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Title: Mixed neuropathology in frontotemporal lobar degeneration.

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Abstract

AIMS: Frontotemporal lobar degeneration (FTLD) is a significant cause of dementia in mid-life and older adults. The extent of interactions between FTLD and other neurodegenerative pathologies is unclear. We reviewed occurrences of mixed pathology in cases of neuropathologically diagnosed FTLD from the UK Brain Bank Network.

MATERIALS AND METHODS: Clinicopathological details of cases of FTLD were extracted from the UK Brain Bank Network database.

RESULTS: Of 515 cases, 30.10% had mixed neuropathology. Concordance between clinical and neuropathological diagnosis was lower in these cases (38.71% v 59.17%). Alzheimer's spectrum pathology was the commonest additional finding. Age at death was higher in mixed neuropathology cases (mean 76.7 years v 72.59.0 years, $p < 0.005$), increasing in tandem with the number of neuropathologies present.

CONCLUSION: Mixed neuropathology is common in FTLD and associated with increased age at death. Our findings suggest that mixed neuropathology influences age at onset and clinical phenotype in FTLD and makes accurate ante-mortem diagnosis more difficult. Further investigation of interactions between neuropathologies and phenotype is warranted, particularly in view of the potential impact on clinical diagnosis and patient selection for clinical trials.

Keywords:

FTLD

Frontotemporal

Tauopathy

TDP-43

Pick's disease

Dementia

Key Points:

- Mixed neurodegenerative neuropathologies commonly occur with frontotemporal lobar degeneration.
- The likelihood of mixed neuropathology with FTLD increases with older age at death.
- Mixed neuropathology could influence the clinical phenotype of frontotemporal lobar degeneration.

Introduction

Frontotemporal lobar degeneration (FTLD) is a devastating form of dementia affecting both mid-life and older adults(1), and one for which no dedicated therapies currently exist. Developing novel therapeutics demands a paradigm shift from classification by clinical phenotype to classification by detailed neuropathological subtype (2). It is well recognised that different neurodegenerative and vascular pathologies often co-exist(3,4). How neuropathologies interact, and the extent to which additional pathologies are additive or synergistic, are areas of keen interest and occasional controversy(5–7).

The frequency of mixed neuropathology in FTLD is an unstudied area. The proteinopathies underlying FTLD are diverse and can involve TAR DNA binding protein (TDP-43), hyperphosphorylated microtubule-associated protein tau, fused-in-sarcoma (FUS), and possibly other, as yet uncharacterised proteins(8). The clinical manifestations of FTLD are equally extensive, including behavioural and language variants of frontotemporal dementia, progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and exhibiting a significant overlap with amyotrophic lateral sclerosis (ALS)(9,10). A neuropathological diagnosis depends not only upon the presence of abnormal proteins, but their relative severity and brain distribution. The mere presence of TDP-43 does not equate to a diagnosis of FTLD TDP-43; a certain threshold of protein burden and brain distribution must be met. Neuronal TDP-43 inclusions are common in older adults with and without dementia, and frequently accompany Alzheimer's pathology(11,12). Similarly, Alzheimer's pathology occurs across a continuum of severity, and many older adults have neurofibrillary tangles and plaques without fulfilling neuropathological criteria for AD. AD with coincidental TDP-43 deposition is therefore fundamentally different from FTLD TDP-43 with coincidental Alzheimer's pathology.

Abbreviations: AD: Alzheimer's disease; aFTLD-U: atypical FTLD with ubiquitinated inclusions; ALS: amyotrophic lateral sclerosis; ALS-FUS: ALS with fused-in-sarcoma proteinopathy; ALS-TDP: ALS with TDP proteinopathy; CAA: cerebral amyloid angiopathy; CBD: corticobasal degeneration; CBS: corticobasal syndrome; CVD: cerebrovascular disease; FTLD: frontotemporal lobar degeneration; FTLD-FUS: FTLD due to fused-in-sarcoma proteinopathy; FTLD-tau: FTLD due to tau proteinopathy; FTLD-TDP: FTLD due to TDP-43 proteinopathy; FTLD-UPS: FTLD with ubiquitin proteasome system positive inclusions; FUS: fused-in-sarcoma; GGT: globular glial tauopathy; HS: hippocampal sclerosis; LBD: Lewy body disease; MND: motor neurone disease; NIFID: neuronal intermediate filament inclusion disease; PSP: progressive supranuclear palsy; TDP /TDP43: Transactive response (TAR) DNA-binding protein 43.

