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ARTICLE

# Early vs late age at onset frontotemporal dementia and frontotemporal lobar degeneration

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## Abstract

### Objective
To examine clinicopathologic correlations in early vs late age at onset frontotemporal dementia (FTD) and frontotemporal lobar degeneration (FTLD).

### Methods
All patients were clinically evaluated and prospectively diagnosed at the UCSF Memory and Aging Center. Two consecutive series were included: (1) patients with a clinically diagnosed FTD syndrome who underwent autopsy (cohort 1) and (2) patients with a primary pathologic diagnosis of FTLD, regardless of the clinical syndrome (cohort 2). These series were divided by age at symptom onset (cutoff 65 years).

### Results
In cohort 1, 48 (25.3%) were 65 years or older at symptom onset. Pathologic causes of behavioral variant FTD (bvFTD) were similar in the early age at onset (EO) and late age at onset (LO) bvFTD groups. In corticobasal syndrome (CBS), however, the most common pathologic substrate differed according to age at onset: progressive supranuclear palsy (42.9%) in LO-CBS and Alzheimer disease (AD; 40.7%) in EO-CBS. In cohort 2, 57 (28.4%) were classified as LO-FTLD. Regarding FTLD major molecular classes, FTLD with transactive response DNA-binding protein of 43 kDa was most common in EO-FTLD (44.4%), whereas FTLD-tau (58.3%) was most common in LO-FTLD. Antemortem diagnosis of a non-FTD syndrome, usually AD-type dementia, was more frequent in LO-FTLD than EO-FTLD (19.3% vs 7.7%, $p = 0.017$). LO-FTLD was also associated with more prevalent comorbid pathologic changes. Of these, moderate to severe AD neuropathologic change and argyrophilic grain disease were overrepresented among patients who received an antemortem diagnosis of AD-type dementia.

### Conclusion
Patients with FTD and FTLD often develop symptoms after age 65, and age at onset represents an important consideration when making antemortem neuropathologic predictions.

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## Glossary

**Aβ** = β-amyloid; **AD** = Alzheimer disease; **ADNC** = Alzheimer disease neuropathologic change; **AGD** = argyrophilic grain disease; **bvFTD** = behavioral variant frontotemporal dementia; **CAA** = cerebral amyloid angiopathy; **CBD** = corticobasal degeneration; **CBS** = corticobasal syndrome; **EO** = early age at onset; **FTD** = frontotemporal dementia; **FTLD** = frontotemporal lobar degeneration; **FUS** = fused in sarcoma; **HS** = hippocampal sclerosis; **LO** = late age at onset; **MND** = motor neuron disease; **NIA** = National Institute on Aging; **PSP** = progressive supranuclear palsy; **PSPS** = progressive supranuclear palsy syndrome; **svPPA** = semantic variant primary progressive aphasia; **TDP-43** = TAR DNA-binding protein of 43 kDa; **UCSF MAC** = University of California San Francisco Memory and Aging Center; **VBI** = vascular brain injury.

Despite attempts to associate frontotemporal dementia (FTD) clinical syndromes with specific frontotemporal lobar degeneration (FTLD) neuropathologic diagnoses, to date no such correlation has proved invariant.[1–3] In patients with early age at onset (EO) dementia, defined by symptom onset before age 65 years, FTD is a leading diagnosis, possibly as prevalent as Alzheimer disease (AD).[4,5] Much less is known about FTD in older patients. Pathologic studies have suggested that late age at onset (LO) FTLD, which has ranged from 18.6% to 25.6% of FTLD cohorts, was diagnosed less frequently than LO-FTD, ranging from 28.3% to 45.5%,[6–9] suggesting that FTD may be overdiagnosed in older patients. These studies, however, were relatively small (n = 70–117), and did not describe the full picture of non-FTLD pathologic changes.[10,11] Interestingly, revised consensus clinical diagnostic criteria for behavioral variant FTD (bvFTD) were found to be more sensitive in EO than LO bvFTD, perhaps because comorbid non-FTLD pathologic changes influenced the clinical picture.[12] Considering that non-FTLD neurodegenerative changes become more prevalent with age, even in the absence of dementia,[13–15] incorporating these factors is an essential step toward understanding clinicopathologic relationships in EO-FTD and FTLD as compared to LO-FTD and FTLD.

In this study, we aimed to determine whether LO-FTD and LO-FTLD had distinctive clinical and neuropathologic features compared to EO-FTD and EO-FTLD. We also compared the clinicopathologic correlations in EO-FTD and LO-FTD. Finally, we examined the hypotheses that LO-FTLD would be accompanied by more frequent comorbid pathology and that these admixtures would affect the clinician's syndromic diagnosis.

## Methods

### Subjects

#### Cohort 1: Clinically diagnosed FTD spectrum

First, we searched the University of California San Francisco Memory and Aging Center (UCSF MAC) database for patients who had been clinically evaluated between 1998 and 2014, diagnosed with an FTD spectrum clinical syndrome, and then autopsied (figure e-1, links.lww.com/WNL/A254). This strategy identified a consecutive series of 190 autopsied patients, representing 61.7% of the 308 patients with an FTD syndrome who died during the search interval. FTD spectrum illnesses included a behavioral variant (bvFTD), semantic variant primary progressive aphasia (svPPA) and nonfluent/agrammatic variant PPA, FTD–motor neuron disease (MND), progressive supranuclear palsy syndrome (PSPS), and corticobasal syndrome (CBS), and were formulated at a consensus conference based on patient and informant interviews, neurologic examination, and neuropsychological testing. Because patients can meet more than one syndrome's diagnostic research criteria, we used the clinicians' single best-fit syndromic diagnosis, as prospectively documented in all cases. For patients diagnosed prior to a shift in syndromic nomenclature (e.g., semantic dementia to svPPA), the most recent naming convention was assigned to improve clarity of the article. Structural imaging, when available, was used to exclude nondegenerative pathologies and supported the clinical syndromic diagnosis. We selected patients based on the last clinical diagnosis before death.[16,17]

