Neuroimaging of Dementia
What to order and when

35th Annual Midwestern Conference on Health Care

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Objectives

Revise imaging findings in

– Normal aging

– Degenerative Dementias
  • Alzheimer’s disease (AD)
  • Lewy body dementia (LBD)
  • Parkinson dementia (PDD)
  • Frontotemporal dementia (FTD)

– Other causes of dementia
  • Vascular dementia *(mixed dementia)*
  • HIV
  • NPH

Discuss indications and strategies for imaging
Normal aging: MRI changes

• Atrophy
  – Preferentially involving gray matter and frontal lobes

• White matter signal hyperintensities: Leukoaraiosis (white matter rarefaction)
  – Correlated with age and hypertension

• Low T2 signal of deep nuclei
  – From iron deposition
Tissue volume changes with aging

Sullivan & Pfefferbaum, BJR 2007
Traditional “exclusionary” approach for imaging in dementia

• Purpose: To identify causes of reversible or treatable dementia

• However, a Meta-analysis by Clarfield in 2003 showed
  – Potential reversible causes in 9%
  – 0.6% actually reversed
Causes of reversible Dementia

- Medications
  - Anticholinergics, AEDs, tricyclic antidepressants, antipsychotics, ...
- Psychiatric (depression)
- Nutritional deficiencies
  - Vitamins B1 (Wernicke’s encephalopathy), B3, B12, ...
- Endocrine
- Metabolic
- Mass lesions (hematomas, tumors)
- NPH
- Infectious – immune mediated
  - HIV, limbic encephalitis, Whipple, meningoencephalitis, ...
- Systemic inflammatory disorders
  - SLE, vasculitis, sarcoidosis, ...
- Other
  - Brain sagging syndrome, vascular
70-year-old female with personality changes for the past 3 years becoming more argumentative and impulsive.

She is more likely to speak her mind irrespective of consequences and is less caring about her appearance.

She is no longer interested in caring for her home or preparing meals.
New “inclusionary” approach for imaging in dementia

• Early detection
  – MCI stage

• Demonstration of specific pathology
  – Medial temporal atrophy in AD
  – Frontotemporal atrophy in FTD
  – Vascular diseases
Classification of dementia based on imaging

F. Barkhof et al., Neuroimaging of dementia, Springer 2011

- A. Primary gray matter loss: Neurodegenerative diseases: AD, FTD, CBD
- B. Vascular dementia (combined gray and white matter damage)
- C. Primary white matter disorder: HIV encephalopathy, metabolic)
- D. With brain swelling: hydrocephalus, encephalitis, AV fistula.
Alzheimer’s disease: neuropathologic staging

Braak & Braak, Neurobiol Aging 1995

transentorhinal stages

STAGE I
Uncus
parasubiculum
subiculum
trans entorhinal region
entorn. region

CA I

STAGE II	
temp.
temporal cortex

limbic stages

STAGE III

STAGE IV

isocortical stages

STAGE V

STAGE VI

Progression of cortical myelination
Progression of Alzheimer's disease related destruction
Imaging in Alzheimer’s disease
Medial temporal atrophy score (MTA)

