PET for Clinicians

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Austin Health

University of Melbourne
PET in dementia is not new but only in recent years, as PET has become more accessible, has a clinical role emerged. **Austin Health, Melbourne does 1000 brain PET per year.**
Clinical Diagnosis of AD

• Sensitivity 80%, Specificity 70%
  (Knopfman, Neurology 2001- average of 13 studies with pathological confirmation)

i.e. diagnosis requires dementia and only has moderate accuracy
Mild Cognitive Impairment (MCI) does not equate to early AD

- Only 50% of MCI will progress to AD dementia
- 15-20% have other dementias.
- 35-40% do not develop dementia.

We need biomarkers for early diagnosis of AD and other dementias!
New Research Criteria for AD (2007)*

- dementia or significant functional impairment is **NOT** required
- clear history of progressive cognitive decline
- objective evidence from psychometric tests of episodic memory impairment
- characteristic abnormalities in the CSF or in neuroimaging studies (MRI, FDG-PET, Aβ PET)

FDG PET in Alzheimer’s disease

Parietotemporal hypometabolism

View in AC-PC plane
bottom of frontal lobe and occipital lobe on same horizontal plane in mid sagittal image

Prefrontal

Primary sensori-motor cortex

Parietal
Reading Brain PET

Compare:

• parietal vs sensori-motor and frontal
• posterior cingulate vs other cortex

• visual association cortex and primary occipital cortex vs frontal and putamen (for DLB)
• check subcortical structures for lacunar infarcts or asymmetry in FTD or CBD

Do not forget the anterior and medial temporal lobes
Reading Brain PET

Compare:

• parietal vs sensori-motor and frontal
• posterior cingulate vs other cortex – SHOULD BE THE BRIGHTEST REGION ON THE SLICE
• visual association cortex and primary occipital cortex vs frontal and putamen (for DLB)

Check subcortical structures for lacunar infarcts or asymmetry in FTD

Do not forget the anterior and medial temporal lobes
Reading Brain PET

Compare:

• parietal vs sensori-motor and frontal
• posterior cingulate vs other cortex –

• visual association cortex and primary occipital cortex vs frontal and putamen (for DLB) –
  MEDIAL OCCIPITAL CORTEX SHOULD BE EQUAL TO STRIATUM

Check subcortical structures for lacunar infarcts or asymmetry in FTD

Do not forget the anterior and medial temporal lobes
Alzheimer’s dementia

NORMAL

Posterior cingulate should be the brightest cortex on the slice!
Dementia with Lewy Bodies (DLB) or Posterior Cortical Atrophy Variant of AD

Temporal, Parietal & Occipital hypometabolism

Cingulate Island Sign

medial occipital < striatum

Lim MS et al. JNM 2009
Frontal Hypometabolism

1. Frontotemporal dementia – Behavioural (Pick’s disease) and PNFA variants.
2. Frontal variant of Alzheimer’s disease.
3. Chronic Schizophrenia
4. Progressive supranuclear palsy
5. Subcortical vascular disease
6. OSA, alcohol, depression

Note: Declines with aging.
Quantification of FDG PET for Clinical Practice e.g. Neurostat 3D-SSP

Alzheimer’s Disease
Quantification can turn a beginner into an expert

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<tbody>
<tr>
<td>1 expert</td>
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<td>67%</td>
<td>84%</td>
<td>83%</td>
<td>97%</td>
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AD (n = 68) vs Normal (n=32)
For FDG – quantitation performs better than visual read.
Positive Likelihood Ratios
AD vs Healthy Controls

Frisoni GB, et al. Neurology 2013
$^{18}$F-Fluorodeoxyglucose (FDG) PET

- Alzheimer's Disease
- Logopenic Aphasia variant of AD
- Dementia with Lewy bodies
- Behavioural subtype of Frontotemporal Dementia
- Progressive Non-fluent Aphasia subtype of FTD
- Semantic Dementia subtype of FTD
Eventual Pathological Diagnosis of AD: Clinical vs FDG PET at initial presentation

<table>
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<td>76%</td>
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<td>PET</td>
<td>84%</td>
<td>74%</td>
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Brain SPECT