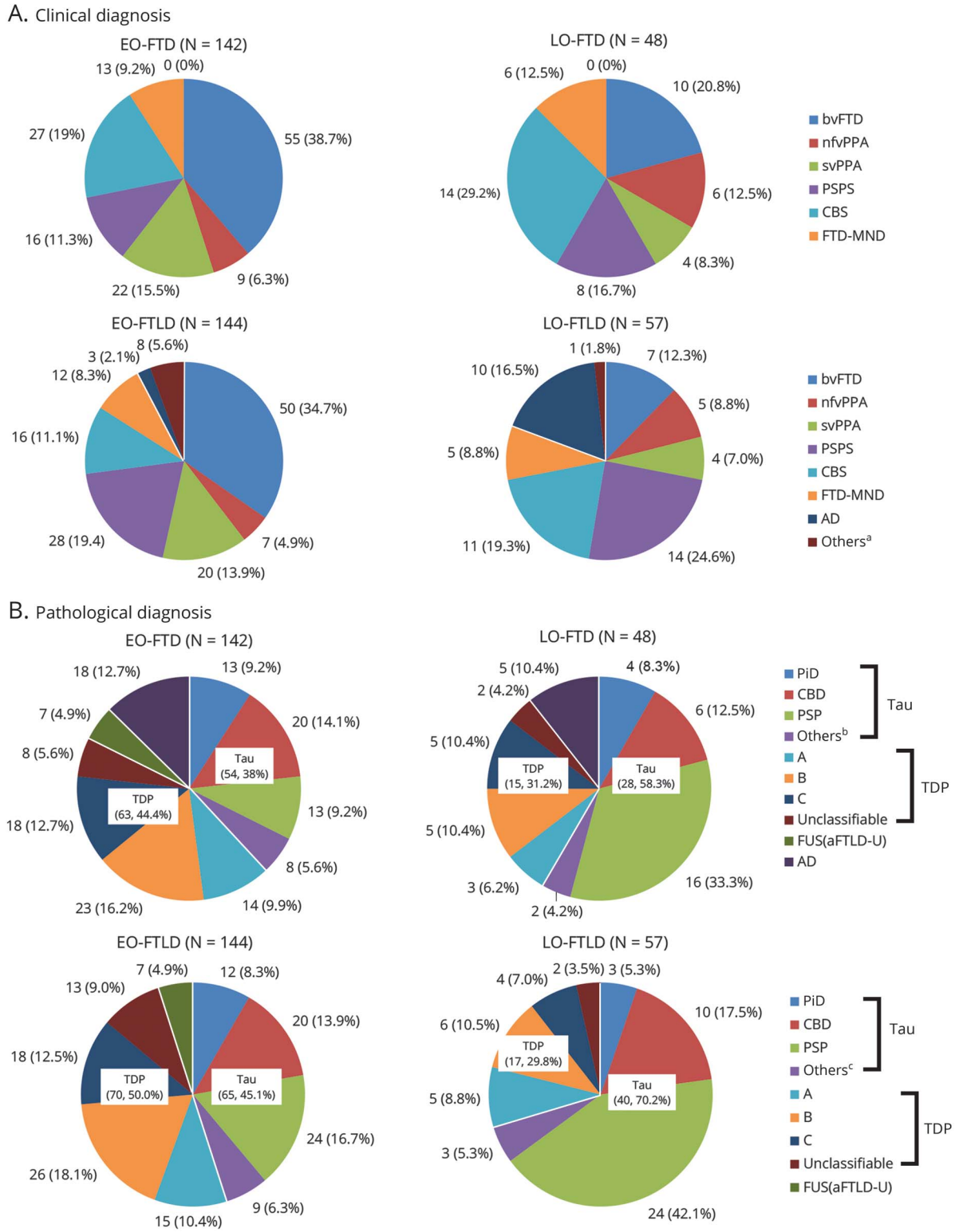
#### Cohort 2: Pathologically diagnosed FTLD spectrum

We searched the UCSF MAC database for patients with a primary neuropathologic diagnosis of FTLD at autopsy regardless of their clinical syndromic diagnosis (figure 1). This search identified a consecutive series of 201 FTLD spectrum cases spanning all major molecular classes (FTLD-tau, TAR DNA binding protein of 43 kDa [TDP-43, FTLD-TDP], and fused in sarcoma protein [FUS, FTLD-FUS]). These pathologic diagnoses were further classified, based on the consensus nomenclature for FTLD,[16,17] as Pick disease, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), FTLD-tau with *MAPT* mutation, multisystem tauopathy, globular glial tauopathy, and unclassified tauopathy for FTLD-tau; TDP-A, TDP-B, TDP-C and unclassifiable TDP (TDP-U) for FTLD-TDP; and atypical FTLD with ubiquitin inclusions for FTLD-FUS. There was one patient whose final diagnosis after reassessment with TDP-43, FUS, and ubiquitin immunohistochemistry remained FTLD with no inclusions. A total of 157 patients were members of both cohorts.

### Age at onset

Patients were divided according to age at onset using a cutoff of 65 years. Age at onset was defined as the age at which

**Figure 1** Clinical and pathologic diagnoses in early age at onset (EO) and late age at onset (LO) frontotemporal dementia (FTD) and frontotemporal lobar degeneration (FTLD) spectrum cohorts




[a]Mild cognitive impairment (1), dementia with Lewy bodies (2), and motor neuron disease only (6). [b]FTLD-tau with *MAPT* mutation (4), multisystem tauopathy (2), and 4R unclassifiable (4). [c]FTLD-tau with *MAPT* mutation (4), multisystem tauopathy (2), 4R unclassifiable (5), and chronic traumatic encephalopathy (1). AD = Alzheimer disease; bvFTD = behavioral variant FTD; CBD = corticobasal degeneration; CBS = corticobasal syndrome; FUS = fused in sarcoma; *MAPT* = microtubule-associated protein tau; MND = motor neuron disease; nfvPPA = nonfluent/agrammatic variant primary progressive aphasia; PiD = Pick disease; PSP = progressive supranuclear palsy; PSPS = progressive supranuclear palsy syndrome; svPPA = semantic variant primary progressive aphasia; TDP-43 = TAR DNA-binding protein 43.

symptoms were first noticed by the patient or a family member. Patients aged 65 years at onset were considered LO. Histograms of age of onset of participants in cohort 1 (A) and cohort 2 (B) are provided in figure e-2 (links.lww.com/WNL/A254).

