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Radionuclide Studies in the Determination of Brain Death: Criteria, Concepts, and Controversies

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Forty years after the publication of a landmark paper by the Ad Hoc Committee of the Harvard Medical School, the general concept of brain death has achieved widespread acceptance. In the United States, irreversible dysfunction of the brain and brainstem are required for the diagnosis of brain death. Although primarily based on clinical evaluation, confirmatory examinations, including radionuclide blood flow studies, play an important role in augmenting the physical examination in special situations when some of its specific components cannot be performed or reliably evaluated. The 2 main radionuclidic techniques used in evaluation of brain death are radionuclide angiography with nonlipophilic radiopharmaceuticals and parenchymal imaging with lipophilic agents. Specific technical guidelines for determination of brain death have been promulgated by professional medical societies. In the vast majority of cases, blood flow examinations are useful in confirming brain death. Nonetheless, on occasion patients clinically diagnosed with brain death will exhibit persistent intracranial blood flow or electrical activity. Existence of these contradictory cases reveals underlying inconsistencies in the definitions of brain death. We hypothesize that the existence of these apparent contradictions is related to differences in sensitivity of the physical examination and the confirmatory examinations, differences in localization of the physical examination and confirmatory tests, and differences between blood flow and cerebral function as markers of brain death.
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Forty years have passed since a landmark paper by the Ad Hoc Committee of the Harvard Medical School appeared in the *Journal of the American Medical Association*, introducing the term "brain death" into the medical and lay lexicon.[1] Controversy regarding brain death persists in the neurologic and imaging literature,[2-6] thereby creating a need for ongoing analysis and commentary. Very few areas of nuclear medicine are as charged with legal and ethical import as the determination of brain death; it is therefore appropriate to periodically review and reformulate our understanding of this topic.

Definition of Death

The definition of death, and therefore the determination of its precise onset, is a societal construct informed by legal, moral, and religious beliefs and is based on underlying scientific hypotheses and facts. The historical definition of death embraced by most western societies is absent circulation and breathing. Before recent medical advances, patients who sustained a neurologic injury that disrupted the central control of respiration would quickly progress to hypoxia, asystole, and classic cardiopulmonary death. With the development of intensive care units and advances in resuscitation, many of these patients were being sustained by artificial ventilation, in some cases leading to prolonged and irreversible coma. Increased use of resources on one hand and need for organs to transplant on the other challenged society to broaden the definition of death and propelled debate on this topic to the national agenda.[7]

Brain Death

In 1968, the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death introduced a new paradigm of death based on "irreversible coma in patients with no discernible central nervous system activity."[1] In the United States, this concept of brain death was further codified into law in the early 1980s by the President's Commission for the Study of Ethical Problems in Medicine, which proposed a Uniform Determination of Death Act that was

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ultimately written into state laws, albeit with regional variations.[8] This Act specifies a definition of death based on irreversible cessation of all functions of the entire brain, including the brain stem, with determination of death in accordance with accepted medical standards. Specific technical guidelines for determination of brain death have therefore been promulgated by professional medical societies. Current recommendations of the American Academy of Neurology[9] and the American Academy of Pediatrics Task Force[10] are summarized in Table 1. In accordance with these guidelines, the term "brain death" in the United States is used to describe the irreversible dysfunction of the entire brain and brainstem, the so-called "whole brain" standard; this convention will be followed in this review as well. Similar or variant formulations of brain death have been adopted throughout the world[11,12]; a "brain stem death" standard used in the United Kingdom is defined as irreversible dysfunction of the brain stem alone.[13]

The American Academy of Neurology's practice parameters for determining brain death in adults defines brain death as "the irreversible loss of function of the brain, including the brainstem."[9] Prerequisites to diagnosing brain death based on physical examination include a sufficient mechanism of injury, lack of confounding factors such as drug intoxication or poisoning, and exclusion of complicating medical conditions that may interfere with clinical assessment, including hypothermia or severe electrolyte, acid-base, and endocrine disturbances.

Three cardinal findings are present in brain death. The first essential finding is coma, with no response to noxious stimuli. The state of coma may derive either from massive injury to the cortex or from injury to the reticular activating system of the brainstem, which mediates wakefulness. The second essential finding is absence of brain stem reflexes. These include reflexes deriving from the midbrain, pons, and medulla, which are tested by examination of the cranial nerves. Finally, apnea testing is performed according to a very spe-

Table 1 Definition of Brain Death

	American Academy of Neurology[9]	American Academy of Pediatrics[10]
Publication date	May 1995	August 1997
Definition	Irreversible loss of function of the brain, including brain stem	Irreversible cessation of all functions of the entire brain including the brainstem
Relevant age	≥18 years	≥Term + 7 days
Prerequisites	Evidence of acute central nervous system catastrophe compatible with brain death	Proximate cause excludes reversible conditions
	Exclusion of confounding conditions (electrolyte, acid-base, endocrine)	No metabolic disorders
	No drug intoxication/poisoning	No sedative-hypnotic drugs or paralytic agents
	Core temp ≥ 32°C	No hypothermia or hypotension
Cardinal findings	Coma	Coma
	Apnea	Apnea
	Absent brainstem reflexes	Absent brainstem function
	Pupils	Pupils
	Ocular movement	Ocular movement
	Facial sensation and motor response; corneal reflex	Facial and oropharynx movement; corneal reflex
	Pharyngeal and tracheal reflexes	Pharyngeal and tracheal reflexes
		Sucking, rooting
		Flaccid tone
Confirmatory tests	Included tests:	Included tests:
	Conventional angiography	Conventional angiography
	EEG	EEG
	^{99m}Tc-HMPAO	Cerebral radionuclide angiography
	Transcranial Doppler	Investigational methods
	Somatosensory evoked potentials	
	Recommended if specific components of clinical testing cannot be performed	Recommended according to table below
Repeat exam	Recommended at arbitrary interval (ie, 6 hours)	7 days to 2 months: 2 exams and EEGs separated by at least 48 hours
		2 months to 1 year: 2 exams and EEGs separated by at least 24 hours*
		≥1 year with irreversible cause: No lab testing. 12 hour observation
		≥1 year with questionable reversibility: 24 hour observation†

*Repeat exam and EEG not needed if radionuclide angiographic study demonstrates no visualization of cerebral arteries.
†Observational period may be reduced with confirmatory EEG or cerebral radionuclide angiography.