- 15% less accurate than PET
- Widely available since 1989
- Use in dementia is limited by low accuracy and low reader confidence

AD, Alzheimer's Disease; FDG, fluorodeoxyglucose; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SPECT, single photon emission computed tomography
Use and Limitations of FDG PET

• Hypometabolism reflects clinical deficits so findings are subtle in MCI
• Mixed clinical features are often associated with mixed FDG findings
• Changes are less clear in the very elderly
• Sensitivity 85%
• Specificity 70-80%
• Many sites only give a visual read
  
  *(i.e. 15% less accurate unless an expert)*
Amyloid and Tau PET
Biomarkers for Alzheimer’s Disease

Pathology Markers
• Beta-amyloid (Aβ) imaging with PET
• CSF Aβ₄₂ assay
• Tau PET

Neuronal damage markers
• MRI
• FDG PET
• CSF Tau assay
Alzheimer’s Pathology

1. Extracellular Beta-amyloid Plaques
   - Beta-Amyloid Plaque
   - Microtubule Subunits Fall Apart
   - Tangled Clumps of Tau Proteins

2. Intracellular Neurofibrillary Tangles (tau aggregates)

2004

2013
IWG-2 research criteria for AD


- Objective episodic memory impairment plus
- Pathophysiologic biomarker for AD
  i.e. CSF (low $A\beta_{42}$ with high tau) or **positive A\beta PET**

FDG and MRI for disease severity and progression
Dementia Specific Patterns

Amyloid PET summary

Normal:
• Sparse to no amyloid neuritic plaques
• High negative predictive value for AD pathology

Abnormal:
• Moderate to frequent amyloid neuritic plaques
• Increases the likelihood of AD
Visual read vs CERAD pathological criteria for AD

*(moderate or frequent neuritic plaques)*

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<tr>
<th></th>
<th>n</th>
<th>sens</th>
<th>spec</th>
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<tbody>
<tr>
<td>Florbetapir</td>
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<td>92</td>
<td>95</td>
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<tr>
<td>Florbetalen</td>
<td>74</td>
<td>98</td>
<td>89</td>
</tr>
<tr>
<td>Flutemetamol</td>
<td>106</td>
<td>91</td>
<td>90</td>
</tr>
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**Sensitivity and specificity >90%**

Clark C. Lancet Neurology 2012; Sabri O. Alz Dementia 2015; Salloway s. Alz Dementia (DADM) 2017
A standardized SUVR is rescaled - 0 Cl in young controls up to 100 Cl in mild AD

- Standard VOIs

  One Cortical VOI (Aβ+ areas after subtracting YC from AD)

  Reference region: Whole cerebellum (WCB)

Available at the Global Alzheimer's Association Interactive Network [http://www.gaain.org](http://www.gaain.org)
The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing

Commenced 2006

Serial Aβ PET and MRI Imaging in 1,550 of 2,200 participants
PiB neocortical SUVR

<table>
<thead>
<tr>
<th>Condition</th>
<th>SUVR Value</th>
<th>Standard Error</th>
<th>N</th>
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<tbody>
<tr>
<td>HC</td>
<td>1.40±0.4</td>
<td></td>
<td>195</td>
</tr>
<tr>
<td>MCI</td>
<td>1.91±0.6</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>AD</td>
<td>2.30±0.4</td>
<td></td>
<td>79</td>
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</tbody>
</table>

(n = 366)
Aβ Deposition Rate

Three - Six year follow-up data with PiB

0.045 SUVR/yr
3.8 CL/yr

Mean AD
(SUVR 2.33; 100 CL)

Threshold for +ve PiB

Mean HC -ve
(1.17; 10 CL)

Aβ PET Alone Cannot Predict Time to Dementia

Neocortical SUVR<sub>cb</sub> vs. Time (years)

AD Mean
Detectable
Other Prognostic Factors

- Cognitive performance
- Hippocampal volume
- Cerebrovascular disease
- Cognitive Reserve – yrs of education
- Genetics – e4, BDNF, other?
- Lifestyle – exercise, diet, high BP, diabetes, smoking
Amyloid Negative Dementias

