity is mainly in the Delta-Theta range. In the Fp2 and Fz leads there is an incipient, but observable, peak in the Alpha band. In the O1 lead, a visible Delta peak is also present. Several power spectral density inter-hemispheric asymmetries are found for homologous EEG leads.

In Figure 4, the power spectral density (PSD) for the whole HRV spectrum is observed for Case 3. Discrete spectral frequencies within the VLF, LF, MF, and HF bands are clearly present (upper panel), in spite of low power spectral density. The bottom panel shows the values of power spectral density expressed as normalized (%) values for each spectral band. Normalized values show a predominance of the HF band.

Figure 5 shows the valid IMFs (left panel), the instantaneous spectral amplitudes (middle panel) and the instantaneous frequency (right panel) values of the respective IMFs for Case 3. Tacograms are presented in
the first diagrams of the 3 panels. Non-continuous lines indicate the instantaneous frequencies’ mean values (right panel). A thick blue vertical line indicates the beginning of the “Mother Talks” stimulus, vs. the “Basal Record.” It is possible to observe ostensible dynamics in the different HRV frequencies, indicating a manifest autonomic reactivity to the mother’s voice stimulus.

Figure 6 shows the PSD (6A) obtained for 65 seconds of artefact-free continuous EEG (follow-up study - April 23, 2016), and the corresponding PSD brain maps (6B) for Case 3.

Figure 7 shows the PSD (7A) obtained for 65 seconds of artefact-free continuous EEG (follow-up study - May 14, 2016), and the corresponding PSD brain maps (7B) all for Case 3. Greater PSD values were observed for this second EEG follow-up study.

Figure 8 (A) shows the power spectral density for the whole HRV spectrum for the equivocal Case 3 (upper panel), (B) for the brain dead state in Case 2 (middle panel), and (C) for the Persistent Vegetative State in Case 1 (lower panel). In Case 3 (upper panel), discrete spectral frequencies within the VLF, LF, MF, and HF bands are clearly present, in spite of low power spectral density. In Case 1 (brain-dead), there is only one remaining peak within the HF band, corresponding to the frequency rate of the mechanical, with ventilator. In Figure 8C, Case 2 (VS/UWS) there are clear discrete frequencies in the HRV whole spectrum with high power spectral density.

Figure 9 shows 65 seconds of EEG from Case 3, Case 1, and Case 2. An EEG record from Case 3 shows a disorganized EEG background, with a prevalence of a diffuse Delta-Theta activity, and ECG contamination. EEG amplitude was clearly over 2 μV of amplitude, excluding a pattern of electro-cerebral inactivity. The EEG record from Case 1 shows no EEG activity over 2 μV of amplitude, and ECG contamination, illustrating a typical pattern of electro-cerebral inactivity. EEG record from Case 2 shows a prevalence of Delta-Theta activity, and several sharp waves; compared with Case 3, where EEG amplitude is higher.
Figure 6. Figure 6A shows the power spectral density (PSD) obtained for 65 seconds of free-of-artefacts continuous EEG (follow-up study - April 23, 2016), and the corresponding PSD brain maps (6B). It is possible to demonstrate evident PSD for all leads, with augmented values for the frontal regions, and interhemispheric PSD asymmetries (Case 3).

Figure 7. Figure 7 shows the PSD (7A) obtained for 65 seconds of free-of-artefacts continuous EEG (follow-up study - May 14, 2016), and the corresponding PSD brain maps (7B). Greater PSD values were observed for this second EEG follow-up study (Case 3).

