The Many Faces of Dementia and Why They Matter

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What I will cover today

- There are many faces of dementia
  - Type of symptoms
  - Underlying pathology
  - Disease stage
  - Concomitant pathologies
  - Demographic variables
- Use of Machine Learning to understand the many faces of dementia
Two amazing persons affected by “Dementia”, but two different presentations

Grandma Dugger
- didn’t remember who I was but could remember to sit in the same pew even though it wasn’t a church she grew up in or was very familiar with before the disease

Grandma Morenski
- dementia with hallucinations and more pronounced personality changes
Clinical Classification of Dementia

Decrease in activities of daily living and cognitive impairment
Clinical presentation vs. underlying disease

DEMENTIA

• Alzheimer’s Disease (AD)
• Dementia with Lewy Bodies (DLB)
• AD & Vascular Dementia (mixed)
• Vascular Dementia (VaD)
• Frontotemporal Dementia (FTD)
• Parkinson’s Disease (PD)
• Huntington’s Disease (HD)
• Other Degenerative Diseases (PSP, ALS with dementia)
• Dementias Secondary to Alcohol
• Depression/Pseudodementia
• Normal Pressure Hydrocephalus (NPH)
• Structural Lesions
• Metabolic Disorders (Hypothyroidism)
• Delirium
• Infections (e.g. neurosyphilis, AIDS, CJD)
• Drug Intoxication
Why we need to understand the underlying disease

Precision Medicine
“Deliver optimally targeted and timed interventions tailored to an individual’s molecular drivers of disease”.

Clinical diagnosis is not an exact science

Low clinical diagnostic accuracy of early vs advanced Parkinson disease
Clinicopathologic study

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ABSTRACT

Objectives: Determine diagnostic accuracy of a clinical diagnosis of Parkinson disease (PD) using neuropathologic diagnosis as the gold standard.

Methods: Data from the Arizona Study of Aging and Neurodegenerative Disorders were used to determine the predictive value of a clinical PD diagnosis, using 2 clinical diagnostic confidence levels, PossPD (never treated or not clearly responsive) and ProbPD (responsive to medications). Neuropathologic diagnosis was the gold standard.

Results: Based on first visit, 9 of 34 (26%) PossPD cases had neuropathologically confirmed PD while 80 of 97 (82%) ProbPD cases had confirmed PD. PD was confirmed in 8 of 15 (53%) ProbPD cases with <5 years of disease duration and 72 of 82 (88%) with ≥5 years of disease duration. Using final diagnosis at time of death, 91 of 107 (85%) ProbPD cases had confirmed PD. Clinical variables that improved diagnostic accuracy were medication response, motor fluctuations, dyskinesias, and hyposmia.

Conclusions: Using neuropathologic findings of PD as the gold standard, this study establishes the novel findings of only 26% accuracy for a clinical diagnosis of PD in untreated or not clearly responsive subjects, 53% accuracy in early PD responsive to medication (<5 years’ duration), and

How does one classify dementias pathologically?

- Looking for the “car accidents”

- A dementia will have abnormal aggregates (i.e. “car accidents”) of specific proteins in specific areas of the brain
abnormal aggregates of Amyloid-β

“Amyloid Plaques” in Alzheimer’s disease
This is how you classify dementia pathologically

Abnormal aggregates of Tau

“Neurofibrillary Tangles” in Alzheimer’s disease

“Tufted astrocytes” in Progressive Supranuclear Palsy

“Pick Bodies” in Pick’s disease

“Astrocytic plaques” in Corticobasal Degeneration
abnormal aggregates of $\alpha$-synuclein

“Lewy bodies” in Dementia with Lewy bodies
In dementias, there are similarities and differences

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical presentation</th>
<th>Pathologic presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease (AD)</td>
<td>Dementia, forgetfulness &amp; word finding difficulties</td>
<td>Plaques and Tangles</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies (DLB)</td>
<td>Dementia, Parkinsonism, hallucinations, fluctuations, REM sleep behavior disorder</td>
<td>Lewy bodies</td>
</tr>
<tr>
<td>Progressive Supranuclear Palsy (PSP)</td>
<td>Dementia, Parkinsonism, Supranuclear gaze palsy, backwards falls (early), dysphagia</td>
<td>Tufted astrocytes</td>
</tr>
<tr>
<td>Corticobasal Degeneration (CBD)</td>
<td>Dementia, Parkinsonism, Asymmetric clumsiness, stiffness or limb jerking, alien limb phenomenon</td>
<td>Astrocytic plaques</td>
</tr>
<tr>
<td>Pick’s Disease</td>
<td>Dementia; inappropriate social behavior, language problems</td>
<td>Pick bodies</td>
</tr>
</tbody>
</table>
Many studies have aided greatly in understanding the relationship between clinical symptoms and underlying pathology. However,

