Fundamentals of Nuclear Medicine Brain Imaging

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EANM Technologist Committee (EANM-TC)

European School of Nuclear Medicine
I must think harder. A mere brain is a mere brain I must.
Overview

• Anatomy & Physiology
• Common Pathologies
• Caring for Patients in Imaging departments
• Positioning & Immobilisation
• Brain perfusion SPECT
• PET in neurological diseases
• PET in brain oncology imaging
• SPECT & PET in movement disorders
• PET/MR
Anatomy & Physiology

- Speech
- Reading
- Somatosensation
- Proprioception

- Vision
- memory

- Balance
- Coordination
- Learning motor tasks

- Olfactory Motor cortex
- Attention Speech
- Decision-making

- Processing & interpreting sounds

- Relays signals between brain and spinal cord
Cerebral blood supply

- Internal carotid & vertebral arteries – provide oxygenated blood to brain
- Superficial & deep veins – carry deoxygenated blood back to heart
- Complex arrangement of arteries to ensure continuous supply, Circle of Willis
- Occlusion leads to stroke (*cerebrovascular accident CVA*)

Source: Gray’s anatomy
Cerebral cortex

- Hills ( gyrus ) & valleys ( sulcus )
- Grey matter – mainly cell bodies (neurons, glia)
- White matter – mainly axons, form major fibre bundles

http://www.candelalearning.com/
Neuronal Communication

- Synaptic clefts
- Neurons communicate by action potential or release of neurochemicals which bind to receptors on the next neuron
- "lock and key" system

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Commonly seen pathologies in Nuclear Medicine

- Dementia e.g. Alzheimer’s
- Movement disorders e.g. Parkinson’s
- Epilepsy
- Brain infections & inflammation (encephalopathy)
- Brain tumours (primary & metastatic)
Dementia

INFOGRAPHIC
The global impact of dementia

Around the world, there will be 9.9 million new cases of dementia in 2015, one every 3 seconds.

46.8 million people worldwide are living with dementia in 2015. This number will almost double every 20 years.

68% 2050

Much of the increase will take place in low and middle income countries (LMICs): In 2015, 58% of all people with dementia live in LMICs, rising to 63% in 2030 and 68% in 2050.

Dementia care costs

The total estimated worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to US$ 2 trillion by 2030.

If global dementia care were a country, it would be the 18th largest economy in the world exceeding the market values of companies such as Apple and Google (source: Forbes 2018 ranking).

This map shows the estimated number of people living with dementia in each world region in 2015.

We must now involve more countries and regions in the global action on dementia.
Alzheimer’s Disease

• Most common form of dementia
• Histopathologic analysis at autopsy is the standard of reference for the diagnosis of AD
• Neuronal loss due to aggregation of insoluble proteins:
  – Amyloid β plaques
  – Intracellular neurofibrillary tangles (consist of tau proteins)
Other Dementia Types

- Dementia with Lewy Bodies (DLB)
  - intracellular aggregations of $\alpha$-synuclein
  - related to Parkinson’s disease
- Vascular Dementia (VD)
  - Occurs because of brain injuries such as microscopic bleeding and blood vessel blockage
- Frontotemporal Dementia (FTD)
  - Affects frontal and temporal lobes
Proteinopathies

- Tau Protein
  - Neurofibrillary tangles
  - Amyloid plaques
  - Lewy Bodies

- β-Amyloid
  - Progressive Supranuclear Palsy
  - Frontotemporal dementia
  - Alzheimers Disease