Scheltens et al, 1992

Radiology 2009;253:174-183
Conversion of MCI to dementia

*Stroke 2009; 40:1269*

<table>
<thead>
<tr>
<th></th>
<th>Nonconverters</th>
<th>Converters</th>
<th>AD</th>
<th>Non-Alzheimer Dementia</th>
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<tbody>
<tr>
<td>MTA</td>
<td>0.7 (0.8)</td>
<td>1.4 (0.9)$</td>
<td>1.4 (1.0)$</td>
<td>1.2 (0.8)$†</td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td>0.6 (0.7)</td>
<td>1.0 (0.8)‡</td>
<td>1.0 (0.7)‡</td>
<td>1.2 (0.9)‡</td>
</tr>
<tr>
<td>PVHs</td>
<td>2.3 (1.7)</td>
<td>2.9 (1.6)</td>
<td>2.6 (1.5)</td>
<td>3.8 (1.5)‡</td>
</tr>
<tr>
<td>DWMHs</td>
<td>4.9 (5.4)</td>
<td>5.4 (5.2)</td>
<td>4.4 (4.6)</td>
<td>8.9 (5.6)‡</td>
</tr>
<tr>
<td>Total WMHs</td>
<td>7.1 (6.9)</td>
<td>8.3 (6.5)</td>
<td>6.9 (5.9)</td>
<td>12.7 (6.9)‡</td>
</tr>
<tr>
<td>Presence of ≥1 lacune, n (%)</td>
<td>15 (19%)</td>
<td>15 (21%)</td>
<td>10 (18%)</td>
<td>5 (31%)†</td>
</tr>
<tr>
<td>Presence of ≥1 lacune BG, n (%)</td>
<td>9 (11%)</td>
<td>13 (18%)</td>
<td>8 (14%)</td>
<td>5 (31%)‡</td>
</tr>
<tr>
<td>Presence of ≥1 MB, n (%)*</td>
<td>11 (15%)</td>
<td>10 (16%)</td>
<td>4 (9%)</td>
<td>6 (38%)†</td>
</tr>
<tr>
<td>Presence of ≥1 infarct, n (%)</td>
<td>5 (6%)</td>
<td>4 (6%)</td>
<td>3 (5%)</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>
Alzheimer’s disease, MCI & controls: ADNI cohort (n=643) 12 month GM loss

Neurobiol Aging 2010;31:1401

a) AD > HC

b) MCI-C > HC

c) MCI-S > HC

d) AD > MCI-S

e) MCI-C > MCI-S

f) AD > MCI-C

p < 0.0001 (unc.) k = 27
Imaging biomarkers for AD
Ewers et al, TINS 2011, in press
Alzheimer’s disease: PET imaging

• Metabolic imaging: 18F FDG
  – Glucose metabolism
  – Temporoparietal hypometabolism in AD

• Amyloid imaging:
  – 11C PIB
    • Predominantly frontal but not medial temporal uptake
    • Does no correlate with cognition
  – 18F-labeled tracers such as [18F]florbetaben, [18F]florbetapir (also called [18F]AV-45) and [18F]flutemetamol.

• 18F FDDNP
  – Labels amyloid and NFTs
  – Medial temporal involvement
Alzheimer’s disease: PET imaging
Nordberg A, Lancet Neurology 2004

control

AD

C11
PIB

F18
FDG
Vascular dementia

- Mixed (AD + vascular dementia) is the most prevalent post-mortem pathology after 85 years.
- Strategic stroke
- Small vessel disease: most common type of VaD
  - White matter T2 hyperintensities (*leukoaraiosis*)
  - Lacunes
  - Microbleeds
  - Enlarged perivascular spaces (etat crible)
Vascular dementia

- Specific types of Microangiopathy
  - With microhemorrhages
    - Sporadic cerebral amyloid angiopathy (CAA)
      - Increasing prevalence with age: 2% at 50 years, 74% above 90 years
      - Leading cause of lobar hemorrhage
      - Feature of AD
    - Hereditary types
      - CADASIL
      - Fabry’s disease
      - Susac’s syndrome
Microhemorrhages and leukoencephalopathy in CAA
Progression of leukoaraiosis

Fazekas et al, Stroke 2007
## Frontotemporal lobar degeneration

**Josephs K, Ann Neurol 2008**

**FTLD CLASSIFICATION**

- **Tauopathies**
  - PID
  - PSP
  - CBD
  - ALS-PDC
  - TDD
  - DNRC
  - AGD
  - MST

- **TDP-43 proteinopathies**
  - **FTLD-U type 1**
  - **FTLD-U type 2**
  - **FTLD-U type 3**
  - **FTLD-U type 4**
  - **FTLD-PLS**

- **Others**
  - DLDH
  - NIBD
  - BIBD
  - FTLD + CHMP2B
  - FTLD-U non-TDP-43

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Fig 1. Classification scheme demonstrating the subdivision of the spectrum of frontotemporal lobar degeneration (FTLD) pathologies into tauopathies versus TAR DNA-binding protein 43 (TDP-43) proteinopathies. Some cases, however, are neither a tauopathy nor a TDP-43 proteinopathy and are therefore classified as “Others.” AGD = argyrophilic grain disease; ALS-PDC = amyotrophic lateral sclerosis-parkinsonism complex of Guam; BIBD = basophilic inclusion body disease; CBD = corticobasal degeneration; DLDH = dementia lacking distinctive histology; DNRC = diffuse neurofibrillary tangle dementia with calcifications; FTLD-U = frontotemporal lobar degeneration with ubiquitin-only-immunoreactive changes; MST = sporadic multisystem tauopathy; MBD = neurofilament inclusion body disease; PiD = Pick’s disease; PSP = progressive supranuclear palsy; TDD = tangle dominant dementia.
TDP-43 proteinopathies: FTLD-U & ALS

