UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Department of Radiology

Division of Nuclear Medicine

Didactic

Brain Death: Clinical Diagnosis and Imaging

Original presentations by:

Rush Chewning MD and Irene Cruite MD

Reviewed by: Manuela Matesan MD

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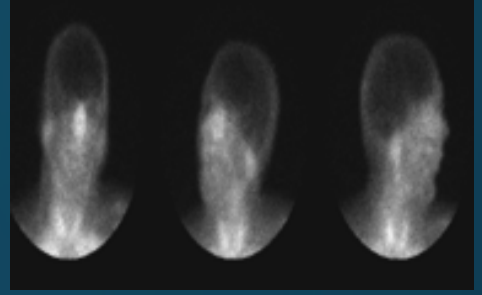
Aims of this lecture

- Outline definition of death and brain death
- Clinical diagnostic of brain death
- Review confirmatory tests of brain death
- Discuss role of radionuclide imaging in brain death

nuclear medicine context



- radionuclide brain death study DOES NOT establish the diagnosis
- the diagnosis is CLINICAL
- radionuclide brain death study may or may not CONFIRM the clinical diagnosis
- society of nuclear medicine procedure guideline for brain death scintigraphy, Feb 25, 2003

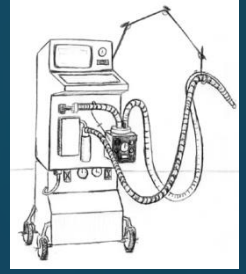
broader context

- WHY DEFINE/DIAGNOSE DEATH?
- trigger for cascade of change (legal, financial, social, moral, etc.)
- impact on medical decisions (physician clarity in planning treatment course, communication with family, conscience of the caregiver)

historical context

- traditional definition of death in west based in ancient religious notion of "vital life fluids"
- for centuries = loss of cardiopulmonary function
- reports of missed diagnosis = buried alive!
- technological advances

medical advances



- technology does not always bring clarity!
- ventilator - traditional cardiopulmonary criteria?
- brain no longer functioning, but heart beating
- “life support”

attempts to clarify

- 1968 ad hoc committee of harvard medical school
- PRACTICAL, not theological or philosophical

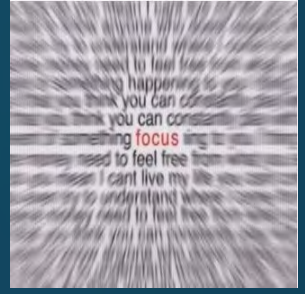
"There are two reasons why there is need for a definition [of brain death]:

(1) Improvements in resuscitative and supportive measures have led to increased efforts to save those who are desperately injured. Sometimes these efforts have only partial success so that the result is an individual whose heart continues to beat but whose brain is irreversibly damaged. The burden is great on patients who suffer permanent loss of intellect, on their families, and on those in need of hospital beds already occupied by these comatose patients.

(2) Obsolete criteria for the definition of death can lead to controversy in obtaining organs for transplantation."

reflected a shift towards neurologic and away from traditional cardiopulmonary criteria

more clarity needed



- "uniform determination of death act" - 1980 by the national conference of commissioners on uniform state laws

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 brain stem, is dead.

A determination of death must be made in accordance with accepted medical standards.

NOTE in preamble: "This Act is silent on acceptable diagnostic tests and medical procedures. It sets the general legal standard for determining death, but not the medical criteria for doing so. The medical profession remains free to formulate acceptable medical practices and to utilize new biomedical knowledge, diagnostic tests, and equipment."

(HOLD THIS THOUGHT!)

federal "clarity"

- "defining death" president's commission for the study of ethical problems in medicine and biomedical and behavioral research - 1981

"Because they were easily measured, circulation and respiration were traditionally the basic 'vital signs.' But breathing and heartbeat are not life itself. They are simply used as signs—as one window for viewing a deeper and more complex reality: a triangle of interrelated systems with the brain at its apex. As the biomedical scientists who appeared before the Commission made clear, the traditional means of diagnosing death actually detected an irreversible cessation of integrated functioning among the interdependent bodily systems. When artificial means of support mask this loss of integration as measured by the hold methods, brain-oriented criteria and tests provide a new window on the same phenomenon."

remember that thought?

- here come the neurologists! (1994 report of the quality standards subcommittee of the american academy of neurology)
- summary statement "determining brain death in adults"
- responding to "need for standardization of the neurologic exam criteria for the diagnosis of brain death"
- same criteria for children, but a bit more strict… (requires confirmatory test(s) and specified interval between exams)

prerequisites

- absence of clinical brain function when the proximate cause is known and demonstrably irreversible

1) clinical or neuroimaging evidence of an acute CNS catastrophe that is compatible with the clinical diagnosis of brain death

2) exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid-base, or endocrine disturbance)

3) no drug intoxication or poisoning

4) core temperature > or = 32 C (90 F)

requirements

- three cardinal findings

1) coma or unresponsiveness

2) absence of brainstem reflexes

3) apnea

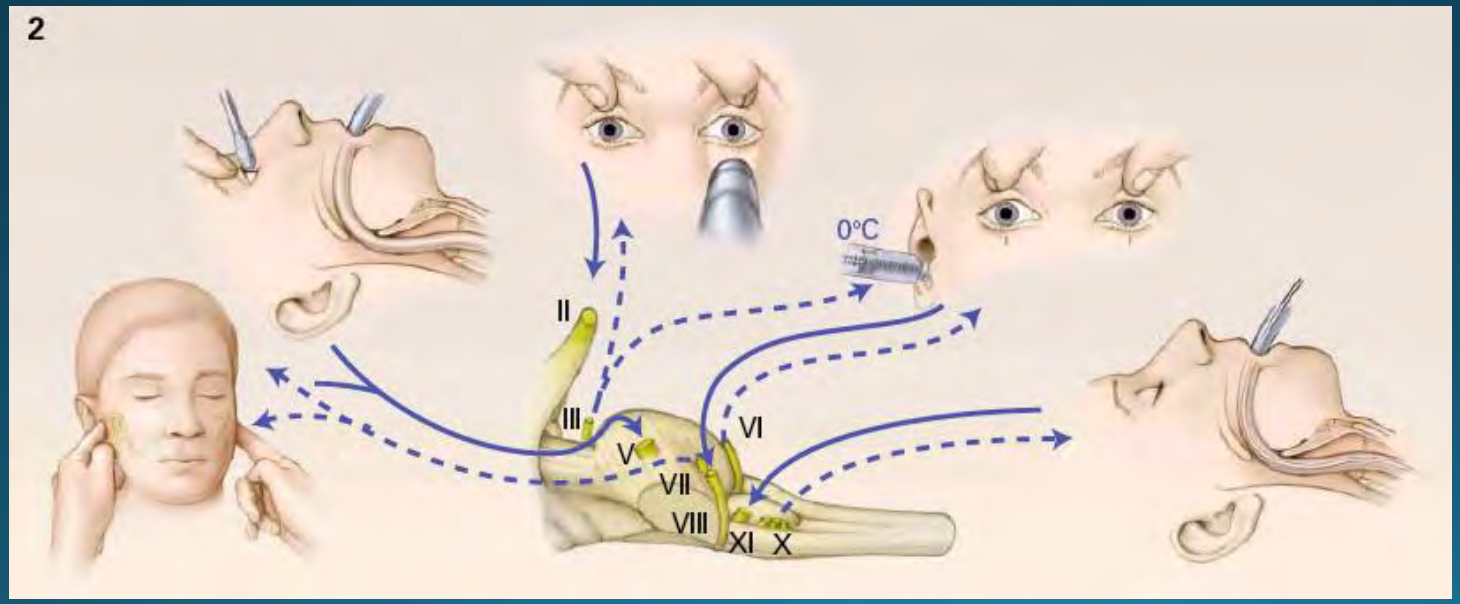
coma or unresponsiveness

- presence or absence of motor responses to a standardized painful stimulus (e.g. nail bed pressure, supraorbital pressure)

picture from: Wijdicks, Eelco, F. M. The Diagnosis of Brain Death, *New England Journal of Medicine* 344, no. 16 (April 19, 2001): 1215-1221.

absence of brainstem reflexes

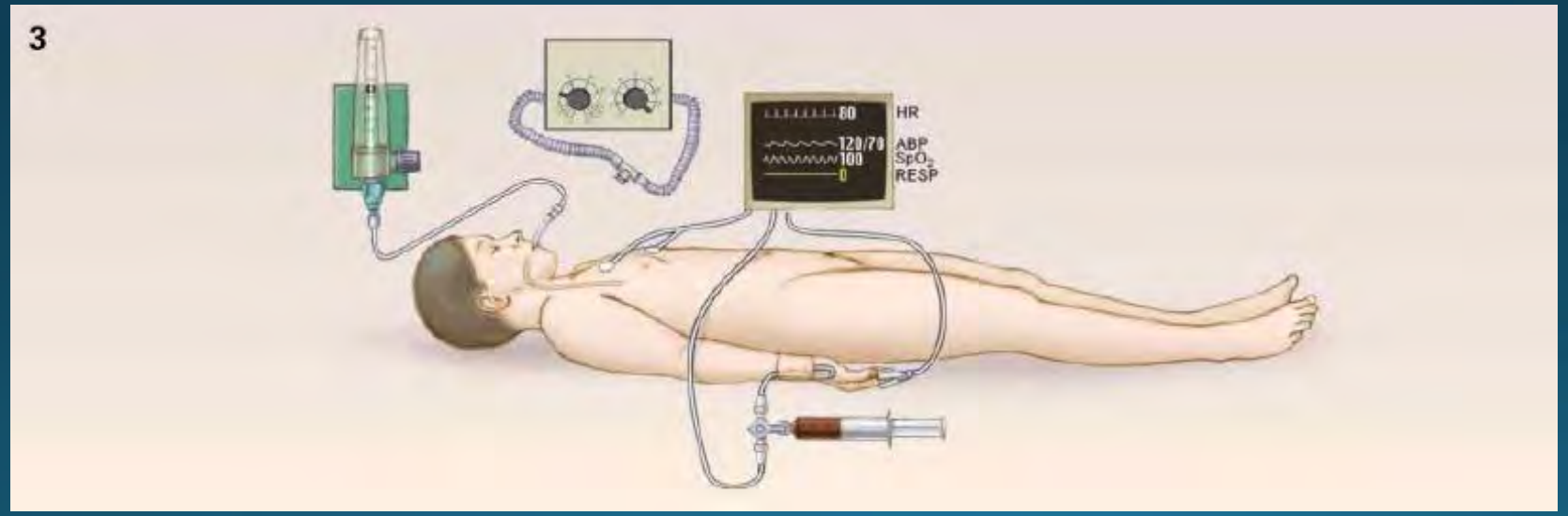
pupils: absent pupillary response to light; mid-sized to dilated
ocular movement: no occulocephalic reflex; no deviation of eyes in response to 50 ml of cold water in ear
facial sensation/motor: absent corneal reflex, jaw reflex, grimace to painful stimuli (sucking, rooting reflexes in infants)
pharyngeal/tracheal: no gag reflex; no cough in response to suctioning



picture from: Wijdicks, Eelco, F. M. The Diagnosis of Brain Death, *New England Journal of Medicine* 344, no. 16 (April 19, 2001): 1215-1221.

apnea

- disconnect ventilator and deliver 100% 02 at 6L per minute into the trachea
- defined as absence of respiratory drive at $PaCO_2$ = 60 mm Hg (or 20 mm Hg above baseline)
- watch for respiration
- measure $PaCO_2$



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Conditions distinct from brain death

- Persistent Vegetative State
- Locked-in Syndrome
- Minimally Responsive State

but wait, there's more!

