Chapter

Ancillary Imaging Tests for Confirmation of Brain Death

Sudharsana Rao Ande and Jai Jai Shiva Shankar

Abstract

Brain death is an irreversible termination of functions of the entire brain including brain stem. The American Association of Neurology has defined brain death with three cardinal criteria, namely cessation of the functions of brain including brain stem, coma or unresponsiveness, and apnea. Ancillary testing is done in situations where clinical criteria of brain death cannot be determined by neurological examination or by apnea test. Ancillary tests for determining brain death can be primarily divided into two groups. One group includes tests that can test brain's electrical functions and the other group includes tests that can document cerebral blood flow in the brain on imaging. In this chapter, we present characteristics of the ideal ancillary test in the diagnosis of brain death and also describe various types of ancillary imaging tests used in the clinical setting for brain death determination and the merits and demerits associated with these techniques.

Keywords: brain death, ancillary imaging test, brainstem function, computed tomography, DSA, nuclear scintigraphy, CT perfusion (CTP), CT angiography (CTA), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), magnetic resonance perfusion (MRP)

1. Introduction

Brain death is defined as permanent cessation of all vital functions of the brain. It is principally established using clinical criteria including coma, absence of brain stem reflexes, and using apnea test. In Canada, two physicians must determine whether particular patient is brain dead or not [1, 2]. The criteria for declaring brain death includes deep unresponsive coma with established etiology, absence of reversible conditions [2]. Absence of brain stem reflexes includes absence of gag, cough, bilateral absence of corneal response, pupillary response to light and vestibule-ocular response, absence of respiratory efforts based on apnea test, and absence of confounding factors [2]. Ancillary imaging tests are necessary in situations when neurological examination or the apnea test cannot be performed or its validity comes into a question [3]. These situations include when patients have resuscitated shock, hypothermia, severe metabolic abnormalities, complex spinal reflexes, peripheral nerve or muscular dysfunctions, high cervical spine injury, craniofacial trauma or if the patient is on sedative drugs such as alcohol, barbiturates, sedatives, and hypnotics.

An ideal ancillary test should not have any false positive results. This is very important in brain death patients. If the ancillary test confirms death, when in fact, patient is not dead, is very dangerous and raises critical social, ethical and legal concerns. The main objective of the ancillary test would be to demonstrate

the absence of cerebral electric activity or cerebral circulatory arrest [4]. Based on this, the first type assesses the electrical functions of the brain, and the other type analyses cerebral blood flow in the brain on imaging. Here, we provide description of cerebral blood flow imaging techniques and compare them.

2. Characteristics of ideal ancillary test for determining the brain death

Young and his colleagues described the attributes of an ideal ancillary test [5]. A reliable ancillary test should meet all the criteria mentioned below.

1. When the test confirms brain death, there should be no one that recovers or have the potential to recover. There should be no false positives.

2. The test should be independently sufficient enough to establish whether brain death is present or not.

3. The test should not be susceptible to external or internal confounding factors such as drug effects and metabolic disturbances.

4. The test should have standardized technology, technique, and classification of results.

5. The test should be inexpensive, safe, and readily applied. Testing should not be restricted to only few tertiary academic centers. It could be applied with any intensive care unit, and the technique should be mastered without difficulty.

3. Ancillary imaging tests used in brain death determination

3.1 Digital subtraction angiography (DSA)

This is considered the gold standard for ancillary imaging test. DSA is the first used modality for determining the cerebral blood flow. It is typically performed with a catheter tip in the aortic arch and contrast injection into each of the four arteries supplying the brain [3]. At least two injections, 20 min apart, must show an absence of filling of four arteries as their course becomes intracranial (**Figure 1**) [3, 6].

This test is capable of detecting dynamic blood flow in the arteries, veins, and capillaries. The criteria for brain death diagnosis using this method include no intracerebral filling at the level of entry into the skull of carotid or vertebral artery and filling of external carotid arteries. But this method does not have the spatial resolution to distinguish the blood flow in the different parts of the brain such as brainstem. Other disadvantages include transportation of patents to the angio suite; requires expert operator to perform; is invasive; and requires injection of contrast medium that may have a potential risk to the patients with kidney diseases. It can have "stasis filling" due to diffusion of contrast in the static column of blood, which can result in false negatives. Thus, it is an expensive procedure and not readily available in many hospitals and may not be easy to interpret in many healthcare facilities.