### Neuropathologic assessment

Brain autopsies were performed at UCSF (n [cohort 1/cohort 2] = 129/147), University of Pennsylvania (49/50), University of Southern California (5/1), Stanford University (2/2), Columbia University (2/0), University of California Davis (1/1), University of California San Diego (1/0), and University of California Irvine (1/0). Pathologic assessments were performed using institution-specific protocols and rendered at consensus conferences, as previously described.[3,18,19] All autopsies included tissue sampling in regions relevant to the differential diagnosis of dementia based on published consensus criteria.[17,20–24] Tissue staining included some combination of hematoxylin & eosin, silver staining with modified Bielschowsky or Gallyas methods, and immunohistochemistry for β-amyloid (Aβ), hyperphosphorylated tau, α-synuclein, ubiquitin, and transactive response DNA-binding protein 43 (TDP-43). AD-related changes were assessed according to the *Thal* amyloid phase,[25] Braak neurofibrillary tangle stage,[26] and Consortium to Establish a Registry for Alzheimer's Disease plaque score.[27] Overall severity of AD neuropathologic change (ADNC) was assigned using the National Institute on Aging (NIA)–Reagan criteria[21] and NIA–Alzheimer Association criteria for AD.[20] Archival cases assessed prior to release of the NIA-AA criteria were re-evaluated to confirm the ADNC level if additional staining was needed and feasible. Where additional staining was needed but not feasible, due to lack of available tissue, we report the range of possible ADNC levels in light of the missing data.

ADNC level was further dichotomized in 2 ways to allow us to compare groups using 2 different AD detection thresholds: (1) not ADNC vs low to high ADNC (low detection threshold) and (2) not to low ADNC vs intermediate to high ADNC (high detection threshold). Coexisting cerebral amyloid angiopathy (CAA), vascular brain injury (VBI), arteriosclerosis, atherosclerosis, argyrophilic grain disease (AGD), Lewy body disease, incidental TDP-43 proteinopathy, and hippocampal sclerosis (HS) were noted when present in the available materials.

### Statistical analysis

Independent sample *t* tests were used to investigate differences in demographics. Fisher exact or $\chi^2$ tests were used to compare groups in terms of clinical and pathologic diagnoses. To investigate differences in the distribution of pathologic diagnoses between EO-CBS and LO-CBS, we performed the Fisher exact test. Also, post hoc analyses were performed using the Fisher exact test with permutation method (n = 1,000) for multiple testing.

To investigate factors affecting AD-type dementia misdiagnosis, logistic regressions were performed in cohort 2 for clinical AD in reference to clinical FTD. In model 1, we entered comorbid (non-FTLD) degenerative pathologic diagnoses as the independent variables and clinical AD (reference to clinical FTD) as the dependent variable after controlling for onset age (continuous variable). In models 2 and 3, we further entered the significant comorbid pathology predictors of clinical AD from model 1 (defined as $p < 0.10$), in order, as independent variables. Among AD-related pathologies, as expected, A and C scores were collinear; we selected C scores for inclusion in the model. Finally, to evaluate the influence of age without a 65-year-old cutoff, we used logistic regression with the frequency of clinical and pathologic diagnoses and comorbid pathologies as dependent variables and age at onset (continuous variable) as an independent variable. Tests were considered significant if they produced $p$ values <0.05 (2-sided tests).

Statistical analyses were performed using the Statistical Package for the Social Sciences 18.0 (SPSS Inc., Chicago, IL).

## Results

### Cohort 1: Clinically diagnosed FTD spectrum

#### Demographics

In cohort 1, 48/190 patients (25.3%) had an age at onset of 65 or greater (LO-FTD) (table 1). In LO-FTD, CBS was the most common clinical diagnosis (29.2%), followed by bvFTD (20.8%) and PSPS (16.7%). In EO-FTD, the most common clinical syndrome was bvFTD (38.7%), followed by CBS (19.0%), and svPPA (15.5%). Direct comparison between EO-FTD and LO-FTD showed that the frequency of bvFTD cases was higher in EO-FTD than in LO-FTD ($p = 0.024$) (figure 1).

#### Clinicopathologic correlation

The most common neuropathologic substrate of LO-FTD was FTLD-tau (58.3%), especially PSP (33.3%), whereas FTLD-TDP (44.4%) was the most common pathologic diagnosis in EO-FTD (figure 1). FTLD-tau overall ($p = 0.014$) and PSP ($p < 0.001$) in particular were significantly more frequent in LO-FTD. Despite increased risk of AD in older individuals, AD was the primary neuropathologic diagnosis at a similar rate in LO-FTD (10.4%) as in EO-FTD (12.7%) (figure 1).

Regardless of onset age, svPPA, PSPS, and FTD-MND suggested specific pathologic diagnoses: TDP-C for svPPA (77.3% and 75.0% in EO-FTD and LO-FTD), PSP for PSPS (75.0% and 87.5%), and TDP-B for FTD-MND (76.9% and 66.7%). bvFTD was associated with the full spectrum of

