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LETTER TO THE EDITOR

Neuroimaging of Intracranial Perfusion and the Clinical Diagnosis of Brain Death: Setting the Gold Standard in Humans

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Dear Editor,

In the article "Computed Tomography Perfusion is a Useful Adjunct to Computed Tomography Angiography in the Diagnosis of Brain Death", Sawicki et al. reported computed tomography perfusion (CTP) findings in 50 patients with the clinical diagnosis of brain death [1]. The gold standard of the study was the clinical diagnosis of brain death based on the following criteria: unresponsiveness, absent brainstem reflexes, and apnea after the exclusion of reversible confounding factors [1]. The assumption of the study was that CTP findings of cerebral blood flow (CBF) <10 ml/100 g/min and cerebral blood volume (CBV) <1.0 ml/100 g was "consistent with threshold of neuronal necrosis" [1]. The above CBF and CBV thresholds were chosen as the cut-off for a positive CTP study and the authors reported that CTP had 100% sensitivity for brain death diagnosis [1]. The authors also reported that, based on CTP findings, neither CBF nor CBV were zero in the study patients with the clinical diagnosis of brain death [1]. Sawicki et al. implicitly assumed that any residual CBF detected on CTP at <10 ml/100 g/min was inadequate to prevent neuronal necrosis and irreversible cessation of functions of the whole brain including the brainstem. The irreversible cessation of the functions of the whole brain, including the brainstem, is the necessary criterion in death determination by neurological criteria [2]. There are several concerns with the study's interpretations.

Firstly, Sawicki et al. did not cite clinical studies to verify that the residual global CBF above zero and <10 ml/100 g/min was consistent with widespread neuronal necrosis. Also, there were no autopsy findings reported in the study to validate the authors' assumption of the presence of neuronal and brain necrosis in patients with positive CTP findings and clinical diagnosis of brain death. Secondly, in a previous study of brain death [3], it was reported that almost 60% of patients that were clinically diagnosed as brain dead had histopathological findings of either normal or minimally ischemic brainstem at autopsy. In another case report, brain magnetic resonance imaging (MRI) and electrophysiological studies were performed 9 months after the initial documentation of clinical brain death and absent CBF on cerebral radionuclide scans [4, 5]. The above studies reported structural and functional preservation of some of the brain structures in a patient fulfilling the clinical criteria of brain death [4, 5]. Another study of the electrophysiological responses of the human cortex to acute reduction and complete cessation of CBF had suggested that even zero blood flow did not necessarily induce irreversible membrane depolarization, necrosis, and cessation of neocortex neuronal electrical activity [6]. Therefore, the early detection of reduction or complete cessation of CBF soon after a clinical diagnosis of brain death may not imply irreversible ischemia and necrosis of the whole brain. Thirdly, the phenomenon of global ischemic penumbra has been documented as a potential mimic of brain death diagnosis resulting in false positive determination of death [5, 7]. The threshold of cerebral ischemic insult in terms of CBF reduction to suppress neuronal synaptic transmission and connectivity is much higher than the ischemic threshold of CBF reduction that will trigger irreversible neuronal membrane depolarization and necrosis (Fig. 1; [8, 9]). These two respective ischemic thresholds of CBF have not been fully elucidated in humans [8]. In global ischemic penumbra, the CBF is below the threshold maintaining supraspinal synaptic transmission in the cerebral cortex and brainstem but the CBF is maintained above the threshold for membrane depolariza-

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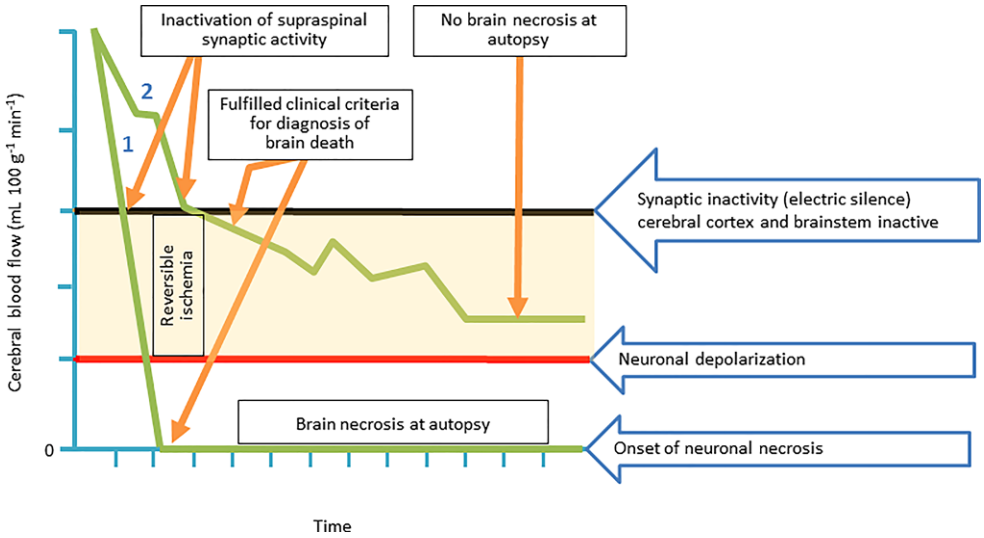