3.2 Nuclear scintigraphy

This is another gold standard ancillary imaging test for determination of brain death. In this technique, a gamma emitting radioactive tracer is intravenously

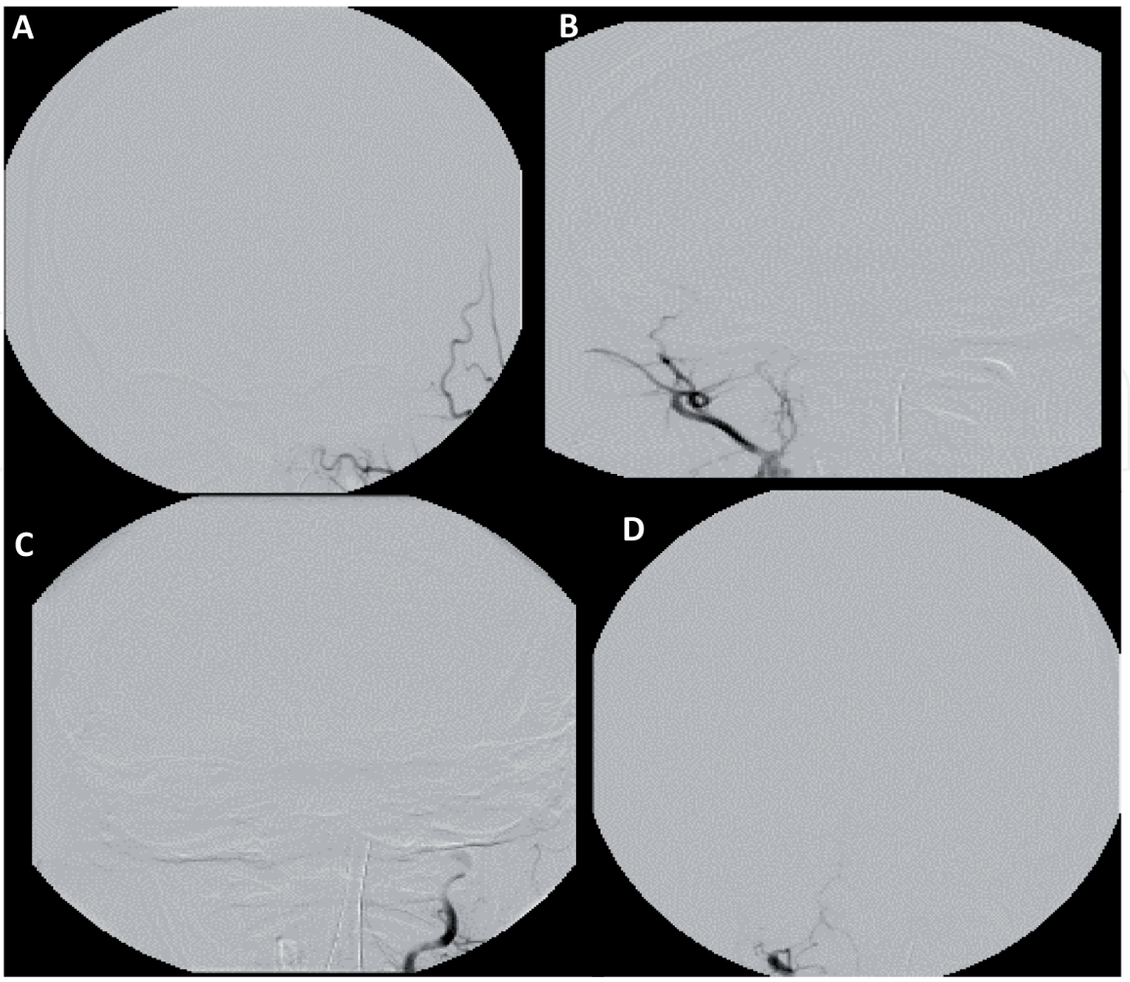

Figure 1.
Digital subtraction angiography image of a brain dead patient showing no intracranial filling on selective (A) left and (B) right common carotid artery as well as (C) left and (D) right vertebral artery angiograms. These show continued filling of the extracranial arteries including (A) left and (B) right external carotid arteries.

injected and is detected by a radio counter in the nuclear medicine. One of the radioactive tracers used is Tc99m-DTPA. After bolus intravenous injection of the tracer, brain vascular flow is estimated. DTPA does not have the ability to cross the intact blood brain barrier, so intracranial blood flow is seen in normal patients. However, Tc99m-DTPA tracer has low resolution for brain vascular flow [7]. There are two other radiopharmaceuticals, namely Tc99m-HMPAO (hexamethylpropyleneamine oxime) and Tc99m-ECD (ethyl cysteinate dimer) [8]. Both of them are brain specific, lipophilic and after intravenous injection, they cross the blood brain barrier. Because of this property, they are accumulated proportional to the blood flow in normal gray matter including brain cells of cerebrum, cerebellum, and brainstem [8]. So, it is not only blood flow but also brain parenchyma is seen in the normal functioning brain. In this method, radioactive isotope is injected 30 min after its reconstitution. Images are taken immediately after injection, after 30 min, and finally after 2 hours. If there is no blood flow, there is no accumulation of tracer in the brain and brain looks hollow, this phenomenon is known as "hollow skull" or "empty bulb" sign (**Figure 2**). These injected radioactive tracer compounds are safe to the patients because they do not interact with their medication and have no associated side effects [8].

Disadvantages of this technique is sometimes posterior fossa may be difficult to visualize, and uptake may be affected by hypothermia and barbiturates [3]. It does not have the spatial resolution to detect isolated brainstem activity. Other disadvantages include associated time delay and availability of this technique. Nuclear

scintigraphy requires instrumentation, an experienced radiologist to interpret the test results, and the radioactive tracer used in this test is expensive and requires a trained pharmacist to reconstitute.