Figure 8. Figure 8 shows the power spectral density (PSD) for the whole HRV spectrum for Case 3 (upper panel), Case 1, (middle panel), and Case 2 (lower panel). In Case 3, discrete spectral frequencies within the VLF, LF, MF, and HF bands are clearly present, in spite of low power spectral density. In the brain-dead case (Case 1), there is only a remaining peak within the HF band, corresponding to the frequency rate of the mechanical ventilator. In the VS/UWS patient (Case 1), there are clear discrete frequencies in the whole spectrum, with higher power spectral density. Different colours represent the VLF, LF, MF, HF, and VHF bands.
Discussion

Three cases offered here are offered for comparison purposes to indicate the need for approaching the definition of death on the basis of position of a patient on a spectrum rather than consciousness evaluation based on the fixed criteria of BD, comatose, VS/UWS, MCS, etc. We here demonstrated clinical features in patients that ranged from clearly brain dead to a VS/UWS to equivocal findings of brain death (Case 3), falling somewhere on the spectrum of consciousness but being not clearly definable. The equivocal BD state (Case 3), included a patient showing an absence of brainstem reflexes, absence of an ability to trigger a ventilator, and requiring permanent mechanical ventilation as did the unequivocally BD patient (Case 1). After nine months of a post-anoxic encephalopathy in Case 3, preservation of intracranial structures was noted as well as remaining brain function in both brainstem and in cerebral hemispheres, as well as demonstrated autonomic reactivity response to Mother’s Voice stimuli when compared to age-matched non-maternal voices.

Case 1 presents a brain-dead patient, showing a complete absence of all HRV bands, with Case 2, being that of a VS/UWS patient, demonstrating preservation of all HRV bands. The patient described in Case 3 shows many features similar to those of a BD state, but falls somewhere else on the clinical spectrum of human consciousness. Case 3 shows clinical features associated with a BD state, but with the preservation of intracranial structures, remaining brain function in both brainstem and in the cerebral hemispheres, as well as an autonomic reactivity response to the "Mother Talks" stimulus, when compared with the voices of other women matched in age with Case 3’s mother. No HRV responses were found, which placed Case 3 on a non-described point on the clinical spectrum of consciousness somewhere between its absence and awake and aware.

In Case 3, preservation of intracranial structures, both in the brainstem and cerebral hemispheres, was observed nine months after intra-operative cardiac arrest resulting in severe brain injury. Neuropathologists have coined the term...
respirator brain to describe the pathological findings in mechanically ventilated brain dead patients. The respirator brain phenomenon results from an arrest of intra-cerebral perfusion, and the time on the ventilator correlates with the extent of brain damage.\textsuperscript{41,42,54,55} Wijdicks recently studied a series of brain-dead patients, and documented that no distinguishing neuropathologic brain death features were found, probably due to the fact that timing to brain fixation has been reduced as a consequence of timely organ transplant protocols.\textsuperscript{43,56}

Case 3 was diagnosed and studied in the USA, and therefore BD diagnosis should be considered under the whole brain criterion.\textsuperscript{25-28}

Another clinical condition where there exists controversy about the use of EEG in BD, is when intracranial pathology is localized in the posterior fossa. Both intracranial blood flow and EEG may persist when a primary-brainstem catastrophe that does not produce markedly raised intracranial pressure is present.\textsuperscript{21,44,57}

Several authors have reported persistent EEG activity in patients declared brain-dead by clinical criteria. The main pathologic findings in these cases demonstrate principal lesions of the brainstem with relative preservation of the cerebral cortex.\textsuperscript{44-46,57-59}

Case 3 showed a large lesion at the pons, extending to the medulla. Therefore, in primary brainstem or cerebellar lesions, under the whole-brain formulation, several BD guidelines have stipulated that ancillary electrical and/or blood flow tests are needed to confirm BD diagnosis.\textsuperscript{57,48,60,61}

In summary, in Case 3 EEG records demonstrated preservation of brain function at the level of the cerebral cortex, denying an ECI, in comparison to an EEG pattern that was illustrated in Case 1 (brain-dead patient). EEG recorded from Case 2 (VS/UWS patient) also confirmed preservation of brain function at the level of the cerebral cortex, as in Case 3.