- α-synuclein
  - Dementia with Lewy Bodies
  - Parkinsons Disease
### Differential Diagnosis of Dementia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pathology</th>
<th>Perfusion SPECT</th>
<th>IOFLUPANE SPECT</th>
<th>IBZM SPECT</th>
<th>PRE-POST SYNAPTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Beta-Amyloid</td>
<td>Temporoparietal bilateral</td>
<td>Normal</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>Lewy-bodies’ dementia</td>
<td>Diffuse Lewy bodies</td>
<td>Temporoparietal bilateral+/- occipital</td>
<td>Diminished similar to PD</td>
<td>Normal</td>
<td>Pre</td>
</tr>
<tr>
<td>Fronto-temporal degeneration</td>
<td>Diffuse cortical bilateral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pick's</td>
<td>Thaupathy 3R</td>
<td>Frontal bilateral</td>
<td>Normal</td>
<td>Normal</td>
<td>?</td>
</tr>
<tr>
<td>DCB</td>
<td>Thaupathy 4R</td>
<td>Assymetric</td>
<td>Diminished</td>
<td>Diminished</td>
<td>Pre &amp; Post</td>
</tr>
<tr>
<td>PSP</td>
<td>Thaupathy 4R</td>
<td>Symmetric</td>
<td>Diminished</td>
<td>Diminished</td>
<td>Pre &amp; Post</td>
</tr>
<tr>
<td>A. Multi-systemic</td>
<td>Astrocytic gliosis</td>
<td>Diffuse hypoperfusion + cerebellum</td>
<td>Diminished</td>
<td>Diminished</td>
<td>Pre &amp; Post</td>
</tr>
<tr>
<td>AMS-C AMS-P</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Lewy bodies (substantia nigra)</td>
<td>Normal</td>
<td>Diminished</td>
<td>Normal</td>
<td>Pre</td>
</tr>
<tr>
<td>Vascular</td>
<td>Multiple Infarcts</td>
<td>Multiple perfusion defects</td>
<td>Normal (often)</td>
<td>Abnormal (often)</td>
<td>Post (often)</td>
</tr>
</tbody>
</table>

- Appropriate treatment depends on specific diagnosis – use of expensive & ineffective medications avoided.
Protein pathology process begins at least a decade before symptoms.

Jack et al. Lancet Vol12, No. 2,
Dementia Symptoms

- **AD** – memory loss, depression, impaired communication, poor judgment, disorientation, behaviour changes and difficulty speaking and walking

- **DLB** - memory loss and thinking problems (like Alzheimer's) sleep disturbances, visual hallucinations, muscle rigidity or other parkinsonian movement features

- **FTD** - Typical symptoms include changes in personality and behaviour and difficulty with language. Patients often present with social impairment & disinhibited and impulsive behaviour
Dementia Symptoms

- Any two people with dementia are unlikely to experience the condition in exactly the same way.
Patients with Parkinson’s Disease

• Condition may vary hour to hour. Patient may appear fine at injection but not at scanning
• Common symptoms:
  – Physical/motor symptoms - stiff rigid muscles, slow movements (bradykinesia), tremor, incontinence
  – Cognitive symptoms - memory problems, hallucinations, difficulty completing day-to-day tasks, problems with reasoning
  – Behavioural symptoms - behavioural inhibition, aggression, mood changes, problems with communicating
Patients with Parkinson’s Disease

- Speak to patient and carer about how best to manage their condition within imaging department
- As Parkinson's disease progresses, it often results in a progressive dementia similar to Dementia with Lewy bodies or Alzheimer's
- *All patients with dementia should be treated with dignity and respect whilst in hospital.*
Preventing Motion

- Keep patients comfortable
- Blankets, straps (feelings of security)
- Patients with cognitive impairment, special support may be needed
- Reassure frequently
- Repeat instructions
- Get help from family/carer
- Sudden waking may cause more motion
Standard brain positioning

- Patient supine, neck relaxed
- Brain in centre of field of view (FOV)
- Use head holder to reduce motion and improve comfort
- Use chin and forehead strap and wedges if required
- Laser position system if available
Brain imaging tracers

• For a tracer to be able to enter the brain it must cross blood brain barrier (BBB)
• Tracers divided into several groups:
  – Regional cerebral blood flow (rCBF) tracers
  – Metabolic tracers
  – Tracers targeting neurotransmission and receptors
  – Tracers targeting amyloid
  – Tracers for brain tumour imaging
rCBF tracers

- rCBF tracers are used for measurement of perfusion of blood to brain
- Must be retained sufficiently in brain in their initial distribution sufficiently long to enable diagnostic imaging
- Two main tracers in EU:
  - $^{99mTc}$ HMPAO
  - $^{99mTc}$-ECD
- Evaluation of cerebro-vascular disease, acute stroke, localisation of epileptogenic foci, traumatic brain injury, infection & inflammation, brain death
rCBF tracers

- $^{99m}$Tc-HMPAO – hexamethyl propylene amine oxime, exametazime, Ceretec®
- $^{99m}$Tc-ECD – ethyl cysteine dimer, bicisate, Neurolite®
- Brain images usually obtained 30-60min post-injection
- Diagnostic reference level = 750MBq, effective dose 6mSv

EANM procedure guideline for brain perfusion SPECT using $^{99m}$Tc-labelled radiopharmaceuticals (2009)
Brain HMPAO SPECT for AD

• Initial stage
  – Hypoperfusion: parietal and/or posterior temporal cortex
  – Unilateral or bilateral