3.3 CT head

Computed tomography (CT) was introduced in 1970, since then it has revolutionized the assessment of head injuries including brain death [9]. It is fast, readily available, and requires no contrast medium. It is a standard imaging test for the patients admitted in the hospital because of brain injuries. Plain head CT scan can visualize brain tissue and lesion. It accurately diagnoses skull fractures, intracranial bleeds, brain contusions, and brain herniation. For diagnosis of brain death, a diffuse loss of gray-white mater differentiation needs to be established (**Figure 3**).

Plain head CT has several limitations in assessment of brain death. Plain head CT does not provide functional information of the brain and does not assess

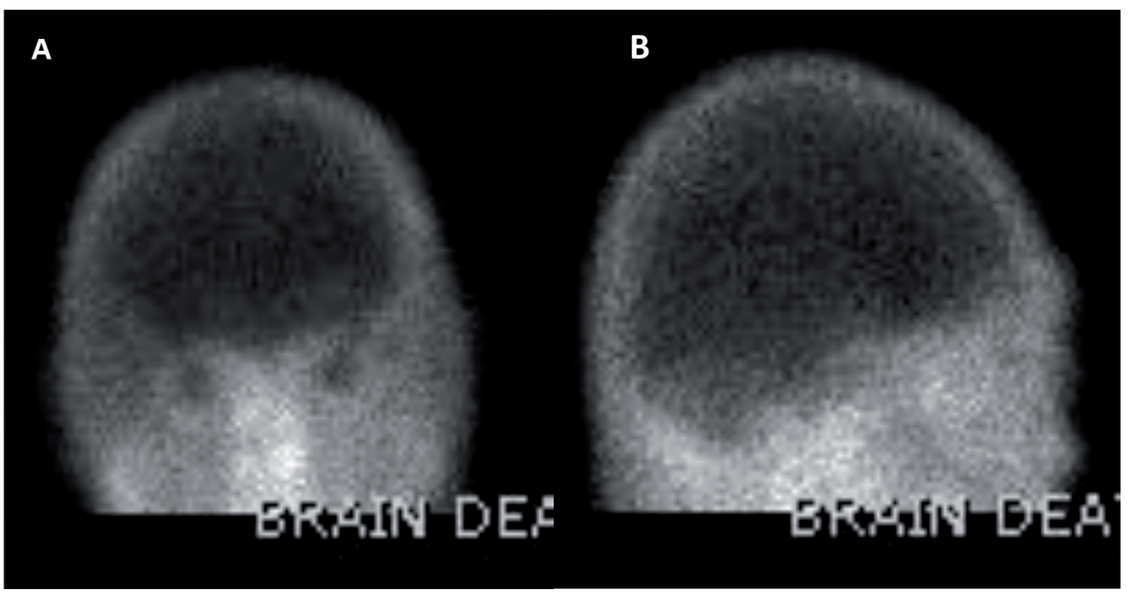

Figure 2.
"Hallow skull"/"empty bulb" sign shown in brain death patient using (A) AP and (B) lateral nuclear scintigraphy imaging. Flow and delayed imaging demonstrated no significant intracranial flow or parenchymal uptake.

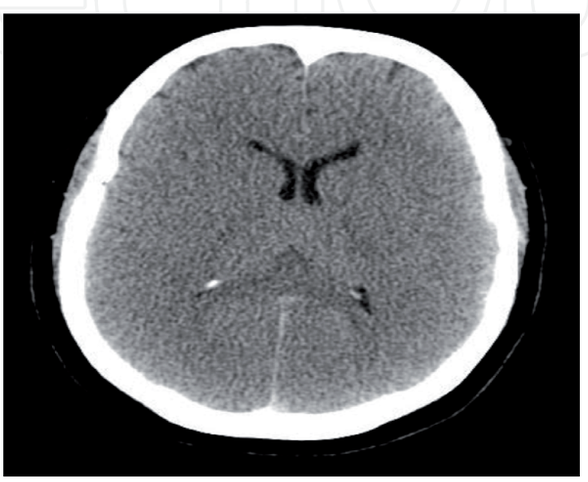

Figure 3.
Plain head CT image of a brain dead patient showing diffuse loss of gray-white mater differentiation.

intracranial blood flow. Diffuse loss of gray-white mater differentiation is likely a late phenomenon and the inter-rater reliability is poor [10].

Contrast enhanced CT of head can be acquired to assess brain blood flow but is delayed compared to CT angiography. Contrast-enhanced CT acquisition requires a delay of 5 min, whereas CT angiography requires only 12–16 seconds. This delay makes the contrast-enhanced CT highly susceptible to "stasis filling" of the brain blood vessels. Thus, plain head CT is not very reliable test in determining brain death.

