ISSN No:-2456-2165

Brain Death or Reversible Coma? Minimizing Misconducting

Sérgio Brasil MD, PhD[1], Paulo Tierno MD[2], Nara Franzin de Moraes MD[2] and Ricardo de Carvalho Nogueira MD, PhD[1].
[1]Division of Neurological Surgery. Hospital das Clínicas, School of Medicine, University of São Paulo, Brazil.
[2]Intensive Care Unity, Hospital Municipal de Barueri, São Paulo, Brazil.

Abstract

- ***Objective:***

We present a case of coma with uncertain inception and brain death (BD) diagnosis misconducting. The definite diagnosis was Bickerstaff syndrome (brainstem encephalitis), with good recovery posterior to immunoglobulin therapy. Situations with potential to challenge coma evaluation are presented and the beneficial role of blood flow ancillary testing is discussed.

- ***Methods:***

Hospitalization report and online literature review.

- ***Discussion:***

Not only acceptance and understanding of death are fraught with variation worldwide, but even medical knowledge and training to perform BD assessment, especially when situations are not ordinary.

- ***Conclusion:***

Performing a blood flow examination prior to initiating BD clinical assessment in uncommon cases may be the best practice.

Abbreviation Key:- *BD: Brain Death, CTA: Computed Tomography Angiography, DSA: Digital Subtraction Angiography, TCD: Transcranial Doppler.*

I. INTRODUCTION

A 37 years old woman with no remarkable health history was referred to the emergency room with headache, psychomotor agitation, nausea, vomiting, diplopia and visual turbidity started 04 days ago, without history of fever and no signs of meningeal irritation. Normal CT scan with and without contrast and cerebrospinal fluid evaluation were previously performed the day before at the original institution, where therapy with methylprednisiolone and acyclovir was implemented.

At admission, patient in regular state, dehydrated, with drowsiness and restlessness, reactive pupils, despite left eye and left hemifacial mobility impairment, dysarthria, and progressive 4-limb dystonia without neck rigidity or skin lesions. In this same day, disclosed awareness level deterioration and hypoventilation, requiring tracheal intubation and ICU support. Computed tomography angiography (CTA) evidenced global erasure of the cerebral convexity grooves, without other alterations. 48 hours later, signs of brain death (BD) were seen, maintaining Glasgow Coma Score (GCS) 3 and absence of brainstem reflexes even after switching off sedation with fentanyl and midazolam and observing a 24 hours period.

The BD protocol was then started after 48 hours from admission, 12 hours after first BD signs, with two complete brainstem assessments performed by different physicians. The Brazilian BD protocol requires two neurological tests, plus apnea test once and an ancillary test. In the present case, the apnea test was performed twice, because target pCO_2 was not reached (Brazilian BD cut-off pCO_2 >55 mmHg) in first attempt. Although no respiratory movements were observed in both attempts, the test was conclusive only in the second when pCO_2 reached 82 mmHg post apnea. A transcranial Doppler (TCD) was then performed and the BD protocol consequently suspended, as neither blood flow impairment was observed, nor signs of intracranial hypertension.

Toxicological tests were negative for morphine, diazepan, cocaine, methamphetamine, barbiturates and amphetamine. The hypothesis of autoimmune encephalitis emerged and immunoglobulin pulse therapy (0.4g / kg / day for 5 days) started. A magnetic resonance angiography (MRA) showed only a mild frontal edema. Electroencephalogram (EEG) disclosed diffuse electrical disorganization, but no epileptic status. Initiated Tazocin due to worsening laboratory.

During immunoglobulin therapy, there were absent oculomotor and corneal reflexes, maintaining discreetly isochoric mydriatic pupils, no photoreaction. The day after, status progressed to GCS 7 and, within a period of further 5 days after the end of immunoglobulin, presented with GCS 10, with motor response to verbal stimulus. After a total of 73 days of hospitalization, she was discharged. Glasgow outcome score at 6 months was 5, with mild gait impairment.

