Imaging in Dementia

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Dementia

• multiple cognitive deficits, including:
  – Memory dysfunction (esp new learning)
  – One additional cognitive deficit
    • Aphasia, apraxia, agnosia or executive dysfunction
• cognitive disturbances must be sufficient and severe enough to cause impairment of occupational or social functioning
• must represent a decline from previous level of functioning
Ddx

1. Alzheimer’s dz (pure 40%, mixed 70%)
2. Vascular Disease (5-20%)
3. Drugs, Depression, Delirium
4. Ethanol (5-15%)
5. Medical / Metabolic Systems
6. Endocrine (thyroid diabetes), Ears, Eyes
7. Neurologic (other primary degenerations)
8. Tumour, Toxin, Trauma
9. Infection, Idiopathic, Immunologic
10. Amnesia, Autoimmune, Apnea
Why image?

- Fixable cause
- Estimation of severity of brain atrophy
- SPECT, PET – estimation of regions of physiologic dysfunction
- Helps family to visualize the problem
Imaging Guidelines in Dementia

• Case by case basis
• Acute mental status changes (affect, behaviors or personality)
  – Abnormal neurological examination
  – Hx of trauma
  – New onset psychosis
  – New onset delirium
  – New onset dementia of unknown etiology
  – Prior to initial course of ECT
Overview

1. Functional image overview
2. Disease-specific imaging findings
3. Dementia mimics
Part I

FUNCTIONAL IMAGING OVERVIEW
Imaging Modalities

- Anatomic
  - CT
  - MRI
- Functional
  - MR techniques
  - PET
  - SPECT
- Fusion imaging
Primary Role of Anatomic Imaging

- Exclude medical or surgically treatable conditions (tumour, SDH, hydrocephalus)
- Diagnosis of patterns
  - Medial temporal lobe atrophy in AD
  - Focal frontal-temporal atrophy of FTD
  - Ischemia/infarction on CV diseases
- Document baseline changes in the brain
- Monitoring disease progression (serial, longitudinal measurements, rate of change of brain volume)
- Prognostication and Identify temporal changes to treatment and response
Subdural hematomas
Tumours
Functional MR (fMRI)

- T2* signal is retained longer (brighter) in areas which have more oxygenated blood, compared to areas with less oxygenated blood.
- Using co-operation of patient, who is told to perform certain task, different brain centers can be activated.
- Area is more active when it has more oxygenated blood.
• MR signal changes in the visual, auditory and sensorimotor cortex have been correlated with rate of stimulation
• Most useful to study processes which can be rapidly turned off and on (i.e., language, vision, memory, hearing, and movement)
• Used to noninvasively map language, motor, and memory function in dementing illness and in patients undergoing neurosurgery
• Not widely available
• Decreased temporal resolution
fMRI blood flow
Magnetized transfer imaging

- Identifies interactions between protons in water and macromolecules in the brain
- When a radiosaturation pulse is combined with a imaging pulse sequence (T2 weighted), a magnetized transfer ratio (MTR) can be measured
- Low MTR indicates low degree of myelination
- Used to measure changes from aging and myelin damage
Multidirection Diffusion MRI

- Measures diffusion of the motion of water molecules
- Used to calculate apparent diffusion coefficient (ADC)
- Low ADC indicates diffusion is restricted (classic example is stroke)
- DTI – diffusion tensor MRI – measure the direction as well as motion of water molecules
  - Used to measure fiber tracts
Perfusion MRI

- Method that measures regional cerebral blood flow
- IV bolus tracking
  - Using magnetic compound and measuring its T2* signal as it travels through the brain over a short time
  - Areas which are more perfused show less T2 signal
  - Injection once during control and during activation task
- Absolute blood flow by arterial spin labelling
  - H+ protons are flipped magnetically as it enters the ROI
  - Can measure absolute RBF
MR Spectroscopy (MRS)

• Signal in MR obtained in the time domain is used to generate images, but in MRS, Fourier transformation of the MR signal is used to get a spectograph of the components that make up the image
• Use MR to noninvasively study biochemistry and cerebral metabolism within a voxel
• Precession frequencies on X axis determines compound, and intensity on Y axis determines amount
Functional Isotope NeuroMR

- Invasive (radioisotopes)
- Expensive (need cyclotron)
- Metabolic activity is measured, using conventional MRI principles and radioisotopes (in bloodstream) to tag molecules of interest
- Emission are then measured
Magnoelectroencephalogram

- Detects changes in the magnetic field of the brain
- Expensive (you need to shield the earth’s magnetic field – overwhelms all signals)
- Special sensors encased in liquid helium
- Good spatial and temporal resolution
Brain region is located using MRI.