3.4 Computed tomography angiography (CTA)

CTA is a valuable ancillary imaging technique for intracranial blood flow. CTA was first reported in 1998 as an ancillary test in diagnosing the brain death [11]. According to Dupas et al., in 14 patients who were diagnosed as brain dead using clinical criteria, the results were confirmed to have 100% sensitivity using CTA [11]. CTA is fast, non-invasive, technically noncomplicated, inexpensive, readily and widely available. It is perhaps the most widely available brain blood-flow test. CTA has a high spatiotemporal resolution and is relatively operator independent. Several European countries have adopted CTA as an ancillary test but not the United States [12, 13].

The technique of CTA involves rapid intravenous administration of iodinated contrast followed by volume scanning of the whole brain. For imaging of brain death at least two acquisitions should be performed, 60 seconds apart [9]. Others have proposed at least three acquisitions-arterial phase scanning after 20 seconds and venous phase scanning after 50–60 seconds [4].

Diagnostic criteria for brain death using CTA include lack of intracranial arterial contrast opacification. Lack of intracranial contrast opacification can be assessed by 4, 7, and 10 point scales. In 4 point scale, M4 (cortical) segments of middle cerebral artery (MCA) and intracerebral vein (ICV) are evaluated for contrast opacification [11]. The 7 point scale included evaluation of MCA-M4, anterior cerebral artery (ACA), ICV, and great cerebral vein (GCV) [14]. In the 10 point scale, all the seven segments of the 7 point scale plus posterior cerebral artery (PCA) and basilar artery are included [6]. In a recent study, Garret et al. assessed statistical performance of CTA in diagnosing brain death. For all the 18 patients included in the study, CTA had sensitivity of 75%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 33% [15]. Another recent study from Macdonald et al. reported the diagnostic accuracy and inter-rater reliability of different ancillary imaging tests used for brain death in 74 patients. They showed that CTA along with CTP and radionuclide scan had a specificity and positive predictive value of 100% [10]. These results certainly add to the growing medical literature that supports the use of CTA as a reliable ancillary imaging test in confirming the brain death. However, systematic reviews do not support use of CTA as an ancillary imaging test for confirmation of brain death [16, 17].

The disadvantages of CTA are that this is not widely available as a bedside test and patient needs to be transported to imaging facility and this is challenging for an intensive care unit (ICU) patient. However, this can be obviated by the use of portable CT scanners in the future. CTA provides incomplete quantitative measurement of cerebral blood flow due predominantly of "stasis filling" (**Figure 4**). It is defined as delayed, weak persistent opacification of proximal cerebral arteries. This phenomenon causes a major problem in the development of reliable CTA protocol for the diagnosis of brain death [6]. There is also potential risk of damage to the organs of the brain death patients because of iodinated

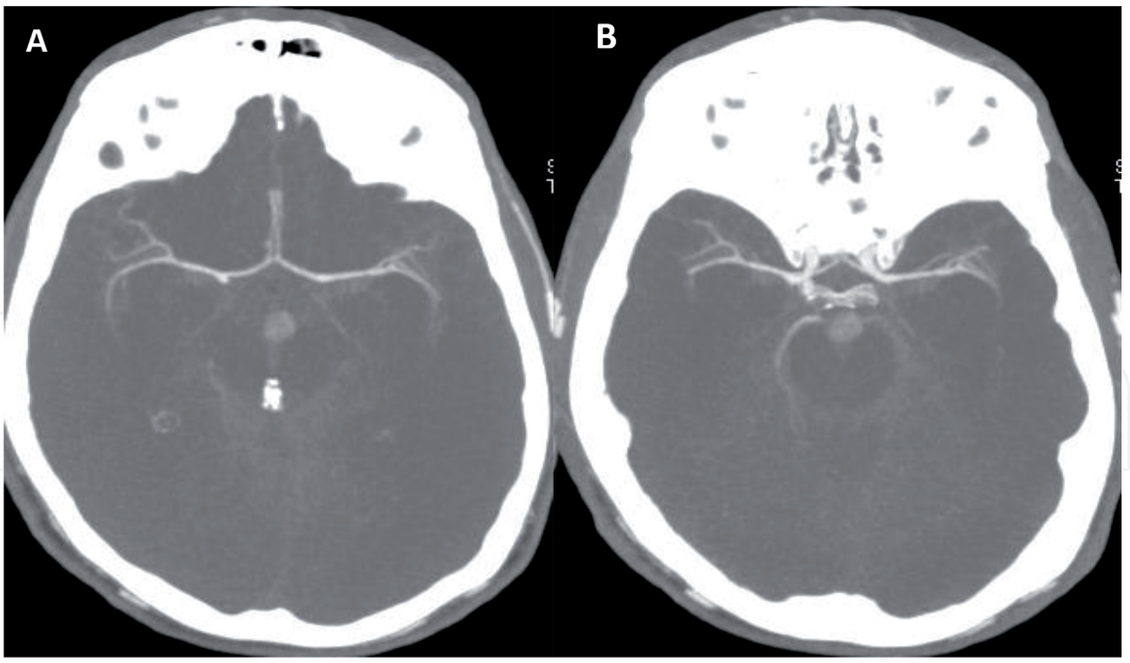

Figure 4.
Axial CTA images (A, B) in patient with clinically confirmed brain death show contrast opacification of bilateral internal carotid arteries, proximal branches of bilateral middle, and anterior cerebral arteries. None of the two images show opacification of M4 or cortical branches of middle cerebral arteries, distal anterior cerebral artery (ACA), internal and great cerebral vein. There is some opacification of only right posterior cerebral artery. There is continued filling of the extra cranial arteries.

contrast media used in CTA. However based on the volume of contrast used for CTA, this is rare or negligible [18, 19].

