Scintigraphy in the confirmation of brain death: Indian context

The concept of brain death has been described in the scientific literature since first published in 1959.[1] In the past few decades, with the advancement of medical technology to enable maintenance of ventilation and perfusion even after the complete cessation of brain function on one hand; and significant increase in the need of donor organs resulting from improved organ transplantation technology on the other; the need for an accurate and timely diagnosis of brain death has gained prominence.

The specific diagnostic criteria for brain death vary from country to country.[2,3] In the USA, most jurisdictions have developed their statutes regarding brain death on the basis of the Uniform Determination of Death Act,[4] which declares "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards." Individual states have statues which are broadly similar but have specific differences regarding the qualifications of personnel declaring brain death.[5]

In India, The Transplantation of Human Organs Act, 1994[6] was passed by the Parliament to regulate organ transplantations in India. It defines "brainstem" death to mean "the stage at which all functions of the brainstem have permanently and irreversibly ceased." As has been pointed out by Sethi and Sethi,[7] this is in line with the practice in United Kingdom of declaring death by loss of brainstem function only, whereas the practice in the USA calls for documentation of the lack of function of the entire brain, including the brainstem. This Act calls for a panel of four physicians to make the diagnosis of brainstem death, composed of (i) physician treating the patient, (ii) physician in charge of the hospital treating the patient, (iii) a specialist physician from an unspecified specialty, and (iv) a neurologist or a neurosurgeon.

Brain death is a complex issue encompassing overlapping areas of medicine, philosophy, ethics, and the law.[8] Brain death declaration needs careful adherence to established protocols and accurate documentation. Yet, occasionally, this process is less than optimum as observed in several papers.[9-11] Several sensational news headlines have appeared recently that have the potential to erode the confidence of the general public.[12-15] Most of these cases appear to be the result of failure to follow protocol and documentation rather than any *malafide* intent. Similar confusion has been reported by Sethi and Sethi[7] in a major super-specialty hospital in New Delhi.

Organ donation rate in India is very low at 0.05 per million deaths compared to about five per million in Hong Kong and 25 per million in the USA.[16] A possibility is that the low rate of organ donation is related to a very low rate of declaration of death by loss of brain function rather than refusal of the deceased's loved ones to donate. Super-specialty hospitals with the capability to declare brain death have performed better. One paper reported 19% of brain dead patients had their organs harvested for transplantation.[17] Religious leaders from major religions in India have voiced their support for organ donation.[16] Organ sharing networks such as Multi Organ Harvesting Aid Network (MOHAN) have been established to facilitate optimum use of harvested organs among different hospitals.[18] Adherence to protocol and perception of fairness have the potential to increase the harvesting rate of organs.

Increased acceptance by the general public of organ donation and the availability of super-specialized facilities can be expected to increase the necessity to make the diagnosis of brain death. It is important, therefore, for the nuclear medicine physician to be comfortable with the potential role of nuclear medicine in the evaluation of brain death. Scintigraphic confirmation of brain death has been well discussed in the medical literature. As pertains to nuclear medicine, the different radiopharmaceuticals used, techniques of imaging and the stand of various professional societies in the USA have been discussed before in detail in review articles.[5,19] Of particular note is the broad classification of tracers to hydrophilic and lipophilic categories. Hydrophilic tracers such as Tc99m diethylene triamine pentaacetic acid (DTPA) do not cross the blood brain barrier, and can be used to provide rapid sequence dynamic anterior images to assess cerebral perfusion. Lipophilic agents such as Tc99m hexamethylpropyleneamine oxime (HMPAO) allow acquisition of dynamic as well as delayed static images and allow for distinguishing between low and absent flows.[20-22]

Even with the availability of well-documented ancillary diagnostic tests, the determination of brain death in most US jurisdictions remains largely a clinical process. The American Association of Neurology (AAN) issued a summary statement in 1995[23] stating the following to be pre-requisites (1) clinical or neuroimaging

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evidence of acute central nervous system catastrophe; (2) exclusion of complicating medical conditions; (3) absence of drug intoxication; and (4) core body temperature of at least 32ºC (90ºF). Once these have been met, a clinical examination to assess for (1) coma, (2) absence of brainstem reflexes, and (3) apnea is performed. These criteria have been reinforced in their more recent report specifically addressing interval developments since the first report.[24] AAN indicates that ancillary diagnostic tests for brain death (previously called confirmatory tests) are needed only when specific components of the clinical examination cannot be performed or to shorten the length of the observation period if such is mandated. The emphasis is on clinical examination. The AAN states that, "Rather than order ancillary tests, physicians may decide not to proceed with the declaration of brain death if clinical findings are unreliable."[24] It has also been argued that confirmatory tests are unnecessary and "a comprehensive clinical examination, when performed by skilled examiners, should have perfect diagnostic accuracy."[25]

Several ancillary tests have been listed by the AAN[24] which could be used to confirm the clinical suspicion of brain death. These include radionuclide brain scan using Tc99m HMPAO, conventional contrast angiography, electroencephalography, and transcranial Doppler ultrasonography. In our institution, the Tc99m HMPAO brain perfusion study has been the commonest ancillary test used to confirm brain death. It is of note that the AAN discussed somatosensory evoked potentials and other "newer" tests such as computed tomography angiography, magnetic resonance angiography, and bispectral index and concluded that "there is insufficient evidence to determine if newer ancillary tests accurately confirm the cessation of function of the entire brain."[24] These tests should therefore be used with caution, if at all, to confirm brain death. This is primarily due to the lack of a scientific study to evaluate their role rather than any theoretical basis to question their effectiveness.