A transcranial magnetic stimulator (TMS) is placed over this region of the cortex.

The TMS coil, shown here in a composite MRI/PET scan photograph, interferes with brain function in the adjacent area.

With the TMS in place, the subject is then placed in a PET scanner where cortical activity is monitored.
PET and SPECT

- Shows blood flow by imaging trace amount of radioisotopes. PET however can measure metabolism also.
- Both PET & SPECT depict the distribution of blood into tissue but PET does with greater accuracy.
- Unlike PET which uses FDG (cyclotron produced and flown in daily from Edmonton), SPECT uses easily available radioisotopes greatly reducing the cost of operation.
Positron Emission Tomography (PET)

- Short-lived isotopes
- Isotope attached to molecules used to locate changes in blood flow, areas of high metabolic activity
- Example: radioactive oxygen (15 O)
  - Can be superimposed on CT or MR
  - High spatial resolution (poor temporal)
  - High radiation
Positron Emitter + Ligand

- $^{18}\text{F}$ + 2-fluoro-2-deoxy-D-glucose (FDG)
$F^{18}$-FDG uptake

**FDG** $\xrightarrow{\text{Glucose Transporters (GLUT)}}$ Intracellular FDG $\xrightarrow{\text{hexokinase}}$ FDG-6-P $\xrightarrow{\text{G-6-P}}$ X
The Physics of Positrons

- Anti-particle of electron
- Protons >> neutrons in nucleus
- $\beta^+$ escapes nucleus, slowed by electron cloud, comes to rest, captures electron
- annihilation produces 2 photons travelling in opposite directions
F18-FDG PET example

Damaged regions don’t pick up FDG
Single Photon Emission Computed Tomography (SPECT)
Tc HMPAO and Tc ECD
Radiopharmaceutical Choice

- Tc HMPAO
  - Reflects blood flow arrival
    - unstable in vitro
      - time since last generator elution <24 h
      - time since Tc eluted <2 h
      - time since cold vial labeled with fresh Tc <20 min
- Tc ECD
  - reflect cellular metabolism
    - stable to at least 4 h
    - freshly eluted Tc not required
    - labeling procedure longer (30 min)
Tracer Uptake Patterns

- Cold
  - CSF
  - edema
  - SOL (blood, tumor, cyst, AVM, post-op)
  - stroke
- Decreased uptake
  - ischemia
  - hypometabolism (deafferentation, diaschisis)
- Increased uptake
  - luxury
  - encephalitis
  - seizure
  - tumor
Brain Perfusion SPECT/PET Patterns

- Temporoparietal hypoperfusion
  - Alzheimer’s
  - Parkinson’s
  - Lewy Body disease

- Frontal (frontotemporal) hypoperfusion
  - Pick’s disease
  - Frontotemporal degeneration
  - PSP

- Multifocal / patchy
  - Multi-infarct dementia
  - AIDS dementia
Part II

DISEASE SPECIFIC OVERVIEW
Alzheimer’s Disease

- Most common cause of dementia in the elderly
- Typically begins with memory impairment
- Diagnosed clinically by deficit of one cognitive domain like memory, plus another after other causes of dementia are ruled out
- Definite diagnosis by autopsy
- >90 percent are sporadic, onset after 65 years
- Family history is a clear risk for development late onset AD
Pathology

- Senile plaques, neurofibrillary tangles, decreased synaptic density, neuron loss and cerebral atrophy
- Plaques vs tangles?
- Genetic evidence implicates derangement in amyloid metabolism
- Tau protein found by breakdown of microtubules are the pathologic substrate of NF tangles
- Neuritic (senile) plaque consisting of central beta amyloid core with inflammatory cells and dystrophic neurites
Progression of Atrophy in AD

- Rostal to caudal
  - Hippocampus
  - Entorhinal cortex
  - Cingulate Gyrus
  - Cerebrum
Atrophy: hemispheric and specific anatomic sites like entorhinal cortex, medial temporal lobe and hippocampus

Volume and linear measurements of hippocampus, interuncal distance and medial temporal lobe limbic structures correlating with age matched controls (painful)

