Beyond Alzheimer’s disease: overview of other major forms of neurodegenerative dementia

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  • Tau Consortium
  • Bluefield Consortium for Frontotemporal Dementia Research
  • Chan-Zuckerberg Initiative

• I have no conflicts of interest related to this presentation
Overview

- Prevalence of the most common neurodegenerative dementias
- Lewy-body disease
  - Parkinson’s disease & Dementia with Lewy bodies
- The frontotemporal lobar degenerations
- Neurodegenerations of aging
  - Hippocampal sclerosis and LATE
- Is dementia one or multiple diseases?
- Chronic traumatic encephalopathy
Prevalence of Alzheimer’s disease

<table>
<thead>
<tr>
<th>Total prevalence</th>
<th>1800/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 yo</td>
<td>72</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>288</td>
</tr>
<tr>
<td>Age 75-84</td>
<td>792</td>
</tr>
<tr>
<td>&gt;85 yo</td>
<td>666</td>
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</tbody>
</table>

Ages of People with Alzheimer's Dementia in the United States, 2018

- 85+ years, 37%
- 75-84 years, 44%
- 65-74 years, 16%
- <65 years, 4%
Prevalence of neurodegenerative dementias

- Alzheimer's disease: 66%
- Vascular dementia: 23%
- Lewy Body Disease: 7%
- Frontotemporal Dementias: 3%
- Other: 1%
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  • Hippocampal sclerosis and LATE
• Is dementia one or multiple diseases?
• Chronic traumatic encephalopathy
Lewy body disease – alpha-synucleinopathy

- Parkinson’s disease
  - Resting tremor
  - Rigidity
  - Bradykinesia
  - Postural instability
  - Asymmetric onset
  - Responsiveness to L-DOPA

- Prevalence:
  - 41/100.000 at age 40-49
  - 1900/100.000 >80 years

- PD dementia
  - 30-40% of all PD cases
  - 80% after 20-years duration

- Dementia with Lewy bodies
  - Attention/executive and visuospatial deficit
  - Cognitive fluctuations
  - Visual hallucinations
  - REM-sleep behavior disorder
  - Parkinsonism

- Prevalence: 7% of all cases of dementia
Other common symptoms of LBD

• Symptoms of autonomic dysfunction (constipation, sweating abnormalities, sexual dysfunction, etc.)
• Decreased sense of smell
• Seborrheic dermatitis
• Anxiety/depression
• Hypophonia
• Decreased facial expression
• Delusional thinking
Braak stages 1 and 2
Autonomic and olfactory disturbances

Braak stages 3 and 4
Sleep and motor disturbances

Braak stages 5 and 6
Emotional and cognitive disturbances

via olfactory bulb
via vagus nerve
pramotor symptoms
motor symptoms

Brainstem Lewy body
Cortical Lewy body
Braak Stages of PD

- **Stage I**: Olfactory bulb, Nuclei IX and X in medulla
- **Stage II**: Intermediate reticular zone, lower raphe, coeruleus-complex
- **Stage III**: Substantia nigra, amygdala, hippocampus
- **Stage IV**: Temporal mesocortex and allocortex
- **Stages V, VI**: High order sensory association areas of neocortex and prefrontal cortex.

Substantia nigra degeneration
Lewy bodies

alpha-synuclein immunohistochemistry
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Frontotemporal Lobar Degeneration (FTLD)

- Neurodegenerative process characterized by predominant neuronal loss and gliosis (atrophy) of the frontal and temporal lobes of the brain
Arnold Pick

- .... circumscribed lobar (frontotemporal) atrophy ....

Pick A. Prager Med Wochenschr
1892;17:165-167
Alois Alzheimer defines Pick’s disease

- .... absence of plaques, presence of round-shaped neurofibrillary tangles (Pick bodies), and swollen neurons ....

Alzheimer A. Z ges Neurol Psychiat 1911;4:356-385
## Prevalence of neurodegenerative dementias

<table>
<thead>
<tr>
<th>Pathological entity</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>1800/100,000</td>
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<tr>
<td>PDD-LBD</td>
<td>~800</td>
</tr>
<tr>
<td>Frontotemporal dementias</td>
<td>15-50</td>
</tr>
</tbody>
</table>

- Common cause pre-senile dementia
  - 1:1 with AD 45–64 years (Ratnavalli 2002)
  - More common than AD <60 years (Knopman 2004)
- Common in elderly?
  - 3% prevalence 80–90 (2003 Skoog)
3 types frontotemporal dementia