• Intermediate stage
  – Hypoperfusion: extensive, parietal, temporal, bilateral

• Advanced stage
  – Diffuse cortical hypoperfusion
  – Less/not affected: motor areas, occipital, basal ganglia, cerebellum
Brain Death

- HMPAO to determine complete absence of brain function
- Clinically diagnosed with legal standards
- Can also be used to determine the viability of internal organs for transplantation
- *Hot nose sign* – absence of internal carotid artery flow increases external carotid artery flow, increases perfusion to nasal region

Creative commons license: Case courtesy of Dr Andrew Dixon, Radiopaedia.org, rID: 19410
$^{18}$F-FDG brain PET

- Alternative to HMPAO SPECT for brain perfusion imaging
- FDG PET superior to SPECT imaging for the early and differential diagnosis of Alzheimer’s and frontotemporal dementia (FTD or Pick’s disease)
- Epilepsy (preoperative evaluation of foci)
- Movement disorders: differentiation between Parkinson’s disease and other syndromes
- Also used in Neuro-oncology
FDG enters cell via GLUT proteins competing with glucose for hexokinase process, undergoes phosphorylation and trapped intracellularly.

- Tumours increase GLUT & hexokinase activity.
**18F-FDG brain PET**

- Healthy subjects
  - Cerebral cortex
  - Basal ganglia
  - Thalamus
  - Cerebellum
  - Subcortical putamen, caudate nucleus, thalamus
  - High uptake in the cortical grey matter
  - Lower uptake in white matter

ACG = anterior cingulate gyrus, CN = caudate nucleus, F = frontal lobe, O = occipital lobe, P = parietal lobe, PCG = posterior cingulate gyrus, PSMS = primary sensorimotor strip, Pu = putamen, T = temporal lobe, Th = thalamus.

$^{18}$F-FDG brain PET

- Fast for at least 4h
- Patient should rest quietly with lights dimmed for 10 minutes prior to injection
- Check medication - psychotropic pharmaceuticals can influence regional metabolic rate
- Uptake in quiet dark room for 30-45 minutes
- During uptake, the patient should remain silent
- 1 bed position - top of skull to base of brain (10 minute acquisition)
- Diagnostic reference level 125-250MBq (eff dose 5mSv)

EANM procedure guidelines for PET brain imaging using FDG v2 (2009)
FDG in Neurology

- Clinical diagnosis for specific types of dementia (FTD, AD, DLB) with characteristic metabolic signatures
- Classic pattern of impaired metabolism - involvement of the posterior cingulate gyri, precuneus, and posterior temporal and parietal lobes
- Determine presence or absence of AD (vascular dementia has similar pattern)
- Differentiate DLB from AD
FDG in Neurology

- FDG PET is useful for imaging regional glucose consumption in the brain, where a pathologic change in neuronal activity is reflected by a corresponding decrease in glucose metabolism.

Normal FDG PET findings in a patient undergoing evaluation for possible AD

Abnormal findings in a patient with known AD and progressive verbal difficulties (marked bilateral temporal hypometabolism)
Epilepsy imaging

- HMPAO, ECD or FDG currently used clinically
- Dual role:
  - Identify focal abnormalities in view of epilepsy surgery
  - Explore mechanism of seizure onset
- Continuous EEG recording is required by telemetry-experienced staff
- Prepared syringes available to ensure quick injection time
- Ictal (immediately after seizure onset) and interictal scans
Interictal $^{99m}$Tc-ECD SPECT (left image) showing the usual hypoperfusion in presumed epileptogenic focus (arrow) in left frontal cortex region, which becomes hyperperfused during ictal SPECT (right image).

**β-Amyloid imaging**

- First amyloid tracer (2004): Carbon-11 labelled Pittsburgh compound B ("PiB")
  - Short $t_1/2$ (20min), widespread clinical use limited
  - Selectively binds to amyloid plaque and cerebrovascular amyloid
  - Significant retention seen in:
    - >90% AD patients
    - Patients with mild cognitive impairment
    - Some “normal” elderly

β-Amyloid imaging

• Recognised need for $^{18}$F amyloid tracer

• Development stages until 2008 – 1st successful $^{18}$F imaging in humans*
  – Florbetapir (Amyvid™)
  – Flutemetamol (Vizamyl™)
  – Florbetaben (NeuraCeq™)*

• All three $^{18}$F current tracers approved by US FDA & EMA, all derived from $^{11}$C-PiB for Mild Cognitive Impairment

**β-Amyloid imaging**

- Interpretation is independent of patient’s clinical features and relies upon recognising unique image features.
- Contrast between white matter (WM) & grey matter (GM).
- Positive scan = GM uptake intense or >WM.