II. REVIEW ON BD MIMICS

It is essential for professionals from emergency rooms and intensive care units to be able to recognize and assess correctly comatose patients. Each potential factor involved must be brought to light, in order to avoid mistaken diagnosis. Several neurological or systemic conditions may mimic BD, as locked-in syndrome, rattlesnakes bites and pufferfish envenomation, Guillain-Barré syndrome variants, hypothermia, exogenous intoxication and hypokalemia[1]. Moreover, spinal reflexes may be complex

and lead to misinterpretations on the BD diagnosis[2-4]. Bellow we synthetized the most common situations reported.

A. Guillain-Barré Syndrome

The Guillain-Barré syndrome (GBS), is commonly an ascending acute inflammatory polyneuropathy, despite this entity may present a wide range of varieties. GBS has been reported mimicking BD[5, 6]. The variant Miller-Fisher syndrome per example, in addition to the limbs palsy, these patients develop ophthalmoplegia, and Bickerstaff encephalitis points to disturbance of consciousness and even brain stem reflexes suppression[7]. The occurrence of a complete "locked-in" syndrome harbored in GBS is not an infrequent situation, been reported previously. The key for avoiding misdiagnosing this condition, and consequently a disastrous outcome, is always to proceed with caution when obtaining clinical history of comatose patients[8, 9].

B. Hypothermia

Hypothermia has been described as the condition most capable of BD simulation, in out of hospital cases or even after post-cardiac arrest hypothermic rescue therapy. Moreover, drug metabolism in this situation is slow, and CNS depressors may last active for longer periods[10]. Deep hypothermia is defined as body temperature less than 30°C, but even with 32ºC is possible the pupils response to light to be absent, with abolition of brain stem reflexes in sequence[11]. However, the encephalic impact on extreme hypothermia may be reversible.

Therapeutic hypothermia post-cardiac arrest has become a standard of care for its neuroprotective effect. Diagnosing BD in these patients is more challenging, and an ancillary test disclosing cerebral circulatory arrest should be performed instead of the EEG[12]. The neuroprotective effect of hypothermia is affiliate to reduction of the cerebral metabolic rate, release of excitatory transmitters, ions influx, lactic acidosis and vascular permeability, mechanisms particularly important in the ischemic penumbra.

The AAN guidelines indicate to exclude assessing patients with hypothermia; the neurological assessment should be performed exclusively after normalization of core temperature[13, 14].

C. Drug Intoxication

Narcotics, benzodiazepines, tricyclic antidepressants, bretylium[15], anticholinergics, and barbiturates have been associated with brain death mimics. Despite absence of brain stem reflexes is possible, but pupillary response to light should remain in drugs overdoses, formal determinations of brain death have been reported in cases of intoxication with tricyclic antidepressants[16], valproic acid[17], baclofen[18-20] and barbiturates[21].

The AAN guidelines[13], recommend excluding the presence of a CNS-depressant drug effect by history, drug screen, and calculation of clearance using 5 times the drug's half-life, provided that the elimination of the drug is not interfered by other drugs, organ dysfunction, or hypothermia. If laboratorial specific measure is available, drug plasma levels must be below the therapeutic range[22].

III. REVIEW ON INTRACRANIAL BLOOD FLOW ASSESSMENT

We presented in this paper a rare cause of brainstem encephalitis mimicking BD. Similar cases have been reported, with BD diagnosis being precluded because of ancillary testing[7, 23]. Otherwise, as one of the most important diagnoses in medical practice, elevation in diagnostic confidence is profitable for physicians, indicating the association of ancillary testing with neurological assessments as the best practice currently, although there is still no consensus about this subject[24] . If ischemic derangement spreads to whole brain after disastrous injury, leading to cell membrane impairment, brain-blood barrier disruption and free entrance of liquid in each brain cell and perivascular compartment, the consequent rise of intracranial pressure will lead to its own circulatory arrest[25]. Thus, the absence of intracranial blood circulation is an affordable proof of brain death, although this assessment is limited under each technique particular features.