Geser F. et al, Neuropathology 2010
Alzheimer’s in comparison to frontotemporal dementia (FTD)

FTD

AD

bvFTD

AD

bvFTD

AD
Clinical subtypes of frontotemporal dementia

Behavioral FTD

Non-fluent Aphasia

Semantic Dementia
Important clinical mimic of FTD

Frontotemporal brain sagging syndrome
An SIH-like presentation mimicking FTD

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ABSTRACT

Background: Behavioral variant frontotemporal dementia (bvFTD) is a relatively well-defined clinical syndrome. It is associated with frontal and temporal lobe structural/metabolic changes and pathologic findings of a neurodegenerative disease. We have been evaluating patients with clinical and imaging features partially consistent with bvFTD but with evidence also suggestive of brain sagging, which we refer to as frontotemporal brain sagging syndrome (FBSS).

Methods: Retrospective medical chart review to identify all patients seen at our institution between 1996 and 2010, who had a clinical diagnosis of FTD and imaging evidence of brain sag.

Results: Eight patients, 7 male and 1 female, were diagnosed with FBSS. The median age at symptom onset was 53 years. All patients had insidious onset and slow progression of behavioral and cognitive dysfunction accompanied by daytime somnolence and headache. Of the 5 patients with functional imaging, all showed evidence of hypometabolism of the frontotemporal regions. On brain MRI, all patients had evidence of brain sagging with distortion of the brainstem; 3 patients had diffuse pachymeningeal enhancement. CSF opening pressure was varied and CSF protein was mildly elevated. A definite site of CSF leak was not identified by myelogram or cisternography, except in one patient with a site highly suggestive of leak who subsequently underwent surgery confirming a CSF leak. In 2 patients with a neuropathologic examination, there was no evidence of a neurodegenerative disease.

Conclusions: This case series demonstrates that FBSS may mimic typical bvFTD but should be recognized as an unusual presentation that is potentially treatable. Neurology® 2011;76:1377-1382
Lewy body dementia

- Second cause of degenerative dementia after AD
- α-synuclein deposition (=Parkinson’s)
- Clinical correlates
  - visual hallucinations
  - parkinsonism
  - clinical fluctuations
- No evidence of medial temporal atrophy
Lewy body dementia

Dopamine transporter imaging
**FP-CIT SPECT in Parkinson’s disease**

Early | Mid | Late

Also positive in:

- Multiple system atrophy
- Progressive supranuclear palsy
- Lewy body dementia
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<th>AD</th>
<th>DLB</th>
<th>PDD</th>
<th>PD</th>
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<tr>
<td>dementia</td>
<td>early</td>
<td>early</td>
<td>late</td>
<td>none</td>
</tr>
<tr>
<td>hallucinations</td>
<td>none/late</td>
<td>prominent</td>
<td>variable</td>
<td>variable</td>
</tr>
<tr>
<td>parkinsonism</td>
<td>none</td>
<td>late</td>
<td>early</td>
<td>early</td>
</tr>
<tr>
<td>plaques</td>
<td>+++ neuritic</td>
<td>+ diffuse</td>
<td>+ diffuse</td>
<td>0</td>
</tr>
<tr>
<td>NFTs</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lewy bodies</td>
<td>only amygdala</td>
<td>diffuse</td>
<td>diffuse</td>
<td>brainstem</td>
</tr>
<tr>
<td>SN loss</td>
<td>minimal</td>
<td>variable</td>
<td>prominent</td>
<td>prominent</td>
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</table>
Tau-related parkinsonian syndromes

- Progressive Supranuclear Palsy (PSP)
  - vertical supranuclear gaze palsy and postural instability with falls
  - Midbrain atrophy on MRI
- Corticobasal degeneration (CBD)
  - Unilateral progressive parkinsonism with “alien limb” syndrome
  - Asymmetric frontoparietal atrophy
Progressive supranuclear palsy - Imaging

control  
PSP

Penguin or hummingbird sign
New and reliable MRI diagnosis for progressive supranuclear palsy