Behavioral variant

Language variants

Semantic variant

Non-fluent variant
International Research Criteria for Behavioral Variant FTD

1. Early (2-3 yrs) behavioral disinhibition
2. Early (2-3 yrs) apathy or inertia
3. Early (2-3 yrs) loss of emotional reactivity/sympathy and empathy
4. Perseverative, stereotyped or compulsive/ritualistic behavior
5. Hyperorality and dietary changes
6. FTD neuropsychological profile

7. Frontal or anterior temporal atrophy on MRI
8. Presence of known mutation

Rascovsky et al. Brain 2011
Regions Involved in Emotion

Insula

Anterior

Amygdala
Emotional Deficits in FTD

- Lack of concern for loved one’s illness
- Cruelty to children, animals elderly
- Lack of concern when others are sad
- Rude comments to others
- Lose respect for intrapersonal space
- “Disgusting” behaviors
- Diminished response to pain
Behavioral Variant FTD
3 types frontotemporal dementia

- Behavioral variant
- Language variants
  - Semantic variant
  - Non-fluent variant
Primary Progressive Aphasia (PPA)

- Semantic dementia  FTD (TDP-43)
- Logopenic – AD (AB42, tau)
- Non-fluent CBD, PSP (tau)

Semantic Dementia vs Controls

Rosen et al. *Brain* 2002;125:2286-2295
Seman:c variant PPA (svPPA)
left-temporal pole degeneration

• Impaired confrontation naming
• Loss of word meaning (more severe for low frequency words)
• Impaired object knowledge (more severe for low frequency items)
• Surface dyslexia (regularization of irregular phonetic words)
  • Colonel, knight, yacht, etc.
• Spared repetition
• Spared grammar
• Often hyper-verbal, fluent aphasia
Animals Become Prototypical
Semantic dementia
Right-temporal pole degeneration
Behavioral variant FTD with additional peculiar features

• Loss of knowledge of famous faces
• Increased interest towards word-search games
• Extremely rigid and stereotypic behavior
• Often cold, distinct, anti-social personality
• Hyper-religiosity
3 types frontotemporal dementia

- Behavioral variant
- Language variants
  - Semantic variant
  - Non-fluent variant
Nonfluent variant PPA (nfvPPA)
left posterior frontoinsular atrophy

• Agrammatism
• Effortful, halting speech with sound errors and distortions
• Impaired comprehension of complex sentences
• Spared single word comprehension
• Spared object knowledge
Nonfluent variant PPA (nfvPPA)
3 types frontotemporal dementia

- Behavioral variant
- Language variants
  - Semantic variant
  - Non-fluent variant
3 more types of frontotemporal dementia...

- FTD with motor neuron disease (FTD-MND)
- Progressive supranuclear palsy syndrome (PSP-S)
- Corticobasal syndrome (CBS)
FTD with motor neuron disease (FTD-MND)

- Amyotrophic lateral sclerosis (ALS)
  - 10% of FTD patients develop ALS
  - Most ALS patients develop cognitive impairment

- Progressive muscle weakness and degeneration leading to death within 3 years on average
Progressive supranuclear palsy syndrome (PSP-S)
Richardson’s syndrome

- Early falls
- Eye movement abnormalities
- Axial rigidity
- Parkinsonian features not responsive to L-DOPA
- Executive dysfunction
- Increased impulsivity
- Disrupted sleep pattern
Corticobasal syndrome (CBS)

- Asymmetric limb rigidity, dystonia, myoclonus
- Oral or limb apraxia
- Cortical sensory deficits
  - astereognosis
  - agraphesthesia
- Alien-limb phenomenon
FTLD-tau: the tauopathies (40% of FTLD)

Pick’s disease

Progressive supranuclear palsy

Corticobasal degeneration

Pick bodies

Tufted astrocyte

Astrocytic plaque
Frontotemporal lobar degeneration (FTLD)

- FTLD-tau
  - Pick's 3R tau
  - CBD 4R tau
  - PSP 4R tau
  - FTDP-17 (MAPT)
  - Other (CTE, AGD, MST)

- FTLD-TDP*
  - Type A
    - (PGRN) (C9orf72)
  - Type B
    - (C9orf72) (TARDP?)
  - Type C
  - Type D
    - VCP
  - Type U
    - (C9orf72)

- FTLD-FUS
  - aFTLD-U
  - BIBD

- FTLD-3 (CHMP2b)
  - NIFID
  - ??? (FUS)

Alzheimer's Disease

svPPA, nfvPPA, FTD-MND, CBS, PSPS

Mackenzie harmonized scheme, 2011
FTLD-TDP43 (55% of FTLD)

Type A

Type B

Type C

Type D
FTLD-FUS: the FUS-opathies (<5% of FTLD)

Atypical FTLD with very early age at onset

Frontotemporal lobar degeneration (FTLD)

FTLD-tau
- Pick's 3R tau
- CBD 4R tau
- PSP 4R tau
- FTDP-17 MAPT
- Other CTE, AGD, MST

FTLD-TDP*
- Type A (PGRN) (C9orf72)
- Type B (C9orf72) (TARDP?)