- *Digital Subtraction Angiography (DSA)*

DSA remains the gold standard for BD diagnosis complementation[26, 27]. This technique was created in 1927 by portuguese physician Egas Moniz[28]. Catheter angiography is an invasive, time consuming procedure, which needs an experienced neuroradiologist, the availability of an angiography suite, patient transportation and the use of high amount of contrast material[29]. As for all techniques that analyses brain blood circulation, it is imperative the blood pressure to be monitored, as such patients can be hemodynamically unstable.

Early recommendations suggested that a certain amount of time, e.g., one minute, should elapse before concluding that the contrast material does not enter the intracranial cavity. A limitation for all techniques in the assessment of brain circulation, is the possibility for brain death to exist without intracranial pressure exceeding mean arterial blood pressure; there can also be a gradual evolution from some intracranial arterial filling, especially in cases of large skull defects and severe damage to the brainstem exclusively[30]. Sawicki et al.[31] investigated the delayed filling phenomenon using CTP and concluded that the mean blood circulation time in this phenomenon is incompatible with neuronal survival.

Radiation exposure isolated to the head is not hazardous in the case of organ donation, and even exposure of the whole body has not been demonstrated to be harmful on transplantable organs to the date. Further limitations of DSA include the need of an expert to perform imaging, the DSA room and device (costly impact), patient transportation.

➢ *Transcranial Doppler (TCD)*

TCD is very sensitive and specific for assessment of brain circulatory arrest[32-35]. A recent prospective and blinded study evaluating 106 comatose patients with CTA and TCD found the latter 96% sensitivity and 100% specificity, 100% of positive predictive value of TCD even performed 24-12 hours prior to the neurological assessment[36]. As this ultrasonographic technique is non-invasive, inexpensive, safe and repeatable, suitable to evaluate both supra and infratentorial vessels, TCD becomes a high reliable tool to aid uncommon cases handling. Unfortunately, this technique depends on TCD operator availability and skills.

➢ *Computed Tomography Angiography (CTA)*

CTA is highly sensitive and as specific as TCD[25, 36, 37]. Similar cases as the illustrated in this paper, with no visible injury on no-contrast CT, are of low degree of difficult to be assessed by experienced neuroradiologists. CTA is not operator dependent, as a technician is able to perform the examination, while a radiologist can evaluate the images remotely. Additional advantages of this technique are the wide availability of devices with 32 channels or more, the readiness in acquiring images, the need of only a single peripheral vein, and its ability for additional scanning of the entire body of a potential organ donor[38]. Hindrances on CTA practice rely on the particular fashion to obtain BD imaging, with adequate under pressure pump injection of contrast, and hemodynamic stability of subjects evaluated. Neurocritical patients, and worse when BD is present, tend to develop labile hemodynamics and may not able to be transported to CTA site.

➢ *Computed Tomography Perfusion (CTP)*

CTP is able to report isolated brainstem death[39]. The technology is capable of discriminating between severe hypoperfusion (2%, 1.2 mL/100 g/minute) from an absence (0%). CTP has been used to evaluate stasis filling phenomenon observed in CTA and DSA, showing nonviability of the brain, indicating that stasis filling does not preclude the diagnosis of BD. Whole-brain CTP is a highly sensitive and specific method for diagnosis of BD. CTP used together with CTA may increase the sensitivity of the test, instead this technique is less available than CTA, also demands patient transportation and contrast administration[40].

➢ *Magnetic Resonance Angiography (MRA)*

As with CTA, the AAN currently does not support the use of MRA as an ancillary test in the diagnosis of BD [13]. Among several digital imaging reconstructions, the apparent diffusion coefficient (ADC) is the main feature in BD[41, 42]. Studies using time-of-flight algorithms or gadolinium enhancement have shown similar results, despite susceptibility weighted imaging disclosed considerably number of false positives. There may be some filling of proximal intracranial vessels, as observed with a variety of blood circulation assessment techniques[43, 44], likewise, observation of large veins in brain dead patients is possible, because of drainage from meningeal vessels[43], although deep cerebral veins are more often absent. The large duration of image acquisition, availability, patient transportation, costs and mainly the inability to recognize blood flow if extreme slow, are main limitations of MRA.