Table 2 Comparison of Confirmatory Examinations

Examination	Availability	Sedative Influence	Bedside	Toxicity	Region of Sensitivity		
					Cerebrum	Cerebellum	Brain Stem
Physical exam	Yes	Yes	Yes	No			+
EEG	Yes	Yes	Yes	No	Superficial		
RN angiography	Yes	No	Possibly*	No	+		
RN parenchymal imaging (planar)	Yes	No	Possibly*	No	+	+	
RN parenchymal imaging (tomography)	Usually	No	No	No	+	+	+
Contrast angiography	Yes	No	No	Yes	+	+	+
Transcranial Doppler sonography	Operator dependent	No	Yes	No	+		

RN, radionuclide; +, sensitive.
*If portable camera is available.

cific protocol that is both rigorous and protective of the patient from hypoxia. The American Academy of Neurology recommends a repeat clinical evaluation 6 hours after the first[9] whereas the American Academy of Pediatrics Task Force[10] requires a repeat examination after a variable interval that depends on the age of the child studied (Table 1). Legal codes in most jurisdictions require performance of a second clinical examination between 6 and 24 hours after the initial examination.

Confirmatory Examinations in Brain Death

Although the cardinal findings in brain death are determined on physical examination, confirmatory examinations, including imaging tests, may be called on in special situations to supplement the physical examination when specific components cannot be reliably performed or evaluated.[9] These include situations in which the proximate cause of injury is

Table 3 Technique

	Society of Nuclear Medicine[17]	American College of Radiology[18]
General method		
Scalp tourniquet	Optional	Optional
Collimator	LEHR or UHR	LEAP or LEHR
Preference	Diffusible radiopharmaceutical	Not recorded
Nondiffusible		
Radiopharmaceutical	DTPA	TcO_4^-, DTPA or GHA
Amount (adult)	555 to 740 MBq	≤925 MBq
Flow Views	Anterior	Anterior
Flow frame duration	1 to 3 sec/frame × 1 minute	1 sec/frame × 1 minute
Static delay	None	None
Static views	Anterior, both laterals, posterior*	Anterior, lateral,† posterior,† submental vertex†
Static duration	5 minutes	300 to 500K counts
Diffusible		
Radiopharmaceutical	HMPAO or ECD	HMPAO or ECD
Amount (adult)	370 to 1110 MBq	≤1110 MBq
Flow Views	Anterior*	Anterior†
Flow frame duration	1 to 3 sec/frame × 1 minute	1 sec/frame × 1 minute
Static delay	≥20 min	15 to 60 min
Static views	Anterior, both laterals, posterior*	Anterior, lateral,† posterior†
Static duration	NS	500 to 1000K counts
SPECT	Optional	Optional

LEAP, Low energy, all purpose; LEHR, low energy, high resolution; UHR, ultra-high resolution; TcO_4^-, ^{99m}Tc-pertechnetate; DTPA, ^{99m}Tc-diethylene triamine penta-acetic acid; GHA, ^{99m}Tc-glucoheptonate; HMPAO, ^{99m}Tc-hexamethyl propylene amine oxime; ECD, ^{99m}Tc-ethyl cysteinate dimer; NS, not specified.
*Recommended.
†Optional.

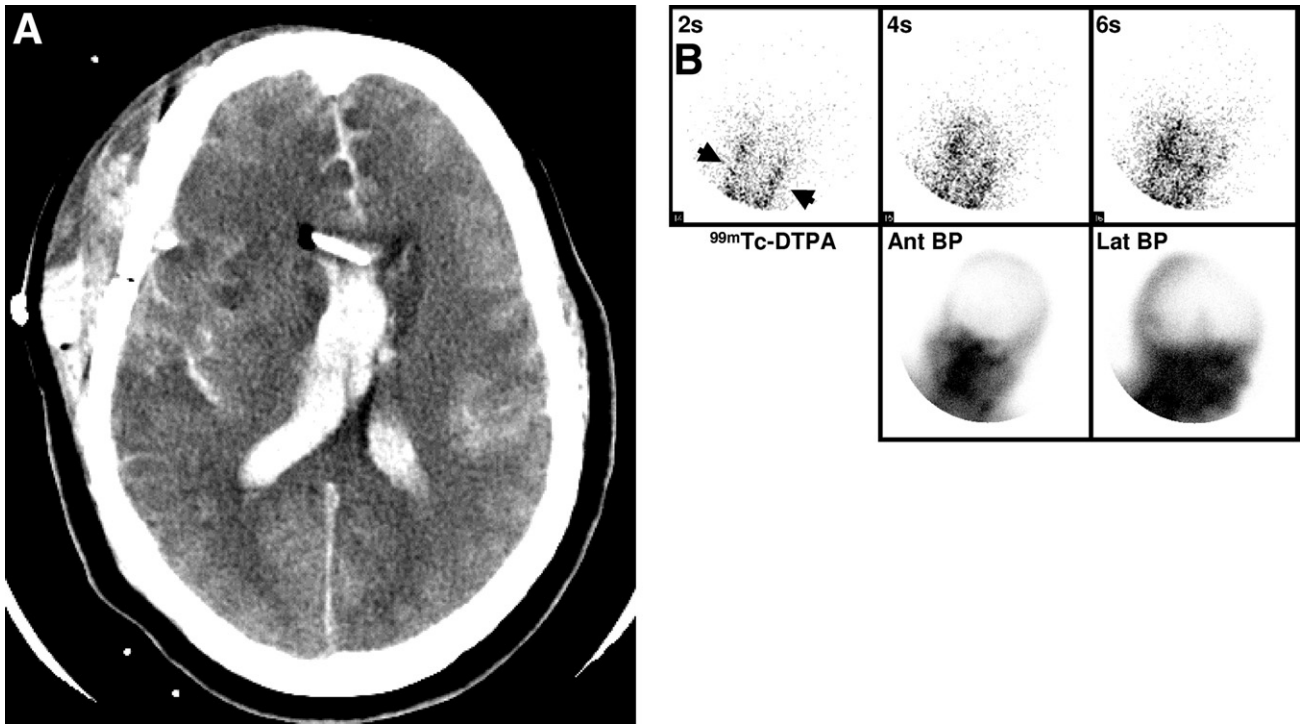

Figure 1 A 47-year-old subject with subarachnoid hemorrhage. The patient is status post right frontal temporal craniotomy with postoperative changes and placement of 2 aneurysm clips in situ. (A) Noncontrast CT scan demonstrates extensive subarachnoid hemorrhage with right-to-left midline shift. There is bilateral frontal edema, greater on the right than the left. Marked intraventricular hemorrhage is present with an intraventricular drainage catheter noted. (B) ^{99m}Tc-DTPA radionuclide angiographic blood flow study demonstrates flow in the common carotid arteries (bold arrows) but no visualization of anterior or middle cerebral arteries indicating lack of intracranial flow. On blood pool images, the superior saggital sinus is not seen, a further confirmation of absent intracranial flow.

unknown, where confounding factors such as elevated levels of central nervous system sedatives or neuromuscular blockers are present, or where a complete examination cannot be performed because of facial trauma or pupillary abnormalities. In these cases, confirmatory examinations can be used in lieu of the missing physical examination components. According to some state laws, confirmatory tests can also serve to replace or expedite performance of a required repeat second clinical examination.