- confirmatory tests: cerebral angiography, electroencephalography, transcranial doppler ultrasonography, cerebral scintigraphy
  - ~ term to 2 months: 2 confirmatory tests required
  - ~ 2 months to 1 year: 1 confirmatory test required
  - ~ above 1 year: confirmatory tests are optional
- intervals between tests: two evaluations required
  - ~ term to 2 months: 48 hours
  - ~ 2 months to 1 year: 24 hours
  - ~ above 1 but under 18 years: 12 hours
  - ~ above 18 years: interval optional (6 hours is common practice)

Confirmatory tests recommended by AAN are:

- Electroencephalography (EEG)
- Somatosensory evoked potentials (SEPs or SSEPs)
- Radiologic examinations of blood flow
  - Conventional contrast angiography
  - Transcranial Doppler US
  - Radionuclide imaging

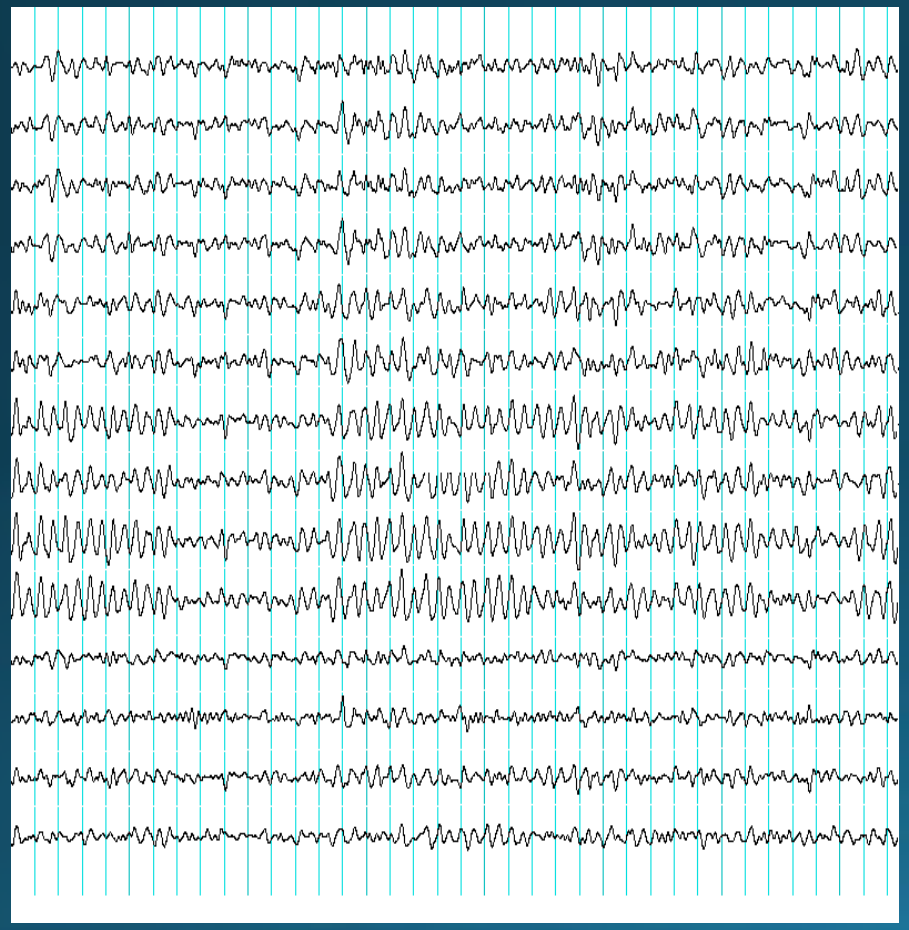
Confirmatory tests in order of sensitivity

- Conventional Angiography
- EEG
- Transcranial Doppler US
- Tc-99m HMPAO brain scan
- Somatosensory evoked potentials

Choice of confirmatory test depends on …

- Availability
- Accuracy across operators and readers
- Ability to perform test at the bedside, and
- Toxicity on organs that may be for transplantation
- Whether affected by drugs or metabolic disturbances
- Whether test is standardized and robust

- Electroencephalography (EEG) – No activity over at least 30mins



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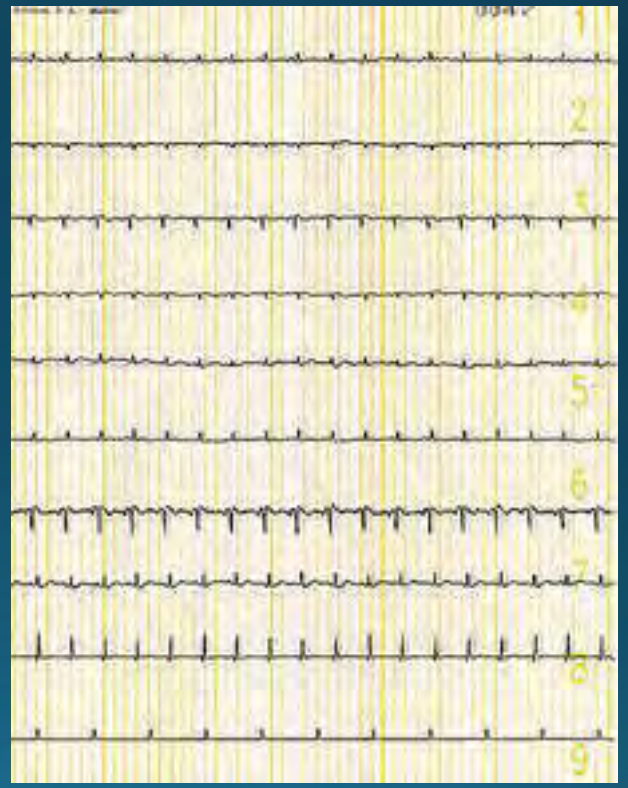
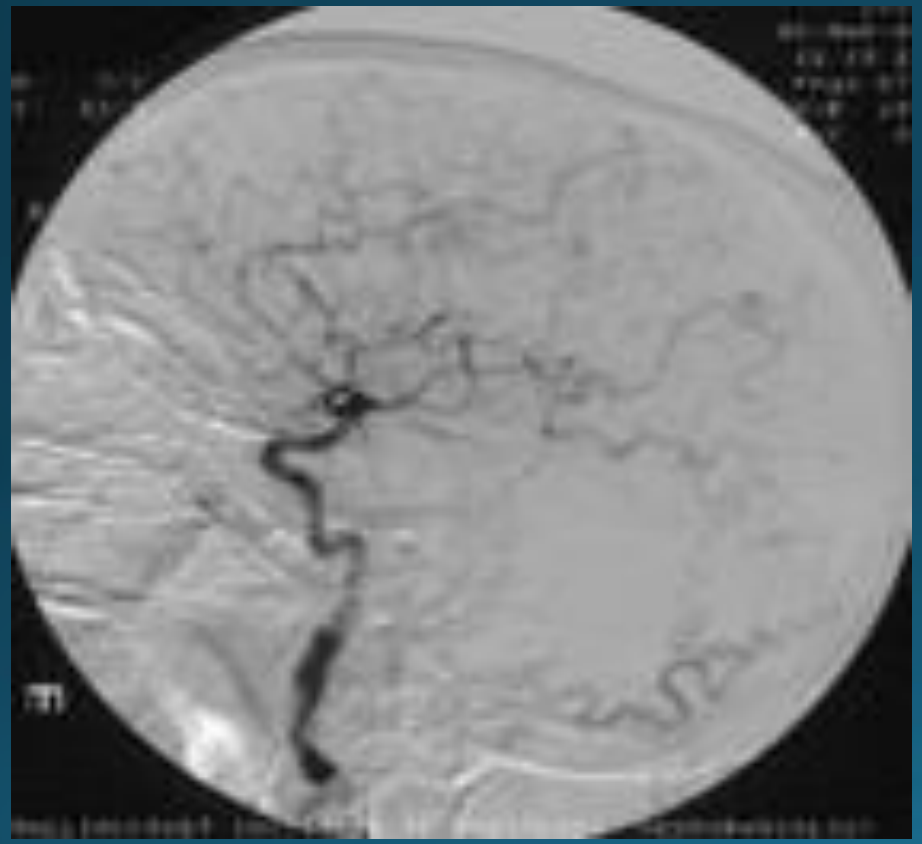


Electrocerebral Silence

Conventional contrast angiography



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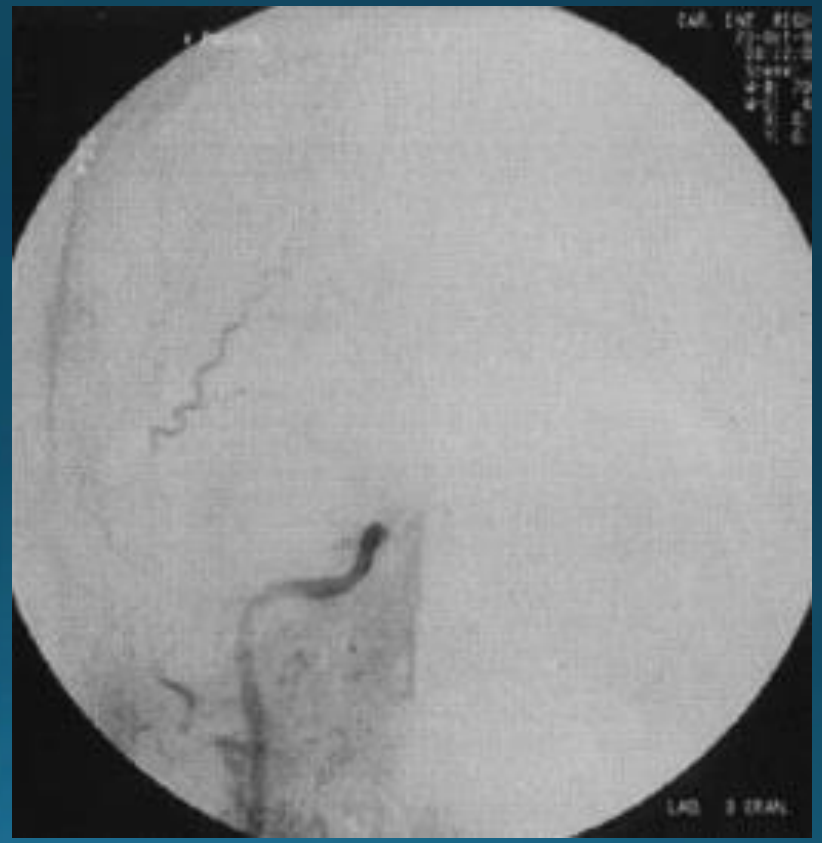
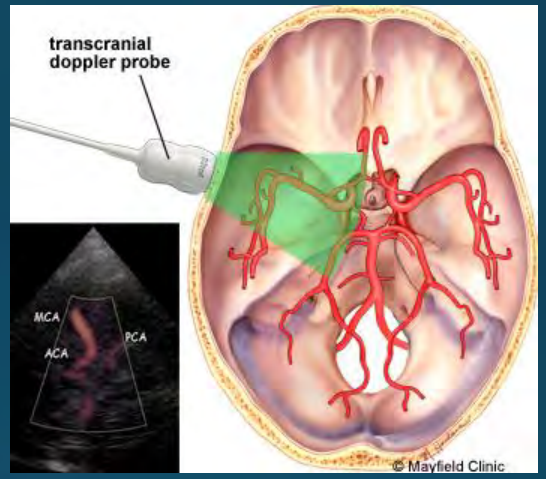
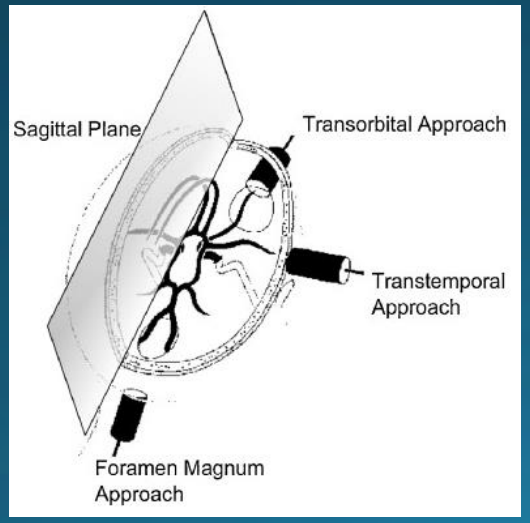
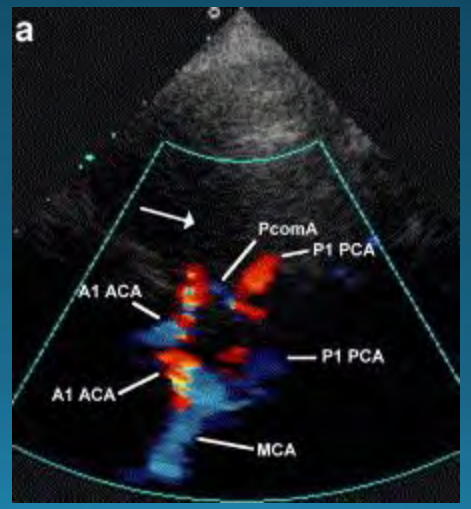