- **primary hippocampal sclerosis** (seen in the very elderly - TDP-43)
- Dementia with Lewy Bodies
- Frontotemporal dementias (**tau** or TDP-43)
- Progressive supranuclear palsy (**tau**)
- Corticobasal degeneration
- Agyrophilic grain disease (**tau**)
- Tangle dominant dementia (**tau**)
- Parkinson’s Disease Dementia
- Pure vascular dementia (rare)
Appropriate Use Criteria for amyloid PET

Alzheimer’s Association/Society of Nuclear Medicine 2013

- Early onset dementia (<65 yrs of age)
  - AD clinical features often atypical and FTD relatively common
- MCI
  - 50% AD, 10% other dementias, 40% not neurodegenerative
- Dementia of uncertain cause after expert assessment

AD, Alzheimer’s Disease; FTD, frontotemporal dementia; MCI, mild cognitive impairment; PET, positron emission tomography
Inappropriate use

- Prior to clinical and cognitive assessment by a clinician experienced in diagnosis of dementia
- When asymptomatic
- When no cognitive deficit is present
- When dementia is present and the clinical features are typical of AD
Aβ PET in Monoclonal Aβ Antibody AD trials

EXPEDITION, BLAZE, and PRIME

SOLA = Fleischer et al., AAIC 2015
CREN = Salloway et al., CTAD 2014
ADUC= Chiao et al., HAI 2016

Change in SUVR

Solvaneuzumab  Crenuzumab  Aducanumab (10 mg/kg)
Aducanumab Phase 1B Trial

Nature September 2016
First Major Dementia Trial Using Adaptive Design. Results from a large Phase II Trial presented in July 2018

BAN2401 Reduces Amyloid Burden

- Dose dependent reduction in amyloid PET values (Florbetapir tracer)
- BAN2401 significantly reduced amyloid PET values across all doses

![Graphs showing PET SUVr and Centiloid improvement over time for different dose groups.](image)

- Similar results with SUVr and Centiloid measures across all reference regions analyzed
  - Reference regions analyzed: SWM, WC mask, WC derived, WC/WM correction, CG, Composite
- Top dose: observed baseline mean (74.5), observed 18-month mean (5.5)

Global Cortical Average versus Whole Cerebellum Reference

*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. †Adjusted mean change from baseline by Mixed Model Repeated Measures (MMRM).

The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MC due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.

For PET analysis N=508 at 12 months and N=277 at 18 months.
Comment in ALZFORUM on Eisai’s BAN2401 Phase II trial results at AAIC July 2018

Randall Bateman
Washington University School of Medicine

“The field is clearly moving forward with the ability of a fourth drug to remove amyloid to a normal level, as measured by PET. Now with aducanumab, gantenerumab, and n3pg (LY3002813), BAN2401 has demonstrated reversal of amyloid plaques to normal levels, representing a milestone in the history of Alzheimer’s disease. This has the potential to slow clinical decline in the symptomatic stage of Alzheimer’s and even more promise to slow, delay, or stop dementia if used before symptom onset.”
AD Cases (all Aβ+ve) (youngest to oldest)

<table>
<thead>
<tr>
<th>Case</th>
<th>MMSE</th>
<th>AGE</th>
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<tr>
<td>29</td>
<td>52</td>
<td>23</td>
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<td>26</td>
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<tr>
<td>27</td>
<td>88</td>
<td>27</td>
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</table>

 Tau PET in AD (MK6240)
NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr., a,*, David A. Bennett b, Kaj Blennow c, Maria C. Carrillo d, Billy Dunn e, Samantha Budd Haeberlein f, David M. Holtzman g, William Jagust h, Frank Jessen i, Jason Karlawish j, Enchi Liu k, Jose Luis Molinuevo l, Thomas Montine m, Creighton Phelps n, Katherine P. Rankin o, Christopher C. Rowe p, Philip Scheltens q, Eric Siemers r, Heather M. Snyder d, Reisa Sperling s