Using HRV methodology, it was possible to reveal the preservation of all HRV bands in Case 3. The HF component is considered to be a marker of the parasympathetic cholinergic central system, with responses mainly generated in the nucleus ambiguous. The LF band is related to vagal and sympathetic influences. The MF band has been correlated to biofeedback of baroreceptor function and Meyer blood pressure waves. Meanwhile, the VLF range has been associated with the pressor arm of the sympathetic adrenergic system, central thermoregulatory centres, and the renin-angiotensin system.\textsuperscript{50,49-51,53,62-66} BD has been characterized by the loss of all HRV power of heart rate.\textsuperscript{52,60} We recently reported a case of brain death in which the VLF oscillations were the last to vanish, possibly related to residual sympathetic vasomotor activity that progressively disappeared due to the extension of necrosis affecting the nervous centres of the lower part of the medulla and the first 2–3 cervical spine segments.\textsuperscript{53,66} Therefore, the preservation of all HRV bands in Case 3 is a clear demonstration of autonomic activity conservancy in the medulla, within vagal, and other autonomic central nuclei.

Another key finding in Case 3 was the autonomic reactivity of “Mother Talks” stimulation when Case 3’s response to Mother’s Voice was compared to aged-matched voice of others. We recently reported the effect of Zolpidem in VS/UWS patients, demonstrating an autonomic reactivity to this drug.\textsuperscript{7,8,19} Lee et al. demonstrated HRV response in a vegetative state patient with music therapy.\textsuperscript{54,67} Several authors have reported brain activation in response to presentation of the patient’s own name spoken by a familiar voice, using fMRI and event related potentials.\textsuperscript{55-57,68-70} We recently published a report of a VS/UWS case assessed by HRV, who demonstrated autonomic reactivity to mother’s voice.\textsuperscript{39,51} These findings demonstrate remaining function at different levels of the central autonomic system in Case 3, and suggest recognition of the mother’s voice, based on residual linguistic processing. Owen et al. found residual cognitive functions in a VS/UWS patient by fMRI.\textsuperscript{38,71} They concluded that the observations provided compelling evidence for residual linguistic processing in a VS/UWS patients, suggesting some preservation of awareness.

In conclusion, Case 3 displayed several clinical features of a BD state, such as the absence of brainstem reflexes, no spontaneous driving to breath and the requirement for permanent mechanical ventilation. Nonetheless, preservation of intracranial structures, and remaining brain function in both brainstem and cerebral hemispheres was demonstrated, showing clear differences compared with Case 1, the brain-dead case. Moreover, the autonomic reactivity findings on “Mother Talks” stimulation in Case 3, demonstrated remaining function at different levels of the autonomic nervous system, placing the patient at some point on the clinical spectrum of consciousness, as she demonstrated a complete absence of brainstem reflexes as did the patient in Case 1, as well as no ability to trigger a ventilator. The patient in Case 3 did not demonstrate intermittent wakefulness, with definable sleep-wake cycles, and did not show preserved cranial-nerve reflexes as did Case 2, which excluded the possibility of being in a VS/UWS or a MCS.\textsuperscript{53,38-40,45,50-52,59,63,72-75} Comparisons of Case 3 with Cases 1 and 2, demonstrated clear differences with brain death and VS/UWS states.

Wijdicks recently stated in an editorial of a special seminar on BD: “I am particularly baffled when it is suggested that patients with no brainstem function might be locked in with functioning thinking parts of the brain”.\textsuperscript{64,76} The findings described for Case 3 confirm that this state can be observed in some suspected brain-dead patients, with no brainstem reflexes but remaining functioning activity in “thinking parts of the brain”.\textsuperscript{64,76} It is important to remark that the authors of this paper defend the concept of BD as synonym of death of the individual.\textsuperscript{21} Although it has been affirmed “that patients who are clinically dead do not need confirmation”.\textsuperscript{64,76} We would ask if there is actually a diagnosis of any disease in
which a confirmatory test (blood test, imaging, etc.) is not used? BD determination is a challenging diagnosis for a physician and exemplifies why is that care must be taken in the clinical evaluation of function on the spectrum of consciousness.

References


