Senescent Changes, Nothing Acute – Unpacking Cerebral Atrophy in Dementia

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Disclosures

• My family and I have no significant financial or other relationship with the manufacturer of any product or service I may discuss
• Off-label use of antipsychotics for the treatment of behavioral symptoms in dementia may be discussed during Q&A. Use of these medications in dementia patients is the subject of two warnings issued by the U.S. Food and Drug Administration
A standardized approach to diagnosing dementia
Is this dementia?

Dementia is a clinical syndrome which has 3 basic elements

- a decline in the level of cognitive functioning from a previous level of performance
- in someone who is alert and cooperative
- which is sufficient to cause functional impairment

All formal definitions of dementia are based on these 3 basic elements

The 2-step approach to diagnosing dementia

- Is this dementia?
  - Clinical history and exam – patient, collateral information (informant, medical records)
  - Cognitive screening: Cognitive decline only = Mild Cognitive Impairment (MCI/ mild NCD)
  - Functional screening: Cognitive + functional decline = Dementia/ major NCD
- What is the etiology of this dementia?
  - Laboratory testing
  - Biomarkers
    - CSF
    - Neuroimaging
  - Genetic studies
Using a standardized approach to diagnosis

• The diagnosis is easily missed without a standardized approach
  • Missed in 76% of patients with moderate-severe cognitive impairment by PCP's in an academic primary care practice in one study
  • In the year after screening, these patients had significantly more hospitalizations, ER visits and mortality, compared to patients with mild or no cognitive impairment
  • In the GP-based DelpHi-MV study in Germany, those who received a formal diagnosis of dementia had approximately a 180% higher chance of receiving anti-dementia treatment
  • Only 30% of all subjects who screened positive for dementia were receiving anti-dementia treatment
  • While another 37% were receiving anti-dementia drugs without a formal diagnosis

Callahan et al., 1995; Wucherer et al., 2015

The NIA-AA criteria for dementia

The NIA-AA updated criteria for the presence of dementia require:

• Cognitive impairment identified from history taking and objective cognitive assessment
• Minimum of 2 cognitive domains: memory, executive, visuospatial, language, and personality/behavior
• Interference with function at work or usual activities
• Decline from previous levels of function
• Not explained by delirium or a psychiatric disorder

McKhann et al., 2011
The DSM-5 criteria for dementia

- Dementia is subsumed under the Neurocognitive Disorders (NCD) in DSM 5
  - A substantial decline in one single cognitive domain can still receive a diagnosis of NCD
  - The term “dementia” implies degenerative dementias in older individuals
- 2 of 5 cognitive domains in DSM-IV – Memory, aphasia, apraxia, agnosia, executive function.
- 1 of 6 cognitive domains in DSM-5 – Learning and memory, complex attention, language, perceptual-motor, social cognition and executive function

American Psychiatric Association, 1994; American Psychiatric Association, 2013

The DSM-5 criteria for dementia

- DSM-5 criteria require
  - Subjective concern about cognition by patient/informant/clinician; and
  - Objective evidence of cognitive decline from expected level from testing or clinical assessment
- DSM-5 also distinguishes between Major and Mild NCD (previously Cognitive Disorder NOS) based on ability to function independently in everyday activities
  - Major NCD – cognitive deficits interfere with independent functioning
  - Mild NCD – cognitive deficits do not interfere with independent functioning as individuals are able to compensate

American Psychiatric Association, 2013
What is the etiology of this dementia?

- Making an etiological diagnosis (as far as possible) is necessary for treatment
- Dementia is a syndrome with multiple potential etiologies -
  “The NCD’s are unique among DSM-5 categories (as they) are syndromes for which the underlying pathology, and frequently the etiology...can potentially be determined”
- But psychiatrists are accustomed to stopping at syndromal level diagnoses

Etiological subtypes in DSM-5

- Coding note for the NCD’s:
  “Code based on medical or substance etiology” (DSM-5, p 603)
- There are 10 specific etiological subtypes of dementia in DSM-5, 8 of which require an additional medical code based on etiology
- “In distinguishing among etiological subtypes, additional diagnostic markers may come into play, particularly neuroimaging studies such as MRI and PET scans” (DSM-5, p 610)

American Psychiatric Association, 2013
Dementia Quality Measurement Set

- Currently undergoing revision, this establishes the current standard of care for dementia
- "Disclosure of Dementia Diagnosis" is the very first measure
- It measures patients/caregiver dyads who have been told
  1. that they have dementia and
  2. what disease is responsible
- Diagnosis is defined as the provider's best current opinion about dementia etiology...may include a disclosure that diagnosis remains unknown or that a previous diagnosis must be revised

From the AAN-APA Draft for Work Group Review and Public Comment, October 28, 2015

Exclusionary approach – Welcome to the 90’s!

