White matter hyperintensities correlate with neuropsychiatric manifestations of Alzheimer’s disease and frontotemporal lobar degeneration

Annual Scientific Meeting - Canadian Geriatric Society

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Presenter Disclosure

Philippe Desmarais, MD, FRCPC, MHSc (c)

- Relationships with financial sponsors: *none*
Presenter Disclosure

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Mitigating Potential Bias

Philippe Desmarais, MD, FRCPC, MHSc (c)

- The sponsors of the study had no role in the study design, data collection, data analysis, or data interpretation.
Background

Alzheimer’s disease (AD)
- Most prevalent neurocognitive disorder with advancing age
- Neuropsychiatric manifestations are frequent and distressing

Frontotemporal lobar degeneration (FTLD)
- Multiple neurodegenerative pathologies with overlapping clinical features
- Various cognitive, neuropsychiatric, and motor manifestations
- Clinical phenotypes:
  - Behavioural variant frontotemporal dementia (bvFTD);
  - Primary Progressive Aphasia (PPA);
  - Corticobasal syndrome (CBS);
  - Progressive supranuclear palsy (PSP).
Background

Gray matter atrophy and clinical manifestations

- Mesial temporal atrophy ➔ episodic memory and learning deficits
  
- Orbitofrontal atrophy ➔ disinhibition, impulsivity

White matter changes

- White matter hyperintensities (WMHs) were associated in AD with:
  
  ➔ *executive dysfunction*
  
  ➔ *mental processing speed impairment*
  
  ➔ *memory deficits*

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Objective

To better understand the relationships between regional white matter hyperintensities and neuropsychiatric symptoms in patients with sporadic Alzheimer’s disease and frontotemporal dementia and related disorders.
Study Design

Cohort series from the Sunnybrook Dementia Study

- Ongoing longitudinal study of subjects with/without cognitive impairment
- Subjects undergo extensive assessments:
  - Neuropsychological batteries: MMSE, MoCA, DRS, and various other tests;
  - Neuropsychiatric batteries: NPI, BEHAVE-AD;
  - Genetic testing: APOEε genotype, others;
  - Brain imaging: standardized MR and SPECT imaging.
Case Selection

Retrospective selection and analysis of autopsy-confirmed cases of:

- Alzheimer’s Disease (AD);
- Frontotemporal dementia (FTD) due to:
  - Tau proteinopathy (i.e. Pick’s disease);
  - TDP-43 proteinopathy;
- Progressive supranuclear palsy (PSP);
- Corticobasal degeneration (CBD).

As well as healthy controls (HC) for comparison purposes.
Data Collection

- Demographic data: sex, age, education level
- Comorbidities: vascular risk factors and cardiovascular events
- Disease: age at onset, age at assessment, pathology findings
- Baseline neuropsychological & neuropsychiatric results:
  - Neuropsychiatric inventory (NPI): total score, caregiver score, and 12 subscale items
- Baseline brain imaging volumetrics obtained on a 1.5 Tesla GE Signa system:
  - T1-, T2-, and PD-weighted axial cuts;
  - 3 mm slice thickness.
Imaging Analysis

- **MR imaging processing included:**
  - Segmentation and parcellation procedures\(^1\);
  - Volumetrics for regional and whole-brain regions;
  - Values adjusted for total intracranial volume (TIV).

\(^1\) Ramirez et al., *NeuroImage*, 2011
Data Analysis

- Linear regressions:
  - dependent variables = items of the NPI;
  - predictors = regional WMH volumes;
  - covariates = age, sex, educational level, and corresponding regional GM volumes
- Statistical analyses were performed with IBM® SPSS® Statistics 24.0
Identified Cases

Sunnybrook Dementia Study

- 53 FTLD cases
  - 27 FTD
    - 17 FTD
      - TDP43α
    - 10 FTD
      - tau
  - 11 CBD
    - 11 CBD
      - tau
  - 15 PSP
    - 15 PSP
      - tau
- 15 AD cases
- 35 HC
## Results

### Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FTLD-TDP 43 FTD (n = 17)</th>
<th>FTLD-tau FTD (n = 10)</th>
<th>FTLD-tau CBD (n = 11)</th>
<th>FTLD-tau PSP (n = 15)</th>
<th>AD (n = 15)</th>
<th>HC (n = 35)</th>
<th>P - value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>8 (47%)</td>
<td>4 (40%)</td>
<td>8 (73%)</td>
<td>6 (40%)</td>
<td>5 (33%)</td>
<td>14 (40%)</td>
<td>0.449</td>
</tr>
<tr>
<td>Hand dominance, R/L/A</td>
<td>16/0/1</td>
<td>7/2/1</td>
<td>10/1/0</td>
<td>13/1/1</td>
<td>15/0/0</td>
<td>16/0/1</td>
<td>0.512</td>
</tr>
<tr>
<td>Education in years, mean (SD)</td>
<td>14.4 (3.3)</td>
<td>15.4 (4.1)</td>
<td>13.5 (3.2)</td>
<td>15.3 (3.2)</td>
<td>16.0 (5.5)</td>
<td>14.4 (3.3)</td>
<td>0.465</td>
</tr>
<tr>
<td>Age at baseline, mean (SD)</td>
<td>66.8 (9.5)</td>
<td>67.4 (9.6)</td>
<td>67.4 (6.6)</td>
<td>71.4 (5.3)</td>
<td>69.1 (10.0)</td>
<td>71.2 (7.8)</td>
<td>0.381</td>
</tr>
<tr>
<td>Age at onset of symptoms, mean (SD)</td>
<td>63.6 (9.3)</td>
<td>63.5 (11.1)</td>
<td>63.9 (6.0)</td>
<td>68.3 (5.8)</td>
<td>65.6 (10.5)</td>
<td>..</td>
<td>0.549</td>
</tr>
<tr>
<td>Disease duration, mean (SD)</td>
<td>3.2 (1.4)</td>
<td>3.9 (3.7)</td>
<td>3.6 (1.7)</td>
<td>3.1 (1.7)</td>
<td>3.6 (2.2)</td>
<td>..</td>
<td>0.881</td>
</tr>
<tr>
<td>MMSE (/30), mean (SD)</td>
<td>21.8 (7.0)</td>
<td>16.9 (10.6)</td>
<td>21.9 (5.8)</td>
<td>24.1 (6.2)</td>
<td>19.9 (6.4)</td>
<td>28.9 (0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Genotype APOE ε4+, n/N (%)</td>
<td>6/12 (50%)</td>
<td>1/9 (11%)</td>
<td>0/8 (0%)</td>
<td>2/12 (17%)</td>
<td>6/13 (46%)</td>
<td>2/6 (33%)</td>
<td>0.067</td>
</tr>
<tr>
<td>Vascular risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (29%)</td>
<td>2 (20%)</td>
<td>3 (27%)</td>
<td>5 (33%)</td>
<td>4 (27%)</td>
<td>9 (26%)</td>
<td>0.988</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4 (24%)</td>
<td>0 (0%)</td>
<td>3 (27%)</td>
<td>2 (13%)</td>
<td>6 (40%)</td>
<td>1 (3%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>2 (18%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Data are n (%) and mean (SD). All percentages were rounded to the nearest whole number.