Contributors †: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg
<table>
<thead>
<tr>
<th>AT(N) profiles</th>
<th>Biomarker category</th>
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</thead>
<tbody>
<tr>
<td>A-T-(N)-</td>
<td>Normal AD biomarkers</td>
</tr>
<tr>
<td>A+T-(N)-</td>
<td>Alzheimer’s pathologic change</td>
</tr>
<tr>
<td>A+T+(N)-</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>A+T+(N)+</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>A+T-(N)+</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change</td>
</tr>
<tr>
<td>A-T+(N)-</td>
<td>Non-AD pathologic change</td>
</tr>
<tr>
<td>A-T-(N)+</td>
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</tr>
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</tr>
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*Alzheimer’s continuum*
- **Alzheimer disease (AD)**—refers to Aβ plaques and pathologic tau deposits, defined *in vivo* by abnormal biomarkers of Aβ and pathologic tau (both are required)

- **Alzheimer’s pathologic change**—early stage of Alzheimer’s continuum, defined *in vivo* by an abnormal Aβ biomarker with normal pathologic tau biomarker

- **Alzheimer’s continuum**—refers to individuals with biomarker designation of either AD or Alzheimer’s pathologic change

- **Alzheimer’s clinical syndrome**—recommended terminology for clinically ascertained multi- (or single-) domain amnestic syndrome or a classic syndromal variant (i.e., what has historically been labeled “possible or probable AD”). It applies to both mildly impaired and demented individuals. The term “Alzheimer’s disease” is reserved for situations where neuropathologic or biomarker evidence of the disease (i.e., Aβ plaques and pathologic tau deposits) is present
**Case Example: Effect of changing diagnostic criteria**

- 88 yr old, MMSE 27, CDR SoB 3.5, CVLT Delay -1.5 SD

<table>
<thead>
<tr>
<th>Year</th>
<th>Diagnosis</th>
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<tr>
<td>1984:</td>
<td>➔ AD</td>
</tr>
<tr>
<td>2007:</td>
<td>➔ AD</td>
</tr>
<tr>
<td>2011:</td>
<td>➔ AD with increased certainty</td>
</tr>
<tr>
<td>2014:</td>
<td>➔ AD</td>
</tr>
<tr>
<td>2018:</td>
<td>➔ NIA/AA Framework</td>
</tr>
</tbody>
</table>

(Likely Amyloid plus Primary Hippocampal Sclerosis)
Imaging of $\alpha$-synuclein related disorders (PD, MSA, DLB)
DAT (dopamine transporters) and VMAT are both reduced in the striatum by more than 50% before signs of Parkinsonism develop.
Clinically Uncertain Parkinsonian Syndrome (CUPS)

- DATScan ($^{123}$I-ioflupane SPECT) changed the diagnosis in 52%
- Two year follow-up confirmed DATScan assisted diagnosis
- DATScan increased clinical confidence and changed clinical management in 72%

Catafau, Movement Disorders 2004
DATScan in Dementia with Lewy Bodies (DLB)

- Decreased binding in DLB but not AD (e.g. Donnemiller EJNM 1997, Walker JNNP 2003)

  8 DLB, 9 AD, 3 other dementia at post mortem.

  DATScan - Sensitivity 88%, Specificity 100%
  vs Clinical review - Sensitivity 75%, Specificity 42%

We have shown similar results with VMAT-2 PET with $^{18}$F-AV133
Imaging VMAT with $^{18}$F-AV133

Example Case

• 71 year old male
• Diagnosed with PD 8 years ago due to tremor and rigidity
• But no functional impairment – musician – and no dyskinesia
• Escalating medication – high dose Sinemet (1.5 gms) plus Comtan plus Sifrol
• Requests deep brain stimulator for tremor
• Neurologist suspicious of psychogenic component
Results: $R_T$ (Z-Score)
Relative to Normal Control

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
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<tbody>
<tr>
<td>Caudate</td>
<td>2.99 (4.44)</td>
<td>3.04 (4.24)</td>
</tr>
<tr>
<td>Put. (Ant.)</td>
<td>3.03 (4.75)</td>
<td>3.62 (4.36)</td>
</tr>
<tr>
<td>Put. (Post.)</td>
<td>3.14 (4.55)</td>
<td>2.93 (3.08)</td>
</tr>
<tr>
<td>Midbrain</td>
<td>1.34 (4.31)</td>
<td>50%</td>
</tr>
</tbody>
</table>
RESULT: Normal scan

Diagnosis: Psychosomatic tremor

Management: Withdrawal of PD medications

Referred for Psychiatric Management

Impact Rating - High
How do I get a FDG, amyloid, tau or VMAT scan?