MR volume measurement of hippocampal atrophy is a sensitive marker for AD, early in the disease – but unfortunately difficult to do properly
Imaging in AD:

- Prediction of AD by a single imaging study (Mayo clinic) using MR measurements
- Longitudinal follow-up of 32.6 months of 80 patients with MCI, 27 developed AD
- Most studies show median rate of atrophy of up to 1.5% against 0.2% in comparable control groups
MRS in Alzheimer’s Disease

- Increase in NAA/creatine ratio in the frontal cortex (1.23 at baseline vs 1.3 after treatment, \( p=0.026 \))

- Increase in the myoinositol/creatine ratio in the occipital cortex (0.61 vs 0.65; \( p = 0.009 \))

- DWI : Increase in diffusion values are seen in AD pts when compares to controls
Brain SPECT

- accuracy of SPECT as high as 88%
- meta analysis, SPECT was superior to clinical exam and clinical criteria (sensitivity 91% vs. 70%)


- value of SPECT in patient with doubtful AD
  - positive SPECT: increased posttest probability of Alzheimer disease by 30%
  - negative SPECT: increased the likelihood of the absence of Alzheimer disease by only 10%.
Perfusion Pattern

- Holman et al. studied 132 patients with pathology in 113 patients
  - 52 patients with Alzheimer's disease
  - 11 with Parkinson's disease dementia
  - 11 with vascular dementia
  - 14 with AIDS dementia
  - 2 with Pick's disease
  - 23 with other diagnoses.

- Bilateral parietotemporal defects with or without additional defects had a probability of 77% and 82% respectively.
  - If Parkinson's disease dementia is excluded, the likelihood of Alzheimer's disease is over 90%.

- Unilateral, frontal or multiple small defects were not predictive of AD.


Perfusion Pattern

- Bilateral parietotemporal involvement (hallmark)
- Usually symmetric, although asymmetry in the degree of perfusion or metabolism is accepted (10%)
- Posterior association cortex is the first cortical region to be affected in AD
- Spreads to the frontal lobes as the disease progresses, with persisting posterior dominance
- Early-onset disease have greater posterior association cortex involvement than patients with late-onset disease
- Primary motor, sensory, and visual cortices are typically spared until the last


Mild Cognitive Impairment (? Early AD)

- memory concern, usually by the patient but preferably corroborated by an informant
- Within 6 years, 80% of individuals diagnosed with MCI will develop full blown AD
- In amnestic MCI, a decrease in perfusion as well as glucose metabolism in the posterior cingulate gyrus and precuneus
  - has been observed with PET or SPECT
- Decrease in medial temporal regions
Decrease in medial temporal areas

- In a SPECT study of patients with mild AD, a significant decrease in perfusion in the amygdala and hippocampus. These areas have been reported to show marked atrophy from the early stage of AD.
- However, PET (better spatial resolution) have not reported such a decrease in the hippocampus.
- Numerous structural MRI studies have demonstrated that atrophy of the medial temporals a sensitive marker of very early AD.

Conversion from MCI to AD (quantification of perfusion)

- 12%–15% of patients have been shown to have converted to dementia per annum
  - incidence is about 10 times higher than the incidence of dementia in the general population
- Using brain perfusion SPECT to compare 52 converters (from MCI to AD) and 24 nonconverters at a 3-y follow-up, Hirao et al. reported reductions in perfusion in the bilateral parietal areas and the precunei in converters relative to nonconverters.
- Reduction in rCBF (perfusion) in the inferior parietal lobule, angular gyrus, and precuneus had high predictive value and discriminative ability.
- Confirmed in an independent study similar report at a 2-y follow-up in a SPECT study demonstrated that converters showed reduced rCBF specifically in the parietal and temporal lobes, precuneus, and posterior cingulate cortex.


Monitoring response to therapy

- Lower lateral orbital frontal and dorsolateral frontal perfusion suggested a good response to donepezil and was significantly related to behaviors of irritability, disinhibition, and euphoria.

- Longitudinal SPECT findings over 15 mo, on average, between stabilized and nonstabilized subjects receiving donepezil treatment.
  - No significant difference was found between the baseline and repeat SPECT data in the stabilized subjects.
  - In the nonstabilized subjects, a significant reduction in perfusion was found in the frontal, temporal, and parietal superficial cortices and in the occipital precuneus in the right hemisphere and in the frontal and mesial temporal cortices in the left hemisphere.