- Typically focus on one diagnosis
  - Importance of:
    Concomitant diagnoses
    Locational aspect of pathology/disease states
- Cohorts mainly “upper middle class white Caucasians”
  - Importance of race/ethnicity:
    Social
    Cultural
    Economic
    Behavioral characteristics
how frequent are concomitant diagnoses?
Multiple diseases can exist in one brain

30% of Alzheimer’s cases have a concomitant clinicopathological diagnosis.

Dugger BN, query of the Brain and Body Donation Program database
A person just doesn’t wake up one day with dementia, it is a process

<table>
<thead>
<tr>
<th>Latency</th>
<th>Prodromal</th>
<th>Full Clinical Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Pathology Stage</strong></td>
<td><strong>Mild Cognitive Impairment</strong></td>
<td><strong>Dementia</strong></td>
</tr>
</tbody>
</table>

**Amyloid-β aggregate staging**

**Tau aggregate Staging**
What of cohort composition?
Diversity in research cohorts

Alzheimer’s Disease Centers

<table>
<thead>
<tr>
<th>Race</th>
<th>Frequency (n)</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>28487</td>
<td>79.6%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>4479</td>
<td>12.5%</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>206</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Native Hawaiian or Pacific Islander</td>
<td>27</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Asian</td>
<td>860</td>
<td>2.4%</td>
</tr>
<tr>
<td>Multiracial</td>
<td>1125</td>
<td>3.1%</td>
</tr>
<tr>
<td>Unknown or ambiguous</td>
<td>584</td>
<td>1.6%</td>
</tr>
<tr>
<td>All</td>
<td>35768</td>
<td></td>
</tr>
</tbody>
</table>

Hispanic ethnicity | Frequency (n) |
--- | --- |
No   | 32905 |
Yes  | 2718  |
Unknown | 145   |
All   | 35768 |

2718/35768 = 7.6%

Dugger, BN unpublished, NACC query July 15, 2017
## U.S. population July 2016 estimates

<table>
<thead>
<tr>
<th>Race and Hispanic Origin</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, not Hispanic or Latino</td>
<td>61.3%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>13.3%</td>
</tr>
<tr>
<td>American Indian and Alaska Native</td>
<td>1.3%</td>
</tr>
<tr>
<td><strong>Hispanic or Latino</strong></td>
<td><strong>17.8%</strong></td>
</tr>
<tr>
<td>Asian</td>
<td>5.7%</td>
</tr>
<tr>
<td>Native Hawaiian and Other Pacific Islander</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

https://www.census.gov/quickfacts/
Diversity matters because dementias can differ based on demographic factors!

Filshtein TJ, Dugger BN et al. Journal of Alzheimer Disease, in press
How can we delve deeper into understanding dementia?
The Age of Machine Learning

Machine learning programs are able to make informed judgements and decisions by recognizing patterns in data.

“We’re looking for someone with your exact qualifications, but a mechanical version.”
Using Machine Learning

https://artsandculture.google.com/
Can we utilize machine learning to aid in understanding the many faces of dementia?
Current standard way of assessing pathologies

Case 123
Amyloid-B
MTG

Mirra S, et al. 1991
Here’s how machine learning can help

Digitize glass slides

Whole slide image

Tile (768 x 768) at 10x

Bounding boxes

~55,000 cropped (128 x 128) tiles

Case 123
Amyloid-B
MTG

Tang, et al. under review
Whole slide heatmaps to see where and how much of each specific pathology is within a slide

Tang, et al. under review
Location of plaques in the brain
What I covered today

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  - Disease stage
  - Concomitant pathologies
  - Demographic variables
- Use of Machine Learning to understand the many faces of dementia
Understanding these different “faces” of dementia matter as it leads to better biomarkers, treatment, and model systems for all who are affected by these devastating diseases.
Alzheimer’s Disease Center

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National Institute on Aging
Thank you!