No Intracranial Flow

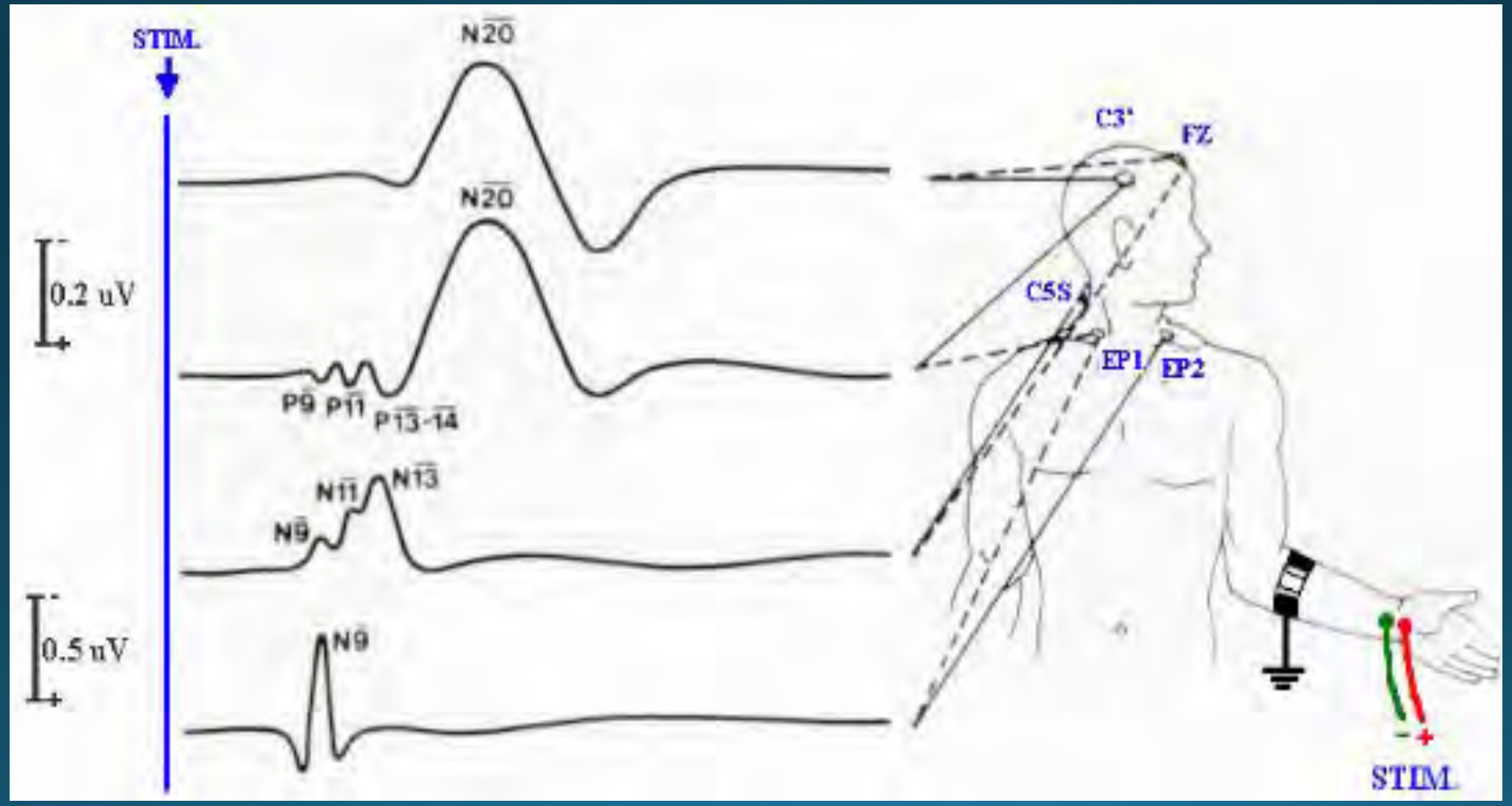
Transcranial Doppler ultrasound





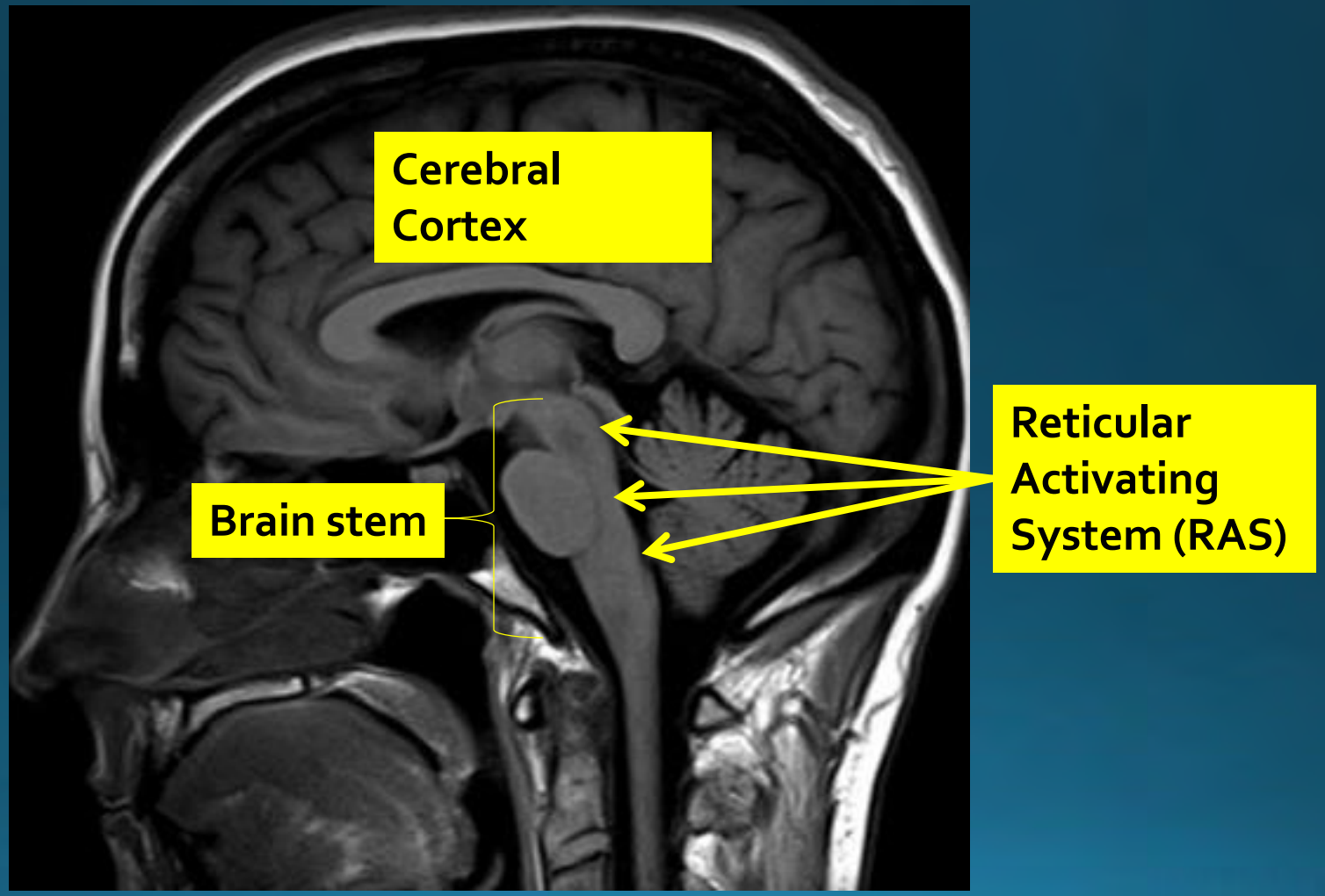


Somatosensory evoked potentials (SEPs or SSEPs)