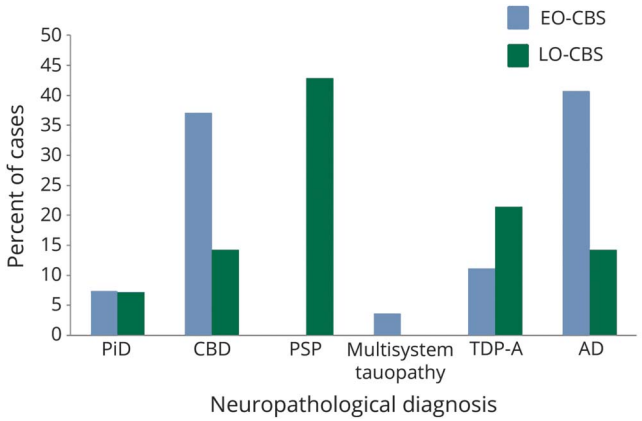
**Table 1** Demographics and pathologic comorbid pathologies in early age at onset (EO) and late age at onset (LO) frontotemporal dementia (FTD) and frontotemporal lobar degeneration (FTLD) spectrum cohorts

| | Cohort 1 (clinically diagnosed FTD) | | | Cohort 2 (pathologically diagnosed FTLD) | | |
|---|---|---|---|---|---|---|
| | EO-FTD (n = 142) | LO-FTD (n = 48) | *p* Value | EO-FTLD (n = 144) | LO-FTLD (n = 57) | *p* Value |
| **Demographics** | | | | | | |
| **Mean age at onset, y** | 55.1 ± 7.2 | 71.4 ± 4.5 | | 54.9 ± 7.9 | 70.9 ± 4.3 | |
| **Mean age at diagnosis, y** | 61.9 ± 7.4 | 76.3 ± 4.8 | | 62.0 ± 7.9 | 76.3 ± 4.7 | |
| **Age at death, y** | 64.2 ± 7.4 | 78.0 ± 5.0 | | 64.1 ± 7.8 | 77.9 ± 4.5 | |
| **Sex, female, n (%)** | 66 (46.5) | 17 (35.4) | 0.182 | 61 (42.4) | 22 (39.6) | 0.625 |
| **Education, y** | 15.8 ± 2.9 | 16.6 ± 2.8 | 0.093 | 15.5 ± 3.9 | 16.4 ± 3.5 | 0.121 |
| **Interval between onset and diagnosis, y** | 6.8 ± 4.9 | 4.9 ± 2.6 | 0.001 | 7.0 ± 6.3 | 5.3 ± 2.6 | 0.004 |
| **Interval between onset and death, y** | 9.1 ± 5.2 | 6.6 ± 2.8 | <0.001 | 9.2 ± 6.6 | 6.9 ± 2.7 | 0.001 |
| **Pathologic comorbid pathologies, n (%)** | | | | | | |
| **AD**[a] | | | | | | |
| **ADNC: low to high** | 78/107 (72.9) | 31/39 (79.5) | 0.418 | 76/110 (69.1) | 36/47 (76.6) | 0.341 |
| **ADNC: intermediate to high** | 22/132 (16.7) | 14/41 (34.1) | 0.016 | 6/134 (4.5) | 14/50 (28.0) | <0.001 |
| **A score of 1–3** | 78/107 (72.9) | 31/39 (79.5) | 0.418 | 76/110 (69.1) | 36/47 (76.6) | 0.341 |
| **A score of 2–3** | 19/82 (23.2) | 10/27 (37.0) | 0.157 | 10/86 (11.6) | 15/36 (41.7) | <0.001 |
| **B score of 1–3** | 86/134 (64.2) | 35/39 (89.7) | 0.002[b] | 82/137 (59.9) | 42/48 (87.5) | <0.001 |
| **B score of 2–3** | 30/132 (22.7) | 17/38 (44.7) | 0.008 | 16/135 (11.9) | 18/48 (37.5) | <0.001 |
| **C score of 1–3** | 47/138 (34.1) | 25/48 (52.1) | 0.027 | 34/139 (24.5) | 26/56 (46.4) | 0.003 |
| **C score of 2–3** | 35/138 (25.4) | 20/48 (41.7) | 0.033 | 19/139 (13.7) | 22/56 (39.3) | <0.001 |
| **CAA** | 26/110 (23.6) | 15/35 (42.9) | 0.028 | 18/112 (16.1) | 16/43 (37.2) | 0.004 |
| **VBI** | 23/111 (20.7) | 8/31 (25.8) | 0.544 | 23/123 (18.7) | 14/39 (35.9) | 0.026 |
| **Arteriosclerosis** | 52/84 (61.9) | 22/26 (84.6) | 0.031 | 54/82 (65.9) | 30/32 (93.8) | 0.002[b] |
| **DLB** | 14/132 (10.6) | 9/45 (20.0) | 0.106 | 14/132 (10.6) | 9/53 (17.0) | 0.323 |
| **AGD** | 21/75 (28.0) | 10/21 (47.6) | 0.089 | 22/76 (28.9) | 17/29 (58.6) | 0.005 |
| **Tau**[c] | 3/88 (3.4) | 4/20 (20.0) | 0.021[b] | 3/62 (4.8) | 4/17 (23.5) | 0.035[b] |
| **HS** | 1/142 (0.7) | 3/48 (6.2) | 0.050[b] | 0/144 (0.0) | 6/57 (10.5) | <0.001[b] |
| **TDP-43**[c] | 2/46 (4.3) | 4/16 (25.0) | 0.034[b] | 2/59 (3.4) | 4/37 (10.8) | 0.201[b] |

Abbreviations: AD = Alzheimer disease; ADNC = Alzheimer disease neuropathologic change; AGD = argyrophilic grain disease; CAA = cerebral amyloid angiopathy; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; DLB = dementia with Lewy bodies; HS = hippocampal sclerosis; TDP-43 = TAR DNA-binding protein 43; VBI = vascular brain injury.
A total of 157 patients overlap between cohort 1 and 2. A score of 1 or 2–3 = *Tha*l amyloid phase 1 or 3–5; B score of 1 or 2–3 = Braak neurofibrillary tangle stage 1 or 3–6; C score of 1 or 2–3 = CERAD neuritic plaque score sparse or moderate to frequent.
[a] AD-related pathologies were categorized in 2 ways: low detection threshold (ADNC: not vs low to high, *Tha* l phase: 0 vs 1–5, Braak stage: 0 vs 1–6, and CERAD: absence vs sparse to frequent) and high detection threshold (ADNC: not to low vs intermediate to high, *Tha* l phase: 0–2 vs 3–5, Braak stage: 0–2 vs 3–6, and CERAD: absence to sparse vs moderate to frequent).
[b] Fisher exact test.
[c] Tau or TDP-43 pathologies in patients who had no primary or contributing diagnoses such as aging-related tau astrogliopathy and incidental limbic TDP-43.