Relationships between TDP-43 and Alzheimer's pathology are being identified, potentially with a synergistic element. James et al.(12) observed an additive, dose-dependent impact of TDP-43 upon Alzheimer's pathology, with the addition of TDP-43 increasing the likelihood of clinical dementia (increased odds ratio from 4.62 to 6.73).

Understanding how FTLT interacts with other common neuropathologies in the ageing brain is important for diagnosis and prognostication, and critical to current efforts to develop effective dementia therapies. The presence of multiple neuropathologies with potential synergistic interactions may limit the prospects for success in clinical trials of agents targeting only one abnormal protein or pathway.

We reviewed the prevalence of mixed neurodegenerative pathology in patients with a neuropathological diagnosis of FTLT, in a large cohort of individuals whose brains were donated to the UK Brain Banks Network. We analysed the prevalence of co-incident AD, Alzheimer's spectrum changes (not meeting full criteria for AD), CVD, LBD, Lewy body pathology (not meeting full criteria for LBD), HS and the concurrence of dual forms of FTLT. Additionally, we examined the interaction of mixed pathology and age at death.

Materials and Methods

Participants: The UK Brain Banks Network is a consortium of 10 brain banks accepting donations from a wide range of individuals with or without a specific clinical diagnosis. Each brain bank has different donor criteria resulting in a mixed cohort, and due to previous emphasis on specified conditions such as dementia there is a bias towards clinically affected individuals. It is not an entirely representative community sample, but recent efforts to increase the collection of control ('healthy') tissue samples have diversified the sampled population. The UK Brain Banks Network currently holds accessible clinical and post-mortem neuropathological data from over 10,500 people in Scotland and England.

Search criteria: Between August 2016 and January 2017 the UK Brain Bank Network database was searched for terms relating to any form of FTLD. The following search terms were used: amyotrophic lateral sclerosis (ALS); ALS with fused-in-sarcoma proteinopathy (ALS-FUS); ALS with TDP proteinopathy (ALS-TDP); corticobasal degeneration (CBD); FTLD; FTLD due to fused-in-sarcoma proteinopathy (FTLD-FUS); FTLD due to TDP-43 proteinopathy (FTLD-TDP); FTLD-TDP types A, B or C; TDP-43 pathology with AD/other disease/ageing; FTLD due to tau proteinopathy (FTLD-tau); atypical FTLD with ubiquitinated inclusions (aFTLD-U); FTLD with ubiquitin proteasome system positive inclusions (FTLD-UPS); Globular glial tauopathy (GGT); Motor neuron disease (MND)/ALS or FTLD gene mutation/polymorphism; Movement disorder with tau pathology; neuronal intermediate filament inclusion disease (NIFID); Pick's disease; progressive supranuclear palsy (PSP). Mutations of the following genes were searched for: *CHMP2B*; *FUS*; *GRN*; *OPTN*; *SOD1*; *SQSTM1*; *TARDBP*; *UBQLN2*; *VAPB*; *C9ORF72* repeat expansion. Cases who died prior to 1990 were excluded.

The category terms are those used in the UK Brain Bank Network database, some of which overlap. Duplicate results were removed after case ascertainment. Cases with a primary diagnosis of argyrophilic grain disease or primary age-related tauopathy were excluded as these do not typically cause clinical frontotemporal dementia. 1 FTD case with co-existent Down's syndrome was excluded due to uncertainty over the primary cause of dementia. All cases were screened to ensure that the neuropathological diagnosis included FTLD and there was clinical evidence of dementia. Cases with sporadic or genetic ALS/MND without evidence of FTLD were excluded. Cases where FTLD was a secondary neuropathological diagnosis were included.

Neuropathological classification: Neuropathology reports were searched for findings of FTLD, ALS/MND, AD, LBD, CAA, HS and CVD. FTLD neuropathological subtype was recorded, as per current diagnostic criteria(13–18).