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Neuro-Oncology imaging

- **SPECT**
  - $^{99m}$Tc-HMPAO, $^{99m}$Tc-ECD
  - $^{99m}$Tc-Sestamibi
  - $^{201}$Thallium chloride
  - Amino acids (e.g. $^{123}$I-methyl-tyrosine)

- **PET**
  - Metabolic: $^{18}$F-FDG, $^{15}$O-water
  - Amino acids: $^{11}$C/$^{18}$F-Methionine, $^{18}$F-DOPA, $^{18}$F-fluorotyrosine (FET)
  - Cell proliferation: $^{18}$F-fluorothymidine (FLT)
  - Phospholipids: $^{11}$C/$^{18}$F-Choline
  - Tumour hypoxia: $^{18}$F-MISO
  - Somatostatin receptors: $^{68}$Ga tracers
Metabolic PET brain imaging

- Main metabolic substrates in the brain are oxygen and glucose: $^{18}$F-FDG (fluorodexyglucose) & $^{15}$O (mainly used in research)
- High background uptake of FDG in normal brain limits its use in primary brain tumour imaging
- Paraneoplastic syndromes
- Common applications - tumour diagnosis, metabolic grading and prognosis, volume estimation and follow-up
- Not useful for assessing treatment response

Metabolic PET brain imaging

- Standard brain positioning and technique as for brain perfusion FDG PET
- Suggested later imaging time for neuro-oncology (better tumour to normal tissue contrast) from 60min to several hours post injection

PET Amino acid analogues

- $^{11}$C- methyl-L-methionine $^{11}$C-MET
  - Drawback is 20min half-life of $^{11}$C » requires on-site cyclotron
  - Cellular amino acid uptake via overexpressed neurochemical transporters & increased metabolism
- $^{18}$F-FET (fluorotyrosine) and $^{18}$F-DOPA (fluorodopa)
- Can assess protein synthesis within malignant lesions
- Superior contrast to FDG
- Low uptake in normal brain
- More tumour specific – not influenced by inflammation

EANM Procedure Guidelines for Brain Tumour Imaging using Labelled Amino Acid Analogues (2006)
PET Amino acid analogues

- Detection of tumour tissue
- Tumour delineation & therapy planning
- Response assessment
- Selection of biopsy site
- FDG better for tumour grading
- Early imaging (i.e. 20 minutes post injection) for brain tumours (tumour uptake near maximum and early enough to avoid peak uptake in striatum)

Glioblastoma with markedly accumulating $^{18}$F-FET in left temporal lobe
18F-DOPA in oncology

18F-DOPA (A), shows an increased uptake in malignant glioblastoma, shown to be comparable to 11C-MET (B) lesions of matching size in temperoparietal, posterior basal ganglia and thalamus.

**18F-Choline**

- Originally developed as 11C-choline (a phospholipid component of cell membranes – increased cellular metabolism ↑ choline uptake)
- 11C-choline or 18F-fluoro-methyl/ethyl choline

**18FDG**

**18F Choline**

Courtesy of Charing Cross Hospital, London, UK


**18F-Choline**

- Low concentration in normal cortex = excellent delineation of the tumour from normal brain
- Shows peri-tumoural uptake in high-grade gliomas
- Differentiate benign lesions from high-grade tumours and metastases

Kwee et.al. Radiology 2007; 244: 2
• 39-deoxy-fluorothymidine (\(^{18}\)F-FLT)
• A marker of cell proliferation
• Assessment of grade and proliferation in gliomas
• Treatment response – shown to correlate with histology markers (Ki-67)
• Uptake in tumors is rapid, peaking at 5–10 min after injection and remaining stable up to 75 min.