- In the 1990’s, the approach was only to rule out acute processes (mostly space occupying lesions)
- Reversible etiologies must be identified and treated – still holds true
- In the absence of a reversible etiology, all dementia was “senile” - due to hardening of arteries (arteriosclerosis) which is age-related, inevitable and incurable - so why bother
  - Auguste D was later shown to have typical NFT’s and amyloid plaques and was ApoE ε3/ε3
- This approach provides little additional information over what is identified clinically

Scheltens, 2001; Graeber et al., 1998
Inclusionary approach – The current standard

The current recommendation is to rule in dementia etiology in order to

- **Guide prognosis and treatment** - of both cognitive and behavioral symptoms in all but the last stages of the disease:
  - Cholinesterase-inhibitor responsive or not
  - Extreme neuroleptic sensitivity or not
  - Anti-amyloid therapy or not (in the near future)
- **Provide closure** - families are becoming increasingly aware of the different etiologies of dementia and routinely seek this information
- **Determine need for genetic testing** - of the patient and, at times, of family members

*Modified from Scheltens, 2001*

Role of biomarkers in the diagnostic evaluation
Why biomarkers?
Lack of clinical-neuropathological concordance

- As one moves from the typical late-onset amnestic AD dementia toward the non-amnestic dementia syndromes:
  "At the single patient level, no clinical pattern is pathognomonic of a specific neuropathology type, highlighting the critical role of biomarkers"
- Curiously, DSM-5 requires biomarker (neuroimaging) evidence to establish a diagnosis of “probable” FT-NCD and Vascular NCD
- But for “Probable” NCD-AD, biomarker (neuroimaging) evidence is only required to rule out mixed etiology

Mesulam et al., 2014; American Psychiatric Association, 2013

The ideal dementia biomarker

Attributes of the ideal ante-mortem dementia biomarker include:
- Ability to detect fundamental features of neuropathology that can be validated at autopsy
- Ability to differentiate one form of dementia from other forms
- Ability to differentiate the stages of disease progression to guide therapy
- Highly reliable, easy to perform, and inexpensive
- Use minimally invasive sample collection, such as from peripheral tissues

Adapted from Khan and Alkon, 2015
Alzheimer's Disease biomarkers
Or how a clinicopathological entity became clinicobiological

- In 2007, the International Working Group (IWG) for New Research Criteria for the Diagnosis of Alzheimer's Disease (AD) first proposed to anchor the diagnosis of AD on the presence of biomarkers.
- For the first time, it was proposed that AD could be diagnosed in vivo and independent of the presence of dementia.
- The 2011 NIA-AA diagnostic guidelines for AD were based on this framework and incorporated biomarker testing.

Dubois et al., 2007; McKhann et al., 2011

<table>
<thead>
<tr>
<th>Pathophysiological</th>
<th>Biomarkers of brain Aβ deposition</th>
<th>Biomarkers of downstream neuronal degeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF Aβ42 Amyloid PET</td>
<td>CSF tau (p-tau and t-tau)</td>
<td></td>
</tr>
</tbody>
</table>

Dubois et al., 2010; McKhann et al., 2011

AD biomarkers – cont’d
Biomarker Trajectory in AD Dementia

Why should all dementia patients have a brain scan?

- Until 2001, a selective approach using prediction rules had been recommended.
- A 2000 analysis of 6 prediction rules found that:
  - The rule with the highest sensitivity (87.5-100%) still had low specificity (37.2-52.9%).
  - At a 5% base rate of potentially reversible dementia (PRD), all rules had a PPV < 15%.
  - Depending on the rule used, 6-44 out of 50 patients with PRD would not undergo neuroimaging.
  - Under-utilization of neuroimaging leads to under-detection of PRD – medico-legal ramifications.

Gifford et al., 2000
Neuroimaging in dementia
Current practice guidelines

- **AAN (2001)** – “...data supports the use of a neuroimaging examination—either a noncontrast CT or MR scan—*under most circumstances at the time of the initial dementia assessment* to identify pathology...” (italics mine)
- **EFNS (2012)** – “Structural imaging should be carried out *at least once* in the diagnostic work-up of patients with cognitive impairment...*MRI is currently the imaging modality of choice*...” (italics mine)

Knopman et al., 2001; Filippi et al., 2012

Does imaging increase diagnostic accuracy?