FTLD subtypes and AD, regardless of age at onset (table e-1, links.lww.com/WNL/A255), with the exception that there were no patients with FTLD-FUS in the LO-FTD group. In contrast, age at onset had a greater influence on underlying pathology in CBS. Fisher exact test showed that there were differences in the distribution of pathologic diagnoses between EO-CBS and LO-CBS ($p = 0.003$). Specifically, post hoc analyses revealed that compared to EO-CBS, LO-CBS showed a higher frequency of a pathologic diagnosis of PSP than CBD ($p = 0.002$), while compared to LO-CBS, EO-CBS showed a higher frequency of a pathologic diagnosis of AD than PSP ($p = 0.002$) (figure 2).

**Figure 2** Clinicopathologic correlations in corticobasal syndrome (CBS) according to onset age




AD = Alzheimer disease; CBD = corticobasal degeneration; EO = early age at onset; LO = late age at onset; PiD = Pick disease; PSP = progressive supranuclear palsy; TDP = TAR DNA-binding protein.

## Cohort 2: Pathologically diagnosed FTLD spectrum

### Demographics

In cohort 2, 57 (28.4%) cases were classified as LO-FTLD (table 1). FTLD-tau (70.2%), especially PSP (42.1%), was the most common pathologic diagnosis found in LO-FTLD, whereas FTLD-TDP (50.0%) was the most common in EO-FTLD (figure 1). Direct comparison between EO-FTLD and LO-FTLD showed that the frequency of FTLD-tau ($p$ = 0.001), especially PSP ($p$ < 0.001), was higher in LO-FTLD than in EO-FTLD, while FTLD-TDP was higher in EO-FTLD than in LO-FTLD ($p$ = 0.009, figure 1).

### Clinicopathologic correlation

In pathologically diagnosed FTLD, clinicopathologic correlations showed a similar pattern to that seen in clinically diagnosed FTD (figure 1). Patients with LO-FTLD, however, were more likely than patients with EO-FTLD to have been diagnosed with a non-FTD diagnosis during life (19.3% of LO-FTLD vs 7.6% of EO-FTLD, $p$ = 0.017). In particular, patients with LO-FTLD were more likely to have been clinically diagnosed with AD-type dementia (17.5% vs 2.1%, $p$ < 0.001). This pattern of AD-type dementia misdiagnosis was seen across several LO-FTLD neuropathologic diagnoses, including CBD (n = 3), PSP (n = 2), other FTLD-tau disorders (n = 2), TDP-A (n = 2), and TDP-B (n = 1) (table 2). In patients with LO-FTLD and a non-FTD clinical diagnosis, atypical AD or mixed syndromic diagnoses were common, including frontal variant AD or AD with mixed vascular or PSP syndromes. Among 9 clinically misdiagnosed AD cases with LO-FTLD in whom ADNC could be assessed, 8/9 had at least low ADNC and 5/9 had intermediate or high ADNC. Seven of 8 patients assessed had AGD. AD-type dementia misdiagnosis in EO-FTLD was seen only in FTLD-TDP.

### Comorbid pathologies

Pathologically diagnosed FTLD often coexisted with other neuropathologic changes, especially in LO-FTLD. LO-FTLD more often had moderate to severe ADNC including A, B, and C scores of 2–3 (table 1). The frequencies of CAA, VBI, arteriosclerosis, AGD, miscellaneous tau-related disorders (PSP, CBD, argyrophilic tau astrocyte cluster, nonspecific tauopathy, and chronic traumatic encephalopathy), HS, and TDP proteinopathy (3 limbic only, 2 with comorbid FTLD-TDP, 1 with TDP-43 colocalized PSP lesions) were also higher in LO-FTLD than in EO-FTLD (table 1). These findings are generally consistent with those observed in clinically diagnosed FTD (cohort 1, table 1).

### Factors affecting AD-type dementia misdiagnosis

In model 1 (after controlling for onset age), clinical misdiagnosis of AD-type dementia was associated (defined as $p$ < 0.10) with A scores of 2–3 ($p$ = 0.033), C scores of 2–3 ($p$ = 0.017), and the presence of AGD ($p$ = 0.083) and HS ($p$ = 0.088). Multivariate logistic regression models showed that older onset age, C scores of 2–3, and AGD independently predicted clinical diagnosis of AD. Including these factors explained a significant proportion of the variance in AD misdiagnosis (table 3).

### Sensitivity analyses

As 65 years is a somewhat arbitrary threshold, we used age at onset as a continuous independent variable in logistic regressions with the frequency of clinical and pathologic diagnoses and comorbid pathologies as outcomes. This approach provided results (table e-2, links.lww.com/WNL/A255) that converged with those produced using the 65 years age at onset cutoff.

# Discussion

Consistent with previous studies, roughly one fourth of patients in these large prospectively diagnosed FTD (n = 190) and FTLD (n = 201) cohorts had a symptom onset of age 65 or older. In contrast with previous studies, this study included both FTD and FTLD cohorts and extensive data about comorbid neuropathologic findings, a key issue in older patients. These strengths enabled us to determine that several clinical FTD syndromes strongly predict specific neuropathologic diagnoses regardless of onset age. In addition, we detected differences in clinicopathologic associations in CBS, with younger patients more often showing AD as the neuropathologic substrate and older patients frequently having PSP. Finally, patients with LO-FTLD had more comorbid pathologic burden, including moderate or severe AD, CAA, VBI, arteriosclerosis, AGD, and HS. Older onset age, moderate to severe density of neuritic plaques, and AGD all contributed to an antemortem misdiagnosis of AD-type dementia in patients with underlying FTLD.

