Journal of Zhejiang University SCIENCE B
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Editorial:

Supplementary tests for confirmation of brain death

Wei-lung CHENG[1], Kao-chang LIN[†‡2]

([1]*Department of Neurology, Chi Mei Medical Center, Taiwan 736, Liouying, Tainan County*)

([2]*Department of Neurology, Chi Mei Medical Center, Taiwan 710, Yungkang, Tainan City*)

[†]E-mail: gaujang@mail2000.com.tw

Received May 30, 2008; revision accepted July 19, 2008

doi:10.1631/jzus.B0870001 **Document code:** E **CLC number:** R742

In 1959, the concept of brain death (BD) or irreversible coma was described by Mollaret and Goulon (1959). The first guideline (the Harvard criteria) for deciding BD was established in 1968 (Ad Hoc Committee of the Harvard Medical School, 1968). This concept has been accepted worldwide although its fundamental meaning is not exactly globally uniform yet. Some countries (e.g., the US) view BD as "whole brain death", while others (e.g., the UK) as brain-stem death. The guidelines for the diagnosis of BD also differ among countries, even among hospitals in the same country. The American Academy of Neurology (AAN) published its guidelines in 1995 (The Quality Standards Subcommittee of the American Academy of Neurology, 1995). This dilemma about the "real" death of physiological or physical basis among the leading neurological hospitals is debating (Greer *et al*., 2008). Surprisingly, adherence to AAN guidelines is variable among those top hospitals.

The role of confirmatory tests differs among countries too. In some countries (e.g., France and the Netherlands), the confirmatory tests are mandatory, while in others (e.g., the US and the UK) they are facultative (Haupt and Rudolf, 1999). According to the AAN guidelines, the confirmatory tests are only required when specific components of the clinical testing cannot be reliably evaluated. Electroencephalography (EEG), evoked potentials (EP), cerebral angiography, transcranial Doppler (TCD), magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and single photon emission computed tomographic (SPECT) brain scintigraphy are the most common confirmatory tests, but none of them is "ideal" for the diagnosis of BD. The EEG, EP, and TCD can be performed at bedside. They are non-invasive, not time-consuming, and easy to carry out. The limitations of them are listed in this article, and the combination for more accurate diagnosis seems promising (The Quality Standards Subcommittee of the American Academy of Neurology, 1995).

As the clinical diagnosis of BD is made, more neurons die over time physiologically. It is reasonable that the sensitivity increases over time in the second examination. However, it is hard to decide which combination is the best without multiple comparisons, confidence interval or inter-quintile range (IQR) in those non-parametrical groups. The sensitivity of TCD to confirm BD varied among studies. In AAN guidelines, the sensitivity and specificity is 91% and 100%, respectively (Sloan *et al*., 2004). In Cuba, using TCD to confirm the BD is allowed by law. By exclusion of specific conditions (e.g., large craniotomy, external ventricular drains), TCD is sensitive and the receiver operating characteristic (ROC) is reliable in our results (Kuo *et al*., 2006). The time-lag between clinical BD and performing TCD is a key to increase the sensitivity, so are EEG and short latency somatosensory evoked potentials (SLSEP). It is

‡ Corresponding author

difficult to decide which combination is more simply by a *P* value without more information (Luo *et al*., 2008). The timing of each test, the younger age, and the sample size may affect the outcome. If EEG, TCD, and SLSEP are carried out in sequence, the sensitivity may be different by the "time-lag" period. In general, more studies are still needed to verify which combination of confirmatory test is the best in the future.

Some physicians view BD as a particular condition in which life support should be legitimately forgone and organs could be retrieved from consenting patients (Zamperetti *et al*., 2004). In a recent neuropathologic study (Wijdicks and Pfeifer, 2008), 41 patients who fulfilled AAN criteria of BD were examined, but no distinctive neuropathologic features were seen. According to this study, neuronal loss was widespread in the brain, but total brain necrosis (called "respirator brain") was not observed. In order to make accurate diagnosis and facilitate legal organ donation, we hope world neurologists to draw up new global evidence-based consensus including specific recommendations to avoid too many tests for the confirmation of BD.

References

Ad Hoc Committee of the Harvard Medical School, 1968. A definition of irreversible coma: report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA*, **205**(6):337-340. [doi:10.1001/jama.205.6.337]

Greer, D.M., Varelas, P.N., Haque, S., Wijdicks, E.F., 2008. Variability of brain death determination guidelines in leading US neurologic institutions. *Neurology*, **70**(4): 284-289. [doi:10.1212/01.wnl.0000296278.59487.c2]

Haupt, W.F., Rudolf, J., 1999. European brain death codes: a comparison of national guidelines. *J. Neurol.*, **246**(6): 432-437. [doi:10.1007/s004150050378]

Kuo, J.R., Chen, C.F., Chio, C.C., Chang, C.H., Wang, C.C., Yang, C.M., Lin, K.C., 2006. Time dependent validity in the diagnosis of brain death using transcranial Doppler sonography. *J. Neurol. Neurosurg. Psychiatry*, **77**(5): 646-649. [doi:10.1136/jnnp.2005.076406]

Mollaret, P., Goulon, M., 1959. Le coma de'passe'. *Rev. Neurol. (Paris)*, **101**:3-15.

Sloan, M.A., Alexandrov, A.V., Tegeler, C.H., Spencer, M.P., Caplan, L.R., Feldmann, E., Wechsler, L.R., Newell, D.W., Gomez, C.R., Babikian, V.L., *et al*., 2004. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*, **62(9)**:1468-1481.

The Quality Standards Subcommittee of the American Academy of Neurology, 1995. Practice parameters for determining brain death in adults [summary statement]. *Neurology*, **45**(5):1012-1014.

Wang, K., Yuan, Y., Xu, Z.Q., Wu, X.L., Luo, B.Y., 2008. Benefits of combination of electroencephalography, short latency somatosensory evoked potentials, and transcranial Doppler techniques for confirming brain death. *J. Zhejiang Univ. Sci. B*, **9**(11):916-920. [doi:10.1631/jzus.B0820123]

Wijdicks, E.F., Pfeifer, E.A., 2008. Neuropathology of brain death in the modern transplant era. *Neurology*, **70**(15): 1234-1237. [doi:10.1212/01.wnl.0000289762.50376.b6]

Zamperetti, N., Bellomo, R., Defanti, C.A., Latronico, N., 2004. Irreversible apnoeic coma 35 years later. Towards a more rigorous definition of brain death? *Intensive. Care Med.*, **30**(9):1715-1722. [doi:10.1007/s00134-003-2106-3]