3.5 Computed tomography perfusion (CTP)

CTP is an advanced CT scan technique that provides both anatomical as well as functional information about the brain. CTP is useful in detecting perfusion even in small vessels such as arterioles, capillaries, and venules [20]. CTP is routinely used for evaluation of cerebral ischemia and vascularization of brain tumors and has the spatial resolution to quantify perfusion in any selected part of the brain [21, 22]. This imaging technique can help in calculation of cerebral blood flow (CBF) and cerebral blood volume (CBV). Normal CBF in the brain is 50–60 ml/100 mg/min and CTP can measure as low as 1.2 ml/100 mg/min [20]. CTP is very sensitive in detecting the blood flow and can detect decreased perfusion as low as 2–3% in CBF and 2% in CBV [23]. In CTP acquisition protocol, patients will undergo whole brain coverage with 80 kVp, 100 mAs resulting in a radiation dose of approximately CT dose index of 189.64 mGy [20]. A minimum scan duration of 60 seconds is recommended to reliably cover the venous phase of the circulation. A total of 40 ml nonionic iodinated contrast medium injected at the rate of 5 ml/seconds, followed by 40 ml of saline flush at the rate of 5 ml/seconds. Regular perfusion analysis is performed if intracranial arteries are seen on the source images [20]. Whole brain death could be seen as no intracranial CBF or CBV (**Figure 5**). Shankar et al. compared CTP and CTA derived from the CTP for confirmation of brain death in a retrospective review of 11 patients clinically suspected of brain death [20]. CTA showed a sensitivity of 72.7% for 7- and 4-point scales, 81.8% sensitivity for opacification of ICV, and 100% sensitivity for CTP scores in the brainstem [20]. They, for the first time, showed that CTP can be a valuable ancillary tool in early detection of brain death. Recently, Sawicki et al. tested the reliability and diagnostic accuracy of CTP over CTA in determining brain death [24]. For whole brain CTP,

they also showed a sensitivity of 100% to confirm the diagnosis of brain death [24]. MacDonald et al. showed similar sensitivity [10].

CTP can also evaluate brain-stem specific CBF [10, 20]. The concept of isolated brainstem death was first proposed by Shankar et al. in clinically confirmed brain death patients (**Figure 6**) [20]. Exact pathophysiological mechanism behind isolated brainstem death is not yet known. This is described when in patients with

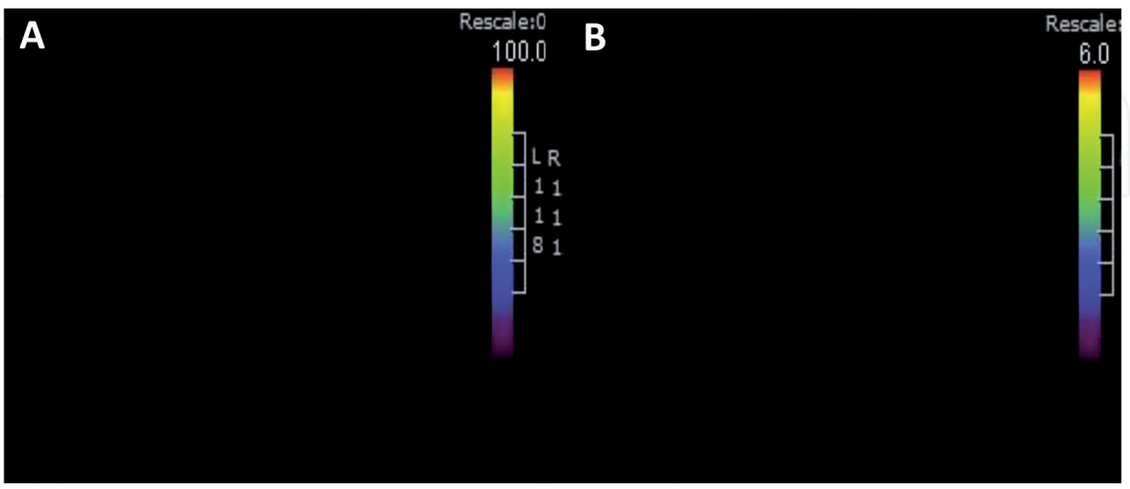

Figure 5.
CT perfusion showing no detectable cerebral blood flow (CBF) (A) and cerebral blood volume (CBV) (B) in the whole brain.