**Table 2** Demographic, clinical, and pathologic diagnoses and combined pathologies of Alzheimer disease (AD)–type dementia misdiagnosis

| Cases | Age at autopsy, y | Onset age, y | Sex | Last clinical diagnosis | First clinical diagnosis | Pathologic diagnosis | ADNC level | *Thal* phase | Braak stage | CERAD score | AGD | Other limbic lesions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **EO-FTLD 1** | 72 | 62 | M | AD | AD | TDP-A | Not | 0 | 0 | Absent | NA | |
| **EO-FTLD 2** | 74 | 62 | F | AD | AD | TDP-B | Not | 0 | 0 | Absent | NA | |
| **EO-FTLD 3** | 73 | 58 | F | Frontal variant AD | Frontal variant AD | TDP-unclassifiable | Low | 4 | 1 | Frequent | Limbic | |
| **LO-FTLD 1** | 83 | 77 | M | AD | AD | CBD | Low | 1–3 | 2 | Absent | Limbic | |
| **LO-FTLD 2** | 80 | 75 | F | AD/vascular mixed | AD/vascular mixed | CBD | NA | NA | NA | NA | NA | |
| **LO-FTLD 3** | 77 | 67 | M | Frontal variant AD | bvFTD | TDP-A | Not | 0 | 1[a] | Absent | Limbic | |
| **LO-FTLD 4** | 77 | 70 | F | AD/vascular mixed | AD/vascular mixed | PSP | Intermediate | 4 | 3 | Frequent | Limbic | |
| **LO-FTLD 5** | 83 | 72 | M | AD | AD | CTE | Intermediate | 2 | 4 | Frequent | Limbic | HS, TDP |
| **LO-FTLD 6** | 79 | 71 | F | AD/PSP mixed | PSP | TDP-A | Low | 4–5 | 0 | Frequent | NA | HS |
| **LO-FTLD 7** | 76 | 68 | F | AD | AD | TDP-B | High | 5 | 5 | Frequent | Limbic | |
| **LO-FTLD 8** | 86 | 77 | M | AD/PSP mixed | AD/PSP mixed | PSP | Intermediate | 3–5 | 4 | Frequent | NA | |
| **LO-FTLD 9** | 83 | 77 | M | AD | AD | CBD | Intermediate | 3 | 3 | Frequent | Limbic | |
| **LO-FTLD 10** | 76 | 65 | F | AD/PSP mixed | PSP | Tau4R unclassifiable | Low | 3 | 1 | Frequent | Absent | |

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; CBD = corticobasal degeneration; CTE = chronic traumatic encephalopathy; EO = early age at onset; FTLD = frontotemporal lobar degeneration; HS = hippocampal sclerosis; LO = late age at onset; NA = not applicable; PSP = progressive supranuclear palsy; TDP-43 = TAR DNA-binding protein 43.
[a] Fisher exact test.

**Table 3** Factors affecting Alzheimer disease (AD)–type dementia misdiagnosis

| | OR | *p* Value | $R^2$ |
|---|---|---|---|
| **Model 1** | | | 0.099 |
| **Onset age** | 1.115 | 0.012 | |
| **C score of 2–3** | 5.053 | 0.017 | |
| **Model 2** | | | 0.224 |
| **Onset age** | 1.212 | 0.023 | |
| **C score of 2–3** | 14.087 | 0.011 | |
| **AGD** | 11.165 | 0.049 | |
| **Model 3** | | | 0.228 |
| **Onset age** | 1.226 | 0.021 | |
| **C score of 2–3** | 17.421 | 0.011 | |
| **AGD** | 13.780 | 0.042 | |
| **HS** | 0.360 | 0.529 | |

Abbreviations: AD = Alzheimer disease; AGD = argyrophilic grain disease; FTD = frontotemporal dementia; HS = hippocampal sclerosis; OR = odds ratio.
Logistic regressions were performed in cohort 2 for clinical AD (reference to clinical FTD). In model 1, we entered each mixed degenerative pathology as the independent variable and clinical AD (reference to clinical FTD) as the dependent variable after controlling for onset age. In models 2–3, we additionally entered the resulting statistically significant mixed pathologies in order from model 1 (defined as $p < 0.10$) as independent variables. C scores of 2–3 = Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque score moderate to frequent.

We found that LO-FTD accounted for 25% of all patients within the clinical FTD spectrum who came to autopsy. Some previous clinical studies without autopsy have suggested that 40% of patients with FTD were over 65 years at disease onset, substantially older than previously assumed.[7–9] Our findings, however, are more aligned with a multicenter FTD study based on 353 pathologically confirmed FTLD cases, which observed EO-FTD in 28% of the cohort, which had only minor overlap with patients in the present study.[6] Furthermore, consistent with 2 pathologic studies,[10,11] our pathologically diagnosed FTLD-spectrum cohort had an onset 65 years or greater in 28%. Overall, our findings show that FTLD should not be dismissed as a candidate cause of an FTD syndrome in older patients.

A previous study based on pathologically diagnosed FTLD suggested no differences in the histopathologic disease spectrum between EO-FTLD and LO-FTLD.[11] The differences between our findings and those of this previous study might relate to differences in study population, as previous work did not include patients with CBS/PSPS or PSP pathology.[9,11] Given, however, that most tau-negative patients have underlying FTLD-TDP, our findings are consistent with a previous study showing that FTLD-tau patients were older at presentation than tau-negative patients.[2] Finally, we found no patient with FTLD-FUS whose symptoms began after 55 years, although patients with LO-FTLD-FUS have been rarely reported in the literature.[11,28]

Consistent with previous studies,[2] we found that some clinical FTD syndromes are better correlated with specific pathologies than others regardless of age at onset: TDP-C for svPPA, PSP for PSPS, and TDP-B for FTD-MND. bvFTD, in contrast, was correlated with diverse FTLD pathologic subtypes regardless of age at onset. Perhaps most importantly, we found just over 10% of clinically diagnosed FTD was due to AD pathology regardless of onset age. Patients with CBS contributed most to this issue, with 32% of CBS cases showing AD at autopsy in the overall cohort.