Confirmatory tests for brain death include tests of electrical activity (electroencephalography [EEG] and somatosensory evoked potentials), as well as radiologic examinations of blood flow (commonly contrast angiography, transcranial Doppler ultrasound, and radionuclide methods, described herein). In addition to EEG and somatosensory evoked potentials, the American Academy of Neurology enumerates 3 confirmatory methods of evaluating blood flow: conventional contrast angiography, transcranial Doppler ultrasonography, and ^{99m}Tc-exametazime (HMPAO) radionuclide scintigraphy.[9] State laws have generally permitted additional methods of evaluation in accordance with accepted medical standards.

Issues of relevance to the clinician in choosing a confirmatory examination include availability on evenings and weekends, accuracy across multiple operators and readers, the ability to perform the examination at the bedside, and potentially deleterious effects of the examination on the patient or patient's organs that may be slated for transplantation. An optimal examination should additionally be unaffected by drug effects or metabolic disturbances, should be relatively standardized, and should be sufficiently robust to establish that brain death is or is not present on its own accord.[3] In these measures, no confirmatory examination is ideal however the radionuclidic examinations have compared favorably to the other available methods (Table 2).

Radionuclidic Examinations of Brain Death

Of relevance to nuclear medicine practitioners, radionuclide studies have been used as confirmatory tests in the determination of brain death for almost 4 decades.[14] Several outstanding reviews have been published regarding these applications,[15,16] and the performance and criteria of interpretation of radionuclide techniques has been standardized in a number of published practice guidelines. Current recommendations of the Society of Nuclear Medicine[17] and the American College of Radiology[18] are summarized in Table 3.

Historically, 2 main radionuclidic techniques have been used in evaluation of brain death, which we will term "radionuclide angiography" and "parenchymal imaging" for consis-

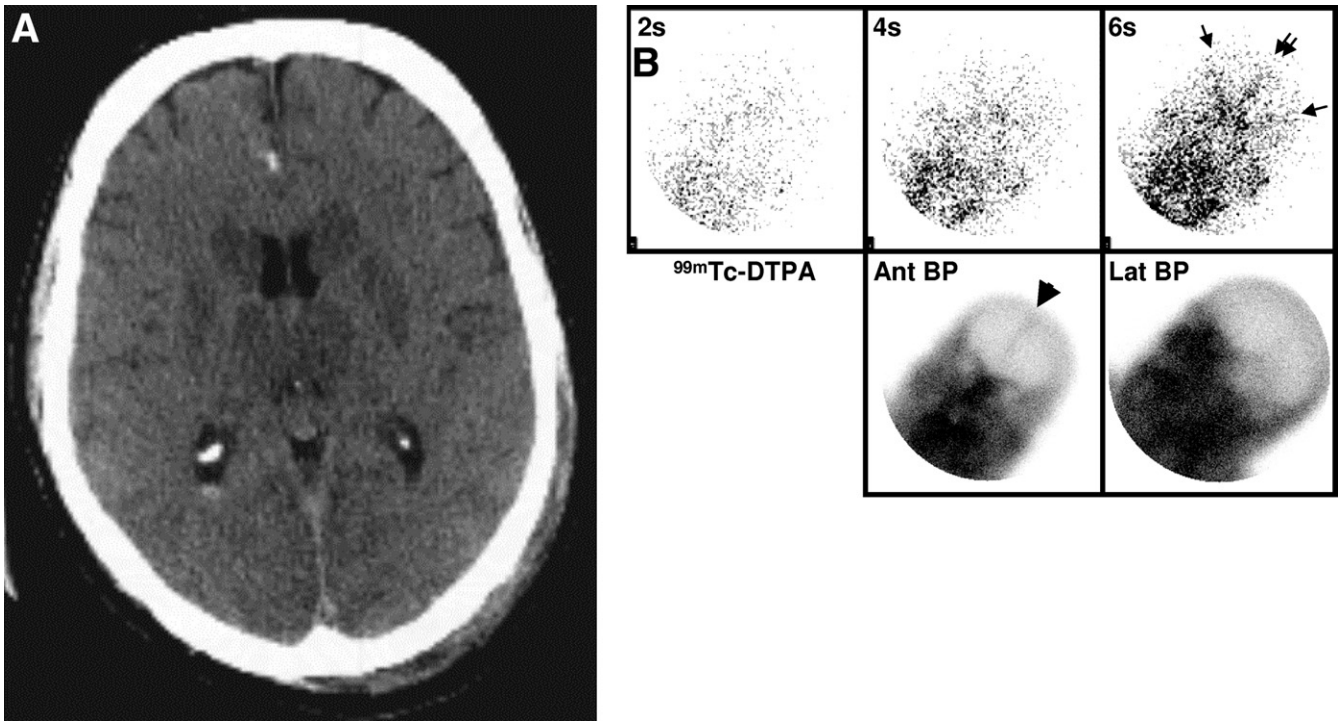

Figure 2 A 35-year-old patient status post seizure and fall. (A) Noncontrast CT scan demonstrates low attenuation of basal ganglia and the occipital cortex consistent with anoxic changes. Subdural hemorrhage along the interhemispheric falx is present. Other findings on this study not visible at this level include bifrontal subarachnoid hemorrhage and a left temporal intraparenchymal bleed. (B) ^{99m}Tc-DTPA blood flow study indicates persistence of flow within the anterior (double arrow) and middle (single arrows) cerebral arteries on the 2-second radionuclide angiographic images (upper row). Anterior blood pool image demonstrates presence of the superior venous sinus (heavy arrow).