The UK Brain Bank Network has harmonised diagnostic protocols, based on the assessment of 13 core formalin-fixed paraffin-embedded blocks (frontal BA46, cingulate BA32/24, superior temporal

BA41/42, amygdala, anterior hippocampus, posterior hippocampus, striatum, thalamus, posterior parietal lobule BA39, primary visual cortex BA17, cerebellar cortex, midbrain, pons, medulla, spinal cord- cervical, thoracic and lumbar). Each block is stained with haematoxylin and eosin and stained with luxol fast blue/cresyl violet. Immunohistochemistry for A β , α -synuclein, phosphorylated TDP-43, etc. is assessed using same antibody clones in each bank. Standard criteria are applied for staging of disease: NIA-AA criteria for Alzheimer's disease(13) including Braak tangle stages(14,15) and Thal amyloid phases(16) and Braak staging of Lewy body diseases(17).

Frontotemporal lobar degeneration (FTLD) is assessed according to MacKenzie et al., 2010(18); in case of FTLD with TDP-43 pathology according to McKenzie et al., 2011(19). Cerebral vascular pathology is assessed according to Skrobot OA et al., 2016(20).

The UK Brain Banks use morphological and immunohistochemical criteria to diagnose MND, as described in Greenfield's Neuropathology(21). The morphological features are motor neuron atrophy and loss and associated astrogliosis, discernible in the anterior horns of the spinal cord, the motor nuclei in the brain stem, and sometimes the primary motor cortex; eosinophilic (rarely basophilic) inclusion bodies within some motor neurons in affected regions; variable corticospinal tract degeneration discernible on staining for myelin and axons. Immunohistochemistry reveals ubiquitin-immunopositive neuronal inclusions in most cases (the inclusions are often also immunopositive for TDP-43 but in some forms of MND may be immunopositive for FUS or neurofilament proteins) and the use of macrophage markers facilitates the detection of corticospinal tract degeneration.

Cases were divided into those for which the sole neuropathological finding was a single type of FTLD ('single neuropathology' cases), and those where FTLD co-existed with other neuropathology that may or may not have contributed to the neurological disease ('mixed neuropathology' cases). This would include (for example) mild vascular disease, or cases with Lewy Body pathology confined to the brain stem, or neurofibrillary tangle pathology limited to the inferomedial part of the

temporal lobe. Small vessel arteriopathy, small and large infarcts were grouped together as CVD. CAA, HS and other findings were listed separately. MND was not considered to be an additional pathology as this is thought to be part of a disease continuum with FTLD-TDP, but HS was. Individuals with neuropathological evidence of more than one type of FTLD were classed as having mixed neuropathology. The presence of malignancy or previous traumatic brain injury was not considered to be an additional pathology in the context of this study.

The number of neuropathologies present was summed (including the type of FTLD present, therefore the minimum number of neuropathologies was 1). Age at death was extracted from the database.

The clinical diagnosis at the time of death was reviewed, and assessed for concordance with the primary neuropathological diagnosis. Cases were considered to show 'partial concordance' if the clinical diagnosis did not match the primary neuropathological diagnosis, but there were secondary neuropathological findings in line with the clinical diagnosis. For example, an individual clinically diagnosed with vascular dementia in whom the primary neuropathological finding was CBD, with additional vascular pathology.

Statistical analysis: Data were assessed for normality using the Kolmogorov–Smirnov test.

Comparison between age at death in mixed and single neuropathology cases was made using paired t-test (normally distributed data) or Mann Whitney U test (non-normally distributed groups). The GGT and FTLD-tau groups were not independently analysed due to small group sizes. Pearson's chi-square test was used for contingency table analyses. Differences in age at death between groups with different numbers of neuropathologies were analysed using Kruskal-Wallis test; Bonferroni adjustment was used for post-hoc Dunn's pairwise comparisons. All statistical analyses were carried out in IBM SPSS Statistics Version 23.

Results

A total of 515 cases of neuropathologically confirmed FTLD were identified. The majority of cases were due to FTLD-tau (359 cases, 69.71%), followed by FTLD-TDP (139 cases, 26.99%). FUS pathology was much rarer, with only 7 cases (1.36%) identified. Other causes included DLDH, and FTLD-UPS. FTLD-UPS is typically due to a *CHMP2B* mutation but apparently sporadic cases have been reported. Genetic analysis was not available for either of the 2 FTLD-UPS cases included here. 20 further cases of genetic FTLD were found (12 *C9ORF72* repeat expansion, 6 *MAPT* mutations and 2 *GRN* mutations). The proportion of each group with mixed neuropathology is shown in Table 1. Overall age at death was similar in FTLD-TDP (mean 72.89 years) and FTLD-tau cases (mean 74.71 years). However, mixed neuropathology was commoner in FTLD-TDP (48.94%) than FTLD-tau (23.68%) (Pearson's chi-square $p < 0.005$).