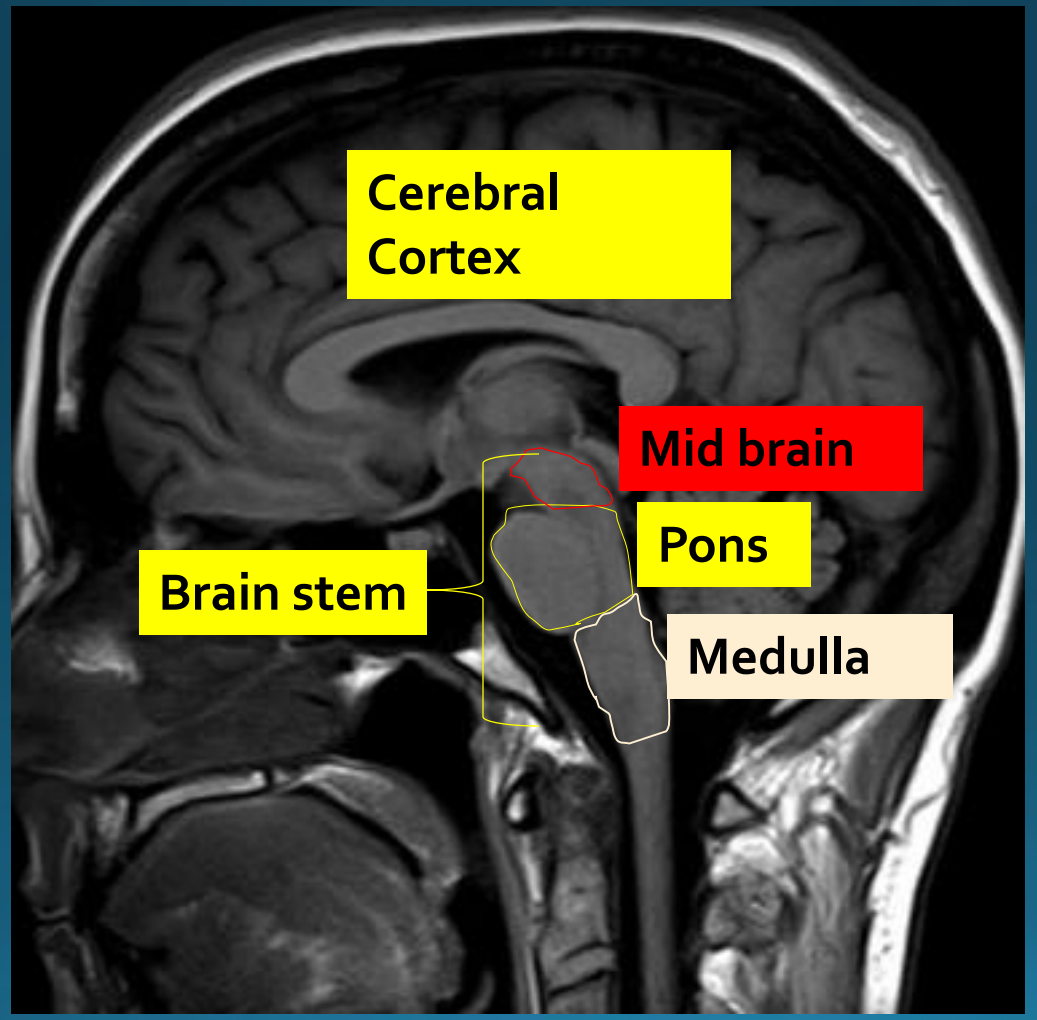


Normal response to arm stimulation

Brain anatomy

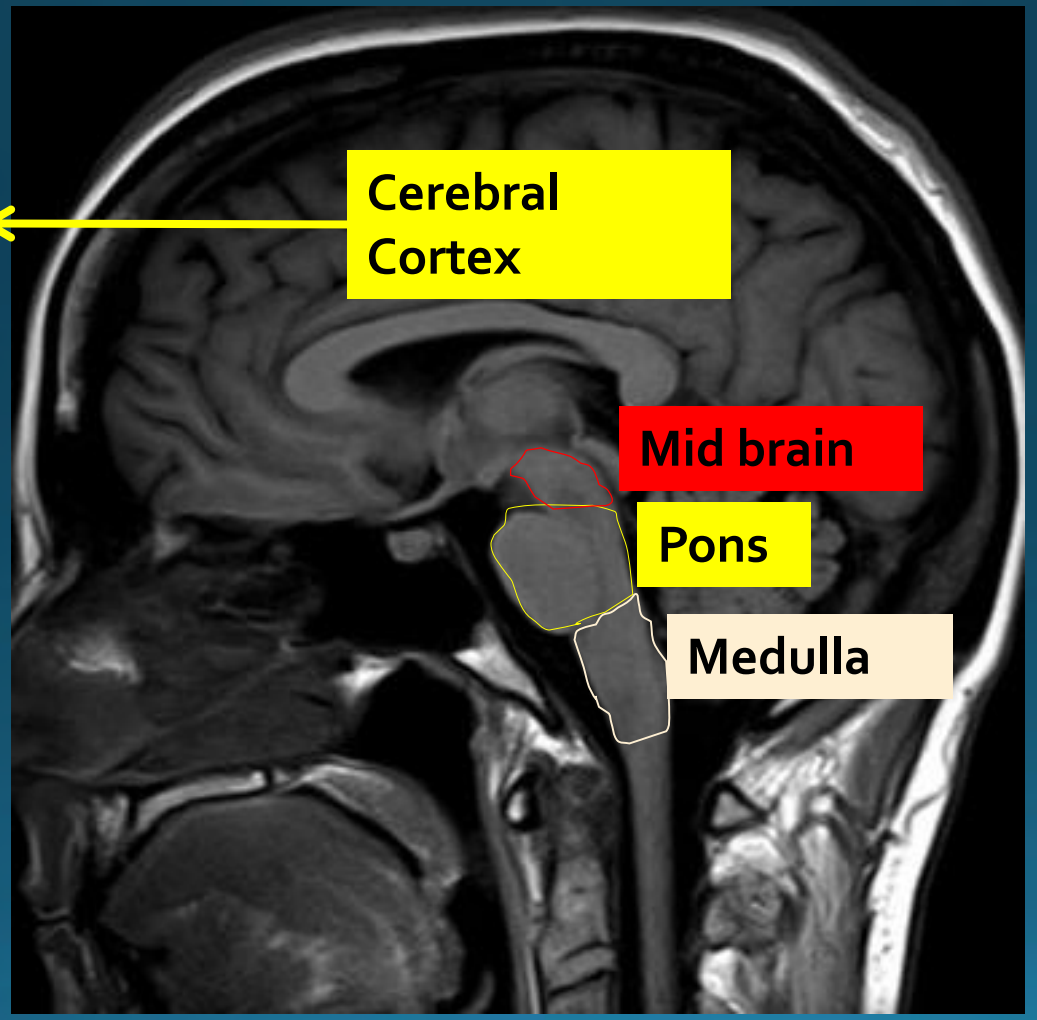


Brain anatomy



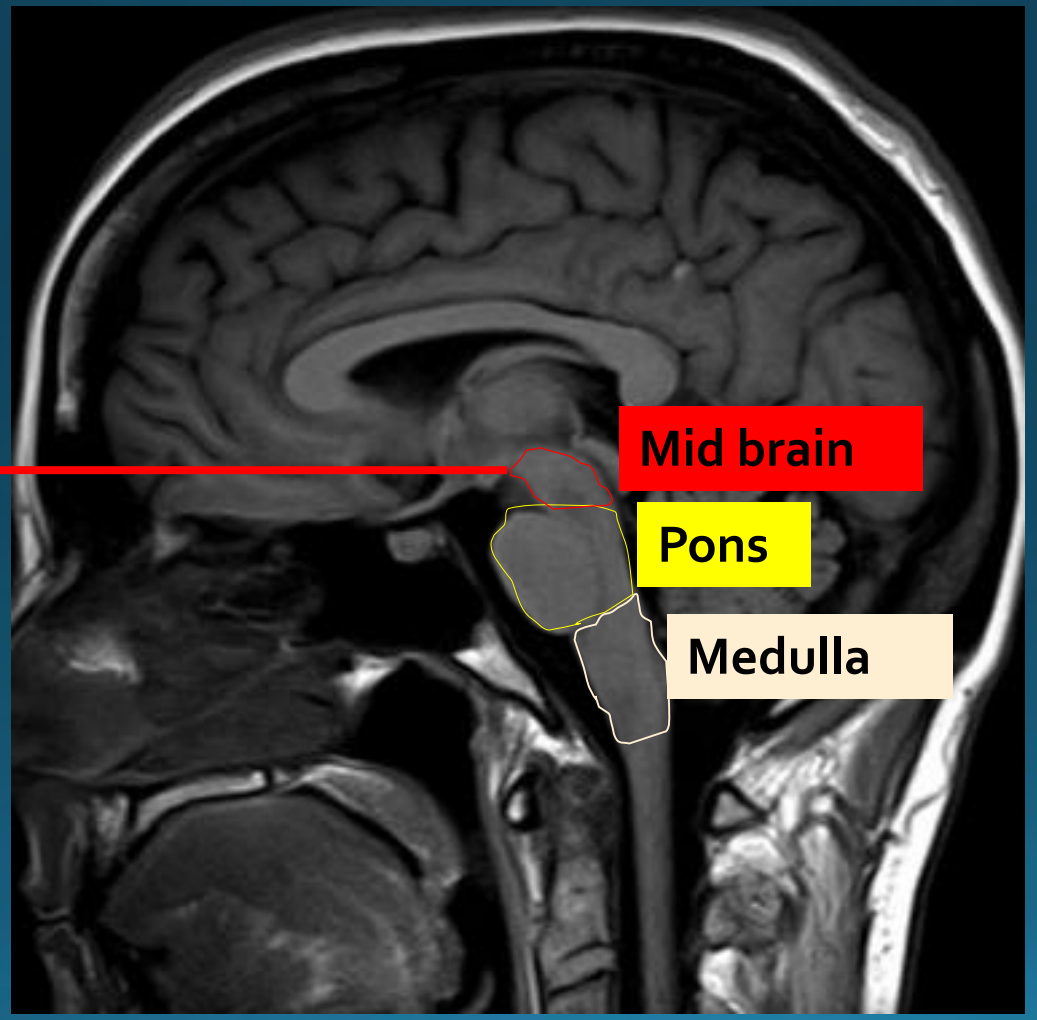
Brain anatomy

- Cognition
- Voluntary movement
- Sensation



Brain anatomy

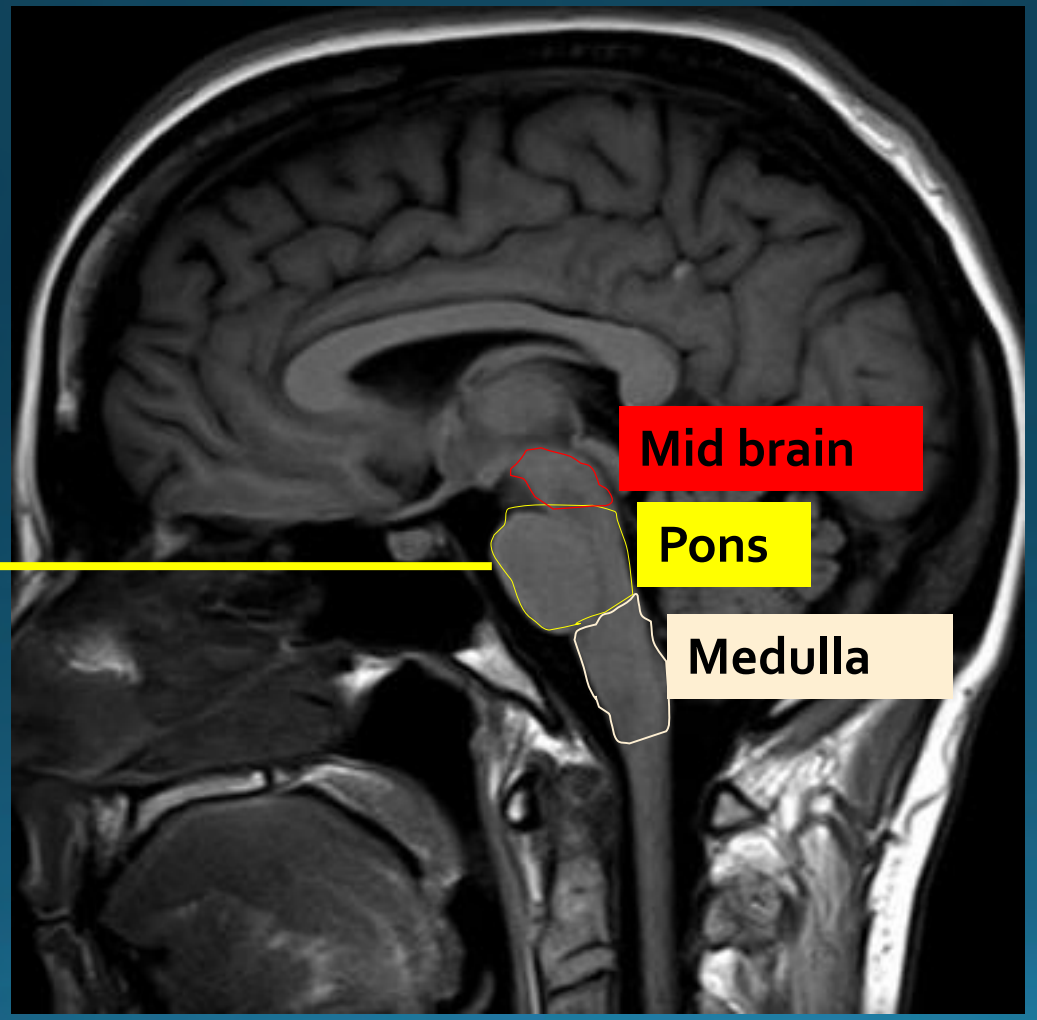
CN III
- Pupillary response
- Ocular movement



CN III – Oculomotor; mainly motor.

Brain anatomy

CN IV, V, VI
- conjugate eye movement
- corneal reflex



CN IV – Trochlear; mainly motor.