- In one study in a specialized memory clinic setting, neuroimaging confirmed, clarified, or contradicted the initial clinical diagnosis in more than 80% of patients.
  - Imaging suggested a complex dementia etiology in 21% of cases clinically thought to be caused by a single process
  - 46% of complex clinical differential diagnoses appeared to reflect a single causal pattern

Borghesani et al., 2010
Neuroimaging modalities

- **Structural imaging**
  - CT
  - MRI – imaging modality of choice
  - Non conventional MRI – H1-MRS, DTI, ASL, resting state fMRI
- **Functional imaging**
  - SPECT scan – DaT scan with 123I-Ioflupane, MIBG cardiac scan
  - FDG-PET scan (CT or MRI)
- **Molecular imaging**
  - Amyloid imaging – PiB, 18F-Florbetapir (2012), 18F-Flutemetamol (2013) and 18F-Florbetaben (2014)
  - Tau imaging - 18F-FDDNP; and many others in development
  - Future – alpha-synuclein imaging, TDP imaging

Why should clinicians read brain scans?

- A brain imaging report by a general radiologist typically contributes little to the diagnostic process in dementia
- General radiologists routinely miss dementia-related focal atrophy
  - In one study where 85% of the scans were performed in academic settings, only in 10% bv-FTD patients was that diagnosis even considered by the radiologist
- Calling an atrophy pattern unremarkable leads to
  - delayed or missed diagnoses
  - unnecessary referrals
  - potentially harmful treatments

Suárez et al., 2009
Clinicians and brain scans – cont’d

• Non-psychiatric providers typically order and read their own scans
  • Most cardiologists read their own echocardiograms
  • 24-38% neurologists depend on their own scan readings alone – this group is increasing in size - the rest use a combination approach
• The referring clinician can best integrate clinical, lab and imaging data meaningfully, improving patient care and safety
  • We read and interpret our own labs, why not imaging?
• If the patient has received a report of the study, he/she may wish to personally review it with the referring clinician
• Finally - The referring clinician may potentially be held liable in a malpractice lawsuit for missed findings on the imaging study
  • That the finding may have been missed by the radiologist as well is not an adequate defense

AAN membership surveys, 1996 and 2005

Structural neuroimaging - CT or MRI?

• MRI is the imaging modality of choice – different pulse sequences greatly enhance sensitivity to focal lesions and brain stem atrophy, no exposure to radiation
• CT still preferred in ER’s to rule out large SOL's and bleeds; preferred modality in
  • Quick in and out situations e.g. advanced dementia with agitation
  • Claustrophobic patients and patients sensitive to noise
  • Patients with metal implants and non-MRI compatible devices e.g. pacemakers
  • Patients who cannot afford an MRI (not covered in their insurance plan, self-pay)
• If only CT is possible, obtain a spiral (helical) CT with MPR in the sagittal and coronal planes
Indications for ordering MRI with contrast

- Rapidly progressive dementia in a young patient
- Suspicion of infection – look for contrast enhancement of inflamed areas
- Suspicion of vasculitis – look for vascular and leptomeningeal enhancement

Adapted from Barkhof et al., 2011

Structured reporting of brain scans in dementia
Structured reporting – basic steps

- First, exclude surgically **treatable conditions** – nothing acute
- Next, assess extent and pattern of **brain atrophy** – senescent changes
- Finally, assess extent and pattern of "**signal change**" – more senescence
- If no abnormality for age, then
  - Reassess after a suitable interval, or
  - Consider CSF biomarker studies or functional imaging

*Adapted from Harper et al., 2014*

Nothing acute –
Excluding surgically treatable conditions
Senescent changes – Assessing the extent and pattern of brain atrophy

Normal senescence

- Global grey matter volume decreases linearly with age at least over the 30–60 year age range (with regional exceptions)
- Grey matter loss appears more prominent in the frontal and parietal cortices
- Ventricular enlargement and hippocampal atrophy rates accelerate after age 70
- White matter volume might even increase throughout middle adulthood, declining only after the age of 50 years

Whole brain volume across ages 31-84 years

From Scahill et al., 2003
Why assess brain atrophy?