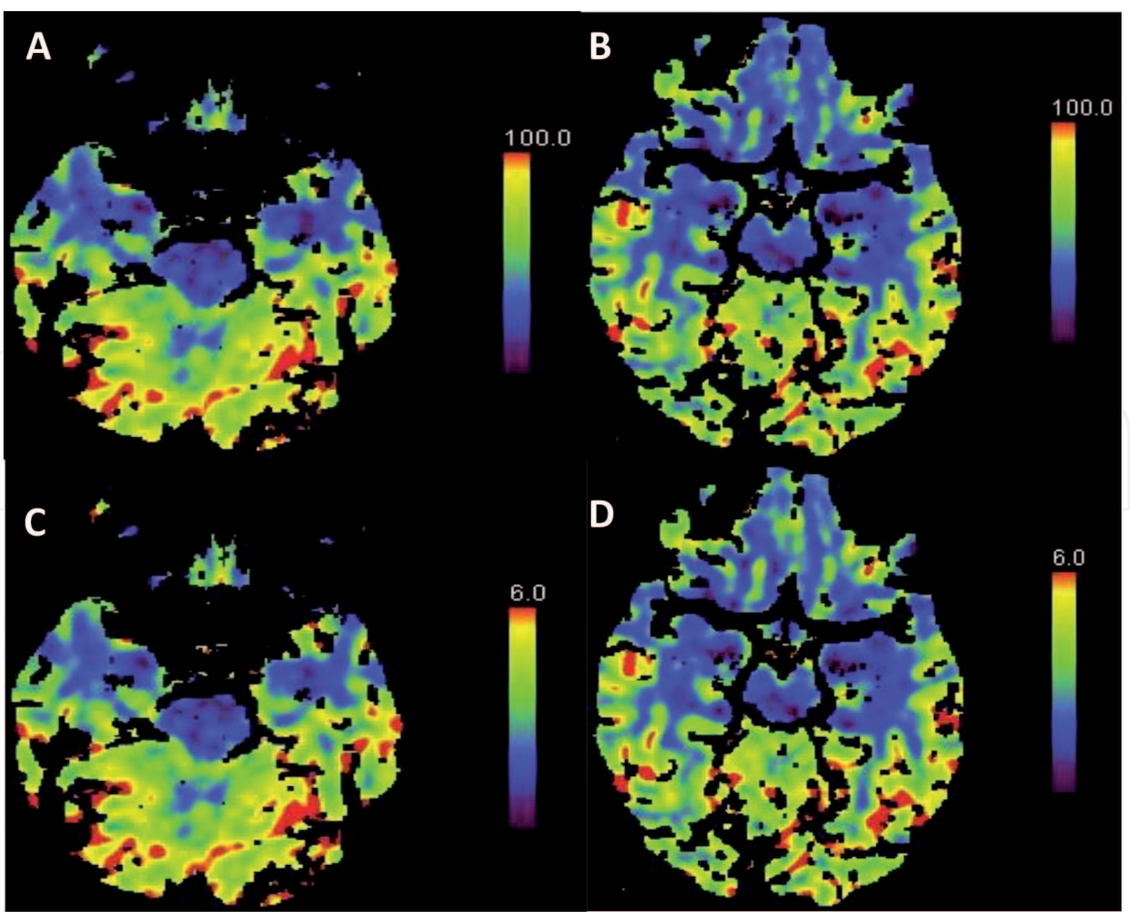

Figure 6.
CT perfusion showing matched defect on cerebral blood flow (CBF) (A and B) and cerebral blood volume (CBV) (C and D) maps in brainstem only. The supratentorial brain as well as cerebellum showed preserved CBF and CBV.

clinically confirmed brain death, there is presence of blood flow in the supratentorial brain and isolated absence of blood flow in the brainstem [10, 20]. Clinical examination does not differentiate between whole brain death and isolated brainstem death. CTP is the first imaging test reported to show the phenomenon of isolated brainstem death [10, 20]. It is suspected that isolated brainstem death is an earlier phenomenon in the process of brain death and may help early declaration of brain death [10]. However, the concept of brainstem death is debatable at the present time, and more studies are needed to establish this phenomenon.

Like CTA, CTP is a widely available tool and with the availability of automated software, CTP is relatively operator-independent [20]. The advantage of CTP is that it can be performed along with CTA. CTP has a presumed risk of contrast induced renal damage in the patients with kidney disease. But, based on the volume of contrast used for CTP, the chances of nephrotoxicity is very rare or negligible [18, 19].

3.6 Magnetic resonance imaging (MRI)

It is a reliable high-resolution imaging of brain and has been used for imaging for brain death. MRI has an advantage of not requiring nephrotoxic contrast material for demonstration of cerebral blood flow. It is noninvasive and accurate in identifying structural abnormalities in the brain. Common MRI findings in brain death patients are variable edema, diffuse cortical high signal intensity, diffuse cerebral white matter injury, and tonsillar herniation [25, 26]. Lovblad and colleagues demonstrated the usefulness of diffusion weighted imaging (DWI) in the diagnosis of brain death [27]. They reported that apparent diffusion coefficient (ADC) values are reduced in brain death patients when compared to the normal individuals [27]. Using DWI and ADC mapping, it is possible to identify areas of cytotoxic damage and ischemic damage [4]. However, this has not been accepted in the imaging guidelines for brain death. The major disadvantages of this method are the length of the scan time and obtaining MRI on ventilated patients as they may have several contraindications to MRI.