Austin Health and recently some other sites offer a CBF-SPECT/FDG PET package with Neurostat analysis at no cost.

Some sites offer user pays FDG brain PET. ($800-1000).

BUT for brain amyloid imaging and dopamine transporter imaging, the required agents are not marketed in Australia due to perceived small market size.
Overseas Status of Amyloid and DAT Imaging

- DATScan ($^{123}$I FP-CIT aka $^{123}$I-ioflupane) marketed by GE Healthcare was approved in Europe (EMA) in 2000 and in USA (FDA) in 2011.

- Florbetapir, florbetaben and flutemetamol were approved for brain amyloid imaging in the US FDA in 2011-14 and Europe in 2013-14. Also approved in Japan and Korea.
New Access at Austin Health

• Austin Health has recently approved the clinical use of brain amyloid and VMAT PET.
• These scans can now be ordered through the Department of Molecular Imaging by a medical specialist.
• BUT – patient must pay for the scan.
Alternatively the recently funded Australian Dementia Network will provide amyloid and tau PET at no cost for patients with MMSE >20 who are suitable for clinical trials.
ADNeT Trials Screening Program

Email the co-ordinator at:
ADNETscreening@florey.edu.au
Case 1: History

• Age 50 - breast cancer treated with surgery and chemoradiotherapy. Tamoxifen continued.

• Age 51 – onset of “memory” lapses. Mother diagnosed with AD at age 64.

• Age 53 – neuropsychology report – “memory entirely unimpaired, deficits in executive function, high level attention and concentration.

**CONCLUSION:** Findings combined with static impairment since chemotherapy IS NOT consistent with Alzheimer’s disease.”
1. Hippocampal atrophy is a reliable feature of early onset Alzheimer’s disease.
2. The MRI scan shows hippocampal atrophy.
3. Medial parietal atrophy is only seen in late onset AD.
4. The MRI scan is within normal limits.

Q: Which of the following is true?
FDG PET was done
Q2: The FDG PET shows

1. Dementia with Lewy Bodies
2. Alzheimer’s disease
3. Frontal Temporal Lobar Degeneration (FTD)
4. “Chemo” brain
Reviewed at 12 months

- Repeat neuropsychology – “stable”
- “FDG PET findings inconsistent with neuropsychology”
- Increased anxiety, stopped teaching.
- “At this stage we cannot make a diagnosis of dementia and in particular there is no evidence of Alzheimer’s disease or any other neurodegenerative disorder.”
Progress

• Age 56 – significant cognitive and functional decline. Rapid forgetting. Scored 1/12 on a memory task.

• FDG PET repeated
Q3: Which statement is true?

1. Severity of hypometabolism correlates well with degree of cognitive impairment
2. Amyloid PET is better than FDG PET for monitoring disease progression
3. Repeating FDG PET in equivocal cases should be done at 3-6 months
4. The repeat scan findings make AD unlikely
Progress

• Clinician still uncertain so an amyloid scan performed.
11C-PiB PET Scan

Healthy Control

Patient’s scan
Progress

- Patient informed after amyloid scan that she has Alzheimer’s disease.
- MMSE 22. Aricept commenced.
- Genetic testing for familial AD genes (PS1, PS2, APP) negative.
Q5: Compared to post mortem diagnosis, FDG PET is more accurate than expert clinical opinion at initial evaluation for detection of Alzheimer’s disease.

1. True
2. False
Eventual Pathological Diagnosis of AD: Clinical vs FDG PET at initial presentation

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Appropriate Clinical Use of PET Imaging

- Early onset dementia (<65 yrs of age) – 
  *AD clinical features often atypical and FTD relatively common.*
- MCI – 55% AD, 15% other dementias, 40% not neurodegenerative.
- Dementia of uncertain cause after expert assessment.

