Factors Associated with Survival Probability in Autopsy-Proven Frontotemporal Lobar Degeneration

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Background: Definition

Frontotemporal lobar degeneration (FTLD):
• Progressive neurodegenerative condition
• Progressive changes in behavior
• Progressive language dysfunction
Background: Brain Regions

- FTLD due to disease of frontal + temporal lobes:
Background: Pathology

- Two major forms of pathology: tau-positive and tau-negative
Background

- FTLD progresses to death more rapidly than Alzheimer’s disease (AD)
- No consensus on the factors contributing to rapid decline in FTLD
Background

Comparison of survival: AD vs FTLD

Product-Limit Survival Function Estimates

Logrank p=0.0004

Time Since Symptom Onset (months)

<table>
<thead>
<tr>
<th></th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>75</td>
<td>100% (75)</td>
<td>0% (0)</td>
<td>108.0 ( 96.0 120.0)</td>
</tr>
<tr>
<td>FTLD</td>
<td>69</td>
<td>100% (69)</td>
<td>0% (0)</td>
<td>75.0 ( 67.0 84.0)</td>
</tr>
</tbody>
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Objective

• Examine factors associated with survival in autopsy-confirmed FTLD
Previous assessments of survival in FTLD:

- Longer survival in tau-positive (Hodges, 2003; Roberson, 2005)
- Equal survival in tau positive + tau negative (Rascovksy, 2005; Josephs, 2005; Kertez, 2005)
Distinct Features of Our Study

• Largest cohort of autopsy-proven FTLD
• Use empirical measure of the actual amount of pathology
• Multivariate analysis of a variety of factors
Inclusion criteria:

• All patients with autopsy-proven FTLD identified at Penn from 1995-2005

• Clinical assessments at Penn or UCSF (N=91)
Study Cohort

Excluded:

• Patients without adequately detailed clinical evaluations (N=15)
• Patients with a clinical diagnosis of motor neuron disease (MND) (N=5).
Study Cohort

• Final analysis cohort included 71 patients with pathologically-proven FTLD.
## Clinical and demographic characteristics of participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Whole Cohort(^4) (N=71)</th>
<th>Tau-negative Group (N=35)</th>
<th>Tau-positive Group (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>34 (48)</td>
<td>16 (46)</td>
<td>18 (50)</td>
</tr>
<tr>
<td>Age at symptom onset (yrs)(^1)</td>
<td>61.0 ± 9.5 (30-80)</td>
<td>60.4 ± 9.5 (43-80)</td>
<td>61.5 ± 9.7 (30-80)</td>
</tr>
<tr>
<td>Education (yrs)(^1,2)</td>
<td>15.0 ± 2.8 (10-20)</td>
<td>14.8 ± 2.6 (10-20)</td>
<td>15.1 ± 3.0 (10-20)</td>
</tr>
<tr>
<td>MMSE at initial clinic visit(^1,2)</td>
<td>23.0 ± 6.8 (4-30)</td>
<td>22.8 ± 6.2 (8-30)</td>
<td>23.2 ± 7.3 (4-30)</td>
</tr>
<tr>
<td>Presence of family history, n (%)(^3)</td>
<td>30 (47)</td>
<td>16 (52)</td>
<td>14 (42)</td>
</tr>
</tbody>
</table>
Survival Time

• Computed from time of symptom onset until death.
  –Symptom onset based on family report of the earliest persistently-abnormal clinical feature
Clinical Signs from Neurological Exam

- Social dysfunction
- Aphasia
- Extrapyramidal features
- Pyramidal signs
Neuropsychological Tests

- Mini-Mental State Examination (MMSE)
- Boston Naming Test
- Animal Fluency
- Word List Recall
- Digit Span Forward
Other factors

- Family history
- Tau haplotype
- Apolipoprotein E genotypic information
Pathology Evaluation

- Semi-quantified Neuropathologic assessment:
  - Tau
  - Amyloid
  - Ubiquitin
- Semi-quantitative grading
  - 0=no or rare pathology
  - 1=low pathology
  - 2=moderate pathology
  - 3=high pathology
Pathology Evaluation: Brain Regions Examined

- Mid-frontal gyrus
- Inferior parietal lobule
- Superior and middle temporal gyri
- Anterior cingulate gyrus
- Hippocampus and entorhinal cortex
- Amygdala
- Thalamus
- basal ganglia
Dichotomized Neuropathology Variables

- Low pathology (grading = 0 or 1)
- Abundant pathology (grading = 2 or 3)
- Cases with low tau pathology are referred to as *tau-negative* (average tau pathology rating ≤ 1)
- Cases with abundant tau pathology are referred to as *tau-positive* (average tau pathology rating ≥ 2)
Pathology Variables Used in Analyses

• Average pathology across all regions for each ascertained protein

• Average pathology reading across tau, ubiquitin, and amyloid for a single brain region
Statistical Analyses

- Survival probabilities from Kaplan-Meier method
- Factors associated with survival from single and multiple covariate Cox proportional hazards regression models:
  - Demographic features
  - Clinical features at the initial visit
  - Neuropsychology variables
  - Family history
  - Genetic
  - Neuropathology features
Results

Median Survival Time Since Symptom Onset

- Whole cohort; CI: 72-84
- tau-; CI: 72-114
- tau+; CI: 60-84
Univariate Factors

- tau-positive pathology had shorter survival than negative pathology
- Hazard ratio of dying = 2.003, 95% CI = 1.209-3.318, p = 0.007
Univariate Factors

Shorter survival time was associated with:

- pathology of any sort in basal ganglia
- pathology of any sort in anterior cingulate
- tau-positive pathology in all cortical region
Multivariate analysis

• Tau Pathology (HR = 3.750, 95% CI: 1.694-8.303; p = 0.001)

• Adjusting for
  – years of education
  – pathology of any sort in basal ganglia
Survival Curves in Tau Pathology Sub-Groups Adjusted for Years of Education and Average Pathology in Basal Ganglia
Discussion: Discrepancies with Other Findings

Some studies have found that tau-negative pathology was associated with shorter survival:

• Previous studies performed only univariate analyses
• Our study used actual empirical burden of tau pathology
• Our cohort had many corticobasal degeneration patients, while other studies had many tau-positive patients with Pick’s disease
Conclusion

• Tau-positive pathology represents a significant risk to survival in FTLD
Reference