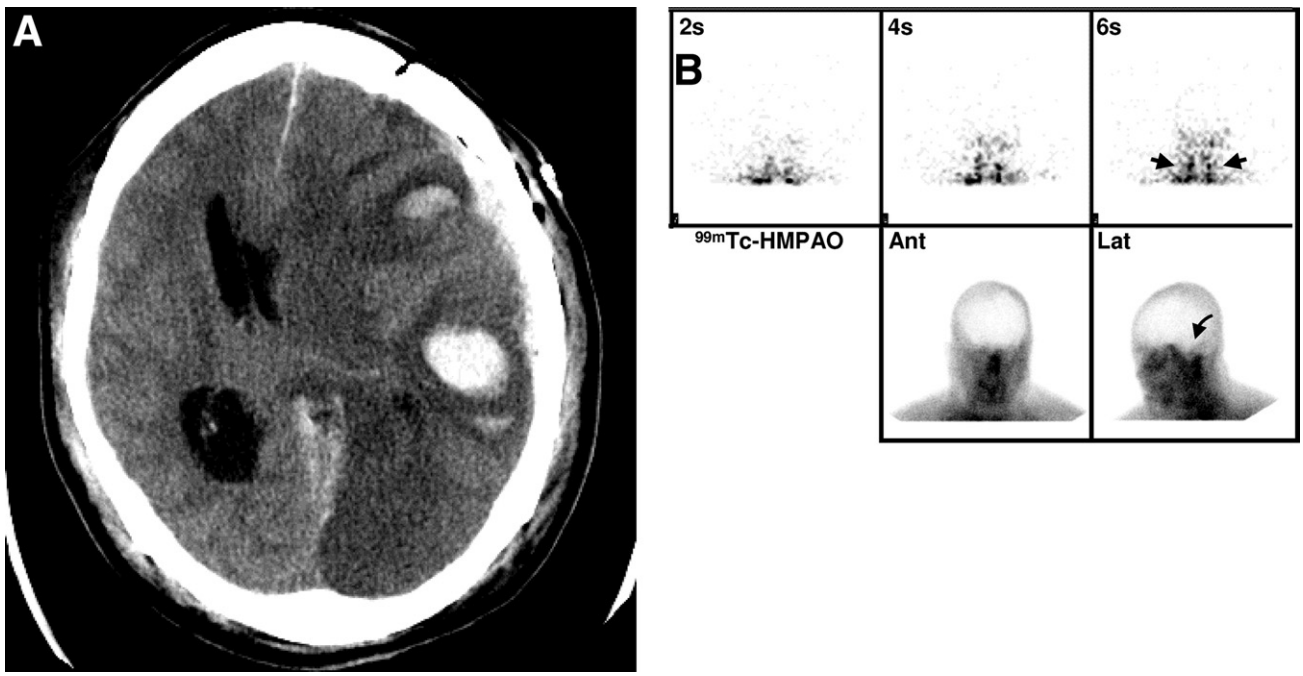

Figure 3 A 53-year-old subject with traumatic brain injury. (A) Noncontrast CT scan shows mass effect and midline shift of the brain to the right. Hematoma is present in the left frontal and parietal regions. An infarct is noted in the distribution of the posterior cerebral artery distribution secondary to herniation. (B) While the common carotid arteries are visualized on representative 2-second ^{99m}Tc-HMPAO flow images (arrows), no anterior cerebral or middle cerebral arterial flow is seen, nor is there parenchymal uptake on delayed views, in either the region of the cerebrum or posterior fossa (curved arrow). Present findings indicate absent intracranial blood flow. Because of overlying parotid gland and other soft tissues, it is difficult to evaluate perfusion of the brainstem on planar examination.

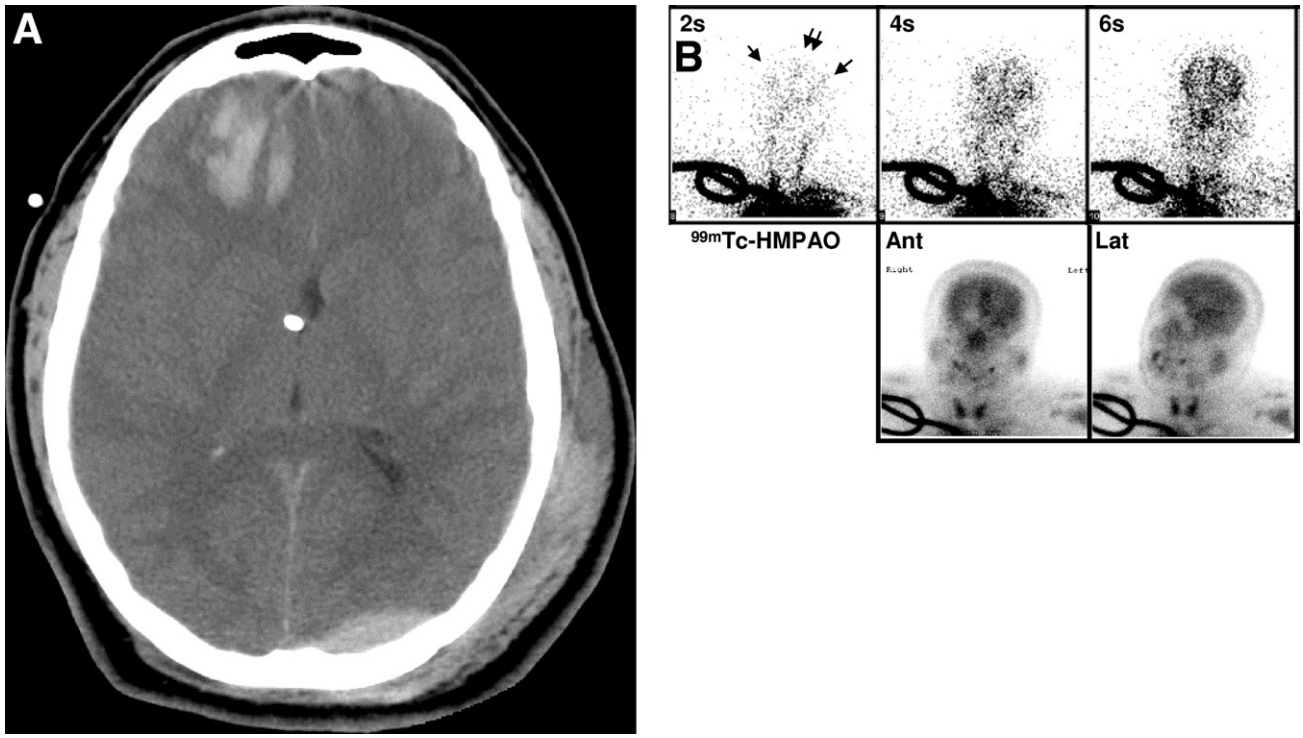

Figure 4 A 19-year-old man after a motorcycle accident with clinical evidence of brain death. (A) Noncontrast CT scan demonstrates a large right frontal lobe contusion and left epidural hematoma of the occiput and posterior fossa with significant mass-effect. A ventriculostomy catheter is seen with its tip in the right foramen of Monro. Other findings on this study not visible at this level include bony fractures, distortion of the left side of the midbrain, and effacement of the supracellar cistern suggestive of incipient supratentorial herniation. (B) Anterior and middle cerebral arterial flow is seen on representative 2-second ^{99m}Tc-HMPAO flow images (arrows), and there is diffuse uptake within the cerebrum and cerebellum on anterior and lateral parenchymal images. Lateral images may be submitted in suboptimal projection due to difficulty in positioning patients with endotracheal tubes and multiple vascular lines.

tency's sake. Radionuclide angiography was the initial radionuclidic imaging method used to evaluate cerebral blood flow.[14] Radiopharmaceuticals with rapid renal clearance (^{99m}Tc-diethylenetriamine-pentaacetic acid or ^{99m}Tc-glucoheptonate) have often been favored to facilitate repeat examinations which are occasionally needed. A bolus of radiopharmaceutical is injected intravenously, and the flow of activity within the internal cerebral artery circulation is assessed on dynamic planar scintigraphy at a rapid temporal resolution of 1 image per 1 to 2 seconds (Figs. 1 and 2). Either portable or stationary gamma-cameras may be used, the former of value in studying critically ill patients within the intensive care unit. Visualization of any activity within the anterior and middle cerebral artery territories indicates presence of intracranial perfusion while absence thereof, in the presence of an adequate common carotid bolus, indicates absent blood flow.