Case 2

- 61 yr old male with 4 years of worsening ability to name objects. Recent decline in comprehension and arithmatic, lacking emotion, rigid thinking, disinhibited. Still working.

- MMSE 26. Memory good. Unable to name animals.

- Suspected diagnosis is FTD – semantic dementia subtype with AD a less likely possibility.

- MRI ordered.
Q. The MRI shows:

1. A normal brain.
2. Hippocampal atrophy.
3. Anterior temporal lobe atrophy.
4. Frontal lobe atrophy.
5. Left stroke.
Progress

• Seen by a specialist in FTD who considers Semantic Dementia likely.

• FDG PET and PiB PET are ordered.
Q: The FDG PET is consistent with?

1. Previous left temporal lobe traumatic injury.
2. A left middle fossa arachnoid cyst.
5. Corticobasal degeneration.
Simple Rules for Classification

AD = Hypometabolism
AD regions > FTD regions

FTD = Hypometabolism
FTD regions > AD regions

98% specificity for FTD in autopsy-confirmed cases; Foster et al. Brain 2007; 130: 2616-35.
PiB Amyloid PET
CASE 3

• Female aged 36 years

• History:
  – Economics graduate
  – 2004 action tremor of the right hand
  – 2005 first signs of ataxic gait
  – Since 2007 wheelchair-bound, lately dysarthria

Clinical Findings:
  – Pyramidal signs
  – Slowing of saccades
  – Peripheral neuropathy
The FDG PET scan is consistent with Spinocerebellar atrophy (SCA) – yes or no
CASE 4

Highly functioning 74 year old woman with progressive cognitive impairment over 3 months, myoclonic jerks and seizures.

Clinical diagnosis - Creutzfeldt Jakob Disease.
But MRI was normal and CSF 14-3-3 negative
MRI in CJD
Increased signal of FLAIR and DWI in cortical ribbon, caudate nucleus, thalamus
Neurostat FDG PET – comparison to normal database

Decreased Metabolism

Increased Metabolism
What is the diagnosis?

A) Alzheimer’s Disease.
B) Limbic encephalitis.
C) Creutzfeldt-Jakob Disease.
D) Fronto-temporal dementia.
E) Herpes Simplex encephalitis.
Q: Which statement is incorrect?

1) A whole body FDG PET/CT may be useful.
2) Biochemistry results may be important.
3) The patient has an untreatable condition.
Whole body FDG PET/CT

Normal
Progress

- Persistent low sodium noted
- Autoantibody screen revealed voltage-gated potassium channel (VGKC) antibodies
- Seizures resolved and cognition returned to normal with corticosteroids and plasma exchange
- Diagnosis: Limbic encephalitis due to VGKC antibodies.
Case: History

- 72 year old retired journalist.
- Two years of memory decline, poor concentration and inappropriate comments.
- Possible closed head injuries >30 yrs ago – hit by a car, hit on head with a hammer, fall from a roof.
- Testing: MMSE 21, CVLT word list delayed recall --2.5 SD, Boston naming Test -5.6 SD “consistent with AD”.
- “Silly, child-like” demeanour and inappropriate jokes during testing.
MRI Report

- Gliosis and atrophy in the anterior temporal lobes, right more than left.
- Severe hippocampal atrophy.
- Enlarged sulci in medial and orbital frontal lobes.
Q1: Differential Diagnosis should include?

1. Alzheimer’s disease
2. Frontotemporal Dementia (behavioural type)
3. Late decompensation post head injury
4. All of the above
FDG PET was done
Q2: The FDG PET shows which one of the following:

1. Frontotemporal dementia
2. Alzheimer’s disease
3. Old head injury
4. Vascular dementia
5. Mixed dementia (i.e. a combination of some of the above)
Appropriate Use Criteria (AUC) for Amyloid PET

- Early onset dementia (<65 yrs of age )
- MCI
- Dementia of uncertain cause after expert assessment
F-18 florbetaben amyloid PET
Q3: Which one of the following is true:

1. The scan shows normal non-specific tracer binding.
2. The scan shows cortical binding that obscures white matter pattern indicating a positive scan.
3. Past head trauma does not increase the risk of Alzheimer’s disease.
4. Only a negative scan can help with diagnosis.
Management Impact

- A diagnosis of Alzheimer’s disease was made and Aricept commenced.
- Legal affairs were put in order.
- Excluded from drug trials because of head injury.
Case : History

• 68 year old engineer with 2-3 years of subtle memory decline. No functional impairment.