- Macrostructural tissue loss (atrophy) is the major substrate of the dementia syndrome
- Atrophy been shown to map accurately to
  - Decline in cognitive performance downstream
  - Microstructural and metabolic changes upstream
- Atrophy can be easily assessed in routine clinical practice
  - Unlike measuring microstructural and metabolic changes in vivo, which require specialized imaging techniques not currently used in clinical practice

What is the neuropathological substrate of atrophy?

- Best studied for Alzheimer’s Disease dementia
- Multiple pathologies converge on brain structures that mediate cognitive decline
- Cortical atrophy is related to both Alzheimer’s and vascular pathology
- Hippocampal atrophy is related to both Alzheimer’s pathology and hippocampal sclerosis
  - This volume loss is directly related to neuronal loss (not shrinkage) in the hippocampus
  - However, AD is not the only pathology that causes neuronal loss in this region
  - Additional pathologies have cumulative effects on hippocampal volume loss

Mungas et al., 2002; Frisoni et al., 2010; Logue et al., 2011
Jagust et al., 2008; Zarow et al., 2005
How should the clinician assess brain atrophy?

- A number of Visual Rating Scales (VRS) have been available since in 1990’s
- While initially constructed for research studies, these can be easily adapted into clinical practice
- VRS focus attention on brain regions particularly susceptible to change in specific dementias
- Use of standard VRS in clinical practice helps quantify the atrophy
  - Patients often understand numbers better
  - Makes the reporting less subjective (gr 3/4 is more meaningful than moderate atrophy)
  - Has better intra-rater reliability as we track progression over time

Why should the radiologist use VRS?

- VRS can be applied directly to clinically acquired images without the use of additional software
- With suitable training, they can easily be used as an adjunct to standard clinical radiology reports
- They can be used to enforce structured image reporting
- They can provide radiologists and non radiology clinicians with a framework for interpreting imaging findings, making visual assessment more consistent and potentially more sensitive

Harper et al., 2015
Pasquier’s Generalized Cerebral Atrophy (GCA) scale

- Rated in the transaxial plane in T1 or T2/FLAIR sequences
- Atrophy is always overestimated in heavily T2-weighted sequences – avoid
- Estimate the overall atrophy and ignore focal changes when estimating GCA
- Can be rated on a visual rating scale from 0 (no atrophy) to 3 (knife blade atrophy)

Pasquier et al., 1996

Pasquier’s GCA Scale – cont’d
Davies-Kipps’ Frontotemporal Atrophy (FTA) scale

- Davies et al devised a visual rating scale to rate atrophy in FTD brains
- Kipps et al extended it to include posterior temporal atrophy
- Rating is done on 2 non-contiguous slices in T1w coronal images
- It is a 5-point visual rating scale
  - The overall rating is the highest score amongst the lobar ratings
  - Score of 2 and above is abnormal

Davies et al., 2006; Kipps et al., 2007

Davies-Kipps’ FTA scale – cont’d

Slice 1 - rate anterior temporal and frontal atrophy at level of temporal pole
Slice 2 - rate posterior temporal atrophy at level of LGN
Davies-Kipps’ FTA scale – cont’d

Kipps et al., 2007

Imaging the Hippocampal formation

The hippocampal axis (D) is slightly oblique to the standard axial slices (B, C). It is best imaged in two planes: parallel to the long axis of the hippocampus and in a slightly oblique coronal plane which is perpendicular to the long axis of the hippocampus.

Szabo et al., 2014; Gardner and Hogan, 2005
Imaging the Hippocampal formation – cont’d

Locating the ERC, TRC and PRC on a coronal section at the level of the cornu ammonis

Scheltens’ Medial Temporal Atrophy (MTA) scale

- Scheltens’ 5-point scale is based on
  - Width of choroid fissure (C)
  - Width of temporal horn of the lateral ventricle (D)
  - Height of hippocampal formation (A)
- Rated in the coronal plane in T1w images on the slice that best depicts both hippocampal formations

Scheltens et al., 1992; Suppa et al., 2015
Schelten’s MTA scale – cont’d

- Duara modified Schelten’s MTA scale to include the perirhinal (PRC) and entorhinal (ERC) cortices.
- A single coronal slice at the level of the mammillary bodies is used for the rating.
- The L or R MTA score is the average score across the 3 structures on that side.
- Rating is done on a 5-point score from 0-4.
- The sensitivity and specificity values are derived from cut-offs for impairment for either L or R MTA.