- Another longitudinal study showed that, before and 1 y after donepezil, perfusion was significantly similar in anterior cingulate gyri, right middle temporal gyrus, right inferior parietal lobule, and prefrontal cortex.

- Treatment with donepezil appeared to reduce the decline in rCBF, suggesting a preservation of functional brain activity.


http://interactive.snm.org/docs/jnm37218.pdf
Brain PET

- F-18 FDG PET (the available type in Canada)
- Sensitivity of 94% and a specificity of 73%.
- Correctly predict a progressive course of dementia with a 91% sensitivity and a nonprogressive course with a 75% specificity.


PET vs SPECT

- Messa et al. performed SPECT and 18F-FDG PET in healthy control subjects and patients with mild to moderate AD
  - similar abilities for delineating reductions in perfusion and metabolism in the temporoparietal cortex
  - similar diagnostic accuracies
- Herholz et al. showed good correspondence between 18F-FDG PET and SPECT for detecting changes in the temporoparietal cortex in mild to moderate AD by using voxel-based statistical image analysis
  - 18F-FDG PET more confidence in separating AD from normal
- Bradley et al. showed SPECT generally more correlated with histopathologic changes in the distribution of neurofibrillary pathology in AD
  - although the results for the medial temporal lobe were discordant

PET: Pittsburgh compound B

- C11 labeled fluorescent analog of thioflavin T
- Targets neurofibrillary plaque of AD
- *sensitivity* of 93.1% and a *specificity* of 93.3%
- As of 2011, FDA approved in the US
Dementia with Lewy Bodies

- Presence of LB in cortical neurons of demented patients. 15-25% of elderly demented patients fit this criteria.
- Cognitive fluctuations, visual hallucinations and spontaneous parkinsonism.
- Absence of medial temporal lobe atrophy in elderly demented patients may suggest DLB rather than AB.
- Functional studies demonstrate frontal lobe dysfunction and loss of visual spatial skills.
Comparison of brain perfusion SPECT images for moderate AD and moderate DLB

DLB showed lower perfusion in the occipital cortex than AD. In contrast, AD showed lower perfusion in medial temporal areas.

Frontotemporal Dementia

- Progressive impairment of executive function and speech but unlike AD, memory and visuospatial skills are preserved until late into the disease
- Primitive reflexes like suck, grasp and snout preserved
- 50-65 with 6-12 yr survival
- Conditions with degenerative of frontal and temporal lobes
3 types of FTD

Pick’s Disease
- Brain shows circumscribed atrophy of frontal and anterior temporal lobes with sparing of the motor cortex and medial temporal lobe

Frontal lobe degeneration
- Grossly same as Pick’s however histopathologically shows sponiform degeneration and microvasculation

FTD with ALS
- Histologically shows overlap between Pick’s and FLD
- Unique feature is loss of neurons and gliosis in substantia niagra and loss of motor neurons in trigeminal and hypoglossal nuclei
Frontotemporal Dementia

- Atrophy or decreased uptake in the frontal or anterior temporal lobes (bilateral or unilateral)
MR findings in late states
Chronic Cerebral Vascular Disease and Dementia

Multiple-infarct Dementia
Cortical infarction due to thromboembolic occlusive disease involving the conducting arterial vessels

Subcortical Ischaemia
vascular disease with dementia, subcortical infarction or ischemia
Part III

Dementia-like conditions
Normal Pressure Hydrocephalus

- 9-14% of elderly in assisted living
- 1.6 per 100,000
- Age > 60 yrs
- 2 M : 1 F
- 5-10% demented patients have NPH
- Full triad in 50-70% of pts

Triad of symptoms

- **Gait Disturbance: Apraxia!! (not ataxia)**
- **Dementia** (frontal lobe –type)
- **Incontinence** (initial immobility, later poor cognition)
In-111 DTPA CSF FLOW STUDY
Prion Disease

- Rapid progressive contagious dementia
- Protein misfolding (and recruitment)
- Most famous – Creuztfield Jacob Disease
  - Sporadic
  - Variant
SPECT/PET
MR
Summary

- Overview of anatomic and functional imaging of the dementing brain
- Perfusion pattern for different dementias
- SPECT is quite effective and helpful in the diagnosis of AD and other dementias
  - Compares with PET
- New compounds (PitB) is the way of the future
- Overview of some dementia mimicks
Thank you for listening!