Dementia - Read with the expert: Brain FDG PET

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Case 1

- Male, DOB 21-AUG-1933

**History:** for >3 years progressive word-finding difficulties, according to wife impaired comprehension of word meaning, whereas the speech output was said to be normal, no described difficulty with calculation, no difficulty with facial recognition, during the last 18 months additional behavioural and personality changes

**Clinical Findings:**

- Mini Mental State Examination (MMSE): 23/30 points
- Cambridge score: 50/100 (Cambridge screen for naming 0/10)
- Pyramids and Palm Trees Test: 20/52 correct
- Neurological examination: no pyramidal, extrapyramidal or cerebellar features, inconspicuous exam of cranial nerves
- Liquor: inconspicuous (including virology)
Case 1

Which is the most likely cause of the clinical situation?

1. Early dementia of Alzheimer Type
2. Bipolar disease
✓ Semantic dementia
4. Dementia with Lewy bodies
5. Herpes Simplex Virus Encephalitis (HSVE)
Case 1  Semantic Dementia (SD)

- also called temporal variant of frontotemporal lobar degeneration (tvFTLD)
- FTLD: second most common cause of dementia in pts < 65 yrs (after AD)
- Clinical Diagnosis based on neuropsychometric findings: MMSE is inconspicuous whereas specific semantic knowledge tests are often abnormal
- MRI shows a characteristic pattern of atrophy in the temporal lobes (predominantly on the left)
- FDG-PET shows hypometabolism in the anterior temporal lobe, often bilaterally, but usually predominantly on the left. Impaired glucose metabolism progresses with disease to lateral temporal lobe regions while other cortical domains usually remain preserved over a longer time

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Case 2

- Female, DOB 04-AUG-1967

**History:** secretary, working since her 23rd birthday, onset of concentration difficulties 2 yrs ago, lately errors of calculation, misplacing things, forgetting where she parked her car

**Family History:** father developed cognitive symptoms at age 33, suffered from a rapidly progressing disease incl. generalized seizures and died at age 48

**Clinical Findings:**

- Mini Mental State Examination (MMSE): 24/30 points
- Neurological examination: no pyramidal, extrapyramidal or cerebellar features, inconspicuous exam of cranial nerves
- Liquor: inconspicuous

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Case 2

3DSSP:

RT.LAT  LT.LAT  SUP  INF  ANT  POST  RT.MED  LT.MED

Date: 2007/09/16

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Case 2

Which of these statements is **wrong**?

1. Predominant atrophy of the parietal lobe is accompanied by bilateral decrease of FDG uptake in lateral and mesial parietal cortex

2. The MRI and PET findings are suggestive of neurodegenerative disease

✓ *Although the pattern of FDG uptake is compatible to AD the patient’s young age excludes this diagnosis*

4. Genetic testing could add to clarification of the diagnosis
Case 2 - Teaching Point

- This patient was tested positive for presenilin-1-mutation!

- Familial AD can occur even at this young age (age onset usually between 45 and 55 yrs). Clinical symptoms may include neurological manifestations like epilepsy.

- Campion et al: prevalence of EOFAD 41.2 per 100,000 (ages 40-59 yrs)

- The phenotype of EOFAD is heterogenous (duration of the disease between 6 and 14 yrs)

Bird TD, Genet Med 2008

<table>
<thead>
<tr>
<th>Causes of Alzheimer disease</th>
<th>Late-onset familial Alzheimer’s disease: molecular genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Locus name</td>
</tr>
<tr>
<td>Chromosomal (Down syndrome)</td>
<td>AD2</td>
</tr>
<tr>
<td>Familial</td>
<td>AD2</td>
</tr>
<tr>
<td>Late-onset familial (AD2)</td>
<td>AD2</td>
</tr>
<tr>
<td>Early-onset familial AD (AD1, AD3, AD4)</td>
<td>AD1</td>
</tr>
<tr>
<td>Unknown (includes genetic/environment interactions)</td>
<td>AD1</td>
</tr>
</tbody>
</table>

Early-onset familial Alzheimer disease (EOFAD): molecular genetics

<table>
<thead>
<tr>
<th>Locus name</th>
<th>Proportion of EOFAD</th>
<th>Gene symbol</th>
<th>Chromosomal locus</th>
<th>Protein name</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD3</td>
<td>20-70%</td>
<td>PSEN1</td>
<td>1q24.3</td>
<td>Presenil-1</td>
</tr>
<tr>
<td>AD1</td>
<td>10-15%</td>
<td>APP</td>
<td>21q21</td>
<td>Amyloid beta A4 protein</td>
</tr>
<tr>
<td>AD4</td>
<td>Rare</td>
<td>PSEN2</td>
<td>1q31-q42</td>
<td>Presenil-2</td>
</tr>
</tbody>
</table>

Bird TD, Genet Med 2008

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Case 3

- Female, DOB 12-SEP-1987

**History:** Progressive cognitive impairment since 2 yrs, psychic alterations esp. irritability and depression, motoric clumpsiness, at birth healthy, early development milestones inconspicuous.