Duara et al., 2008
Duara’s MTA scale – cont’d

Duara et al., 2008

ERC v ERC

Relatively normal ERC and PRC on the L, atrophied ERC and PRC on the R scan
Duara’s MTA scale – cont’d

<table>
<thead>
<tr>
<th>Mean Medial Temporal Atrophy Score</th>
<th>Prodromal AD (MCI - AD) v NCI</th>
<th>Probable AD v NCI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>MTA &gt; 1.0</td>
<td>91.1%</td>
<td>70.1%</td>
</tr>
<tr>
<td>MTA &gt; 1.33</td>
<td>82.2%</td>
<td>82.1%</td>
</tr>
<tr>
<td>MTA &gt; 1.67</td>
<td>62.2%</td>
<td>89.7%</td>
</tr>
<tr>
<td>MTA &gt; 2.0</td>
<td>53.3%</td>
<td>95.7%</td>
</tr>
</tbody>
</table>

Kim’s Medial Temporal Atrophy (MTA) scale

- Kim’s 5-point scale (0-4) is based on:
  - Width of the hippocampus + PHG (A’)
  - Width of the perimesencephalic cistern (C’)
  - Width of the temporal horn (D’)
- Obtained by transposing Scheltens’ T1w-coronal rating scale onto T1w axial images
- The authors found a high kappa value between the T1W-axial and T1W-coronal VRS's

Kim et al., 2014
Kim’s MTA scale – cont’d

Koedam’s Posterior Atrophy (PA) scale

- Rated 0-3 by examining T1w images in all 3 planes
  - Width of the PCS
  - Width of the POS
  - Atrophy of the precuneus
  - Sulcal dilatation in the parietal lobes
- Best used in combination with an MTA scale

Koedam et al., 2011; Lehmann et al., 2012
More senescence -
Assessing the extent and pattern of “signal change”

Upcoming attraction!!

Structural neuroimaging signatures of the dementias
How to integrate this information to diagnose the degenerative dementias
“Typical” Late-onset AD (LOAD)

- Neurodegeneration begins in the hippocampo-entorhinal region (trans-entorhinal cortex)
- ApoE4 is a major risk factor
- No consistent hemispheric asymmetry is present
- Symptoms usually emerge after the age of 65
- Females tend to be overrepresented

Core clinical phenotypic criterion – episodic memory profile characterized by a low free recall that is not normalized by cueing (amnestic syndrome of the hippocampal type)
  - Vis-à-vis frontal-related retrieval deficit which is normalized by cueing

Mesulam et al., 2014; Dubois and Albert, 2004

Neuroimaging signature of “typical” LOAD

- 2011 NIA-AA criteria for AD included 2 neuroimaging biomarkers – structural MRI and FDG-PET
- Usually presents with medial temporal atrophy (MTA)
- MTA is very sensitive but not specific for AD
  - MTA is a sensitive indicator of any underlying hippocampal pathology
  - Right hippocampal atrophy may be more specific for AD than left
- MTA score of >1 is considered abnormal in age <75; score >2 in age above 75
- Medial temporal pathology can include AD, DLBD, FTD, HS, PART, vascular lesions or any combinations thereof

McKhann et al., 2011; Scheltens et al., 1992; Lehmann et al., 2012
The “Atypical” AD spectrum
Early Onset? Non-amnestic? Hippocampal sparing? Type 2?

- Typical AD Dementia is comprised of amnestic (hippocampal) and non-amnestic (focal cortical) deficits
- The 2011 NIA-AA criteria were first to allow 3 non-amnestic presentations of AD
- DSM-5 criteria for NCD-AD do not allow a diagnosis of non-amnestic presentations
- Non-amnestic presentations account for about 6-14% of all AD cases
- Early-onset AD (EOAD) is simply defined as onset before age 65, regardless of clinical phenotype (more often non-amnestic)
- AD age at onset is a substantially heritable trait; with increasing age at onset, the heritability of AD declines

McKhan et al., 2011; Dubois et al., 2014; Koedam et al., 2010; APA, 2013; Wingo et al., 2012

EOAD – Single disease entity?

From van der Flier et al., 2011
Unlikely!!