Interestingly, clinicopathologic correlations in CBS differed according to age at onset. Previously, CBS has been associated with multiple underlying pathologies,[29] but our findings showed that 43% of LO-CBS was due to PSP, whereas none of the 15 EO-CBS patients had PSP. Furthermore, in our study, 41% of EO-CBS was due to pathologic AD, whereas just 14% of LO-CBS was due to AD. A previous meta-analysis suggested that about 40% of patients with CBS 60–80 years of age were amyloid PET–positive. Amyloid positivity in CBS decreased, however, by about 20%, in patients aged 80 years and older.[30] This study did not demonstrate, however, that amyloid positivity indicates a primary pathologic diagnosis of AD. Our findings therefore suggest that clinicians should strongly consider AD as an underlying cause of CBS, especially in younger patients.

Compared to EO-FTLD, LO-FTLD had higher rates of mixed pathologic diagnoses, including moderate to severe AD, CAA, VBI, arteriosclerosis, AGD, and HS, which influenced AD-type dementia misdiagnosis in patients with LO-FTLD. Overall, we found a high rate of coexisting ADNC in EO-FTLD (69.1%) and LO-FTLD (76.6%), in contrast with a previous study, which found that only 26% of patients with FTLD showed some Aβ deposition, which was sparse in most instances.[31] This discrepancy might be explained by differences in regional sampling or staining methods. Importantly, LO-FTLD was more often diagnosed as clinical AD than was EO-FTLD (17.5% vs 2.1%). This misdiagnosis rate compares favorably to that reported in a previous LO-FTLD sample[32] (45.5%, 5/11 cases), possibly due to the larger sample size, advances in FTD diagnosis,[12,33] or the advent of AD biomarkers, which were available to clinicians at our center during the later phases of this study and could have influenced diagnostic thinking. In this study, greater densities of neuritic plaques, but not neurofibrillary tangles, predicted the misdiagnosis of clinical AD-type dementia in patients with FTLD. Thus, the presence of moderate to high densities of neuritic plaques may at times lead clinicians away from a diagnosis of FTD in older patients with FTLD evaluated at our center. Consistent with a previous study,[34] the presence of AGD was also associated with AD-type dementia misdiagnosis, perhaps owing to the localization of these pathologic findings to the medial temporal memory system. Interestingly, neuritic

plaques and AGD independently predicted AD-type dementia misdiagnosis regardless of onset age, suggesting that our findings were driven by mixed pathology rather than clinicians' bias toward a clinical AD diagnosis in older patients. Furthermore, combining these mixed pathologies had an additive effect on the prediction of AD-type dementia misdiagnosis. The higher rate of comorbid neuropathologic changes in LO-FTLD vs EO-FTLD is not surprising given the strong correlation between these changes and aging.[13–15,32]

The major limitations of this study relate to the small sample sizes within subsets of patients with early vs late age at onset for each clinical or pathologic diagnosis. Some archival cases were not assessed as completely as more recent cases and could not be reassessed due to the lack of appropriate materials. Furthermore, an age cutoff of 65 years is a conventional but arbitrary threshold for partitioning early and late age at onset FTD. As shown in figure e-2 (links.lww.com/WNL/A254), our sample had a unimodal age distribution, and a cutoff of 65 years corresponds to roughly the top quartile for age at onset in our cohort 1 (65 years) and cohort 2 (66 years). Clinical articles often compare the top quartile with the rest of the sample to show the characteristics of the 2 groups. Concerns about the arbitrariness of the cutoff are mitigated to some degree by our sensitivity analyses, which produced a similar overall pattern of results when modeling age at onset as a continuous independent predictor variable. Furthermore, inclusion of this cutoff here will enable comparisons to previous studies that used this approach.[7–9,11,32] Despite these caveats, this study represents one of the largest consecutive series of autopsied patients with FTD or FTLD to date and provides important insights into the causes of FTD across the lifespan. Our findings should raise awareness of FTD in the geriatric population and help improve antemortem prediction of pathology. The wide variety of pathologies underlying the FTD clinical spectrum emphasizes the need for molecule-specific biomarkers to improve antemortem prediction and the purity of future clinical trial cohorts.

## Author contributions

Conception and design of the study: S.W.S., M.-P.T., W.W.S., H.J.R. Acquisition and analysis of data: S.W.S., M.-P.T., D.C.P., A.H., M.S., I.S., J.N.S.V., S.E.G., G.D.R., K.D., A.L.B., J.H.K., H.J.R., M.L.G.-T., L.T.G., E.J.H., S.J.D., J.Q.T., B.L.M., W.W.S. Drafting of the manuscript: S.W.S., J.Q.T., M.-P.T., D.C.P., J.N.S.V., B.L.M., W.W.S. Obtained funding: J.Q.T., W.W.S., B.L.M. Study supervision: W.W.S., B.L.M.