Uptake of \(^{11}\)C-MET and of \(^{18}\)F-FLT in gliomas of low grade (top row) and high grade (bottom row). Uptake of \(^{18}\)F-FLT is especially high in malignant glioma and also demonstrates infiltration into surrounding tissue. Wolf-Dieter Heiss et al. JNM 2011;52:1585-1600
Newly diagnosed glioblastoma. (A) MRI (contrast-enhanced T1-weighted image) shows large area of contrast enhancement in right frontal lobe. Both $^{18}$F-FDG PET (B) and $^{18}$F-FLT PET (C) show increased uptake in same area.
$^{18}$F-MISO

- $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO)
- Evaluation of tissue hypoxia = relative resistance to radiation therapy
- Hypoxia predicts poor treatment response of malignant tumours
- Oxygen consumption is lowered in most brain tumours
- Greater $^{18}$F-FMISO uptake is generally observed in high grade gliomas compared to low grade lesions
- $^{18}$F-FMISO uptake associated with a decreased response to therapy and a worse prognosis
(A–C) $^{15}$O-H$_2$O PET perfusion images in 3 patients with glioblastoma. 
(D–F) Corresponding late $^{18}$F-FMISO PET images show tumour hypoxia in low perfusion, in intermediate perfusion with an inverse pattern compared with hypoxia, and in high perfusion.

ESNM European School of Nuclear Medicine
Gallium-68 tracers

- Somatostatin receptor peptide imaging
- Some intracranial tumours express SSTRs
- $^{68}$Ga-DOTATATE shows high binding affinity for receptor type 2 (SSTR2)
- DOTATOC/DOTANOC also available (different SSTRs)
- $^{68}$Ga $T_{1/2} = 68$ minutes
- Requires $^{68}$Ga generator on-site or near-site

Medial temporal/sphenoidal meningioma (arrow) beneath pituitary gland (arrowhead)
Dopaminergic system

- Most common SPECT/PET tracers for mapping dopamine neurons:
  - $[^{123}]$FP-β-CIT
  - $[^{18}]$F-DOPA

Dopamine receptors divided into D1 & D2. Majority D2 located post-synaptically, most commonly 123I-IBZM SPECT and 18F-fallypride PET

$^{123}\text{I}}$-DaTSCAN

- $^{123}\text{I}$-Ioflupane manufactured by GE
- High binding affinity for presynaptic dopamine transporters in the striatal region of the brain
- Used to assess pre-synaptic striatal uptake in basal ganglia of brain
- Can differentiate Parkinsonian syndromes from essential tremor and Dementia with Lewy Bodies (DLB) from Alzheimer’s disease

Normal scan: crescent or comma
**123I-DaTSCAN**

- Thyroid blocking required
- Potassium iodide or iodate tablets 100mg >1hr before (or Lugol’s solution)
- DRL 185MBq
- Effective dose 4mSv
- Comes in referenced vial
- Imaging at 3-6 h p.i
- Imaging takes ~40 minutes

$^{123}$I-DaTSCAN

- Head motion – Lateral shift has significant effect
- Striatum should appear bilaterally on same slice
Separate axial images of caudate heads and putamen (superimposed to illustrate semicolon appearance)


• Mild sagittal tilt has little effect

Forward head tilt results in slices (red) through caudate head that do not include putamen

Correct positioning - all slices through caudate head also include putamen

• Severe sagittal motion can cause “semicolon” appearance
123I-DaTSCAN

• Display raw data as cine loop to check for movement during acquisition
• Check for alignment and motion before patient leaves, repeat acquisition may be necessary
• Look out for “kissing caudates”
• Contingency measures required for repeat scans

Images courtesy of Birmingham City Hospital
**18F-DOPA**

- 6-[18F]-Fluorlevodopa: amino acid analogue which measures dopamine synthesis & neuron density
- Marker of presynaptic dopaminergic system
- Useful for studies requiring repeated measures such as examinations of the course of a disease and the effect of treatment
- 4 hr fasting, imaging at 60-90min post injection

Healthy control (left). Patient with PD (right) - reduced uptake in right putamen and in posterior left putamen, uptake asymmetry between the heads of the two caudate nuclei

PET/MR in brain imaging
PET/MR – challenges

- Different specs than conventional PET-CT
- Technical difficulties (e.g. attenuation correction)
- Staffing requires comprehensive understanding of both PET & MR
- Resource intensive, limited throughput
- 2016 - ~70 scanners worldwide, very expensive
- 2016 - Optimal applications & diagnostic medical benefits still being identified
Conclusions

• Vast number of tracers used in brain imaging
• Tracers are being used for diagnosis, tracking disease and measuring therapeutic effect in oncology
• Increasing used of PET tracers – but there remains a strong clinical use for SPECT tracers
• Amyloid PET allows diagnosing AD before dementia (in future - tau PET?)
• PET/MR opening a whole new field
Thank you for your attention

https://www.pinterest.com/pin/195695546282421074/
- All the staff in the Nuclear Medicine & PET-CT Department at King’s College Hospital, London, UK
- BCNM/HSNM-MI organising committees
- EANM-TC