From Mendez, 2012

Parietal atrophy in EOAD

- Age at onset modulates the distribution of cortical involvement
- In one study of pathologically-confirmed AD
  - 33% of EOAD subjects had PA only (v. 18% LOAD subjects)
  - 9% EOAD subjects had MTA only (v. 46% LOAD subjects)
  - 24% EOAD subjects had no atrophy (v. 0% LOAD subjects)
- Adding PA scores to MTA ratings significantly improved the discrimination
  - of EOAD from age matched controls
  - but not of LOAD from controls

Karas et al., 2007; Lehmann et al., 2012; Filippi et al., 2012
52 y o female with AD and APOE ε3/ε3 genotype

From van der Flier et al., 2011

The Non-amnestic → Amnestic AD continuum

<table>
<thead>
<tr>
<th>Younger age</th>
<th>Older</th>
<th>Oldest-old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-amnestic (~60%)</td>
<td>Amnesia + focal cortical deficits</td>
<td>Non-amnestic (~6%) “Preserved social graces”</td>
</tr>
<tr>
<td>Predominantly male</td>
<td>Male and female</td>
<td>Predominantly female</td>
</tr>
<tr>
<td>Rapid progression</td>
<td>Slow progression</td>
<td>Very gradual progression</td>
</tr>
<tr>
<td>PA &gt;&gt; MTA</td>
<td>PA and MTA</td>
<td>Severe MTA</td>
</tr>
<tr>
<td>Heritability 92-100% - 10% AD; rest AR?</td>
<td>Heritability 60-80% - highly polygenic</td>
<td></td>
</tr>
<tr>
<td>Phenocopies include amnestic-FTD</td>
<td>Phenocopies include HS, PART, AGD</td>
<td></td>
</tr>
</tbody>
</table>
Parkinsonian syndromes

- Synucleinopathies
  - Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD)
  - Multisystem atrophy (MSA)
- Tauopathies
  - Corticobasal syndrome (CBS) and corticobasal degeneration (CBD)
  - Progressive supranuclear palsy (PSP)
  - Frontotemporal dementia with parkinsonism (FTDP-17)
  - Pick's disease

Modified from Boeve, 2007

Neuroimaging in DLB

- There is no structural neuroimaging signature of DLB
- In pure DLB cases, there is relative preservation of medial temporal lobe structures compared to AD of comparable clinical severity on CT/MRI
- Other (non-structural) imaging strategies listed in the 2005 DLB diagnostic criteria
  - Low dopamine transported uptake in the basal ganglia (DaT scan, PET)
  - Reduced occipital activity on PET/SPECT
  - Abnormal myocardial MIBG scintigraphy
- FDG-PET scan can be diagnostic, but CMS does not reimburse
  - Occipital FDG-PET hypometabolism accurately classifies coincident DLB (80% sens and 100% spec)
- Differential dx – Dementia with delirium, LB variant of AD, PCA variant of AD, Heidenhain variant of CJD, VaD

Filippi et al., 2012; McKeith et al., 2005; Toledo et al., 2013
The Frontotemporal Lobar Degeneration (FTLD) spectrum

- Behavioral variant FTD (bv-FTD), including the benign (phenocopy) and late-onset variants
- The language dementias - Primary Progressive Aphasia (PPA)
  - Semantic variant (sv-PPA or PPA-S)
  - Non-fluent or agrammatic variant (nfv-PPA or PPA-G)
  - Logopenic variant (lv-PPA or PPA-L)
- Right temporal variant FTD (rtv-FTD) – sv-PPA or orphan syndrome?
- FTD with motor features
  - FTD-ALS
  - FTD with atypical parkinsonism – PSP, CBD

Modified from Miller, 2014

Diagnosing behavioral variant-FTD

- DSM-5 criteria for FT-NCD only include a behavioral and a language variant
  - In at least 10% of autopsy-proven bv-FTD subjects, an amnestic presentation has been reported
  - In another 10% patients, the bv-FTD phenotype is due to AD
  - If prominent axial rigidity and gaze disturbance, think CBD or PSP
- Presence of signature neuroimaging findings is necessary for “probable” FT-NCD
  - A phenocopy syndrome (male predominance with negative early imaging findings, slowly progressive course and better overall prognosis) has been described

APA, 2013; Hodges et al., 2004; Chare et al., 2014; Davies et al., 2006; Gossink et al., 2016
Neuroimaging in bv-FTD

- Traditional teaching is asymmetric atrophy of the right frontal, orbito-insular and anterior cingulate cortex, dilatation of the frontal horn and an anterior → posterior gradient of atrophy
- DLPFC becomes involved later
- Best seen on T1w coronal images
- More posterior temporoparietal (IPL) atrophy is more characteristic of AD than FTD

Seeley, 2009; Barkhof et al., 2011

Diagnosing language variant-FTD

“Primary Progressive Aphasia (PPA)”