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## Disclosure

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## References

1. Knopman DS, Boeve BF, Parisi JE, et al. Antemortem diagnosis of frontotemporal lobar degeneration. Ann Neurol 2005;57:480–488.
2. Josephs KA, Petersen RC, Knopman DS, et al. Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP. Neurology 2006;66:41–48.
3. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal dementia: clinicopathological correlations. Ann Neurol 2006;59:952–962.
4. Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol 2003;62:1087–1095.
5. McMurtray A, Clark DG, Christine D, Mendez MF. Early-onset dementia: frequency and causes compared to late-onset dementia. Demen Geriatr Cogn Disord 2006;21:59–64.
6. Johnson JK, Diehl J, Mendez MF, et al. Frontotemporal lobar degeneration: demographic characteristics of 353 patients. Arch Neurol 2005;62:925–930.
7. Borroni B, Agosti C, Bellelli G, Padovani A. Is early-onset clinically different from late-onset frontotemporal dementia? Eur J Neurol 2008;15:1412–1415.
8. Shinagawa S, Toyota Y, Ishikawa T, et al. Cognitive function and psychiatric symptoms in early- and late-onset frontotemporal dementia. Demen Geriatr Cogn Disord 2008;25:439–444.
9. Ye BS, Choi SH, Han SH, et al. Clinical and neuropsychological comparisons of early-onset versus late-onset frontotemporal dementia: a CREDOS-FTD study. J Alzheimers Dis 2015;45:599–608.
10. Shi J, Shaw CL, Du Plessis D, et al. Histopathological changes underlying frontotemporal lobar degeneration with clinicopathological correlation. Acta Neuropathologica 2005;110:501–512.
11. Baborie A, Griffiths TD, Jaros E, et al. Pathological correlates of frontotemporal lobar degeneration in the elderly. Acta Neuropathol 2011;121:365–371.
12. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134:2456–2477.
13. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol 2011;70:960–969.
14. Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging 1991;12:295–312.
15. Thal DR, Grinberg LT, Attems J. Vascular dementia: different forms of vessel disorders contribute to the development of dementia in the elderly brain. Exp Gerontol 2012;47:816–824.
16. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the work group on frontotemporal dementia and Pick's disease. Arch Neurol 2001;58:1803–1809.
17. Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol 2010;119:1–4.
18. Murray ME, Cannon A, Graff-Radford NR, et al. Differential clinicopathologic and genetic features of late-onset amnestic dementias. Acta Neuropathologica 2014;128:411–421.
19. Magaki S, Yong WH, Khanlou N, Tung S, Vinters HV. Comorbidity in dementia: update of an Ongoing autopsy study. J Am Geriatr Soc 2014;62:1722–1728.
20. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012;8:1–13.
21. Mendez MF, Perryman KM, Miller BL, Swartz JR, Cummings JL. Compulsive behaviors as presenting symptoms of frontotemporal dementia. J Geriatr Psychiatry Neurol 1997;10:154–157.

22. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiol Aging 1998;18:S1–S2.
23. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. Neurology 2005;65:1863–1872.
24. Roman GC, Tatemichi TK, Erkinjuntii T. Vascular dementia: diagnostic criteria for research studies. Neurology 1993;43:250–260.
25. Thal DR, Rüb U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 2002;58:1791–1800.
26. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol 2006;112:389–404.
27. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): part II: standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479–486.
28. Urwin H, Josephs KA, Rohrer JD, et al. FUS pathology defines the majority of tau- and TDP-43-negative frontotemporal lobar degeneration. Acta Neuropathol 2010;120:33–41.
29. Ling H, O'Sullivan SS, Holton JL, et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. Brain 2010;133:2045–2057.
30. Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA 2015;313:1939–1949.
31. Mann DM, McDonagh AM, Pickering-Brown SM, Kowa H, Iwatsubo T. Amyloid beta protein deposition in patients with frontotemporal lobar degeneration: relationship to age and apolipoprotein E genotype. Neurosci Lett 2001;304:161–164.
32. Baborie A, Griffiths TD, Jaros E, et al. Frontotemporal dementia in elderly individuals. Arch Neurol 2012;69:1052–1060.
33. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006–1014.
34. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer disease centers, 2005-2010. J Neuropathol Exp Neurol 2012;71:266–273.

FULL-LENGTH ARTICLE NPub.org/y3voqu

# Early vs late age at onset frontotemporal dementia and frontotemporal lobar degeneration

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## Study question

Does the age at onset in patients with frontotemporal dementia (FTD) or frontotemporal lobar degeneration (FTLD) influence clinicopathologic correlations?

## Summary answer

Age at onset has important implications for antemortem prediction of pathologic diagnosis.

## What is known and what this paper adds

Attempts to associate FTD syndromes with specific FTLD diagnoses have yielded mixed results, but differences related to ages at onset in FTD and FTLD have attracted attention. This study presents findings that elucidate the association between age at onset and the clinicopathologic features of FTD and FTLD.

## Participants and setting

This study identified participants by searching the databases of the University of California San Francisco Memory and Aging Center for patients who were clinically evaluated between 1998 and 2014 and then autopsied. Cohort 1 comprised 190 patients diagnosed with FTD, and Cohort 2 comprised 201 patients with a primary neuropathologic diagnosis of FTLD. There were 157 patients who belonged to both cohorts.

## Design, size, and duration

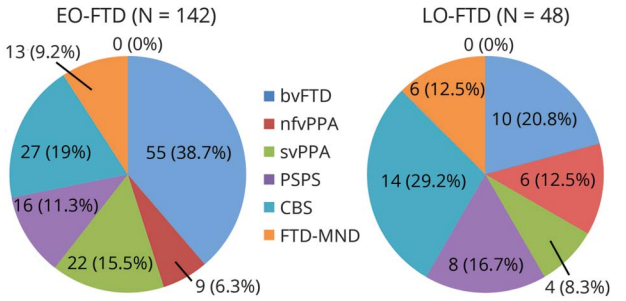
Patients were divided into early-onset (EO) cases with symptom onset before the age of 65 years and late-onset (LO) cases diagnosed later. The patients' brains were autopsied according to institution-specific protocols at various universities.

## Primary outcomes

The primary outcomes were neuropathologic differences between each cohort's EO and LO subgroups.

## Main results and the role of chance

In Cohort 1, 48 (25.3%) patients had LO-FTD. For patients with LO-FTD, the most common specific diagnosis was corticobasal syndrome (29.2%), but for patients with EO-FTD, it was behavioral variant FTD (38.7%). In Cohort 2, 57 (28.4%) patients had LO-FTLD. Compared to patients with EO-FTLD, patients with LO-FTLD were more likely to have an antemortem diagnosis of a non-FTD syndrome (7.7% vs 19.3%, $p = 0.017$).




## Bias, confounding, and other reasons for caution

The study had small sample sizes within patient subsets. Earlier autopsies were sometimes not as thorough as later cases. The cut-off age of 65 years is arbitrary.

## Generalizability to other populations

This study analyzed 2 large cohorts of patients, which provides some confidence in the generalizability of the results.

## Study funding/potential competing interests

This study was funded by the NIH, the Korean National Research Foundation, the Consortium for Frontotemporal Dementia Research, and the Tau Consortium. Dr. Trojanowski and Dr. Seeley received funding from the NIH and various non-profits and revenue from various pharmaceutical companies. Dr. Trojanowski is also a stakeholder in patents submitted by the University of Pennsylvania. Go to Neurology.org/N for full disclosures.

*A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.*