Static blood pool imaging of the skull, immediately after dynamic imaging, is typically performed as a component of this examination. Normally, static images portray blood pool of the intracranial venous sinuses and soft tissues of the face and skull. Nondiffusible radiopharmaceuticals do not cross the blood–brain barrier and consequently do not appear within the brain parenchyma.

In the context of a brain death study, nonvisualization of the venous sinuses further confirms absent intracranial blood flow.[19] According to most experts, the presence of activity in the region of the venous sinuses does not necessarily imply intracranial blood flow as visualization may occur via collateral flow; visualization of the venous sinuses therefore does not preclude brain death.[20-25]

Radionuclide angiographic studies have been extensively validated in the clinic over numerous years,[21,23,24] and lack of flow has also been correlated with specific pathologic changes of the brain ("respirator brain").[23,26] In reality, many of these published series have been performed exclusively with patients exhibiting clinical evidence of brain death; by definition specificity of the brain death findings cannot be evaluated in this population. In fact, based on the inability of radionuclide angiography to evaluate the posterior fossa, specificity may not be as high as desirable for a brain death study. This serious flaw has been substantiated in a limited clinical evaluation.[27]

The initial practice of using nondiffusible radiopharmaceuticals for brain death studies has been largely supplanted by use of lipophilic compounds, specifically HMPAO (Figs. 3 and 4).[28-32] This radiopharmaceutical passively crosses the blood–brain barrier and becomes stably trapped within the brain parenchyma in proportion to regional perfusion.[33,34] Although the determination of brain death with lipophilic

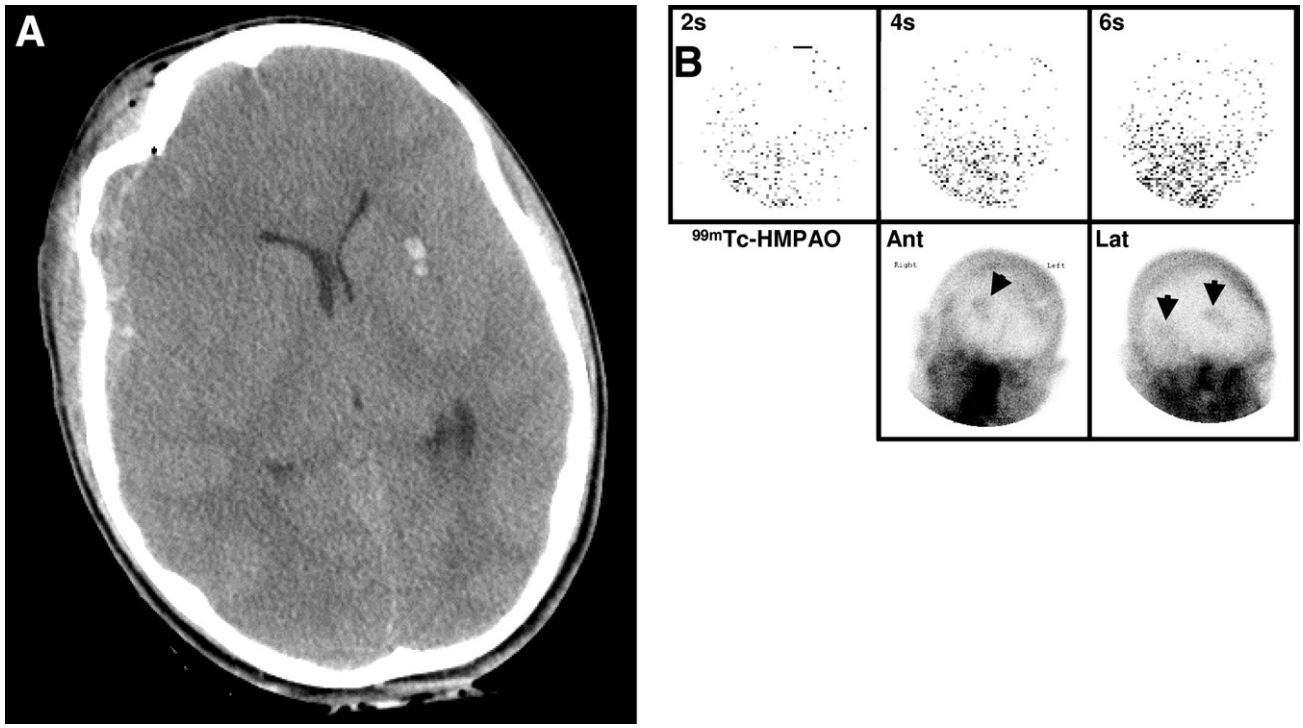

Figure 5 A 17-year-old man, status post motor vehicle accident. Recent neurological examination demonstrated no brainstem reflexes. Noncontrast CT scan demonstrates presence of a right-sided frontal skull fracture that is comminuted and depressed with associated subdural hemorrhage. Hemorrhage is noted in the left basal ganglia. Findings at other levels include bifrontal and temporal contusions as well as effacement of the cisternal spaces secondary to cerebral edema and herniation. (B) ^{99m}Tc-HMPAO examination demonstrated absent flow; however, trace parenchymal uptake was noted (arrows). Patient died within 1 day of study.

compounds has primarily been validated with HMPAO, it appears reasonable to extend the concept to a second commercially-available ^{99m}Tc-labeled lipophilic radiopharmaceutical, ^{99m}Tc-bicisate (Neurolite).[17,18,35] Cerebral uptake is quantitatively similar with these 2 compounds.[36]

When performing blood flow studies with diffusible radiopharmaceuticals, multiple planar views of the brain are obtained to assess perfusion. Lack of localization of lipophilic compounds within the brain indicates absent blood flow. If any activity is visualized within parenchyma of the brain or brainstem, there is incontrovertible evidence of blood flow. In several studies, HMPAO uptake has shown to be in excellent agreement with clinical evaluation of brain death, with specific exceptions discussed below.[32,37] If available, a portable camera can be used for planar imaging of diffusible radiopharmaceuticals at the bedside.[38] Moving the patient to a stationary gamma camera also enables performance of tomographic (ie, single-photon emission computed tomography [SPECT]) imaging at the risk and difficulty of transporting the critically ill patient to the nuclear medicine suite.[28,37,39,40] Although not well studied, it is likely that SPECT imaging has improved imaging characteristics over planar imaging and appears to be the only imaging method that can be used to visualize the brainstem clearly.[39-41]