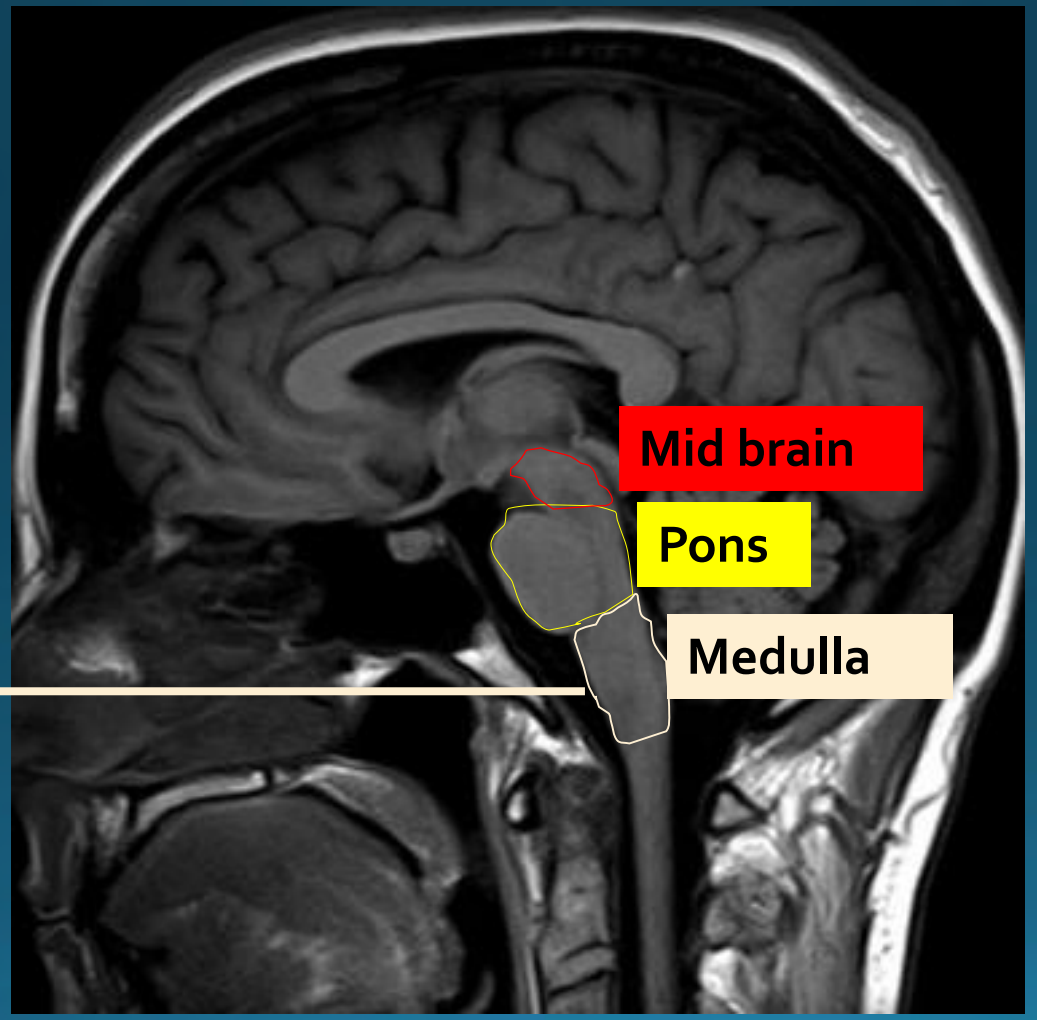
CN V – Trigeminal; sensory and motor

CN VI – Abducens; mainly motor

Brain anatomy

CNs IX, X
- Pharyngeal (Gag) Reflex
- Tracheal (Cough) Reflex

Respiration

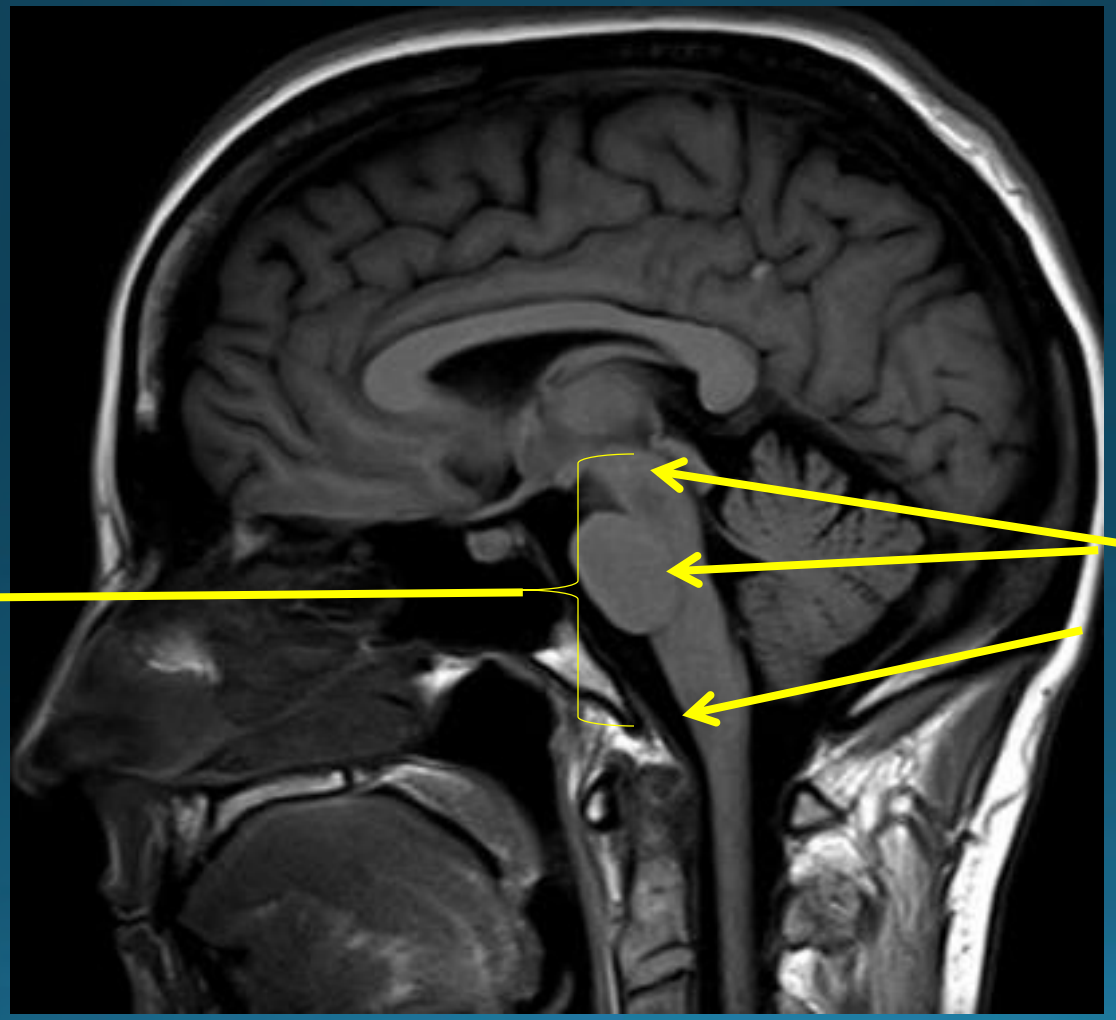


CN IX – Glossopharyngeal ; Sensory and motor.

CN X – Vagus; sensory and motor.

Normal brain anatomy

- Receives multiple sensory inputs
- Mediates wakefulness



Reticular Activating System (RAS)

Pathophysiology of brain death on scintigraphy

- Trauma – necrosis – edema – increased intracranial pressure > systemic blood pressure – decreased brain perfusion
- If calvarium is no longer a closed space - blood flow may persist despite clinical brain death:
  - Open fontanelles
  - CSF shunts
  - ventricular drains
  - Skull defects

Pathophysiology of brain death on scintigraphy

- If perfusion imaging is done soon after insult, brain edema may not have developed sufficiently to cause a decrease in perfusion
- Flow studies are therefore recommended at least 6 hours following clinical finding of brain death and repeat studies after sufficient time (such as 12 hours)

Three sets of published guidelines, similar but differ in details:

- American Academy of Neurology (AAN) 1995
- American College of Radiology (ACR) 1995
- Society of Nuclear Medicine (SNM) 2003

Radionuclide Imaging

- ACR guidelines: “to determine if there is cerebral blood flow,”
- SNM guidelines: “to assess brain blood flow.”
- AAN guidelines- lack of tracer uptake in the brain parenchyma on “static” Tc-99m HMPAO images (“hollow skull” phenomenon)

Confirmatory Tests – Radionuclide Imaging

- ACR and SNM recommended tracers:
  - Hydrophilic tracers (excluded by the BBB)
    - Tc-99m pertechnetate
    - Tc-99m DTPA
    - Tc-99m glucoheptate
  - Lipophilic tracers(brain-avid)
    - Tc-99m HMPAO
    - Tc-99m ECD
- AAN recommended tracer:Tc-99m HMPAO

Confirmatory Tests – Radionuclide Imaging

Radionuclide imaging as a confirmatory test for brain death can be divided into two categories:

- Radionuclide angiography
- Parenchymal imaging

Confirmatory Tests – Radionuclide Imaging

- Radionuclide angiography:
  - Hydrophilic agents – non-diffusible, do not cross BBB, rapid renal clearance thus can repeat exam
  - Static blood pool images are also acquired to distinguish ICA from ECA flow
    - No brain parenchyma uptake – do not cross BBB
    - Uptake in venous sinuses and soft tissues – blood pool
    - Non-visualized venous sinuses = No intracranial blood flow
    - Visualized venous sinuses do not preclude brain death

Confirmatory Tests – Radionuclide Imaging

- Radionuclide angiography:
  - Evaluates anterior cerebral and middle cerebral artery territories
  - Does not evaluate posterior fossa (cerebellum and brain stem) because dynamic images are acquired in anterior projection

Confirmatory Tests – Radionuclide Imaging

- Radionuclide angiography - confirmation of a clinical diagnosis of brain death:
  - Absent cerebral flow (ACA and MCA territories)on anterior projection during dynamic imaging
  - Absent venous sinus visualization on static images

Confirmatory Tests – Radionuclide Imaging

- Radionuclide angiography has 98.5% sensitivity for confirmation of brain death
- False positives from visualization of dural sinuses
  - External carotid fills the sinuses via emissary veins, or via vessels supplying falx and tentorium
    - Head tourniquets recommended by earlier researchers
    - SNM guidelines – a tourniquet should not be used unless there is "adequate monitoring of intracranial pressure or there is little reason to expect an elevation of intracranial pressure."

Confirmatory Tests – Radionuclide Imaging

- Advantages of radionuclide angiography
  - Fast
  - Noninvasive
  - Bedside study
  - No electrical interference
  - No iodinated contrast
- Disadvantages
  - False positive studies: visualization of venous sinuses
  - Inability to assess posterior fossa (cerebellum and brain stem): images are acquired in an anterior projection
  - Sensitivity to bolus injection technique

Confirmatory Tests – Radionuclide Imaging

- Imaging with lipophilic agents Tc-99m HMPAO and Tc-99m ECD
  - Passively cross the BBB and become trapped within brain parenchyma in proportion to regional perfusion
  - Multiplanar imaging enables assessment of posterior fossa
  - No false positives seen with hydrophilic agents from dural sinuses visualization

Confirmatory Tests – Radionuclide Imaging

- Imaging with lipophilic agents
  - Both Tc-99m HMPAO and Tc-99m ECD have similar cerebral kinetics and initial distribution:
    - Rapid uptake by gray matter
    - Distribution correlates with brain perfusion
    - Once trapped, distribution changes little with time
  - HMPAO is widely used
  - ACR and SNM mention use of Tc-99m ECD, AAN does not

Confirmatory Tests – Radionuclide Imaging

- Tc-99m HMPAO preparation:
  - Mo-99/Tc-99m generator must have been eluted within 24 hours preceding current elution for reconstitution of Tc-99m HMPAO (for purity)
  - If methylene blue stabilization is used, the dye must be used within 30 minutes of formulation
  - Stabilized Tc-99m HMPAO must be used within 4 hours
  - If methylene blue stabilization is not used, Tc-99m HMPAO must be used within 30 minutes

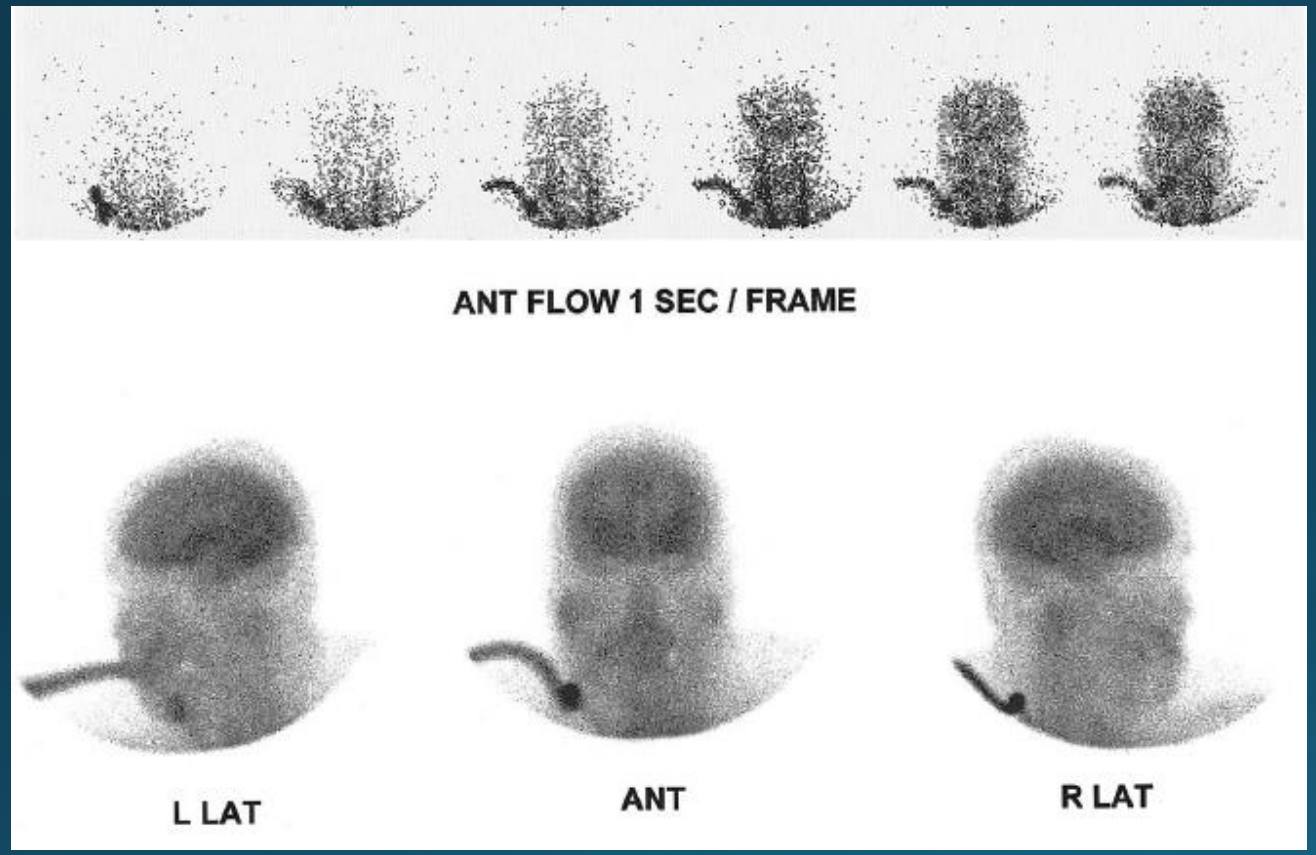
Confirmatory Tests – Radionuclide Imaging

- Angiography with Tc-99m HMPAO
  - Optional procedure by some
  - Supportive information and quality assurance by some
- SPECT imaging
  - Reduces effect of scalp, parotid and muscle activity
  - Accurate evaluation of posterior but the need to move patient to imaging table offsets this advantage
  - ACR and SNM mention potential use of SPECT ; AAN does not

Confirmatory Tests – Radionuclide Imaging

- Confirmation of brain death with Tc-99m HMPAO:
  - No flow on angiogram and
  - No brain uptake
- Patterns precluding brain death confirmation:
  - Preserved flow, metabolism in cerebrum & cerebellum
  - Preserved cerebellar uptake without cerebral uptake (a "step in the brain death phenomenon")
  - Preserved cerebral uptake without cerebellar uptake