* P-value for One-Way ANOVA.
Results

Neuropsychiatric symptoms at baseline

Total NPI score

One-Way ANOVA  \( P = 0.004 \)

Caregiver score

One-Way ANOVA  \( P = 0.069 \)
Results

Neuropsychiatric symptoms at baseline

![Graph showing mean scores for various symptoms at baseline.](image)

- Delusions
- Hallucinations
- Agitation
- Depression
- Anxiety
- Euphoria
- Apathy
- Disinhibition
- Aberrant motor behaviours
- Irritability
- Night time behaviours
- Appetite/eating changes

*Mean score (points)*

* p < 0.05

- **TPD-43** - FTD
- Tau - FTD
- Tau - CBD
- Tau - PSP
- AD

**Note:** Specific symptoms and their comparison for TPD-43, FTD, Tau, CBD, PSP, and AD are depicted in the graph. The asterisk (*) indicates significance at p < 0.05.
Results

Volumetrics at baseline

Healthy controls

Normal gray matter

Normal white matter

White matter hyperintensity

$\text{Volumetrics (mm}^3\text{)}$

$\text{Age (years)}$

$r = 0.002$

$p = 0.783$

$r = 0.172$

$p = 0.016$

$r = 0.395$

$p < 0.0001$
Results

Volumetrics at baseline

Neurodegenerative disorders

![Graphs showing volumetrics at baseline for normal gray matter, normal white matter, and white matter hyperintensity.](image_url)
Results

White Matter Hyperintensities

Data were adjusted for total intracranial volume. * Student’s T-test p < 0.05 compared to HC.
**Results**

**White Matter Hyperintensities**
Clinico-radiological Correlations

Anxiety & WMH:

- TDP-43+ cases: right medial frontal
  \( \beta = +0.431, p = 0.008 \)

- PSP cases: left lateral frontal
  \( \beta = +0.720, p = 0.004 \)

- AD cases: right lateral frontal
  \( \beta = +1.315, p = 0.012 \)
Clinico-radiological Correlations

Euphoria & WMH:

- TDP-43+ cases: left medial frontal
  - $\beta = +0.901$, $p = 0.015$
- PSP cases: left lateral frontal
  - $\beta = +0.680$, $p = 0.041$
Clinico-radiological Correlations

Eating Changes & WMH:

- TDP-43+ cases: left lateral frontal
  \[ \beta = +0.439, p = 0.023 \]
- PSP cases: left lateral frontal
  \[ \beta = +0.720, p = 0.041 \]
Discussion

Highlights & Interpretation

- FTD due to TDP-43+ was associated with significant increased in total WMHs:
  - Progranulin mutation linked to WMHs\(^1\)

- WMH distribution was different between AD and FTLD pathologies:
  - More frontotemporal regions for TDP-43+
  - More periventricular regions (anteriorly and posteriorly) in AD

- Specific regions of WMHs correlated with specific neuropsychiatric symptoms:
  - Previous positive correlations in psychiatric disorders, such as depression\(^2\) and bipolar disorder\(^3\)
  - White matter changes in frontal region linked to frontostriatal dysfunction\(^4\)

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\(^1\) Caroppo et al., JAMA Neurology, 2014; \(^2\) Firbank, et al., American Journal Geriatric Psychiatry, 2004; \(^3\) Tighe et al., Bipolar Disorder, 2012; \(^4\) MacFall et al., Biological Psychiatry, 2000
Discussion

Strengths

- Large cohort of autopsy-confirmed cases of FTLD
- Quantitative measures of white matter hyperintensities

Limitations

- Underpowered for some subgroup comparisons
- Correlation relationships ≠ causation relationships
  - WMHs → neuropsychiatric sx vs. neuropsychiatric sx → WMHs ?
Future Directions

WMH volumetrics could be used as:

- Diagnostic biomarkers to differentiate between FTD-\(\text{tau}\), FTD-\(\text{TDP-43}\), and AD pathologies
- Surrogate markers for pharmacological trials
- Potential predictive markers for clinical response to psychotropic medications
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Thank you!

Questions?