A small number of cases had evidence of more than one FTLD-related neuropathology. A primary tauopathy and secondary TDP-43 deposition was recorded in 9 cases, whilst 4 had a primary diagnosis of FTLD-TDP but with additional tauopathy (in 3 instances this had features of PSP). In 1 case both PSP and CBD were reported, and in a further case FUS and tau pathology co-existed. LBD was seen in 13 cases: with PSP in 2 cases, CBD in 4, Pick's disease in 1 and TDP-43 in 4 sporadic and 2 genetic cases (1 with a progranulin mutation and 1 with C9ORF72 repeat expansion). LBD was described as the primary pathological feature in the 2 cases with PSP and 3 of the CBD cases.

Table 2 shows the prevalence of different neuropathologies within sub-types of FTLD. Changes on the AD spectrum (not meeting consensus criteria for AD itself) were very common, affecting almost half of the mixed cases. AD itself was less frequent. Vascular disease (including small vessel disease, lacunar or large infarcts) was almost as common as Alzheimer's type changes. No cases of with co-existent vascular dementia were found. Lewy bodies and LBD were infrequent findings. HS was more than twice as prevalent with FTLD-TDP as with FTLD-tau. The number of neuropathologies recorded in addition to FTLD was between 1 and 5 (only 1 individual had 5 additional neuropathologies). Most of those with mixed neuropathology had 1 or 2 additional neuropathologies.

Overall those with mixed neuropathology died at an older age than those with isolated FTLD (mean age at death 76.74 years v 72.59 years; Mann-Whitney U = 21315.5, $p < 0.005$). Mean age at death was 73.80 years in FTLD-tau and no other neuropathology, compared to 77.67 years in those with FTLD-tau plus mixed neuropathology (Mann-Whitney U test, $p < 0.005$). In TDP-43 cases, those with isolated FTLD had a mean age at death of 69.59 years, vs 76.34 years in people with FTLD-TDP and mixed neuropathology (Mann-Whitney U = 1581.5, $p < 0.005$).

Age at death increased in tandem with the number of neuropathologies present, with significant between group difference in age at death (one way ANOVA $F(4,510) = 11.07$, $p < 0.005$), (Figure 1). This finding was unchanged by the removal of cases with co-existent MND (one way ANOVA $F(4, 448) = 10.37$, $p < 0.005$). In cases with co-existent MND, there was no significant difference in age at death between those with different numbers of neuropathologies present (one way ANOVA $F(3,58)=2.65$, $p=0.057$). The presence of MND impacted on age at death in the overall FTLD-TDP group (Table 3), being significantly younger in those with concurrent MND (Mann-Whitney U = 1290.0, $p < 0.005$). When considering only those FTLD-TDP cases with single neuropathology, there was no difference in age at death between those with and without MND (Mann-Whitney U=447, $p = 0.038$). In cases without MND, there was no significant difference in age at death between the FTLD-TDP group and the FTLD-tau group (t test, df 439, $p = 0.259$).

HS was significantly commoner in those with FTLD-TDP compared to FTLD-tau (17.91% v 6.98%, Chi-square $p < 0.005$), as was AD (22.40% v 8.10%) although the difference in AD occurrence did not survive correction for multiple comparisons (Chi-square $p = 0.037$, corrected threshold for significance 0.025). There was no difference in the occurrence of other neuropathologies between the FTLD-TDP and FTLD-tau groups.

The clinical and primary neuropathological diagnosis was concordant in 59.17% of cases with a single neuropathological diagnosis, and 38.71% of those with mixed neuropathology. A further 21.94% of mixed neuropathology cases had partial concordance between clinical and neuropathological

diagnosis. The type of dementia was not specified in 19.44% of cases with single neuropathology, and 16.13% of those with mixed neuropathology. There was no concordance between clinical and neuropathological diagnosis in 22.50% of the single neuropathology cases, and 23.23% of the mixed neuropathology cases.