➢ *Nuclear Medicine Perfusion Test (NMPT)*

Radionuclide imaging techniques are frequently applied to brain death assessment[45, 46]. The agents penetrate brain parenchyma in proportion to regional blood flow with SPECT, being currently 99mTc- labelled hexamethylpropyleneaminoxime (HMPAO) or ethyl cysteinate dimer utilized, because these agents remain per hours in the parenchyma. This technique demonstrates the presence or absence of brain perfusion even of the posterior fossa[47], which is more interesting than displaying encephalic circulation exclusively[48, 49].

Despite a promising technique, studies on this subject to the date are few and of small samples[50]. Bertagna et al. have shown persistence of viable spots of brain tissue in patients clinically brain-dead on SPECT[51]. Such findings are in accordance with the understanding of BD as a process, with circulation and still some minimum perfusion occurring in a deceased organ, and the dependence on the intracranial pressure to these techniques obtain optimal sensitivity. Obviously, the main limitation of this method is the lack of availability and practicality, since it demands a short half-life radioisotope to be performed and being also high costly.

IV. DISCUSSION

➢ *Security in Diagnosing BD*

Finally, in cases whether drug abuse or the cause of coma is unclear, but in the absence of CNS depressors high BD suspicion persists, the patient should be observed for 48 hours to determine whether a change in brain stem reflexes occurs; if no change is observed, a test of cerebral blood supply should be performed before apnea test[52, 53]. A circulatory arrest observed, plus neurological assessment (even better if performed more than once by different trained physicians) and apnea test also positive will indicate BD with no possibility of mistaken, to the date knowledge.

V. CONCLUSION

For challenging situations when BD is suspected, cerebral blood circulation evaluation provides guidance for next steps and should always be performed prior to the apnea test.

ACKNOWLEDGMENTS

Dr. Brasil prepared this manuscript. Drs. Brasil, Moraes and Tierno collected data. Dr. Nogueira reviewed the manuscript and provided technical help.

DISCLOSURES

The authors declare no conflicts of Interest. Declaration of informed consent was obtained from study participant.

