Nuclear Neurology

Jennifer S. Jurgens, MD
Walter Reed Army Medical Center
Washington, DC
Uniformed Services University of the Health Sciences
Bethesda, MD
Nuclear Neurology

• Functional Neuroanatomy
• Brain Scintigraphy
  – Perfusion and Metabolism
  – Clinical Applications
• Brain Death Scintigraphy
• CSF Flow Scintigraphy
Functional Neuroanatomy
Lobes of the Brain

- **Frontal**
  - Central sulcus anterior to frontal pole
  - Above the lateral sulcus
- **Parietal**
  - Central sulcus posterior to occipital lobe
  - Superior to temporal lobe
- **Temporal**
  - Temporal pole to occipital lobe
  - Below the lateral sulcus
- **Occipital**
  - Posterior to a line connecting the parieto-occipital sulcus and the pre-occipital notch
- **Insula**
  - Buried within the lateral sulcus
- **Limbic**
  - C-shaped structure of the medial hemispheric surface
  - Encircles the corpus callosum and the lateral aspect of the midbrain

Afifi, Functional Neuroanatomy, McGraw-Hill 2005
Functional Anatomy

- **Frontal Lobe**
  - Reasoning, planning, parts of speech, movement, problem solving, emotions
- **Parietal Lobe**
  - Movement, orientation, recognition, perception of stimuli
- **Occipital Lobe**
  - Visual processing
- **Temporal Lobe**
  - Perception and recognition of auditory stimuli, memory, speech

www.BrainHealthandPuzzles.com
Homunculus

Sensory

Motor

(After W. Penfield and T. Rasmussen, 1950)
Key Deep Structures

- Caudate
- Putamen
- Globus Pallidus
- Thalamus

Blood Supply

- Circle of Willis
- Anterior Cerebral Artery
- Middle Cerebral Artery
- Posterior Cerebral Artery
Perfusion and Metabolism
Perfusion Imaging
SPECT Agents

- Lipophilic agents with low molecular weight and negative charge
- Brain extraction proportional to blood flow
- Become fixed in brain with little redistribution
Perfusion Imaging
SPECT Agents

- Tc99m HMPAO (hexamethylpropyleneamine oxime)
- Tc99m ECD (ethyl cysteinate dimer)
Tc99m-HMPAO

- Lipid soluble
- 40% bound, 60% available for brain uptake
- 80% (of 60%) first pass extraction
- peak uptake in 1-2 minutes followed by a rapid wash out over 10-15 minutes.
- 3.5-7% of dose remains in brain because of conversion by glutathione to a hydrophilic form.
- Distribution remains constant for many hours after injection
Tc99m-ECD

- peak activity in 2 minutes
- 6-7% injected dose retention
- retention via ester hydrolysis (de-esterfication)
- better target to background activity than HMPAO
- Clears slowly from the normal brain
  - 10% left in blood at 2 minutes
  - 5% left in blood at one hour
  - Asymmetric washout
- Show significant regional variation in clearance
  - Gray and white matter contrast decreases at 2 hrs
  - Gray matter activity becomes significantly decreased at 4 hours
Glucose Metabolism
F18-FDG PET

• Brain predominantly uses glucose
• Active transport
• Peak localization: 30 minutes
Clinical Applications

• Evaluation for suspected dementia
• Epilepsy – surgical evaluation
• Cerebrovascular disease
• Mapping the distribution of brain perfusion during interventions
• Evaluation of brain injury
• Characterize primary brain tumors
• Detection and localization of recurrent brain tumor
Dementia
Dementia

- **Cortical**
  - Subcortical structures are spared; motor dysfunction is not prominent
    - Present with apraxia, aphasia, memory loss, and abnormal affect
  - Alzheimer’s dz, Pick’s dz

- **Subcortical**
  - Basal ganglia, thalami, and brain stem are affected
    - Present with motor dysfunction (posture, tone, tremor, gait disturbances) and cognitive dysfunction
  - Huntington’s, Wilson’s, MS, NPH

- **Mixed**
  - Multi-infarct dementia, Creutzfeldt-Jakob, hypoxic encephalopathy
Functional Imaging in Dementia Perfusion and Glucose Metabolism