Discussion

Over a quarter of this large, UK based cohort had mixed neuropathology, with various combinations of Alzheimer's spectrum changes, Lewy bodies, vascular disease, and HS. Formal diagnoses of AD or LBD were relatively uncommon. Over half of those with FTLD-TDP had additional neuropathology, compared to only 23.68% with FTLD-tau. In line with previous reports, HS most often appeared with FTLD-TDP. Alzheimer's pathology and vascular disease were also more frequently reported with FTLD-TDP, and were commoner findings than HS.

Those with mixed neuropathology had an older age at death than those with isolated FTLD. The most probable explanation for this is that survival to a higher age allowed the accumulation of greater burden of age-related degenerative neuropathologies. We did not set a minimum severity level for the degree of mixed neuropathology, therefore are likely to have captured age-related changes. If or how different neuropathologies interact is unclear. Evidence from the AD literature suggests that having additional neuropathology increases the likelihood of clinical dementia (11,12,22).

Tauopathies are frequently seen as co-existent or incidental pathologies in patients with other forms of neurodegeneration(23,24) but the incidence of mixed pathology in those with a primary tauopathy is understudied. An autopsy series of 33 people with neuropathologically diagnosed CBD, coexisting Alzheimer's spectrum pathology was seen in 3 cases (25). An archival review of 66 cases of Pick's disease identified proteinopathy consistent with low or intermediate level probability of AD in 3 cases, and occasional alpha synuclein immunopositivity(26). In our cohort, most of those with FTLD-tau had no other neuropathology present. Why mixed neuropathology is less frequent in FTLD-tau than FTLD-TDP-43 is unclear; this discrepancy was not explained by age at death, or by an excess of any one particular neuropathology with FTLD-TDP.

Concordance between clinical and neuropathological diagnosis was lower in cases with mixed neuropathology, which suggests that reaching an accurate diagnosis in life is more challenging in the face of mixed neuropathology, due to alteration of dementia phenotype.

This study was a retrospective review of data collated by the UK Brain Banks, and as such, a potential weakness is the possibility of inter-operator variability in neuropathological reporting. The UK Brain Banks do actively harmonise neuropathological sampling, diagnostic approaches and reporting across the UK Brain Banks Network, but there remains potential variability which should be considered when interpreting these findings and comparing them to those in other cohorts. The present study encompassed a broad range of individuals from across the UK, but as with many cohort studies the results are liable to selection bias. Some UK brain banks originally targeted specific populations such as those with AD or parkinsonian disorders. There may also be self-selection by volunteers for brain donation. An analysis of socioeconomic and health characteristics of UK Biobank participants found them to be older, in better health and resident in more affluent areas than the general UK population(27). The UK Brain Bank cohort is also at risk of a 'healthy volunteer' bias, potentially leading to artificially low levels of neuropathologies linked to lifestyle risk factors. Although all the UK brain banks broadly recruit persons with neurodegenerative disease, there are differences in specific recruitment remits. This may lead to over-ascertainment of conditions which are actively recruited (in particular parkinsonian conditions, an area of particular interest for 3 of the 10 UK brain banks). These factors may contribute to differences between our findings and those of Dugger et al, who investigated mixed neuropathology in adults with parkinsonian disorders from the Arizona Study of Aging and Neurodegenerative Disorders cohort(28). Dugger et al. reported a higher prevalence of AD and vascular pathology amongst individuals with PSP and CBD. However, the CBD group reported by Dugger et al. contained only 6 individuals, so the results should be interpreted with caution. Their PSP group was on average 9 years older at death than that in the current study, which is likely to affect the burden of age-related neuropathology seen. There is also potential for variability in interpretation of neurofibrillary tangles

in PSP and CBD, as to whether these represent additional Alzheimer's pathology or not. Dugger et al. also reported that a large proportion of recruits came from neurology clinics, potentially creating a bias towards people with more unusual clinical syndromes resulting from mixed neuropathology.

Robinson et al. investigated the prevalence of mixed neuropathology in a broad cohort, including cases of CBD, Pick's disease, PSP and FTLD-TDP(29). They reported a high prevalence of mixed neuropathology with CBD (52% showing mixed neuropathology), Pick's disease (27%), PSP (71%) and FTLD-TDP (45%). In the present UK cohort the proportions with mixed neuropathology were CBD 36.59%, Pick's disease 9.43%, PSP 20.95% and FTLD-TDP 25%. The differences cannot be explained by age at death, which was higher in each of the UK groups. More detailed reporting of TDP-43 co-pathology in the Robinson et al. study may partly explain this difference. Comparing different cohort studies is challenging due to differences in cohort characteristics and study methodology, and a clear overview of potential limitations and biases is vital to allow valid conclusions to be drawn.