REFERENCES

[1]. Hitawala AA, Garg P, Jain A, Nahar A. Severe Hypokalemia Mimicking Brain Death. Indian J Crit Care Med 2018;22:674-677.
[2]. de Freitas GR, Lima MA, Andre C. Complex spinal reflexes during transcranial Doppler ultrasound examination for the confirmation of brain death. Acta Neurol Scand 2003;108:170-173.
[3]. Dosemeci L, Cengiz M, Yilmaz M, Ramazanoglu A. Frequency of spinal reflex movements in brain-dead patients. Transplant Proc 2004;36:17-19.
[4]. Arbour RB. Brain death: assessment, controversy, and confounding factors. Crit Care Nurse 2013;33:27-46.
[5]. Ravikumar S, Poysophon P, Poblete R, Kim-Tenser M. A Case of Acute Motor Axonal Neuropathy Mimicking Brain Death and Review of the Literature. Front Neurol 2016;7:63.
[6]. Kang BH, Kim KK. Fulminant guillain-barre syndrome mimicking cerebral death following acute viral hepatitis a. J Clin Neurol 2007;3:105-107.
[7]. Tan CY, Ahmad SB, Goh KJ, Latif LA, Shahrizaila N. Overlap of Bickerstaff brainstem encephalitis/Guillain-Barre syndrome simulating brain death. Neurol India 2018;66:1475-1480.
[8]. Ortiz-Corredor F, Silvestre-Avendano JJ, Izquierdo-Bello A. [Locked-in state mimicking cerebral death in a child with Guillain-Barre syndrome]. Rev Neurol 2007;44:636-638.
[9]. Rigamonti A, Basso F, Stanzani L, Agostoni E, Lauria G. Guillain-Barre syndrome mimicking brain death. J Peripher Nerv Syst 2009;14:316-319.
[10]. Streat S. 'Reversible brain death'--is it true, confounded, or 'not proven'? Crit Care Med 2011;39:1601-1603.
[11]. Spinello IM. Brain Death Determination. J Intensive Care Med 2015;30:326-337.
[12]. Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. Crit Care Med 2011;39:1538-1542.
[13]. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM, American Academy of N. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74:1911-1918.
[14]. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. There is no reversible brain death. Crit Care Med 2011;39:2204-2205; author reply 2206.
[15]. Thompson AE, Sussmane JB. Bretylium intoxication resembling clinical brain death. Crit Care Med 1989;17:194-195.
[16]. Yang KL, Dantzker DR. Reversible brain death. A manifestation of amitriptyline overdose. Chest 1991;99:1037-1038.
[17]. Auinger K, Muller V, Rudiger A, Maggiorini M. Valproic acid intoxication imitating brain death. Am J Emerg Med 2009;27:1177 e1175-1176.
[18]. Koker A, Arslan G, Ozden O, et al. An intoxication mimicking brain death: baclofen. Acta Neurol Belg 2018.
[19]. Sullivan R, Hodgman MJ, Kao L, Tormoehlen LM. Baclofen overdose mimicking brain death. Clin Toxicol (Phila) 2012;50:141-144.
[20]. Ostermann ME, Young B, Sibbald WJ, Nicolle MW. Coma mimicking brain death following baclofen overdose. Intensive Care Med 2000;26:1144-1146.
[21]. Grattan-Smith PJ, Butt W. Suppression of brainstem reflexes in barbiturate coma. Arch Dis Child 1993;69:151-152.
[22]. Marik PE, Varon J. Prolonged and profound therapeutic hypothermia for the treatment of "brain death" after a suicidal intoxication. Challenging conventional wisdoms. Am J Emerg Med 2010;28:258 e251-254.
[23]. Ragosta K. Miller Fisher syndrome, a brainstem encephalitis, mimics brain death. Clin Pediatr (Phila) 1993;32:685-687.
[24]. Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology 2002;58:20-25.
[25]. Brasil S, de-Lima-Oliveira M, Bor-Seng-Shu E, Teixeira MJ. Letter to the Editor. Determining brain death using computed tomography angiography. J Neurosurg 2018;128:653-654.
[26]. Savard M, Turgeon AF, Gariepy JL, Trottier F, Langevin S. Selective 4 vessels angiography in brain death: a retrospective study. Can J Neurol Sci 2010;37:492-497.
[27]. Kricheff, II, Pinto RS, George AE, Braunstein P, Korein J. Angiographic findings in brain death. Ann N Y Acad Sci 1978;315:168-183.
[28]. Artico M, Spoletini M, Fumagalli L, et al. Egas Moniz: 90 Years (1927-2017) from Cerebral Angiography. Front Neuroanat 2017;11:81.
[29]. van der Lugt A. Imaging tests in determination of brain death. Neuroradiology 2010;52:945-947.
[30]. Alvarez LA, Lipton RB, Hirschfeld A, Salamon O, Lantos G. Brain death determination by angiography in the setting of a skull defect. Arch Neurol 1988;45:225-227.
[31]. Sawicki M, Bohatyrewicz R, Safranow K, et al. Dynamic evaluation of stasis filling phenomenon with computed tomography in diagnosis of brain death. Neuroradiology 2013;55:1061-1069.
[32]. Walter U, Schreiber SJ, Kaps M. Doppler and Duplex Sonography for the Diagnosis of the Irreversible Cessation of Brain Function ("Brain Death"): Current Guidelines in Germany and Neighboring Countries. Ultraschall Med 2016;37:558-578.
[33]. Kasapoglu US, Haliloglu M, Bilgili B, Cinel I. The Role of Transcranial Doppler Ultrasonography in the Diagnosis of Brain Death. Turk J Anaesthesiol Reanim 2019;47:367-374.
[34]. Lange MC, Zetola VH, Miranda-Alves M, et al. Brazilian guidelines for the application of transcranial