3.7 Magnetic resonance angiography (MRA)

It is a reliable test for cerebral blood flow [28] and can detect intracranial arterial blood flow and flow voids (**Figure 7**). However, MRA has not yet been proven as an ancillary test in assessing the brain death. Time of flight MRA is relatively immune to "stasis filling" when compared to CTA or DSA. Like any MRI, the patient needs

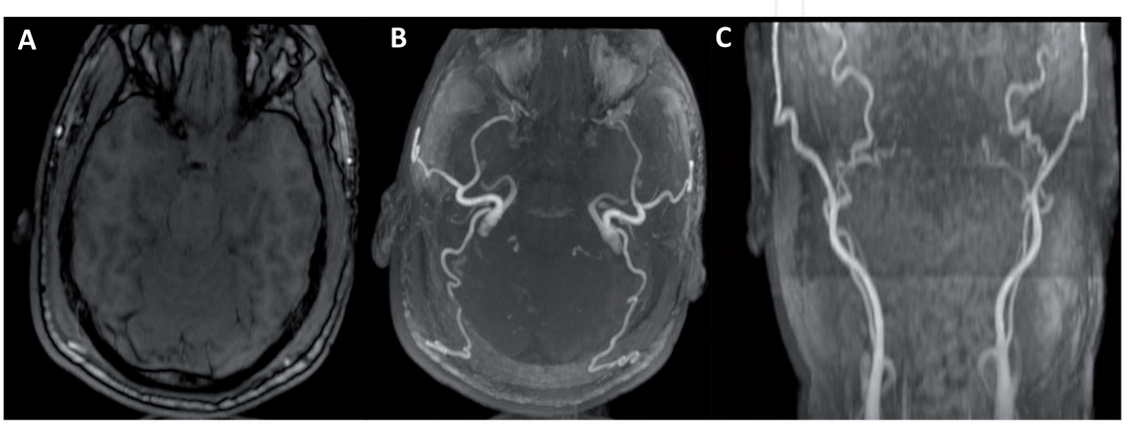

Figure 7.
Time of flight MR angiography image of a brain dead patient showed no intracranial flow but preserved extracranial flow on source image (A), axial (B), and coronal (C) maximum intensity projection images.

transportation to the radiology department, and the length of time for MRA is longer than that for CTA or CTP. There is requirement of having specialized critical care equipment in a scanner.

3.8 Magnetic resonance perfusion (MR perfusion)

MRP is noninvasive and can be used to detect intracranial arterial blood flow. It can also detect perfusion parameters of affected brain tissues such as cerebral blood flow and cerebral blood volume. There are not many reports in the literature that used MR perfusion as an ancillary imaging tool, and more research studies are needed to establish the reliability of this technique in the clinical setting.

4. Conclusions

For clinical confirmation of brain death, the three essential criteria are apnea, absence of brain stem reflexes, and coma. In situations where brain death cannot be confirmed by one of these clinical tests or there are uncertainties around the reliability of clinical examination, ancillary imaging techniques are required to confirm brain death. We describe different ancillary imaging tests commonly used and reported to confirm the brain death. More research is required to validate these tests to become gold standards in the clinical practice.

Conflict of interests

Jai Shankar is the co-PI of ongoing INDEX study for prospective evaluation of CT perfusion for confirmation of brain death.

Author details

Sudharsana Rao Ande and Jai Jai Shiva Shankar*
Division of Neuroradiology, Department of Radiology, University of Manitoba, Winnipeg, MB, Canada

*Address all correspondence to: shivajai1@gmail.com

References

[1] Heran MKS, Heran NS, Shemie SD. A review of ancillary tests in evaluating brain death. Canadian Journal of Neurological Sciences. 2008;**35**(4):409-419

[2] Shemie SD, Doig C, Dickens B, Byrne P, Wheelock B, Rocker G, et al. Severe brain injury to neurological determination of death: Canadian forum recommendations. Canadian Medical Association. 2006;**174**(6):S1-S13

[3] Busl KM, Greer DM. Pitfalls in the diagnosis of brain death. Neurocritical Care. 2009;**11**(2):276-287

[4] Sawicki M, Wojczal J, Birkenfeld B, Cyrylowski L. Brain death imaging. In: Saba L, Raz E, editors. Neurovascular Imaging. New York, NY: Springer; 2014. pp. 1-33. Available from: http://link.springer.com/10.1007/978-1-4614-9212-2_26-1

[5] Young GB, Shemie SD, Doig CJ, Teitelbaum J. Brief review: The role of ancillary tests in the neurological determination of death. Canadian Journal of Anesthesia. 2006;**53**(6):620-627

[6] Sawicki M, Bohatyrewicz R, Safranow K, Walecka A, Walecki J, Rowinski O, et al. Dynamic evaluation of stasis filling phenomenon with computed tomography in diagnosis of brain death. Neuroradiology. 2013;**55**(9):1061-1069