• Depression with “pseudodementia” in 2012 that improved with treatment but some memory impairment persisted.

• 2015: memory impairment on testing. Classified as MCI.

• 2016: MMSE 26, CVLT delayed word list recall -2.5 SD. Other cognitive domains normal. Still classified as MCI.
Q1: Which of the following statements is true?

1. The MRI is normal.


3. Small hippocampi in normal older persons are a reliable predictor of future Alzheimer’s disease.

4. White matter hyperintensity is rare in the elderly.
FDG PET was done
Q2: The FDG PET demonstrates one of the following:

1. Early frontotemporal dementia
2. Significant precuneus and posterior cingulate gyrus hypometabolism indicative of AD
3. Left temporal lobe hypometabolism due to semantic dementia
4. No significant abnormality
Amyloid PET Scan
Q3: Which of the following is not true:

1. The patient has >70% likelihood of developing dementia within 5 years.
2. There is >90% likelihood that the patient has enough amyloid plaques to meet histopathological criteria for Alzheimer’s disease.
3. The amyloid scan is strongly positive.
4. The normal FDG PET has no prognostic value.
Case:

- 74 year old female with progressive aphasia
- Language deficit most prominent feature for first two years but now some memory impairment
- MMSE 22
Which one of the 3 major forms of Primary Progressive Aphasia does this patient have?

1. Semantic
2. Nonfluent/agrammatic
3. Logopenic
Primary Progressive Aphasia

*International Consensus Criteria*

1. Semantic
2. Nonfluent/agrammatic
3. Logopenic

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FTLD (TDP43)

FTLD (Tau > TDP43)

Alzheimer’s Disease

(beta-amyloid and tau)
Case

- 58 year old male accountant.
- Progressive difficulty with calculation, writing and speech (non-fluent).
- Clumsy right hand e.g. not able to put key in lock but normal strength.
- Memory and personality intact.
- MRI – parietal atrophy. No stroke.
Q1. The scan shows

1. Asymmetrical hypometabolism of frontal and parietal association cortex.
2. Right striatal hypermetabolism.
3. Incidental cerebellar stroke missed by MRI.
4. Dementia with Lewy Bodies.
5. Hypometabolism of the posterior cingulate and precuneus and therefore is diagnostic of Alzheimer’s disease.
Q2: Which of the following investigations may assist diagnosis?

1. DATScan
2. PiB scan
3. D2 receptor scan
4. Brain biopsy
5. All of the above
Beta-amyloid $^{11}$C-PiB
The PiB amyloid scan is negative. DATScan shows reduction in striatal binding (left worse than right).

Q3: The diagnosis is

1. Frontotemporal dementia
2. Dementia with Lewy Bodies
3. Cortico-basal degeneration
4. Alzheimer’s disease variant
5. Progressive Supranuclear Palsy
Corticobasal Ganglionic Degeneration

Rare progressive **neurodegenerative disease** involving the **cerebral cortex** and the **basal ganglia**.

- Parkinsonism – DDx IPD (normal FDG), PSP (frontal hypometabolism)
- Alien Hand Syndrome (asymmetric)
- Apraxia (difficulty with complex movements)
- Aphasia (non-fluent and eventually mute)

PET/SPECT – **asymmetric** deficits in posterior frontal and parietal cortex, **basal ganglia** and **thalamus**
Case 5

- 53 year old female with 18 months of worsening personality change, repetitive behaviours, marked reduction in speech.
- Neuropsychology identified language and executive dysfunction worse than memory impairment.
Q: What is the diagnosis?

A) Frontotemporal dementia – Semantic Dementia subtype.
B) Frontotemporal dementia – Behavioural subtype or Pick’s disease.
C) Frontal variant of Alzheimer’s disease.
D) Schizophrenia
E) Progressive supranuclear palsy
Poor quality as patient climbed out of scanner after 5 minutes