- Pattern of abnormality generally associated with the presence of dementia is reduced tracer uptake
  - Certain types: absent tracer uptake
- Distribution of reduced uptake
  - Severity of disease
  - Most prevalent type of cognitive impairment seen on clinical and neuropsychological examination
  - Related to pathophysiology of disease
Alzheimer’s Type Dementia

• 75% of the dementias in the elderly
• Present:
  – Short term memory loss
  – Visuospatial problems
Alzheimer’s Type Dementia

- Relatively preserved blood flow and metabolism
  - Subcortical gray matter
  - Sensorimotor and occipital cortices
  - Cerebellum

- Significant reduction of cerebral perfusion and metabolism
  - Temporal and posterior parietal lobes
  - Posterior cingulate cortex
  - Frontal lobes in more advanced cases
Alzheimer’s Type Dementia

• Functional changes precede the atrophy seen on structural imaging
  – Sometimes by years
  – Are more specific

• Specificity and sensitivity of posterior parietal perfusion defect for Alzheimer’s disease is approx 90%
  – Can also be seen in NPH, Parkinson’s, Bilateral structural abn, CJD, AIDs
Alzheimer’s Type Dementia

• Unilateral or more asymmetric radiotracer distribution
  – Early in the course of the disease
  – Younger patients
• Good correlation between the asymmetry and the cognitive deficits noted on neuropsychological testing
• Degree of decreased activity correlates with severity of symptoms
Hallmark of Alzheimer’s Dz

• **Senile Plaques**
  – Extracellular deposits of amyloid
    • Surrounded by dystrophic axons and processes of astrocytes and microglia
  – Amyloid throughout neuropil and in walls of cerebral blood vessels

• **Neurofibrillary tangles**
  – Filamentous inclusions
  – Poorly soluble hyperphosphorylated isoforms of tau
  – Alter cytoskeleton

• **Key for future:**
  – Pittsburgh Compound B (PiB)
  – Binds to amyloid

Dementia with Lewy Bodies

• Clinical: parkinsonian dementia syndrome
  – Presenting feature is usually the cognitive impairment
    • Similar to AD
    • Visuospatial function and visual memory are impaired more severely
  – Later emergence of parkinsonism
    • Rarely asymmetrical
    • Resting tremor is less prominent
  – Key:
    • Fluctuations and visual hallucinations (80%)
    • Marked neuroleptic sensitivity (sleep disturbances, falls, syncopal episodes)
Dementia with Lewy Bodies

• Temporoparietal pattern (similar to AD)

• Addition of more posterior changes including the visual cortex (usually spared in AD)
  – Occipital metabolic changes distinguished DLB vs AD with 90% sensitivity and 80% specificity

• Minoshima et al, Ann Neurol 2001;50:358-365
Frontotemporal Dementia

Pick’s Disease

- FTD = group of disorders
  - Pick’s Disease is most common

- Progressive dementia
- Presents with personality changes, emotional disturbances, and deterioration in behavior and judgment
- Clinically different than AD except in very early disease
Pick’s Disease

• Decreased frontal or frontotemporal uptake bilaterally
  – Mesial frontal lobe = most common
  – May be asymmetric
• Lesser degree in the basal ganglia
• Uptake in the parietotemporal cortex is preserved
Pick's disease
Multi-infarct Dementia

• Characterized clinically:
  – Stepwise progression of the symptoms, attributable to repeated episodes of infarction
  – Sometimes the “stepwise” is subtle and the presentation can be similar to Alzheimer’s
  – Alz and vascular dementia can co-exist

• Usually have evidence of infarcts on CT/MRI
  – Presence of infarcts of different age is highly suggestive of that diagnosis
Multi-infarct Dementia

Functional Imaging Findings

• Global cerebral perfusion and glucose metabolism are reduced to a greater extent than in pts with Alz

• Multifocal areas of decreased uptake

• Sensorimotor cortex can be involved
  – Spared in Alz
Huntington’s Disease

• Characterized by: gradual onset and subsequent progression of chorea and dementia

• Autosomal dominant
  – Offspring of an affected individual have 50% chance of developing the disorder

• Symptoms do not appear until adulthood (30-50 yrs)
Huntington’s disease

• Decreased flow and metabolism in the caudate nucleus
  – FDG PET has shown reduced glucose utilization in an anatomically normal caudate nucleus.