A radionuclide angiogram may also be acquired during injection of the lipophilic radiopharmaceutical as an additional diagnostic component of the examination, but is of secondary importance to the delayed parenchymal images. Prima fascia, sensitivity for detecting blood flow is greater on the delayed phase than on the angiographic phase as several-hundred-thousand-count static images offer superior statistical discrimination to 2-second flow images. Furthermore, delayed imaging is less dependent on bolus technique and timing of injection compared to dynamic imaging. In clinical studies, blood flow has been observed more often on parenchymal imaging than on the angiographic phase.[29,31,32,41,42] If these findings are extrapolated to the similar issue of estimating the relative sensitivity of nondiffusible versus diffusible radiopharmaceuticals in determining blood flow, one would predict that parenchymal imaging using diffusible radiopharmaceuticals would be superior to angiographic imaging of the nondiffusible radiopharmaceuticals. In fact, in the only direct evaluation of ^{99m}Tc-diethylenetriamine-pentaacetic acid versus HMPAO imaging as confirmatory blood flow examinations, complete agreement was noted between the diffusible and nondiffusible methods in 14 patients with brain death and 12 with persistent flow.[43] HMPAO was considered the more technically forgiving despite its higher cost. The Society of Nuclear Medicine Procedure Guideline for Brain Death Scintigraphy[17] lists the relative accuracies of brain-specific (lipophilic) and nonspecific (nonlipophilic) agents among issues that require further clarification, although it advocates performing brain death examinations with lipophilic radiopharmaceuti-

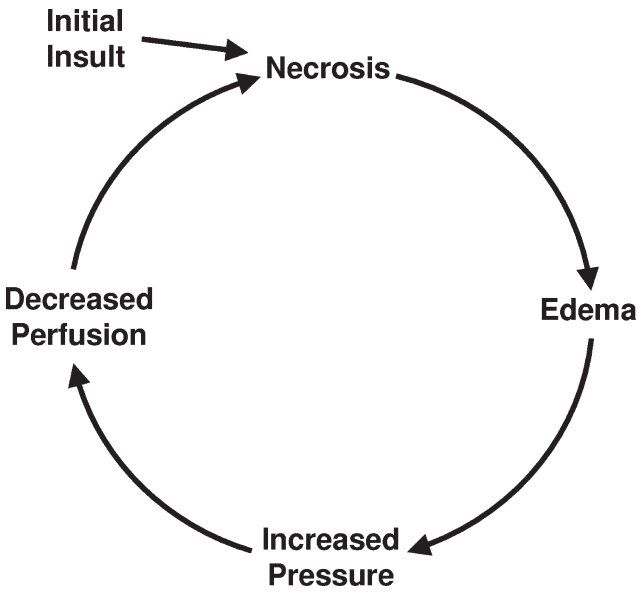

Figure 6 Typical sequence of events after central nervous system catastrophe in a patient with intact calvarium. The necrosis and edema after a major insult leads to elevated intracranial pressure, reduced cerebral perfusion pressure, and additional infarction and necrosis.

cals. The American Academy of Neurology guidelines reference only lipophilic radiopharmaceuticals,[9] while the ACR Practice Guideline[18] does not express an opinion in this regard.

Problems in Reconciling the Clinical Examination with Findings on Confirmatory Studies

In the remainder of this review, we wish to critically consider the contribution of confirmatory examinations to the diagnosis of brain death. Essentially, 2 definitions of brain death have been established—a purely clinical diagnosis, and one that is complimented by confirmatory examinations. An overarching theme in all critiques is that these definitions are not perfectly congruent, with internal inconsistencies that ultimately lead to contradictory conclusions. This problem is punctuated by persistent reports in the literature of patients in whom the physical examination unequivocally demonstrates brain death, yet specific confirmatory tests indicate presence of blood flow, electrical activity, or other phenomena.[32,44-48] It is obvious that confounding factors, such as drug intoxication or complicating medical conditions, may interfere with clinical assessment and cause a discrepancy between physical examination and blood flow examinations; however, in the cases we are discussing these trivial causes have been excluded. Discrepancy may also be the result of physician or technical error; however, published cases generally reflect carefully reviewed findings and not mere mistakes. In our own recent review of 188 brain death studies using diffusible radiopharmaceuticals performed over a 4 year period at University Hospital, Newark, we noted 21 patients with persistent brain perfusion where retrospective chart review confirmed a neurologic examination consistent with brain death. The pattern of parenchymal uptake was trace in 4 patients (Fig. 5), irregular in 5 patients, and grossly intact in 12 patients (Fig. 4). In the following discussion, we will consider 3 possible causes of discrepancy between the physical examination and confirmatory tests: differences in test sensitivity, differences in anatomic localization, and differences based on neuronal function versus blood flow.

Differences in Sensitivity: How Much Brain Is Not Enough?

The first possibility to consider is that the threshold amount of tissue needed to demonstrate flow on the radionuclide study or electrical activity on the EEG differs from that needed to demonstrate function on the physical examination. It would be naïve to believe that lack of electrical activity on the EEG indicates complete cortical cell necrosis, absent visualization of blood flow correlates with an absolute lack of flow or that lack of cranial nerve reflexes on the physical examination indicates complete necrosis of the brainstem. A priori, virtually no examination is perfectly sensitive, and as such, a negative examination only indicates that the parameter being studied has not achieved a specific threshold of detection.

To a large degree, the characteristics of radionuclidic blood flow examinations have not been rigorously studied, and little is known regarding the minimal blood flow needed for visualization. An experimental study in anesthetized cats compared radionuclide angiography using a semiquantitative method with absolute flow as determined by radiolabeled microspheres.[49] 80% reductions in flow were considered significant. In this experimental model, radionuclide angiography was neither overly specific nor highly sensitive as compared with the gold-standard of microspheres.

One generally does not encounter patients with absent flow on radionuclide confirmatory studies who have preserved cranial nerve function; however, this reflects a referral bias—patients are usually not studied with radionuclidic methods unless the physical examination is consistent with brain death. The converse finding is that of patients with clinical evidence of brain death but persistent evidence of function or blood flow on confirmatory studies. As mentioned, this has been described in radionuclidic, angiographic, and electrical examinations of brain activity. To the degree these patients have only minimal blood flow or electrical activity, it is possible that discrepancies arise out of differences in sensitivity of the examinations in detecting small areas of non-necrotic tissue.