Fig. 1 The phenomenon of global ischemic penumbra and the mimic of brain death. "The figure illustrates 2 distinct temporal patterns of CBF (cerebral blood flow) in 2 hypothetical patients (patient 1 and patient 2). With the initial reduction in CBF, an early inactivation of supraspinal synaptic activity and suppression of the cerebral cortex and brainstem will result in developing the clinical criteria for the diagnosis of brain death (i.e., unresponsiveness, absent brainstem reflexes, and apnea) in both patients. Prolonged complete cessation of CBF induces irreversible ischemia and neuronal depolarization in patient 1. Brain necrosis is observed at autopsy in patient 1, confirming the irreversibility of whole-brain ischemia. In patient 2, the acute reduction of CBF induces reversible ischemia without triggering irreversible neuronal depolarization or the onset of necrosis (i.e., global ischemic penumbra). Autopsy in patient 2 demonstrates normal or minimal ischemia of brain structures and no evidence of necrosis. The temporal reversibility of the clinical findings of brain death associated with global ischemic penumbra in patient 2 is unknown." Figure and legend reproduced and adapted from the source [9] under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made

tion and neuronal necrosis. Patients with global ischemic penumbra can have the clinical manifestations of brain death (unresponsiveness, absent brainstem reflexes, and apnea) and also have normal or minimally ischemic brain structures at autopsy (i.e., reversible ischemia) (see Fig. 1). The phenomenon of global ischemic penumbra can mimic brain death and explain the preservation of brain structures and functions found on neuroimaging and neurophysiological studies performed in some brain dead patients who are continued on supportive medical care for several months after the clinical diagnosis of brain death [4, 5]. In patients who die soon after clinical diagnosis of brain death, the presence of normal or minimally ischemic brain structures at autopsy may be related to the phenomenon of global ischemic penumbra mimicking brain death in these patients [3–5, 7, 9].

In conclusion, the presence of residual CBF <10 ml/100 g/min on CTP in brain death may not imply the onset of neuronal necrosis but may represent the phenomenon of global ischemic penumbra and may not confirm the irreversibility of ischemia and cessation of all functions of the human brain. Residual CBF that is detected on neuroimaging modalities should not be ignored after the clinical diagnosis of brain death. This residual CBF may be inadequate to maintain neuronal connectivity and clinical function acutely, but it may be adequate to maintain neuronal viability and perhaps subsequent recovery of some neuronal functions. It is urged that histopathological examination of the brain structures at autopsy should be adopted as the gold standard to validate neuroimaging modalities threshold in detection of CBF reduction to confirm irreversible ischemia and necrosis in brain death.

Compliance with ethical guidelines

Conflict of interest M.Y. Rady declares that he has no competing interests.

Ethical standards For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case. For images or other information within the manuscript which identify patients, consent was obtained from them and/or their legal guardians.

References

1. Sawicki M, Sołek-Pastuszka J, Chamier-Ciemińska K, Walecka A, Walecki J, Bohatyrewicz R. Computed Tomography perfusion is a useful adjunct to computed Tomography Angiography in the diagnosis of brain death. Clin Neuroradiol. 2019;29:101–8.
2. Dalle Ave AL, Bernat JL. Inconsistencies between the criterion and tests for brain death. J Intensive Care Med. 2018; https://doi.org/10.1177/0885066618784268.
3. Wijdicks EF, Pfeifer EA. Neuropathology of brain death in the modern transplant era. Baillieres Clin Neurol. 2008;70:1234–7.

4. Machado C, DeFina PA, Estévez M, Leisman G, Rodríguez-Rojas R, Prestigiacomo C, Fellus J, Halpe J, Chinchilla M, Aubert E, Machado Y, Machado-Ferrer Y. A reason for care in the clinical evaluation of function on the spectrum of consciousness. Funct Neurol Rehabil Ergon. 2017;7:89–99.
5. Shewmon DA. Truly reconciling the case of Jahi McMath. Neurocrit Care. 2018;29:165–70.
6. Dreier JP, Major S, Foreman B, Winkler MKL, Kang EJ, Milakara D, Lemale CL, DiNapoli V, Hinzman JM, Woitzik J, Andaluz N, Carlson A, Hartings JA. Terminal spreading depolarization and electric silence in death of human cortex. Ann Neurol. 2018;83:295–310.
7. Coimbra CG. Implications of ischemic penumbra for the diagnosis of brain death. Braz J Med Biol Res. 1999;32:1479–87.
8. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral Ischemia—the Ischemic penumbra. Stroke. 1981;12:723–5.
9. Verheijde JL, Rady MY, Potts M. Neuroscience and Brain Death Controversies: The Elephant in the Room. J Relig Health. 2018;57:1745–63.