[7] Munari M, Zucchetta P, Carollo C, Gallo F, De Nardin M, Marzola MC, et al. Confirmatory tests in the diagnosis of brain death: Comparison between SPECT and contrast angiography. Critical Care Medicine. 2005;**33**(9):2068-2073

[8] Zuckier LS, Kolano J. Radionuclide studies in the determination of brain death: Criteria, concepts, and controversies. Seminars in Nuclear Medicine. 2008;**38**(4):262-273

[9] Rosenblum ML, Hoff JT, Norman D, Weinstein PR, Pitts L. Decreased mortality from brain abscesses since advent of computerized tomography. Journal of Neurosurgery. 1978;**49**(5):658-668

[10] MacDonald D, Stewart-Perrin B, Shankar JJS. The role of neuroimaging in the determination of brain death. Journal of Neuroimaging. 2018;**28**(4):374-379

[11] Dupas B, Gayet-Delacroix M, Villers D, Antonioli D, Veccherini MF, Soulillou JP. Diagnosis of brain death using two-phase spiral CT. American Journal of Neuroradiology. 1998;**19**(4):641-647

[12] Wijdicks EFM. Brain death worldwide: Accepted fact but no global consensus in diagnostic criteria. Neurology. 2002;**58**(1):20-25

[13] Beltramello A, Casartelli Liviero M, Bernardi B, Causin F, Di Paola F, Muto M, et al. Computed tomography angiography: A double step methodology in brain death confirmation. Minerva Anestesiologica. 2014;**80**(7):862-863

[14] Leclerc X, Taschner CA, Vidal A, Strecker G, Savage J, Gauvrit JY, et al. The role of spiral CT for the assessment of the intracranial circulation in suspected brain-death. Journal of Neuroradiology. 2006;**33**(2):90-95

[15] Garrett MP, Williamson RW, Bohl MA, Bird CR, Theodore N. Computed tomography angiography as a confirmatory test for the diagnosis of brain death. Journal of Neurosurgery. 2018;**128**(2):639-644

[16] Kramer AH, Roberts DJ. Computed tomography angiography in the

diagnosis of brain death: A systematic review and meta-analysis. Neurocritical Care. 2014;**21**(3):539-550

[17] Taylor T, Dineen RA, Gardiner DC, Buss CH, Howatson A, Pace NL. Computed tomography (CT) angiography for confirmation of the clinical diagnosis of brain death. Cochrane Database of Systematic Reviews. 2014;**3**:CD009694

[18] Hopyan JJ, Gladstone DJ, Mallia G, Schiff J, Fox AJ, Symons SP, et al. Renal safety of CT angiography and perfusion imaging in the emergency evaluation of acute stroke. American Journal of Neuroradiology. 2008;**29**(10):1826-1830

[19] Krol AL, Dzialowski I, Roy J, Puetz V, Subramaniam S, Coutts SB, et al. Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography. Stroke. 2007;**38**(8):2364-2366

[20] Shankar JJS, Vandorpe R. CT perfusion for confirmation of brain death. American Journal of Neuroradiology. 2013;**34**(6):1175-1179

[21] Shankar JJS, Woulfe J, Silva VD, Nguyen TB. Evaluation of perfusion CT in grading and prognostication of high-grade gliomas at diagnosis: A pilot study. American Journal of Roentgenology. 2013;**200**(5):W504-W509

[22] Shankar JJS, Langlands G, Doucette S, Phillips S. CT perfusion in acute stroke predicts final infarct volume-inter-observer study. Canadian Journal of Neurological Sciences. 2016;**43**(1):93-97

[23] Uwano I, Kudo K, Sasaki M, Christensen S, Østergaard L, Ogasawara K, et al. CT and MR perfusion can discriminate severe cerebral hypoperfusion from perfusion absence: Evaluation of different commercial software packages by using digital phantoms. Neuroradiology. 2012;**54**(5):467-474

[24] Sawicki M, Sołek-Pastuszka J, Chamier-Ciemińska K, Walecka A, Bohatyrewicz R. Accuracy of computed tomographic perfusion in diagnosis of brain death: A prospective cohort study. Medical Science Monitor. 2018;**24**:2777-2785

[25] Ishii K, Onuma T, Kinoshita T, Shiina G, Kameyama M, Shimosegawa Y. Brain death: MR and MR angiography. American Journal of Neuroradiology. 1996;**17**(4):731-735

[26] Karantanas AH, Hadjigeorgiou GM, Paterakis K, Sfiras D, Komnos A. Contribution of MRI and MR angiography in early diagnosis of brain death. European Radiology. 2002;**12**(11):2710-2716

[27] Lövblad KO, Bassetti C, Basssetti C. Diffusion-weighted magnetic resonance imaging in brain death. Stroke. 2000;**31**(2):539-542

[28] Drake M, Bernard A, Hessel E. Brain death. The Surgical Clinics of North America. 2017;**97**(6):1255-1273