Oba et al, Neurology 2005;64:2050
Corticobasal degeneration Imaging
Tokumaru et al, AJNR 2009

Asymmetric cortical atrophy
Subcortical white matter degeneration
Subthalamatic hyperintensity
65 year old man with dementia and progressive left sided weakness, dystonia, apraxia and “alien limb”
65 year old man with dementia and progressive left sided weakness, dystonia, apraxia and “alien limb”

Corticobasal degeneration
Multiple system atrophy (MSA)

- Glial \(\alpha\) synuclein inclusions
- Clinically, combination of:
  - MSA-Parkinsonism (MSA-P) (striatonigral degeneration)
  - MSA-Cerebellar type (MSA-C)
  - Autonomic involvement (Shy Drager syndrome)
MSA - Imaging

MSA - P

MSA - C

Hot cross bun sign
46 year old man with severe vertigo and progressive cerebellar syndrome

MSA - C
Huntington Disease

- Autosomal dominant (chromosome 4)
- Excess CAG repeats
- Onset 30-40 yrs; death ~ 10-20 yrs
- Progressive chorea, dementia
- Caudate > putaminal involvement
- No known treatment
Huntington disease (juvenile variant)

From Howard Rowley
Pantothenate Kinase-Associated Neurodegeneration

**PANK** (formerly Hallervorden-Spatz disease)

- **Clinical presentation**
  - Typical: Childhood onset of progressive extrapyramidal signs, pigmentary retinopathy and dementia.
  - Atypical: later / slower course

- **Pathology**
  - Iron deposition – globus pallidus

- **PANK2 gene defect** (Ch 20p13)
Pantothenate Kinase-Associated Neurodegeneration

From Howard Rowley
Wilson Disease (Hepatolenticular degeneration)

- Autosomal recessive (3/100,000)
  - Gene product ATP7B on ch 13
  - Hepatocyte copper trafficking

- Cu deposition: liver, brain, ocular

- Peak age 8-16 years (range 5-50)

- Hepatic, psychiatric & neurologic findings

- Treatment: Penicillamine
Wilson Disease

Kayser-Fleischer rings

Giant panda sign

Jacobs, Neurology 2001
Wilson Disease - Imaging

- Putamen > caudate
- Thalamus, brainstem
- “face of the giant panda” sign
- T2 bright claustrum sign
- Late: cortical atrophy
- T2 hyperintensity
- No enhancement

From Castillo and Mukherjee
Normal pressure hydrocephalus

- Clinical triad
  - Cognitive decline
  - Gait disturbance
  - Incontinence

- MRI triad
  - Out of proportion enlargement of the ventricular system
  - Periventricular halo
  - Prominent CSF flow void in the aqueduct
Two pathogenic theories for NPH

– Impaired CSF resorption from prior SAH or meningitis
– Decreased white matter elasticity from leukoaraiosis
HIV Encephalopathy


- HIV-associated dementia (HAD) is the most common cause of dementia worldwide ≤ 40 years old.

- The most common reported imaging finding is cerebral atrophy.
  - The predominant pattern of atrophy may be central (ventricular dilatation)
  - peripheral (sulcal dilatation)
  - or mixed (central and peripheral)

- White matter lesions are the second most common MR imaging finding in patients who have HAD
HIV (Leuko)Encephalopathy

Creutzfeldt Jakob disease

• 1 case per million
• Accumulation of abnormal prion protein
• Rapidly progressing dementia with myoclonus
• Invariably fatal in 6 months
• Most cases are sporadic
• Variant CJD is considered to originate from BSE infection
• 6 genetic types described for the sporadic variant
Creutzfeldt Jakob: FLAIR and DWI

From Howard Rowley
3 MRI patterns in sCJD

Meissner B, AJNR 2008

- Cortex and basal ganglia: 58%
- Only cortex: 33%
- No signal abnormalities: 7%

Variant CJD
Imaging Strategy in diagnosis of Dementia

F. Barkhof et al., Neuroimaging of dementia, Springer 2011

- Clinical suspicion of dementia
- Rule out metabolic/psychiatric (depression) causes

**Structural Imaging**

- **CT**
  - Pacemaker
  - Claustrophobia
  - Very old age

- **MRI**
  - Young age
  - Rapid progression

If negative, consider SPECT/PET