Confirmatory Tests – Radionuclide Imaging

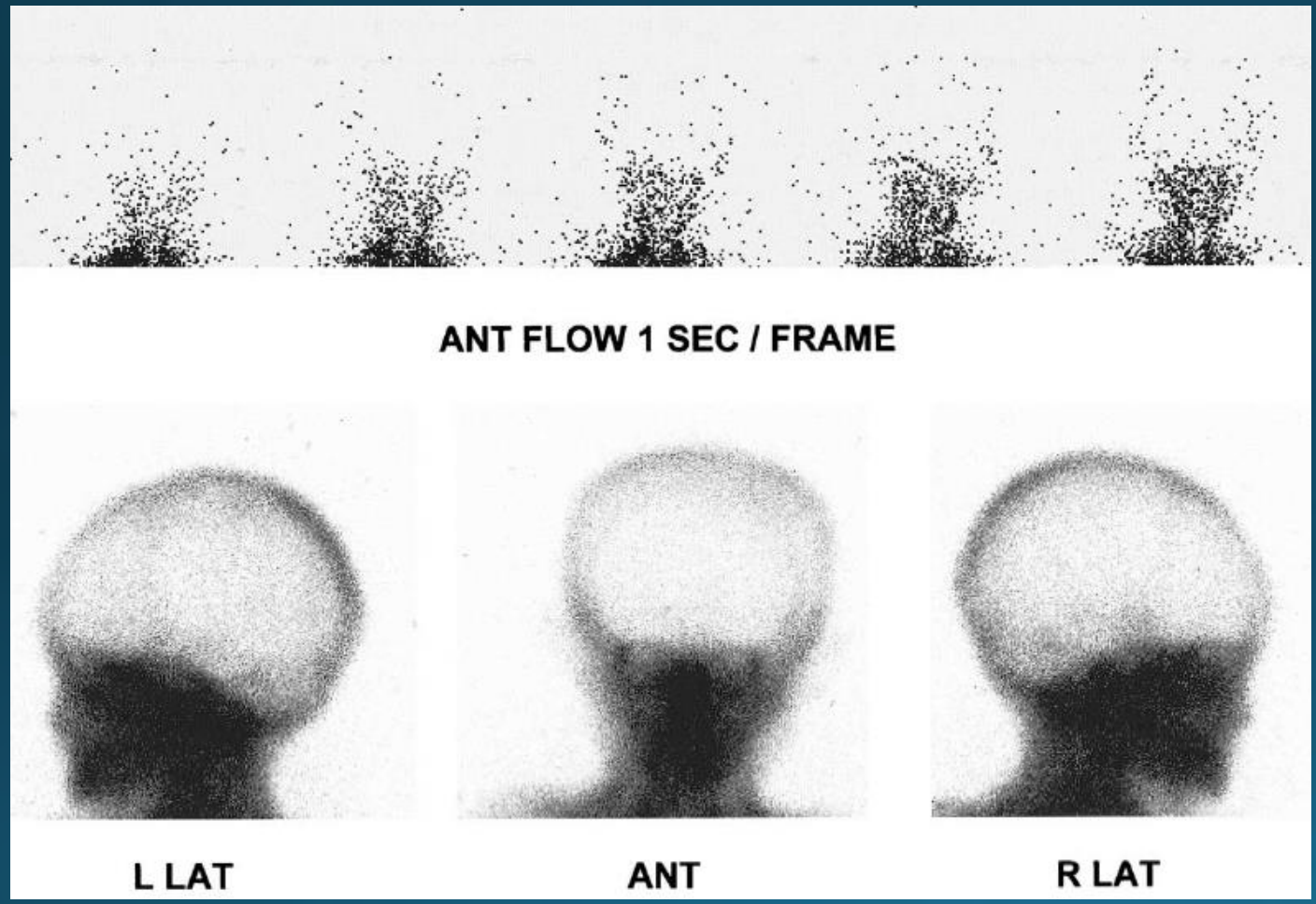


Tc-99m HMPAO
Dynamic images:
Flow present in ACA and MCA distribution

Static Images:
Tracer metabolism within cerebral hemispheres and cerebellum but appears decreased in latter

Preservation of cerebral flow and metabolism
Clinical diagnosis of brain death not confirmed

Confirmatory Tests – Radionuclide Imaging

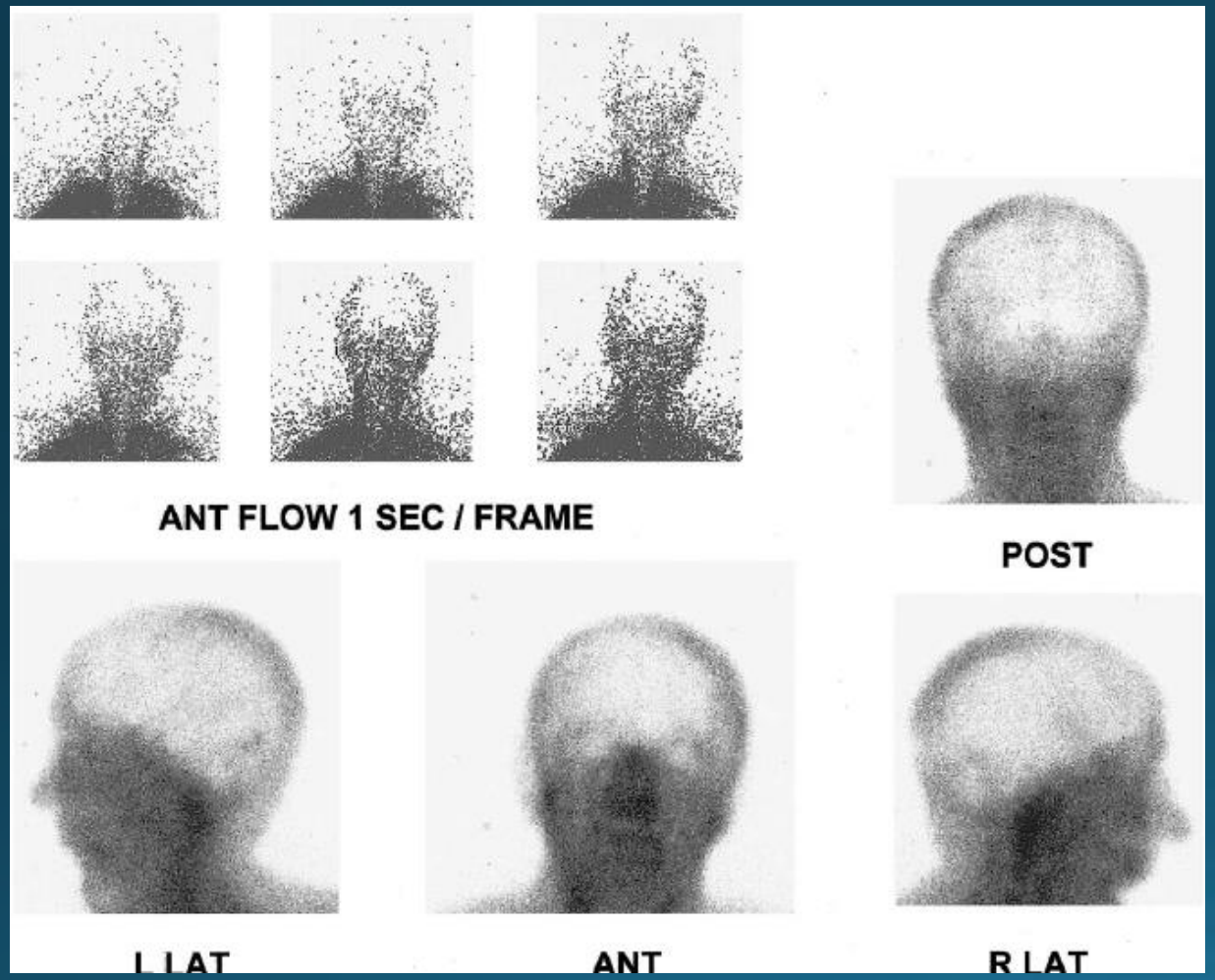


Tc-99m HMPAO
Dynamic images:
No flow

Static Images
No tracer uptake

No cerebral flow or metabolism
Clinical diagnosis of brain death confirmed

Confirmatory Tests – Radionuclide Imaging



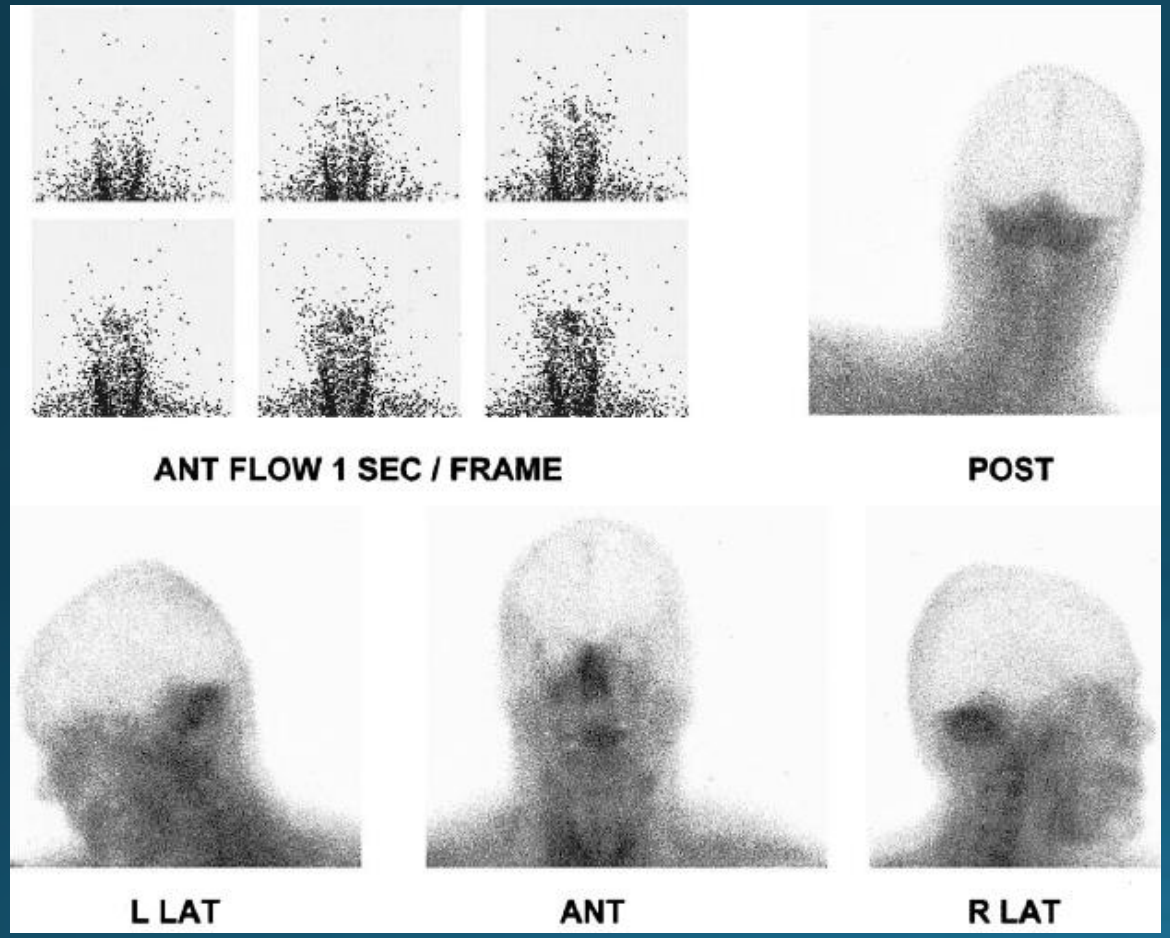
Tc-99m HMPAO
Dynamic images:
Flow in CCA and ECA. No flow in ACA and MCA distribution

Static Images:
No tracer within cerebral hemispheres and cerebellum.