FTLD-FUS
- aFTLD-U
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FTLD-3 CHMP2b

Alzheimer's Disease

svPPA

nfvPPA

FTD-MND

CBS

PSPS

FTD-MND

bvFTD

nfvPPA

FTD-MND

CBS

PSPS

FTD-MND

bvFTD

nfvPPA

FTD-MND

CBS

PSPS

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PSPS

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Neurodegeneration of aging

Limbic-predominant age-related TDP-43 encephalopathy (LATE)

25% of cases in dementia autopsy series

Nelson et al. Brain 04/30/2019
Brain atrophy associated with autopsy-confirmed LATE-NC: Data from Rush University ROS-MAP community-based autopsy cohorts
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Neuropathological lesions in the very old: results from a large Brazilian autopsy study

Suemoto et al. Brain Pathology 2019
Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated


BRAIN 2018: 141; 2181–2193
Table 2 Prevalence of co-pathologies by neurodegenerative disease group

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Proteinopathy</th>
<th>Co-pathology prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tau</td>
<td>Amyloid-β</td>
</tr>
<tr>
<td>Minimal</td>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>MPG</td>
<td>72</td>
<td>67</td>
<td>93</td>
</tr>
<tr>
<td>Amyloid-β</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iAD</td>
<td>46</td>
<td>46</td>
<td>100</td>
</tr>
<tr>
<td>hAD</td>
<td>201</td>
<td>201</td>
<td>100</td>
</tr>
<tr>
<td>Tau</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PiD</td>
<td>15</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>CBD</td>
<td>29</td>
<td>29</td>
<td>100</td>
</tr>
<tr>
<td>PSP</td>
<td>51</td>
<td>51</td>
<td>100</td>
</tr>
<tr>
<td>TDP-43</td>
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<tr>
<td>ALS</td>
<td>108</td>
<td>95</td>
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<td>FTLD-TDP</td>
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<td>hTDP</td>
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<tr>
<td>α-Synuclein</td>
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<tr>
<td>MSA</td>
<td>26</td>
<td>24</td>
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<tr>
<td>bLBD</td>
<td>20</td>
<td>19</td>
<td>95</td>
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<tr>
<td>ILBD</td>
<td>37</td>
<td>37</td>
<td>100</td>
</tr>
<tr>
<td>nLBD</td>
<td>81</td>
<td>81</td>
<td>100</td>
</tr>
</tbody>
</table>

MPG = minimal pathology group.
Table 2

A statistical analysis of attributable risk from research volunteers in two clinical-pathological studies of ageing from Rush University

<table>
<thead>
<tr>
<th>Neuropathological indices</th>
<th>Fraction attributable % (95% CI)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease (ADNC)</td>
<td>39.4 (31.5–47.4)</td>
</tr>
<tr>
<td>Vascular disease pathology$^b$</td>
<td>24.8 (17.3–32.1)</td>
</tr>
<tr>
<td>LATE-NC</td>
<td>17.3 (13.1–22.0)</td>
</tr>
<tr>
<td>α-Synucleinopathy/Lewy body pathology</td>
<td>11.9 (8.4–15.6)</td>
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Chronic traumatic encephalopathy
Chronic traumatic encephalopathy

• 99% autopsy prevalence among NFL players
• multiple repeated head trauma/concussions is highest risk factor
• can present as a behavioral syndrome
  • irritability
  • explosive aggressive behavior
  • depression leading to suicide
• can manifest as a late-onset amnestic syndrome indistinguishable from Alzheimer’s disease
• Prevalence is possibly 1/3 in subject with significant h/o contact sport participation and virtually absent in subject with no contact sport history regardless of h/o single head trauma
Take home messages

• Alzheimer’s disease is the most common but not the only cause of dementia throughout the lifespan
• Frontotemporal dementias are as common as AD in subjects aged 65 and more common than AD in people younger than 60-year old
• Dementia is very unlikely caused by a single pathologic process
• Coexistence of multiple pathologies is the rule, and their number increases with age
• The likelihood of developing cognitive symptoms is directly associated with the number of different diseases together affecting the same brain
• Chronic traumatic encephalopathy is a newly recognized cause of cognitive impairment. Its impact is high in subjects with h/o contact sports but likely minimal in subjects with no h/o repeated head trauma
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