- Language network includes the dominant inferior frontal gyrus, superior temporal gyrus, supramarginal gyrus (arcuate fasciculus) and anterior temporal lobes
- 2011 PPA classification included 3 subtypes (including lv-PPA for the first time)
  - “Aphasia must be the most prominent deficit at symptom onset and for the initial phases... in the absence of prominent initial episodic memory, visual memory, visuospatial and behavioral disturbances... that cause impaired ADLs... not accounted for by other disorders”

Mesulam, 2013; Gorno-Tempini et al., 2011
Diagnosing PPA subtypes

- 3 PPA subtypes in the 2011 PPA classification
  - Non-fluent or agrammatic variant (nfv-PPA or PPA-G)
  - Semantic variant (sv-PPA or PPA-S)
  - Logopenic variant (lv-PPA or PPA-L)
- DSM-5 has a “language variant” of FT-NCD with a very basic definition
  - The 3 subtypes of PPA are mentioned only in the text
  - Ignores the fact that about 40% of PPA patients have Alzheimer’s and not FTLD pathology

Gorno-Tempini et al., 2011; American Psychiatric Association, 2013

Neuroimaging in nfv-PPA

- Agrammatism (inferior frontal gyrus, arcuate fasciculus)
- Without decreased verbal fluency (aslant tract)
- Imaging shows asymmetric atrophy of the dominant fronto-insular regions
- Best seen in early cases in T1w coronal images as an asymmetric left perisylvian atrophy with peak atrophy in the left inferior frontal gyrus

Catani et al., 2013; Mesulam et al., 2014, Mesulam, 2013; Miller, 2014
Neuroimaging in sv-PPA

- Profound impairments in object naming and single word comprehension
- Preserved grammatical structure and fluency
- Dominant temporal pole is the repository of semantic information about objects
- Uncinate fasciculus connects it to the IFG
- Peak atrophy is confined to the dominant anterior temporal lobe
  Mesulam et al., 2014, Mesulam, 2013; Miller, 2014

Neuroimaging in rtv-FTD

- rtv-FTD is the right temporal counterpart of sv-PPA but presents quite differently
- No diagnostic criteria and no specific name yet
- Long psychiatric prodrome in many patients
- Non dominant temporal lobe is the repository of more abstract semantic concepts
- Loss of empathy in early stages leading to alienation of loved ones may be a core feature
- Fails to recognize faces and emotions of others
- Refuse medical consultations, so half as common as sv-PPA in clinical settings
- Lose social warmth and become disagreeable
  Miller, 2014
Neuroimaging in lv-PPA

- Hallmark is word-retrieval impairments on a background of relatively intact grammatical abilities, word comprehension, and motor components of speech
- About 60-80% have AD pathology
- Peak atrophy is confined to the posterior part of the language network and the dominant lateral temporoparietal region
- In study that included both early and late-onset lv-PPA and AD dementia patients
  - Left lateral temporal atrophy best differentiated lv-PPA from AD dementia
  - Right medial temporal atrophy best differentiated AD dementia from lv-PPA

Mesulam et al., 2014; Mesulam, 2013; Madhavan et al., 2013

Vascular Cognitive Impairment (VCI)

- The term VCI was adopted in 2003 by the International Psychogeriatric Association after a consensus meeting
- It is an umbrella term for all forms of cognitive impairment “associated with and presumed to be caused by cerebrovascular disease”
- “Vascular dementia” is a more restrictive diagnosis under this umbrella
- Any diagnostic workup of VCI necessarily includes structural brain imaging
  - NINDS-AIREN (1993) – “structural brain imaging is an essential element for the diagnosis of vascular dementia, and without it vascular dementia will be ‘possible’ at best” (italics mine)
  - Neuroimaging evidence is a criteria for diagnosing “probable” Vascular NCD in DSM-5

O’Brien et al., 2003; Gorelick et al., 2011; Wright and Flores, 2015; Román et al., 1993; APA, 2013
Diagnosing Vascular Cognitive Impairment (VCI)

- Post stroke dementia
- Vascular dementia (VaD)
  - Multi-infarct (cortical) dementia (MID) – VaD type I
  - Subcortical ischemic vascular dementia (SIVD) – VaD type II
  - Strategic infarct dementia (SID) – VaD type III
  - Hypoperfusion dementia – VaD type IV
  - Hemorrhagic dementia – VaD type V
  - Dementia caused by specific arteriopathies (e.g. CADASIL)
- Mixed (Alzheimer’s disease and Vascular) dementia – VaD type VI
- Vascular MCI (minor NCD)

Adapted from O’Brien et al., 2003; O’Brien, 2006

Why bring up VCI in a talk on cerebral atrophy?