There exist some differences among the recommendations of various professional societies, AAN,[24] American College of Radiology (ACR),[26] and the Society of Nuclear Medicine (SNM)[27] regarding the role of scintigraphy in brain death.

AAN recommends planar anterior and both lateral images of the head obtained immediately, between 30 and 60 min and at 2 h following the intravenous administration of Tc99m HMPAO. Single photon emission computed tomography (SPECT) imaging is performed at unspecified time-points.

ACR in its 2007 practice guidelines recommended the use of Tc99m HMPAO or Tc99m ethylene cysteine diethylester (ECD) to assess "cerebral blood flow." Dynamic imaging is recommended but optional. Lateral and posterior images are obtained as needed. SPECT imaging is recommended if technically feasible.

SNM recommends the use of Tc99m HMPAO, Tc99m ECD, or Tc99m DTPA to assess "brain blood flow" but suggests that brain specific agents such as Tc99m HMPAO or Tc99m ECD be used to allow for delayed imaging to assess brain blood flow. The SNM recommends planar or SPECT imaging if brain-specific agents are used but notes that, "SPECT is rarely, if ever, used in these patients who are often unstable and on life support equipment, which may be incompatible with SPECT acquisition."

INDIAN CONTEXT

In India, brainstem death needs to be documented before the declaration of brain death. The brainstem consists of the midbrain, pons, and the medulla. Clinical examination of pupillary reflexes and eye movement for oculomotor function serves as a check for midbrain viability as the oculomotor nerve nuclei are located in the midbrain. Similarly, testing for trochlear, trigeminal, and abducens nerve function checks for pontine viability and testing for glossopharyngeal and vagus nerve function checks for medullary viability. Apnea testing to assess for central respiratory drive is considered a critical part of testing for brain death. It is considered safe[28] and tests for respiratory drive to increasing concentration of carbon dioxide and effectively assesses the functional integrity of the respiratory centers located in the pons and the medulla.

It is important to note that in India, documentation of irreversible loss of brainstem function is all that is necessary for the declaration of brain death. This approach differs from some countries, including some jurisdictions in the USA where it is necessary to document absent function of all parts of the brain before the declaration of brain death. Failure to keep this in mind can lead to situations as described by Sethi and Sethi where the deceased's relatives were confused and angry about conflicting opinions by medical experts.[7]

Brain scintigraphy using current planar techniques works well to document the absence or presence of blood flow to the cerebrum, basal ganglia, thalami, and cerebellum.[29-31] We have, in our practice, used scintigraphy to specifically assess perfusion at these structures after lack of brainstem function has been confirmed by the clinical services. The brainstem is difficult to assess by planar scintigraphy due to multiple reasons such as its size and location with superimposition of overlying high activity structures such as parotid glands and neck muscles which are supplied by the external carotid artery and typically have preserved perfusion. SPECT imaging, by virtue of its cross-sectional nature, can be thought of to have the theoretical advantage of being able to visualize the brainstem. But as has been discussed in detail by us earlier,[19] SPECT imaging of the brain stem may not be reliable to document the absence of tracer uptake. This is primarily because the transverse size of the adult brainstem approaches the resolution limits of SPECT systems and the technical difficulties of performing a high quality SPECT examination in the context of brain death evaluation. In such a situation, visualization of tracer presence in the brainstem can be conclusive to determine blood flow to the brainstem, but the reliability of SPECT to definitively exclude the absence

of perfusion to the brainstem remains to be established on a scientific basis. Current nuclear medicine techniques to evaluate brain flow using Tc99m HMPAO or Tc99m ECD may therefore have limited applicability to confirm brain death in the Indian context.

18-Fluorodeoxyglucose (FDG) positron emission tomography (PET) with its superior spatial resolution as compared to planar or SPECT imaging and the capability to directly visualize brainstem metabolism have the potential to overcome the problem of adequate visualization of the brainstem. It has been described in the literature,[32] but is not specifically mentioned by any of the professional societies in the USA as a recommended method for the confirmation of brain death. We are not aware of any study designed specifically to evaluate the utility of FDG PET scans in the confirmation of brain death. In addition, the logistic difficulties of performing a FDG PET scan for this purpose may limit the use of FDG PET scans for this purpose.

CONCLUSION

Organ transplantation surgeries are expected to keep their rising trend in India and along with it, the need for cadaveric donors. Facilitation of organ transplantation by the establishment of dedicated inter-hospital networks such as MOHAN will allow for more organs being harvested for transplantation. Accurate and timely declaration of brain death is a critical part of this process. Definition of brain death varies across different countries of the world. Strict adherence to the local laws and careful documentation of the brain death declaration process are mandatory to maintain public confidence. In India, brainstem death is equated with brain death. Brainstem function is best assessed clinically and the clinical assessment is mandatory for the declaration of brain death. Planar and SPECT imaging to assess perfusion of the cerebrum and cerebellum is well established. Reliability of currently available SPECT imaging to specifically assess brainstem perfusion is yet to be scientifically validated.

Partha Sinha, Gary R Conrad

Department of Radiology, Division of Nuclear Medicine,
800 Rose Street, HX-313D, University of Kentucky, USA.
E-mail: psinh2@email.uky.edu

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