• Findings present in asymptomatic gene carriers
  – May be helpful in identifying those family members with the disease who have not yet expressed the gene clinically
DEGENERATIVE DISEASES

NORMAL  PARKINSON'S  ALZHEIMER'S  HUNTINGTON'S
DISEASE  DISEASE  DISEASE

FDG  FDG  FDG  FDOPA

Bradley, Neurology in Clinical Practice 3rd Ed, Butterworth-Heinmann, 2000
Epilepsy
Seizures

- Generalized
  - Tonic-Clonic, Absence, Myoclonic
- Partial (Focal)
  - Simple or complex
  - Temporal lobe epilepsy = 2/3 rds
    - Mesial temporal = most common
  - Extratemporal epilepsy
    - Fontal > Parietal > Occipital
Temporal Lobe Seizures

- Mesial temporal lobe
  - Visceral sensations
  - Fear
  - Anxiety
  - Olfactory disturbances
  - Psychic phenomena

- Neocortial temporal
  - Auditory hallucinations
  - Complex visual phenomena
Epilepsy

• Surgical evaluation
  – Medically resistant after 1 – 2 treatments
  – Structural abnormality on MRI (MTS)
• MTLE has more favorable response to surgery vs neocortical epilepsy
• Keys:
  – localize ictal focus and
  – exclude multiple/bilateral foci
Seizures

• **Ictal:**
  – Both regional cerebral perfusion and metabolism are increased

• **Interictal:**
  – Both decreased

• FDG PET imaging is more sensitive for demonstration of the seizure focus in the inter-ictal state
• 99mTc-HMPAO/ECD is more suitable for ictal administration because of its rapid first pass uptake
• **Highest sensitivity and specificity for localization:** ictal perfusion SPECT combined with interictal F18-FDG PET
A: F18-flumazenil

Bradley, Neurology in Clinical Practice
3rd Ed, Butterworth-Heinmann, 2000
Cerebrovascular Disease
Acute Ischemia

• Auto regulation initially intact
• Local brain perfusion pressure decreases (CBF, OEF constant)
  – → local vasodilatation
  – → decreases resistance
  – → maintains flow
• Perfusion pressure decreases significantly
  – → maximal vasodilatation
  – → local perfusion pressure falls
• To compensate for decrease in perfusion → increase oxygen extraction
Acute Ischemia

- Further decrease in perfusion following max OEF
  - Metabolism decreases
  - Signs and symptoms in patient
  - Regulation of blood flow is disturbed
    - Blood flow is a poor marker of tissue viability beyond the initial acute ischemic phase

- Resolve (TIA) vs Infarct
Stroke

**Misery Perfusion**
- Relative decreased perfusion compared to glucose and oxygen metabolism
- Decreased perfusion -> increased OEF

**Luxury Perfusion**
- Perfusion usually improves, but the symptoms and cerebellar diaschisis persist
- Decoupling of metabolism and perfusion

**Penumbra**
- Surrounds the infarcted area; ischemic
- Demonstrates decreased perfusion but increased oxygen extraction fraction
- If perfusion is restored in a timely manner, irreversible damage will not occur
Left hemiparesis and visual spatial dysfunction


Slides are not to be reproduced without permission of author
Stroke

• Regions that show decreased perfusion and metabolism distant to the region of interest:
  – **Cortical infarcts:**
    • Contralateral cerebellar hemisphere (crossed cerebellar diaschisis)
    • Ipsilateral thalamus and caudate nucleus
  – **Thalamic infarcts:**
    • Cortical hypometabolism that is dependant on the specific nuclei.
Interventions
Mapping the distribution of brain perfusion during interventions

• Evaluate hemodynamic reserve
  – TIA, Stroke, AVM

• Acetazolamide [Diamox]
  – Carbonic anhydrase inhibitor
  – Increases cerebral blood flow 30-40%
  – Ischemic areas have decreased reserve
  – Beware: sulfa allergy

• Temporary balloon occlusion of the internal carotid artery
  – Pre op eval to tolerate vessel sacrifice
Right hemiparesis and recurrent TIAs

Baseline

Diamox

Slides are not to be reproduced without permission of author
Moyamoya Disease

- Occlusion of MCA
- Extensive collateral circulation develops
- High risk of stroke / hemorrhage
- Treatment: extra-intracranial bypass surgery
Brain Injury
Mechanisms of Brain Injury

• Contact
  – Object striking the head
  – Contact between the skull and the brain