- Hippocampal (and cortical) atrophy appears to be the substrate for dementia in VCI, including CADASIL
- Hippocampal atrophy may result from a mixture of ischemic and degenerative pathologies
- Entorhinal cortex is spared in the absence of AD pathology
- Caution: All these studies used pre-DSM-5 criteria to diagnose dementia

Fein et al., 2000; O’Sullivan et al., 2007; Gemmell et al., 2012
Cerebral atrophy plays a central role in VCI

From O’Brien, 2006

The “Dementia Protocol”
Common MRI protocols

Neuroimaging departments typically have

• Stroke protocol (non-contrast)
• ICH protocol (contrast)
• Tumor protocol (contrast)
• MS protocol (contrast)

BUT NO DEMENTIA PROTOCOL!!

MRI Dementia Protocol

Adapted from Barkhof et al., 2011

Brain Imaging Order Form

Please obtain the studies checked off below:

☐ MRI-brain using the following multisequence protocol:
  ○ M-T1 oblique coronal with multiplanar reconstructions
  ○ M-T1 sagittal with multiplanar reconstructions
  ○ Axial FLAIR (preferably 3D dataset)
  ○ Axial T2+FLAIR
  ○ Axial T2+GE
  ○ Axial DWI
  ○ Please quantify all deep and periventricular white matter hyperintensities using the Fazekas or similar scale, whenever possible.

Diagnosis: 331.0 331.19 331.82 290.4 294.9

☐ PET-brain to differentiate between Alzheimer’s Disease and Fronto-temporal Dementia.
The OHSU MRI Dementia Protocol
(Special thanks to Dr Jeff Pollock!)

- Finally uploaded into Epic smart order sets (Ambulatory MRI Brain Imaging) in Nov 2015
- Go to the Advanced Protocols section
- Option of choosing MRI brain wo or wwo contrast
- Protocol includes
  - 3D T1 sagittal with multiplanar reconstructions (cor, sag) - needs to be from the neuroquant protocol so we can potentially do volumetrics.
  - 3D Sag Flair with axial MPR
  - Axial T2 (T)SE
  - Axial SWI
  - Axial DWI with ADC map

How to find the OHSU MRI Dementia Protocol
Screenshot from Epic
Scan was obtained and reviewed personally today. It shows evidence of generalized cerebral atrophy, in addition to which regional atrophy is evident in the *** lobe(s). Hippocampal atrophy was graded ***/4 using the Scheltens' scale. Medial parietal atrophy was *** with wide posterior cingulate sulci ***. White matter hyperintensities were graded ***/3 using the Fazekas’ scale. The T2*GRE sequence showed *** evidence of cerebral microbleeds. Overall, the scan was thought to be consistent with *** in the appropriate clinical setting.

Final word and Take home points
Etiology of Dementia
Occam’s Razor or Hickam’s Dictum?

- “Patients can have as many diseases as they d--- well please” (John Hickam, MD)
- Principle of parsimony does not apply in geriatrics – look for multiplicity, not a unifying hypothesis
- Autopsy study of first 22 consecutive ADNI subjects diagnosed with AD dementia or AD-MCI
  - Amnestic, cognitively impaired, subjects without any cognitive signs or symptoms suggestive of non-AD pathologies and a low vascular risk profile
  - Only 4 were found to have a “pure” AD pathology on autopsy
  - 45% had comorbid Lewy Body disease, 23% had comorbid vascular pathology and 40% had comorbid mixed pathology
- BUT - in the 90+ autopsy study, no neuropathology was found in 22% of 63 patients with DSM-IV dementia

Toledo et al., 2013; Corrada et al., 2012

Take home points

- A good dementia work-up must include 1 or more biomarkers
- History and exam with an MRI using the dementia protocol, is usually adequate
- In young-onset and questionable cases, use of 2 disparate biomarkers is advised
- You must know how and when to order and how to interpret biomarkers if you work with dementia patients
  - Even if you are “opposed” to ordering them in your own practice, patients will come to you with biomarker study reports from other centers and expect you to interpret them
- Structural and functional neuroimaging reports by community radiologists have variable reliability in dementia cases
- The final responsibility (clinical, legal and ethical) rests with the clinician who must know how to integrate biomarker results with clinical and other diagnostic data
Questions?

May email me: aga@ohsu.edu