**Clinical Findings:** broad-based gait, limb ataxia, brisk tendon reflexes on the four limbs, flexor plantar responses
Case 3

Date 2006/09

RT.LAT  LT.LAT  SUP  INF
L       R       R       L
GLB

Date 2007/07

RT.LAT  LT.LAT  SUP  INF
L       R       R       L
GLB

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Case 3

What is the most probable diagnosis?

1. Creutzfeldt-Jakob Disease
2. Progressive supranuclear palsy (PSP)
3. Huntington’s Disease
4. Corticobasal degeneration
5. Frontal lobe dementia
Case 3 - Teaching Point

- FDG PET revealed rapidly progressive hypometabolism in the striatum with no significant cortical affection
- This patient had a positive family history for Huntington’s Disease
- Genetic testing showed 92 CAG-repeats
- This constitutes an early manifestation of Huntington’s Disease (typically between 35 and 45 yrs)
- Age of onset and severity of disease are inversely correlated with the number of CAG repeats
- Large expansions over 60 repeats may result in Juvenile Huntington’s Disease (onset before 20 years of age)
Case 3 - Teaching Point

control  Huntington‘s Disease  MRI

early stage  advanced stage

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Case 4

• Female, DOB 25-JUN-1974

History: economics graduate, working as a consultant, 2004 kinetic 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
Case 4

3DSSP:

RT.LAT  LT.LAT  SUP  INF  ANT  POST  RT.MED  LT.MED

GLB

Date: 2008/01/18

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Case 4

What is the most probable diagnosis?

1. Sydenham chorea
2. \textit{Spinocerebellar Ataxia (SCA)}
3. Corticobasal degeneration
4. Cerebellar atrophy following alcohol abuse
5. Cerebellar affection after chronic ecstasy abuse
Case 4 - Teaching Point

- FDG PET shows a severe hypometabolism of the entire cerebellum and the brainstem
- The patient’s paternal family history was unknown
- Genetic testing revealed Spinocerebellar Ataxia Type 2 (SCA2)
- Autosomal Dominant Cerebellar Ataxias: prevalence in Europe 1-2/100,000
- SCA1-29 (so far)

Table 1

<table>
<thead>
<tr>
<th>Classification of spinocerebellar ataxias (SCAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
</tr>
<tr>
<td>SCA2</td>
</tr>
<tr>
<td>Machado-Joseph disease/SCA3</td>
</tr>
<tr>
<td>SCA4</td>
</tr>
<tr>
<td>SCA5</td>
</tr>
<tr>
<td>SCA6</td>
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<td>SCA7</td>
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<tr>
<td>SCA27</td>
</tr>
<tr>
<td>SCA28</td>
</tr>
<tr>
<td>SCA29</td>
</tr>
</tbody>
</table>

Rare (<1%) | Unknown

Schols et al. Lancet Neurol 2004
Soong et al. Curr Opin Neurol 2007
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Case 5

- Male, DOB 18-OCT-1931

**History:** retired teacher, since 2 years progressive gait disturbance, affective disorder, urinary incontinence, since 2 months increasing drowsiness, episodic headaches sometimes accompanied by blurred vision

**Clinical Findings:**

- MMSE 26/30 points
- MRI (with motion artefacts): ventricular dilation
Case 5

3DSSP:

RT.LAT  LT.LAT  SUP  INF

L  R  R  L

GLB

THL

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Case 5

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Case 5

Which of these statements is **wrong**?

1. Cortical hypometabolism largely normalization artefact due to a previously unknown pituitary tumor
2. Diagnosis can be confirmed by high volume tapping of CSF
3. Diagnosis is compatible with a normal pressure hydrocephalus
   ✓ *Cortical hypometabolism caused by psychoactive drugs*
4. Findings are not compatible with frontotemporal dementia
Case 5 - Teaching Point

3.0T GEMSMR01
Ex: 5984
say
Se: 402/9
Im: 18/24
Sag: L3.8 (COI)

256 x 256
Mag: 2.1x

ET: 1
TR: 4.5
TE: 1.8
8HRBRAIN
1.0thk/-1.0sp

pituitary tumor: 1.5 x 1.2 cm

radiologie LMU Grosshadern
1931 Oct 18 M 0021510196
Acc: 0047570178
2008 May 23
Acq Tm: 11:23:57

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Case 5 - Teaching Point

- Serum prolactin level 898 mU/l (normal range <324 mU/l)
- FDG PET shows an intense hypermetabolism in the pituitary gland
- Initial MRI imaging did not reveal the tumor mainly due to motion artefacts
  → high-field thin-section (sagittal) MR of the sella revealed a pituitary adenoma
- Due to the pituitary hypermetabolism cortical FDG uptake appeared significantly reduced → masking the pituitary focus shows a widely unaffected cortical glucose metabolism

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Case 5 - Teaching Point

<table>
<thead>
<tr>
<th>scan: original</th>
<th>scan: masked pituitary gland</th>
</tr>
</thead>
</table>

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Case 6
66 year old female

**History:** Since 7 months progressive speech disorder, rigor of the right arm, apraxia. Mental confusion and memory loss.