In actuality, the persistence of localized regions of functional tissue in patients with catastrophic brain injuries is a fairly unusual occurrence based on physiologic considerations. The brain is contained within the rigid bony calvarium and, in the usual circumstance, there is very little capacity for edema. As soon as increase in brain volume exceeds the capacity of the cisternal and gyral spaces, a rapid increase in intracranial pressure ensues. Elevation of intracranial pressure to levels greater than systemic blood pressure will result

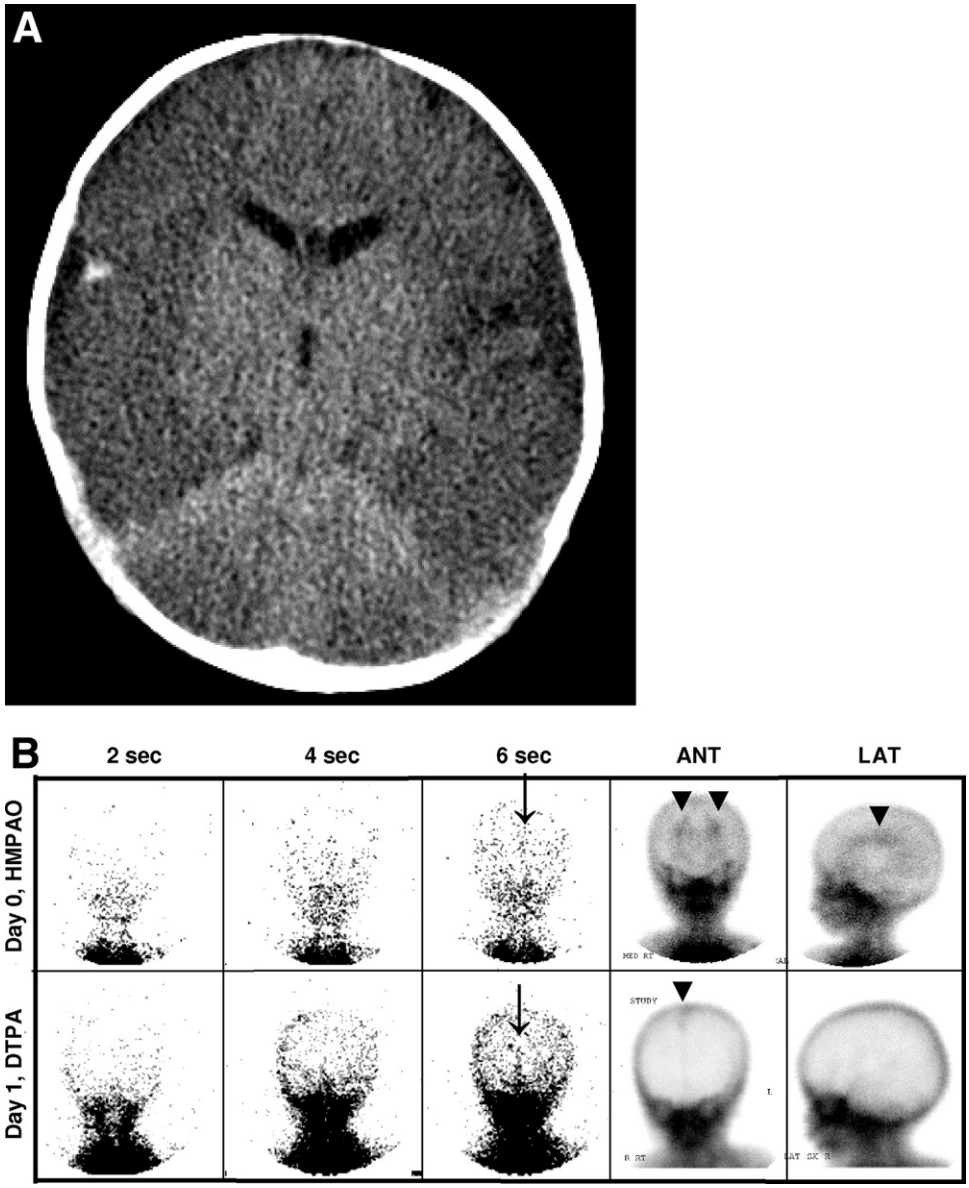

Figure 7 A 2-month-old child with head injury and clinical brain death. (A) Noncontrast CT scan shows diffuse loss of the gray–white matter differentiation and sulcal effacement consistent with bilateral infarction with sparing of the basal ganglia and brainstem. (B) Initial study with ^{99m}Tc-HMPAO (top row) demonstrates a suggestion of arterial flow in the anterior cerebral artery distribution (arrow). Parenchymal images clearly demonstrate periventricular uptake of radiopharmaceutical (arrowheads), indicating trace residual blood flow. Follow-up study the following day was performed with ^{99m}Tc-DTPA (bottom row). Anterior cerebral artery flow is clearly visualized (arrow). Activity is also noted in the region of the saggital sinus on blood pool image (arrowhead).

in a global lack of perfusion to the brain.[50] This anatomic constraint ensures that once a significant degree of intracranial damage takes place, the increase in intracranial pressure will extinguish any further blood flow which, in turn, creates further brain infarction (Fig. 6). Under these conditions, small areas of functioning tissue cannot persist.

An exception prevails when the calvarium is no longer a closed space and the volume-pressure relationship is no longer operative. In fact, many of the case reports of persistent blood flow in the context of clinical brain death occur under these circumstances (reviewed in Flowers[51]), in patients with open fontanelles (Fig. 7) cerebrospinal fluid shunts, ventricular drains, or skull defects.[37,52-54] An additional exception to this phenomenon would be if insufficient time has elapsed after brain insult for the cycle of edema, increased pressure, and infarction to ensue. This is reflected in other reports in the literature where persistent regions of perfusion are noted in patients with clinical evidence of brain death when blood flow studies are performed relatively soon after the neurologic event.[38,45,55] To avoid discrepant cases, it has been suggested that blood flow studies be delayed for at least 6 hours following the clinical finding of brain death.[45] Repeat studies after sufficient time (such as 12 hours) generally reveal complete absence of blood flow (Fig. 8).