• Acceleration / Deceleration
  – Unrestricted movement of the head
  – Pressure gradients within the skull
  – Shear, tensile, and compressive strains
Types of Brain Trauma

- **Focal**
  - Fracture to skull
  - Contusions
  - Hemorrhage
  - Hematoma
  - Tissue tears

- **Diffuse**
  - Diffuse axonal injury
  - Ischemic injury
  - Complications of brain edema
  - Vascular injury
  - Late appearing neurodegeneration of Alzheimer’s type
Contusional TBI Injuries

Osborn; Diagnostic Neuroradiology 1994

Moore, Anatomy 1992
Diffuse Axonal Injury

- Focal alterations of axolemma
- Influx of normally excluded extracellular ions
- Activation of cystein proteases, calpain, and caspase
- Disrupt cytoskeleton
- Swelling
- Collapse and detachment of axon at focal point of swelling
Diffuse Axonal Injury

Osborn; Diagnostic Neuroradiology 1994
Brain Perfusion SPECT in TBI

• Generally more sensitive than traditional CT/MRI in detecting abnormalities
  – More lesions
  – Lesions larger in size
  – All severities of injury
  – Any duration
Brain Perfusion SPECT
Abnormality Locations

- Focal hypoperfusion:
  - Basal ganglia and thalami
  - Frontal lobes
  - Temporal lobes
  - Parietal lobes
  - Insular and occipital lobes

- Diffuse supratentorial hypoperfusion

- Focal hyperperfusion
  - Adjacent to intraparenchymal anatomic lesions
FDG-PET and TBI

- Cerebral dysfunction can extend far beyond the confines of anatomical lesions
- 33% of anatomical lesions associated with larger and more widespread metabolic abnormalities
- 42% of FDG-PET abnormalities are not associated with any anatomical lesions

Alavi, J Neuropsychiatry, 1989
TBI

- Extensive hypometabolism
- Contre-coup
- Crossed diaschisis
Tumor Evaluation
Brain Tumors

• Primary Brain Tumors
• Metastatic Disease
• Radiation Necrosis versus Tumor Recurrence
Brain Tumors

- **FDG PET imaging:**
  - Differentiate recurrent high-grade tumor from radiation necrosis
  - Differentiate high-grade from low-grade glioma
  - Site selection for biopsy
  - A high degree of uptake in high-grade gliomas is a poor prognostic factor
Brain Tumors
FDG PET

• Exceptions:
  – Pilocytic astrocytomas
  – Benign pituitary adenomas

• High FDG uptake is not specific for brain tumors
  – Florid inflammatory lesions
  – Subclinical seizures
Grade II Astrocytoma
Brain Tumors

• Brain Metastases:
  – Can be hypometabolic, isometabolic or hypermetabolic
  – Sensitive of FDG PET imaging for detection of brain mets is relatively low (68%).
  – MRI with gad remains the most sensitive imaging modality
    • the standard of care for detection of brain metastases
Recurrent Tumor vs Radiation Necrosis

• Present with clinical deterioration
• Often difficult to distinguish on MRI
• FDG-PET
  – Radiation necrosis = hypometabolic
  – Tumor recurrence = hypermetabolic
• Range of sensitivities and specificities
Thallium 201

- Normal: BBB intact and no activity in the cerebral cortex
- Diseases of the brain cause a breakdown in the blood brain barrier that allow entry into cortex
  - Brain tumors
  - Cerebrovascular disease
  - Infection
- KEY: Thallium has additional tumor localization properties (K+ analog)
Brain Death Scintigraphy
Brain Death

• Clinical Diagnosis
  – Institutions have guidelines
  – All correctable major systemic biochemical abnormalities should be addressed

• Scintigraphy: tool that can assist in the diagnosis
Brain Death Scintigraphy

• Patient Preparation
  – Stable blood pressure
  – Normal ventilation
  – Headband / Tourniquet
    • Around the scalp, encircling the head just above the eyebrows, ears, and around the posterior prominence of the skull
    • Diminish scalp blood flow
    • Do not use if head trauma or potential to exacerbate injury
Brain Death Scintigraphy

- **Brain Specific Agents**
  - Tc99m-ethyl cysteinate dimer (ECD)
  - Tc99m-hexamethylpropylene amine oxime (HMPAO)