Note sagittal, transverse, and sigmoid venous sinuses

No cerebral flow or metabolism
Clinical diagnosis of brain death confirmed

Confirmatory Tests – Radionuclide Imaging

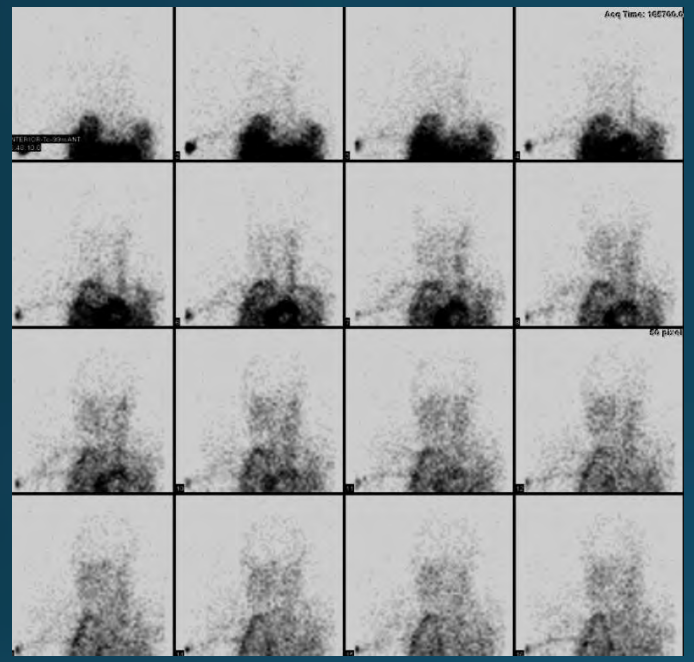


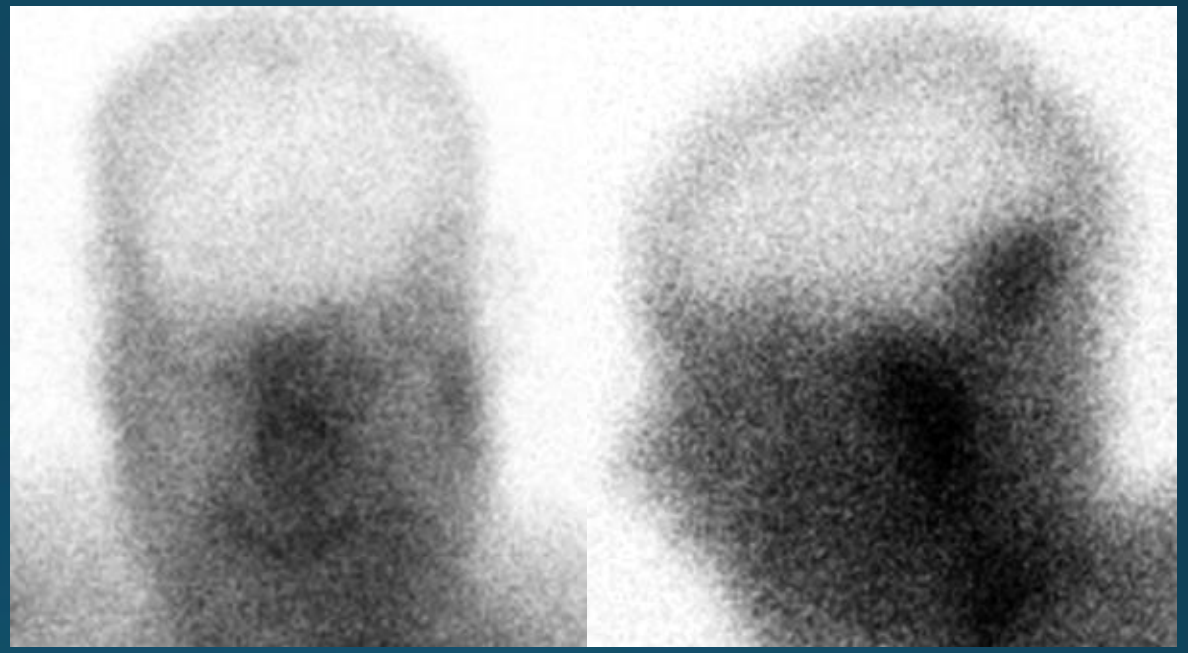
Tc-99m HMPAO
Dynamic images:
No intracranial flow

Static Images:
No tracer metabolism in cerebral hemispheres; tracer metabolism is present within cerebellum.

Metabolism present within cerebellum
Clinical diagnosis of brain death not confirmed

Confirmatory Tests – Radionuclide Imaging



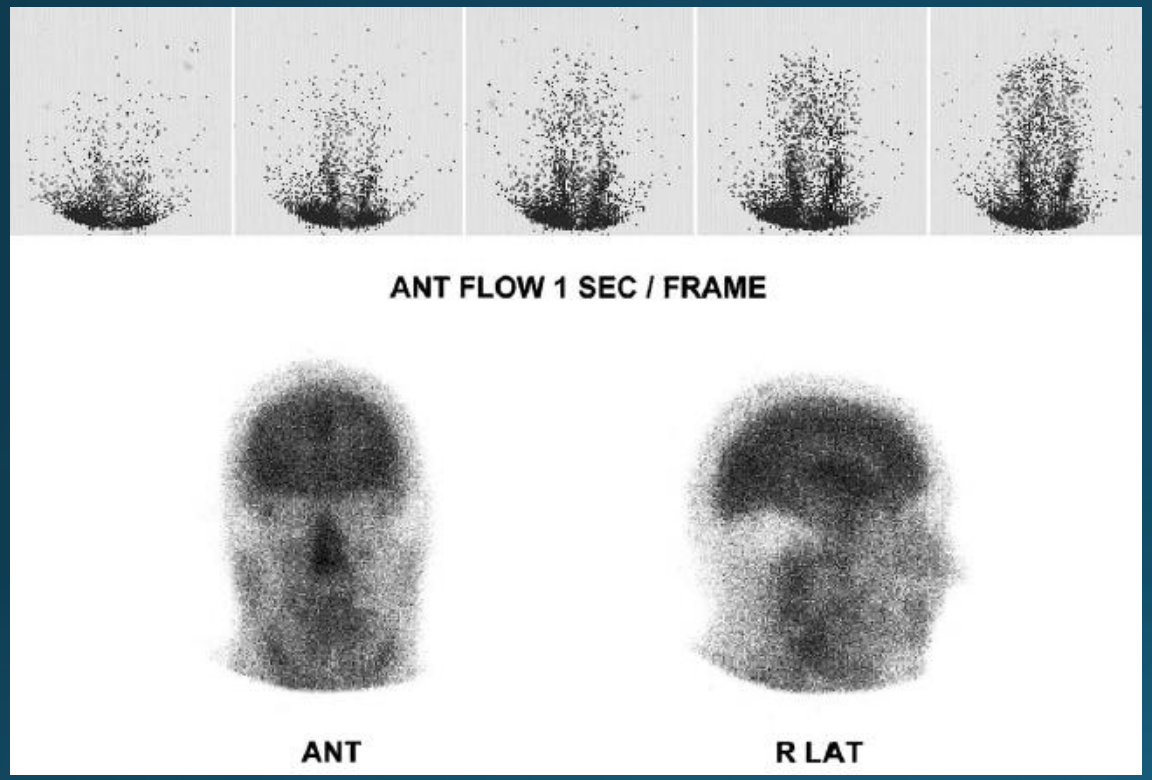


Tc-99m HMPAO

- Dynamic images: No intracranial flow
- Static Images: No tracer metabolism in cerebral hemispheres; tracer metabolism present within cerebellum
- Clinical diagnosis of brain death not confirmed

Case courtesy of Shana

Confirmatory Tests – Radionuclide Imaging

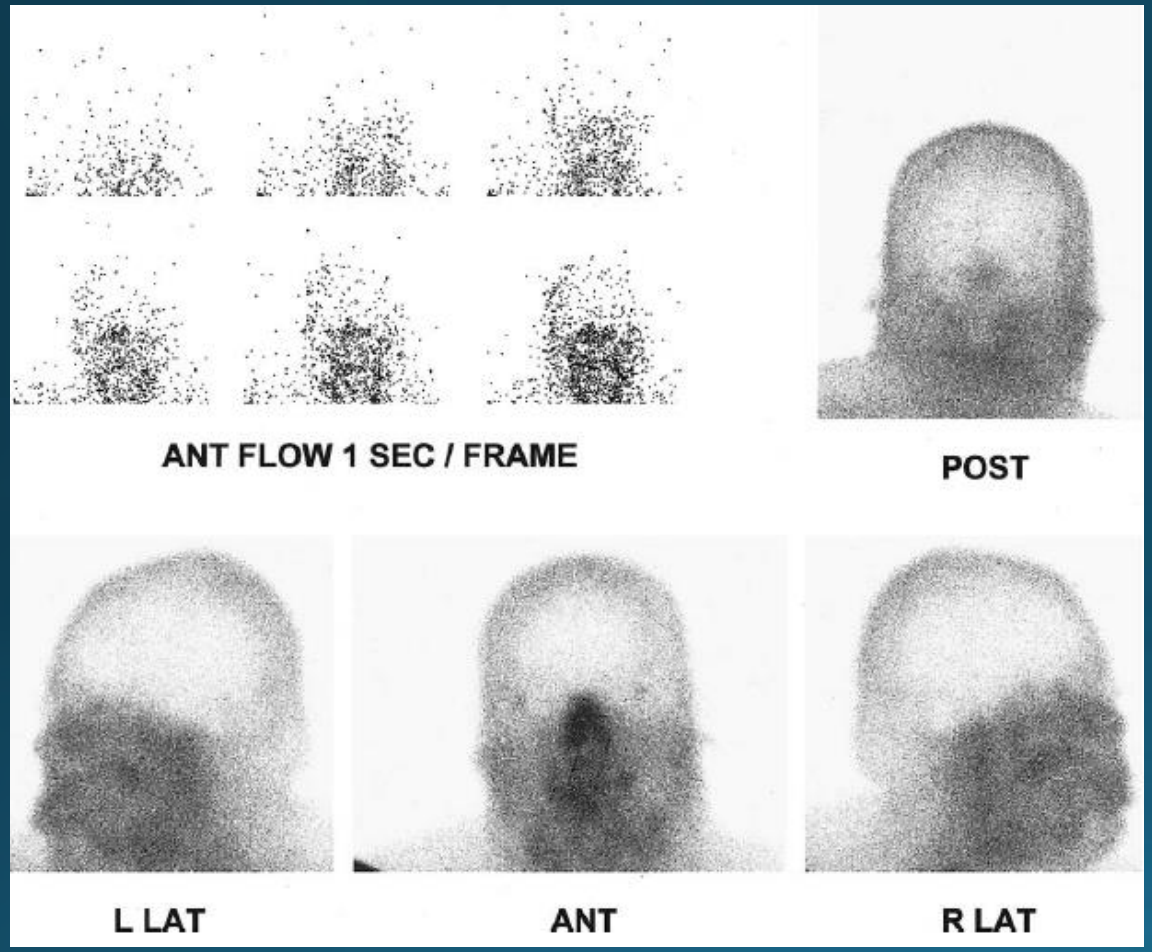


Tc-99m HMPAO
Isolated cerebellar death: Disassociation between cerebral and cerebellar flow from cerebellar infarction.

No tracer metabolism in cerebellum; tracer metabolism present in cerebral hemispheres. H/o vertebral artery dissections with occlusion.

Clinical diagnosis of brain death not confirmed

Confirmatory Tests – Radionuclide Imaging



Tc-99m HMPAO
"Hot nose sign" - in 52% of patients with brain death; also in other disorders not associated with brain death

Refers to increased activity in nasopharyngeal area in patients with internal carotid artery obstruction

It's a secondary sign that is supportive but not diagnostic of brain death

Confirmatory Tests – Radionuclide Imaging

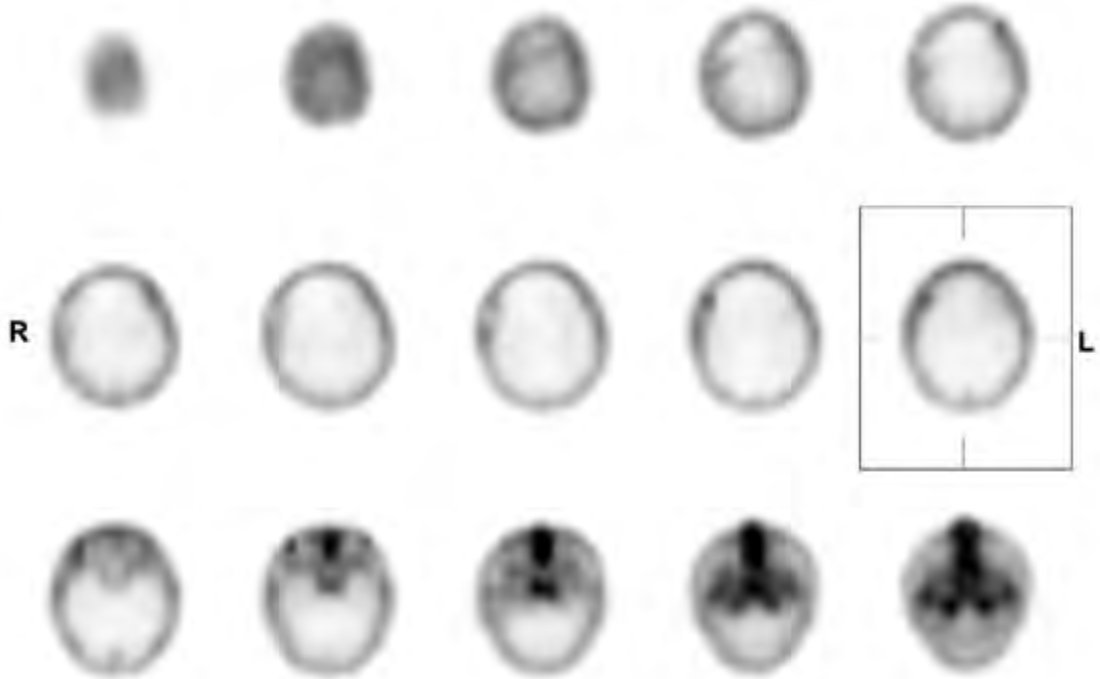


Figure 3 SPECT imaging of the brain performed 60 minutes after the intravenous administration of 30.8 mCi (1140 MBq) Tc99m HMPAO. Clinical examination was consistent with brain death. No tracer uptake is noted in the cerebrum or cerebellum. Brainstem is not visualized, either. An incidental note is made of the SPECT equivalent of the "hot nose" sign.