**Clinical findings:** Right hyperreflexia with a mild ipsilateral hemiparesis and hypertonicity of the right arm. Severe dysarthria and discrete hypomimia. Moderate cognitive impairment. Loss of graphesthesia (ability to identify a letter drawn in the palm).

**MRI:** Global atrophy without any focal lesions.
Case 6
18F-FDG PET:

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Case 6

FP-CIT-SPECT:

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Case 6
18F-FDG PET:

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Case 6

Question

What is the most likely cause of the present clinical situation with respect to the FDG PET / FP-CIT SPECT findings?

1. Cerebrovascular disease
2. Corticobasal degeneration
3. Lewy body disease
4. Creutzfeld-Jakob disease
5. Huntington’s disease

✓ Corticobasal degeneration
Case 6

Findings

FDG PET: Glucose hypometabolism in the frontal and parietal cortex (left >> right) as well as in the left striatum and thalamus

FP-CIT: Decreased dopamine transporter (DAT) binding in the left putamen >> caudate

Interpretation: The asymmetrical FDG-hypometabolism in the left frontal and parietal cortex as well as in the striatum and thalamus together with the decreased DAT binding in the left striatum (contralateral side to the most affected limb!) is compatible to the diagnosis of a corticobasal degeneration.
Teaching Points CBD Case 6

⇒ FDG-PET (relative cortical and basal ganglia hypometabolism contralateral to the most affected side!) and to some extent FP-CIT (asymmetrically reduced DAT binding in the striatum contralateral to the most affected side!) are helpful tools in the differential diagnosis of CBD

⇒ limited diagnostic value of postsynaptic D2-receptor imaging (e.g. IBZM, Racloprid) in the differential diagnosis of CBD since striatal PET/SPECT findings can be similar in:

• Progressive supranuclear palsy (PSP)
• Multiple system atrophy (MSA)
Remember: Corticobasal degeneration (CBD):

A slowly progressive disorder characterized by neurodegenerative changes of cortical and subcortical regions: particularly the prefrontal and parietal lobe and parts of the basal ganglia.
The changes are frequently asymmetrical.

The combined loss of brain tissue in these areas causes the complex symptoms:

CBD symptoms are similar to those found in Parkinson‘s disease combined with cognitive and visual-spatial impairments or apraxia (loss of the ability to make familiar, purposeful movements)
Case 7
54 year old male

**History:** Rapidly progressive mental confusion and memory loss, impaired vision, clumsiness right arm and both legs, unstable atactic gait, dysarthria

**Clinical findings:** Moderate cognitive impairment. Patient awake and oriented, decelerated horizontal and absent vertical optokinetic nystagmus

**EEG:** Continuous left frontal and bitemporal background deceleration; left hemispheric development of periodic sharp waves

**Liquor:** cells/glucose normal, discrete increase of protein/albumin, verification of protein 14-3-3 in Western Blot
Case 7

18F-FDG-PET:

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Case 7

MRI/PET:

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Case 7
Question

What is the most likely cause of the present clinical situation with respect to the FDG PET / MRI findings?

1. Cerebrovascular disease
2. Corticobasal degeneration
3. Multisystem Atrophy
   ✓ Creutzfeld-Jakob disease
4. Huntington’s disease

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Case 7

Findings

FDG PET: Pronounced glucose hypometabolism in the left frontal and parietal cortex and subcortical in the left thalamus and striatum. Moderate glucose hypometabolisms in the right-hemispheric neocortex. Glucose hypometabolism of the right cerebellar hemisphere.

MRI: Asymmetrical hyperintensity of the left striatum in T2-FLAIR and diffusion weighted sequences. Hyperintensity of the left frontal superior and medial gyri in FLAIR and diffusion weighted sequences.
Case 7

Interpretation and Teaching points

Rapidly progressive clinical findings, variable cortical / subcortical FDG hypometabolisms concomitant with MRI hyperintensities and verification of protein 14-3-3 in the liquor are suspicious of:

⇒ Creutzfeld-Jakob disease

In this case primarily left hemispheric neocortical hypometabolism with contralateral cerebellar involvement!

⇒ crossed cerebellar diaschisis (functional deactivation of contralateral cerebellar hemisphere due to disruption of cortico-ponto-cerebellar fibres!)

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