- **Non-brain-binding Agents**
  - Tc99m-diethylenetriaminopentaacetic acid (DTPA)
  - Tc99m-glucoheptonate (GH)
  - Requires a good bolus

- **Caution:** Tc99m pertechnetate can have salivary and choroid plexus activity interfere with interpretation
Brain Death Scintigraphy

- Lack of flow: MCA, ACA, PCA
  - External carotid likely remains patent
- Lack of tracer activity in the superior sagittal sinus
- Brain specific agents: no tracer uptake in the brain on delayed images
CSF Flow Imaging
Imaging the CSF

• Intrathecal administration of a substance
  – Miscible with and diffusible in the CSF
  – Remains in the CSF compartment until absorbed through the normal pathways
  – Nontoxic
  – Nonpyrogenic
    • Strict pyrogen testing of all intrathecally administered agents should be routinely performed
CSF Radiotracer

• Any non-soluble agent will work to visualize CSF flow, if it is small and easily transported by normal flow patterns

• In-111 DTPA is current agent of choice for CSF flow dynamics (NPH)
  – medium-length half-life
  – relatively low dosimetry compared to I-131 HAS or Yterbium-169

• Tc-99m-DTPA can be used for some applications (leaks, shunt patency)
CSF PRODUCTION/ABSORPTION

Normal Examination
Lumbar Injection

- Basal cisterns by 1 hour
- Frontal poles and sylvian fissure area by 2-6 hours
- Cerebral convexities by 12 hours
- Arachnoid villi in the sagittal sinus by 24 hours
- Radiotracer does not normally enter the ventricular system because the flow is in the opposite direction
Normal Examination
Ventricular Injection

• Rapid clearance of the tracer into the basal cisterns by 30-60 minutes
• Sylvian fissures by 2-4 hour
• Over the cerebral hemispheres by 6-12 hours
• Negligible tracer should remain in the ventricles at 24 hours
Clinical Applications

- Common indications include:
  - **Evaluation for Normal Pressure Hydrocephalus** (communicating hydrocephalus)
  - **CSF Leak detection** (post op, post traumatic, spontaneous)
  - **Shunt Patency**

- Anatomic imaging not always able to answer question.

- A combination of anatomic and physiologic studies sometimes necessary for adequate evaluation.
Normal Pressure Hydrocephalus

• Clinical triad
  – Ataxia
  – Dementia
  – Urinary incontinence

• CSF shunting from the ventricular system may provide relief of symptoms in selected patients
Normal Pressure Hydrocephalus

- Early entry of the radiopharmaceutical into the lateral ventricles at 4-6 hours
- Persistence of lateral ventricular activity at 24, 48, and even 72 hours
- Considerable delay in the ascent to the parasagittal region
  - With or without delayed clearance of activity from the basilar cisterns
Slides are not to be reproduced without permission of author.
6 hours
24 hours
48 hours
Shunt patency

- May use Tc99m-DTPA
  - Short duration of examination
- Inject the radiopharmaceutical into the shunt reservoir or tubing under strict antiseptic conditions
- Distal shunt patency:
  - Rapid passage of the radiopharmaceutical through the distal limb of the shunt
  - Activity is noted in the peritoneal cavity or right atrium within minutes; should diffuse
  - Clearance half-time from a reservoir with a patent distal shunt limb: less than 10 min
Cerebrospinal Fluid Leaks

- Substantiate the presence of a CSF leak from the nose or ear
- Localize more precisely the site of a leak.
- Leak must be active at the time of examination
- Early imaging
  - Image the CSF leak at the time the radioactivity reaches the suspected site of origin of the leak
- Pledgets
  - Ratio to serum: normal < 1.3
SPONTANEOUS CSF LEAK

<table>
<thead>
<tr>
<th>RT</th>
<th>ANT</th>
<th>LT</th>
<th>LT</th>
<th>POST</th>
<th>RT</th>
<th>RT</th>
<th>ANT</th>
<th>LT</th>
<th>LT</th>
<th>POST</th>
<th>RT</th>
</tr>
</thead>
</table>

20 MINUTES POST INJECTION
4CM/MIN SCAN
Additional Radiotracers

- 123 I-N-isopropyl-p-iodoamphetamine (IMP): perfusion
- 123 I-IBZM: D2 receptor imaging
- 123 I-B-CIT: dopamine transporter
- 123 I-FP-CIT: serotonin transporter