Confirmatory Tests – Radionuclide Imaging

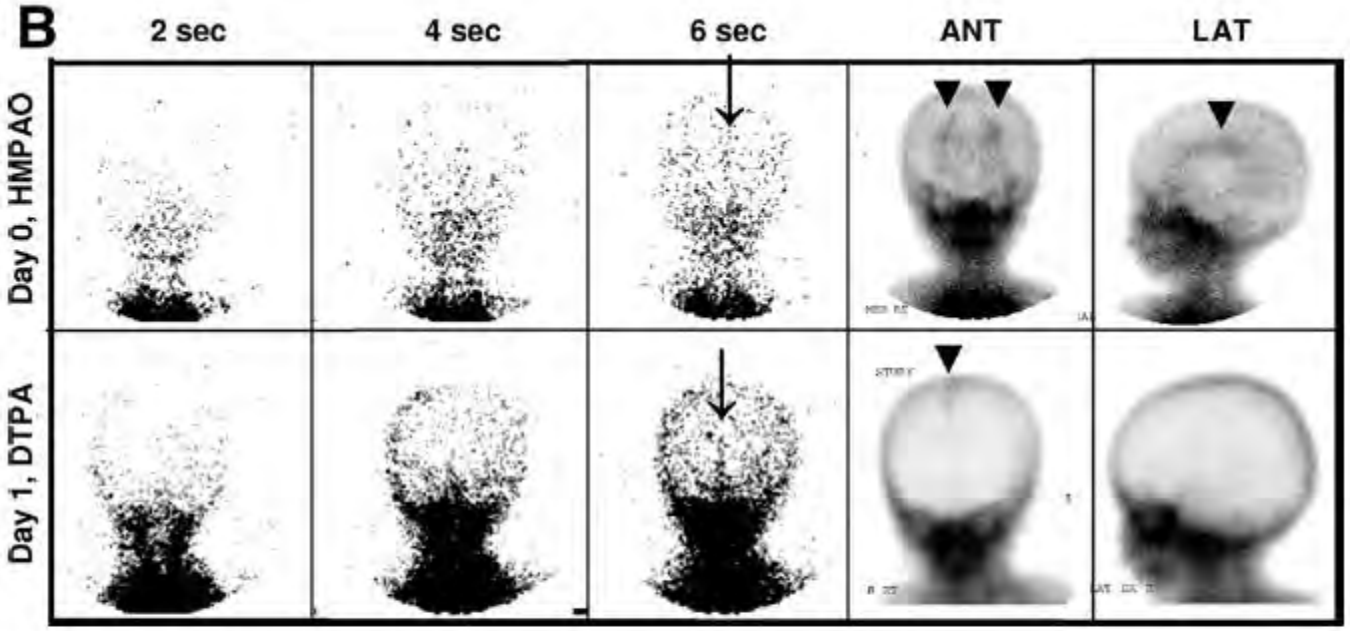


Figure 7 A 2-month-old child with head injury and clinical brain death. (A) Noncontrast CT scan shows diffuse loss of the gray–white matter differentiation and sulcal effacement consistent with bilateral infarction with sparing of the basal ganglia and brainstem. (B) Initial study with ^{99m}Tc-HMPAO (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).

Brain Death Confirmatory Tests – Radionuclide Imaging

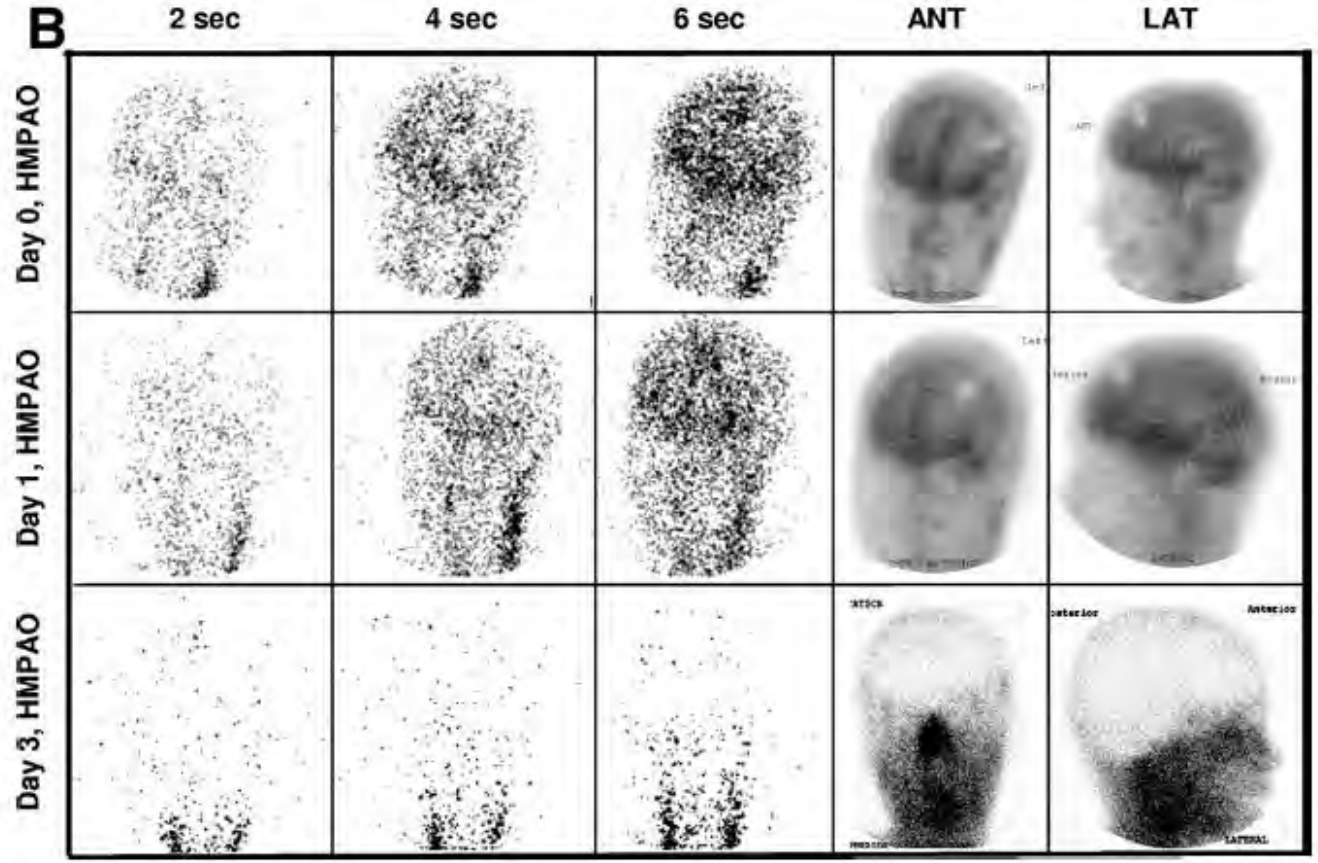


Figure 8 A 31-year-old woman with neurologic evidence of brain death. (A) Noncontrast CT scan demonstrates diffuse cerebral edema. A right-sided shunt catheter is in place. There is blurring of gray–white matter differentiation with a relatively dense-appearing posterior fossa (not seen on this image), 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).

Advantages of imaging with Tc-99m HMPAO:

- Immediate and delayed “static” imaging can be done
- Insensitive to intravenous bolus techniques
- Allows assessment of individual brain regions
- Allows assessment of posterior fossa
- Distinguishes between low and absent flow
- Not affected by metabolic disturbances including hypothermia to 30°C

Brain Death
Summary

- Brain death is a clinical diagnosis that should be based on history and physical examination findings
- Nuclear medicine is not, and should not be a primary method for diagnosing brain death
- Radionuclide imaging provides a safe, reliable, and widely available confirmatory test to clinical diagnosis of brain death

Brain Death Summary

- Radionuclide angiography with nondiffusible hydrophilic agents has largely been replaced with parenchymal imaging using lipophilic agents
- Parenchymal imaging allows assessment of the cerebellum and brain stem
- SPECT imaging may not be possible for all patients although better than planar imaging for brainstem

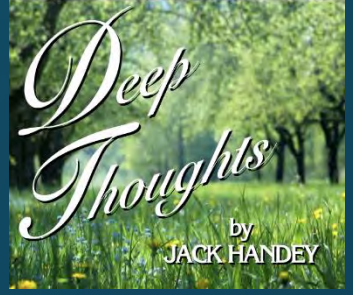
Brain Death – Standard Medical Record Documentation (AAN)

- Etiology and irreversibility of condition
- Absence of brainstem reflexes
- Absence of motor response to pain
- Absence of respiration with $PCO_2 \geq 60$ mm Hg
- Justification for confirmatory test and result of confirmatory test
- Repeat neurologic examination - interval is arbitrary, but usually 6 hours

conclusion

- context for and history of defining death
- technological advances led to shift towards neurologic criteria
- brain death is a clinical diagnosis (coma/unresponsive; absence of brain stem reflexes; apnea)
- confirmatory testing

going forward



- current definition involves whole brain (including brain stem), but some argue for "higher brain" cerebrum only definition
- point in time vs. process…
- "It is not surprising that many people seem to think that 'brain death' is a separate type of death that occurs before 'real' death. This confusion is reinforced when hospital personnel state — and journalists repeat — that 'life support' is being removed from such patients." alexander capron

Suggested Articles

1. Huang AH. The hot nose sign.Radiology 2005. 235: 216-217
2. Uliel L, et al. Radiographics 2013;. Nuclear medicine in the acute clinical setting: indications, imaging findings, and potential pitfalls. 33: 375-396
3. Society of Nuclear Medicine Procedure Guideline for Brain Death, Scintigraphy version 1.0, approved February 25, 2003
4. **Brain Death Determination**, J Intensive Care Med. 2015 Sep;30(6):326-37. doi: 10.1177/0885066613511053. Epub 2013 Nov 12.
5. **Pitfalls in the diagnosis of brain death**, Neurocrit Care. 2009;11(2):276-87. doi: 10.1007/s12028-009-9231-y. Epub 2009 May 15.
6. **Brief review: the role of ancillary tests in the neurological determination of death**, Can J Anaesth. 2006 Jun;53(6):620-7.
7. **Brain blood flow in the neurological determination of death: Canadian expert report**, Can J Neurol Sci. 2008 May;35(2):140-5.

Suggested articles

1. Tom L. Beauchamp, James F. Childress Principles of Biomedical Ethics, Oxford University Press, 2001
2. Brody, Baruch A. How Much of the Brain Must Be Dead? In Ethical Issues in Modern Medicine, eds. Bonnie Steinbock, John D. Arras, and Alex J. London, 277-282.New York: McGraw-Hill, 2003
3. Broyde, Michael J. The Diagnosis of Brain Death, Letter, New England Journal of Medicine 345, no. 8 (August 23, 2001): 617
4. Capron AM Brain death--well settled yet still unresolved., N Engl J Med. 2001 Apr 19;344(16):1244-6.
5. Emanuel, Linda L. Reexamining Death, Hastings Center Report 25, no. 4 (July/Aug. 1995): 27-36.
6. Hardwig J. Is there a duty to die?, Hastings Cent Rep. 1997 Mar-Apr;27(2):34-42. Review.
7. National Conference of Commissioners on Uniform State Laws . *Uniform Determination of Death Act*, Annual Conference Meeting in its eighty-ninth year: Kauai, Hawaii, 1980.
8. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Defining Death*, In Ethical Issues in Modern Medicine, eds. Bonnie Steinbock, John D. Arras, and Alex J. London, 259-268. New York: McGraw-Hill, 2003.
9. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *Definition of Irreversible Coma*, JAMA 205, no. 6 (Aug. 5, 1968): 337-340.
10. Society of Nuclear Medicine Procedure Guideline for Brain Death, Scintigraphy version 1.0, approved February 25, 2003