ultrasound as a diagnostic test for the confirmation of brain death. Arq Neuropsiquiatr 2012;70:373-380.
[35]. Brasil S, Bor-Seng-Shu E, de-Lima-Oliveira M, et al. Role of computed tomography angiography and perfusion tomography in diagnosing brain death: A systematic review. J Neuroradiol 2016;43:133-140.
[36]. Brasil S, Bor-Seng-Shu E, de-Lima-Oliveira M, et al. Computed tomography angiography accuracy in brain death diagnosis. J Neurosurg 2019:1-9.
[37]. Garrett MP, Williamson RW, Bohl MA, Bird CR, Theodore N. Computed tomography angiography as a confirmatory test for the diagnosis of brain death. J Neurosurg 2018;128:639-644.
[38]. Tache A, Badet N, Azizi A, Behr J, Verdy S, Delabrousse E. Multiphase whole-body CT angiography before multiorgan retrieval in clinically brain dead patients: Role and influence on clinical practice. Diagn Interv Imaging 2016;97:657-665.
[39]. MacDonald D, Stewart-Perrin B, Shankar JJS. The Role of Neuroimaging in the Determination of Brain Death. J Neuroimaging 2018;28:374-379.
[40]. Sawicki M, Solek-Pastuszka J, Chamier-Cieminska K, Walecka A, Bohatyrewicz R. Accuracy of Computed Tomographic Perfusion in Diagnosis of Brain Death: A Prospective Cohort Study. Med Sci Monit 2018;24:2777-2785.
[41]. Luchtmann M, Beuing O, Skalej M, et al. Gadolinium-enhanced magnetic resonance angiography in brain death. Sci Rep 2014;4:3659.
[42]. Selcuk H, Albayram S, Tureci E, et al. Diffusion-weighted imaging findings in brain death. Neuroradiology 2012;54:547-554.
[43]. Karantanas AH, Hadjigeorgiou GM, Paterakis K, Sfiras D, Komnos A. Contribution of MRI and MR angiography in early diagnosis of brain death. Eur Radiol 2002;12:2710-2716.
[44]. Sohn CH, Lee HP, Park JB, et al. Imaging findings of brain death on 3-tesla MRI. Korean J Radiol 2012;13:541-549.
[45]. Berenguer CM, Davis FE, Howington JU. Brain death confirmation: comparison of computed tomographic angiography with nuclear medicine perfusion scan. J Trauma 2010;68:553-559.
[46]. Shappell CN, Frank JI, Husari K, Sanchez M, Goldenberg F, Ardelt A. Practice variability in brain death determination: a call to action. Neurology 2013;81:2009-2014.
[47]. Sinha P, Conrad GR. Scintigraphy in the confirmation of brain death: Indian context. Indian J Nucl Med 2012;27:1-4.
[48]. Munari M, Zucchetta P, Carollo C, et al. Confirmatory tests in the diagnosis of brain death: comparison between SPECT and contrast angiography. Crit Care Med 2005;33:2068-2073.
[49]. Palaniswamy V, Sadhasivam S, Selvakumaran C, Jayabal P, Ananth SR. Single-photon emission computed tomography imaging for brain death donor counseling. Indian J Crit Care Med 2016;20:477-479.
[50]. Joffe AR, Shemie SD, Farrell C, Hutchison J, McCarthy-Tamblyn L. Brain death in Canadian PICUs: demographics, timing, and irreversibility. Pediatr Crit Care Med 2013;14:1-9.
[51]. Bertagna F, Barozzi O, Puta E, et al. Residual brain viability, evaluated by (99m)Tc-ECD SPECT, in patients with suspected brain death and with confounding clinical factors. Nucl Med Commun 2009;30:815-821.
[52]. Bernat JL, Dalle Ave AL. Aligning the Criterion and Tests for Brain Death. Camb Q Healthc Ethics 2019;28:635-641.
[53]. Walter U, Fernandez-Torre JL, Kirschstein T, Laureys S. When is "brainstem death" brain death? The case for ancillary testing in primary infratentorial brain lesion. Clin Neurophysiol 2018;129:2451-2465.