The issue of mixed neuropathology in neurodegenerative disease is a pressing one. How different proteinopathies interact, and the influence of multiple neuropathologies on clinicopathological phenotype, is largely unknown. There is emerging evidence of association between TDP-43 and AD, and some evidence that this causes a cumulative deficit, with earlier cognitive decline and dementia(7,22,30). We have little information on the prevalence of subclinical FTLD pathology in older communities, and its impact on dementia risk. Mixed neuropathology has major implications for development and trialling of novel agents targeting neurodegeneration. Targeting a single pathogenic protein may not be an effective strategy given the high frequency of multiple neuropathologies in older adults with cognitive decline. Likewise, trials of agents effective at modifying one specific cause of neurodegeneration may be undermined by other cognitive co-morbidities. A clearer understanding of how different neuropathologies interact is urgently needed to improve public health advice and prognostication, to inform research into new therapies, and refine entry criteria, stratification and monitoring of patients in clinical trials.

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Table 1. FTLD neuropathology by sub-group.

Neuropathological Diagnosis		Number of cases	Percentage of overall cohort	Percentage of each sub-group with mixed neuropathology*
FTLD-tau	CBD	82	15.92	36.59
	FTLD-tau [†]	11	2.14	45.45
	GGT	3	0.58	33.33
	Pick's disease	53	10.29	9.43
	PSP	210	40.78	20.95
FTLD-TDP	TDP A [‡]	33	6.41	63.64
	TDP B [‡]	28	5.44	35.71
	TDP C	16	3.11	37.50
	TDP type unknown [‡]	54	10.49	55.56
	FTLD-MND	8	1.55	25.00
FUS	aFTLD-U	3	0.58	33.33
	FUS	3	0.58	33.33
	NIFID	1	0.19	0.00
Other	DLDH	1	0.19	0.00
	FTLD (TDP negative)	1	0.19	0.00
	FTLD-U	4	0.78	0.00
	MND-ID	2	0.39	0.00
	UPS	2	0.39	0.00
TOTAL		515	100	30.10

* The presence of MND was not considered to be an additional pathology.

[†] *MAPT* mutation present in 6 of the FTLD-tau cases.

[‡] *C9ORF72* repeat expansion present in 3 cases with TDP A, 3 with TDP B and 6 with TDP type unknown. *GRN* mutation was present in 1 case with TDP A, and 1 case with TDP B.

Table 2. The frequencies of different mixed neuropathologies in FTLD subtypes (percentage of cases with each finding shown)

FTLD type	AD	Alzheimer features (not meeting criteria for AD)	Vascular disease	CAA	LBD	Lewy bodies (not meeting criteria for LBD)	HS	Other*	Average no. pathologies present †
CBD (N=82)	3.66	14.63	20.73	12.20	4.88	0.00	4.88	10.98	2.97
PSP (N=210)	1.90	11.43	7.62	4.76	0.95	2.86	0.48	4.29	2.67
Pick's disease (N=53)	0.00	5.67	7.55	3.77	0.00	1.89	0.00	0.00	3.5
All tauopathy cases (N=359)	1.95	11.98	11.42	6.13	1.91	1.91	1.67	5.01	2.85
TDP-43 A (N=33)	21.21	33.33	18.18	12.12	6.06	6.06	18.18	3.03	2.86
TDP-43 B (N=28)	10.71	17.86	25.00	10.71	7.14	3.57	3.57	0.00	3.20
TDP-43 C (N=16)	6.25	12.50	75.00	56.25	6.25	0.00	0.00	6.25	2.83
All TDP-43 cases (N= 139)	10.79	25.18	20.86	12.95	4.32	5.76	8.63	3.60	2.88

* Other pathologies co-existing with tauopathies: PSP (with CBD), AGG, TDP-43, post-encephalitic PD

Other pathologies co-existing with TDP-43: PSP, tau, AGG

Other pathology co-existing with FUS: tau

† This includes the primary FTLD pathology but excludes MND; average no. pathologies present in mixed cases is shown.

A. All cases

B. Cases without MND

Figure 1. Box and whiskers plot of age at death by number of neuropathologies present.