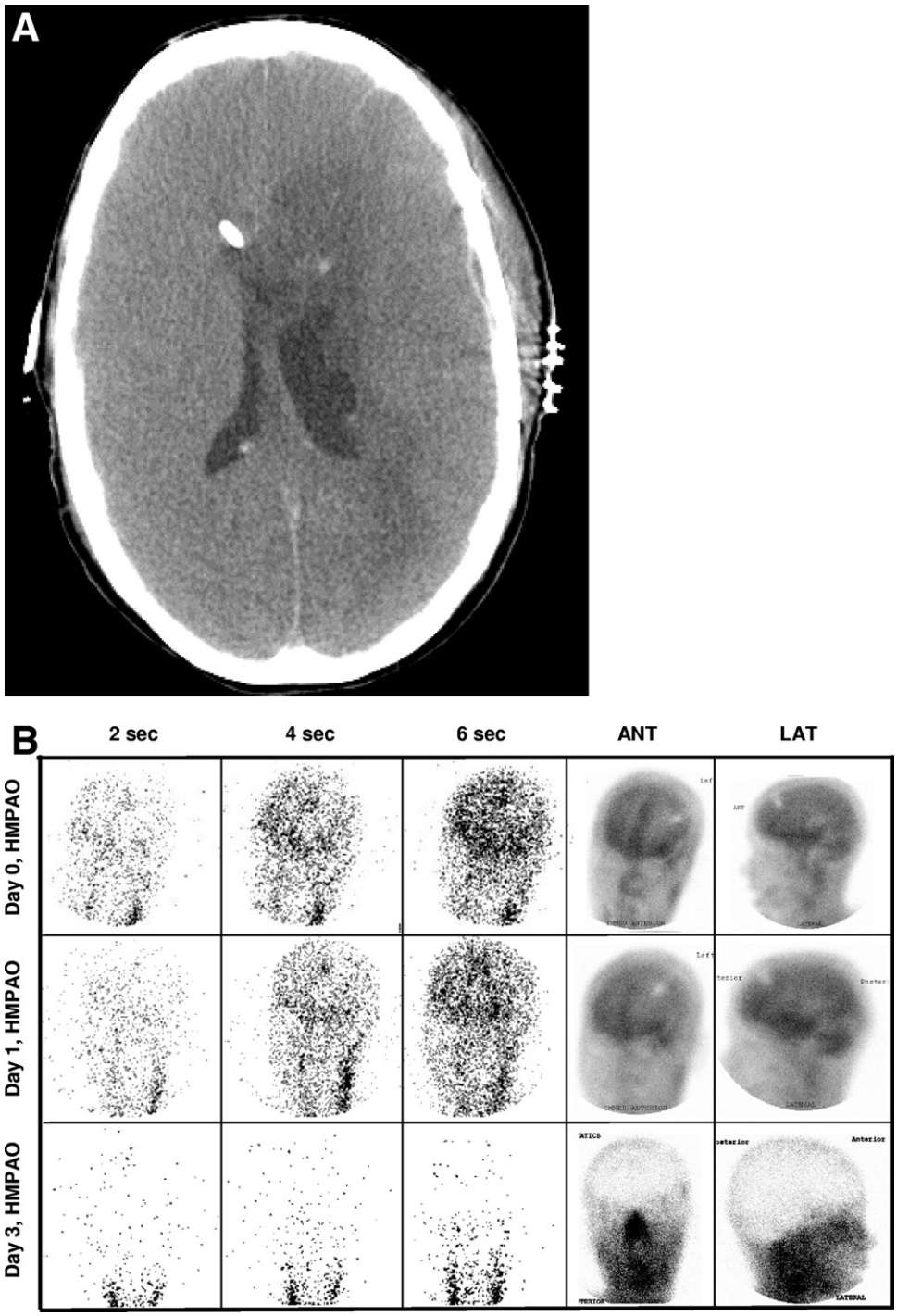

Figure 8 A 31-year-old woman with neurologic evidence of brain death. (A) Noncontrast CT scan demonstrates diffuse cerebral edema. A right-sided shunt catheter is in place. There is blurring of gray–white matter differentiation with a relatively dense-appearing posterior fossa (not seen on this image), findings that are consistent with diffuse anoxic brain injury. (B) All 3 studies were performed with HMPAO. Both initial study (top row) and second study performed the following day (second row) demonstrated evidence of brain perfusion on angiographic and parenchymal phases of the examination. The study converted to absent perfusion on the third day (third row).

Anatomic Localization: Brainstem Versus Brain in the Diagnosis of Brain Death

Discrepancies between physical examinations, which indicate brain death, and confirmatory examinations, which demonstrate blood flow or electrical activity, can simply be understood as differences between evaluation of the brainstem and the cerebral cortex. With respect to the physical examination, examination of cranial nerves and apnea testing evaluate the brainstem and not the cerebrum. The presence of coma does not prove a primary abnormality of the cortex

because this condition can also be mediated by disturbance of the reticular activating system within the brain stem. According to this approach, presence of cortical blood flow or electrical activity does not contradict the physical examination which is focused on the brain stem.

It is interesting to note that, conversely, many confirmatory studies that evaluate the cerebrum and cerebellum do not evaluate the brain stem (Table 2). EEG is only used to evaluated the superficial cortex. With respect to radionuclide angiography, only the territories of the anterior and middle cerebral arteries are adequately visualized and no information regarding the posterior fossa or brain stem is conveyed.[56] In the case of parenchymal imaging with diffusible radiopharmaceuticals imaged by planar techniques, the cerebral cortex and cerebellum are well-visualized however perfusion of the brain stem is not well evaluated.[41] The examination which is most thorough in evaluating the cerebrum, cerebellum and brainstem is parenchymal imaging with SPECT, although this entails transporting the patient to the nuclear medicine suite, with its inherent risks.

This understanding raises fundamental questions as to appropriateness of testing protocols for determination of brain death. If we insist on a whole-brain definition of brain death, can we determine brain death on the physical examination alone if it does not adequately evaluate the cerebral cortex? Young has suggested that most insults that would destroy the entire brainstem would also devastate the more vulnerable cerebral hemispheres; however they stress that this is not always the case as some disorders primarily affect the brainstem sparing large amounts of the cerebral hemispheres.[3] As a second question, if the physical examination is incomplete due to drug intoxication or injury which precludes its completion, how can lack of electrical activity or blood flow in the cortex augment an incomplete examination of the brainstem?

Function Versus Blood Flow

A final explanation of the discrepancy between the physical examination and confirmatory tests is that it is due to differences between blood flow and function as indicators of irreversible loss of function of the brain. There would be little disagreement that loss of integrity of cell membranes indicates irreversible death of the tissue. The goal of a brain death examination; however, is to diagnose irreversible loss of function before frank cell necrosis. Because blood flow is needed to deliver substrates to living tissue, continued absence of blood flow has been considered a reliable marker of brain death, thereby creating a role for blood flow examinations in the evaluation of brain death. The converse is not necessarily true, in that presence of blood flow does not necessarily imply presence of function. If we accept this fact then permanent brain dysfunction on physical examination, indicative of brain death, and regions of perfusion on radionuclide confirmatory studies can harmoniously coexist. According to this approach, blood flow studies are considered specific but not sensitive for brain death.

Because of the appropriate hesitancy to declare brain death in the face of any uncertainty, and in concert with many written recommendations, most physicians are not willing to declare a patient brain dead based on a positive physical examination in the presence of blood flow on radionuclide examinations.

Conclusion

Radionuclide examinations have become standard confirmatory examinations in the determination of brain death. The original angiographic method, using nonlipophilic radiopharmaceuticals, has largely been replaced with parenchymal imaging of lipophilic radiopharmaceuticals. In the vast majority of cases, blood flow examinations are useful in confirming brain death. Occasional instances of patients with persistent blood flow in the face of a clinical examination diagnostic of brain death raise questions regarding the consistency of brain death definitions. One possible understanding of these findings is that blood flow studies provide a better evaluation of the cerebrum and greater evidence of permanence than the physical examination alone and some have therefore advocated expanding the use of confirmatory studies to offer greater certainty in the evaluation of brain death.[4] Parenchymal radionuclidic studies appear to be unique in offering the ability to evaluate both the brain and brain stem.

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