### Title

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### Journal

Journal of neuropathology and experimental neurology, 79(7)

### ISSN

0022-3069



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### Publication Date

2020-07-01

### DOI

10.1093/jnen/nlaa045

Peer reviewed

*J Neuropathol Exp Neurol*
Vol. 79, No. 7, July 2020, pp. 809–812
doi: 10.1093/jnen/nlaa045

ORIGINAL ARTICLE

# Expanding the Phenotype of Frontotemporal Lobar Degeneration With FUS-Positive Pathology (FTLD-FUS)

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**Abstract**

Atypical frontotemporal lobar degeneration with ubiquitin-positive inclusions (aFTLD-U) is an uncommon cause of frontotemporal dementia characterized by *fused in sarcoma*-positive inclusions. It is classified as a subtype of frontotemporal lobar degeneration with FUS pathology. Cases with aFTLD-U pathology typically display an early onset of symptoms and severe psychobehavioral changes in the absence of significant aphasia, cognitive-intellectual dysfunction or motor features. This phenotype is regarded as being sufficiently unusual and consistent as to allow antemortem diagnosis with a high degree of accuracy. In this report, we describe 2 cases with aFTLD-U pathology that broaden the associated phenotype to include later age of onset, milder behavioral abnormalities and early memory and language impairment.

**Key Words:** aFTLD-U, Frontotemporal dementia, Frontotemporal lobar degeneration, FTLD-FUS, Fused in sarcoma.

## INTRODUCTION

Frontotemporal dementia (FTD) is a heterogeneous clinical syndrome characterized by progressive abnormalities of personality, behavior, and/or language (1). There is often an associated pyramidal or extrapyramidal movement disorder, and up to 40% of cases are familial. The neuropathology underlying clinical FTD is also heterogeneous and is broadly referred to as frontotemporal lobar degeneration (FTLD), which is further subclassified based on the identity of the major protein that forms cellular inclusions (2). Although most FTLD cases are characterized by the abnormal intracellular accumulation of either tau protein (FTLD-tau) or the transactive response DNA-binding protein MW 43 (TDP-43, FTLD-TDP); there remains a small subset of cases (~5%) in which the pathological protein was recently identified as being fused in sarcoma (FUS) (3). FTLD-FUS includes 3 distinct clinicopathological entities; the most common is atypical FTLD with ubiquitin-positive inclusions (aFTLD-U), while neuronal intermediate filament inclusion disease (NIFID) and basophilic inclusion body disease (BIBD) are relatively rare (4).

The original reports described aFTLD-U as having an unusual and highly characteristic phenotype (5, 6). All cases were sporadic and presented at a young age (mean = 38 years). Although patients typically fulfilled diagnostic criteria for behavioral variant FTD (bvFTD), they usually presented with severe, progressive psychobehavioral manifestations, often including antisocial and aggressive behavior, even criminal activity, requiring early institutionalization. Memory impairment, other cognitive-intellectual dysfunction and motor features were all uncommon. Language abnormalities were usually absent or occurred late in the disease, and manifest more as frontal lobe dysfunction with decreased output, lack of spontaneity and stereotypy, rather than true aphasia.

The neuropathology underlying these aFTLD-U cases was also reported to be highly consistent (5, 6). All showed marked cerebral atrophy (<1000 g) with severe degeneration of frontal cortex, hippocampal CA1/subiculum, striatum and substantia nigra (Table). Microscopically, the affected regions were characterized by small round or crescentic neuronal cytoplasmic inclusions (NCI) and unique "vermiform" neuronal intranuclear inclusions (NII) that were originally identified using ubiquitin immunohistochemistry (IHC) and later found to be immunoreactive (-ir) for FUS (3) and the other members of the FET family of proteins (Ewing's sarcoma, EWS and TATA-binding protein-associated factor 15, TAF-15) (7). NCI and NII were most abundant in the hippocampus and neocortex, with subcortical regions showing less consistent and

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This study was supported by the Canadian Institutes of Health Research (I.R.M.). H.V.V. is supported in part by the Department of Neurology and the Mary Easton Alzheimer Disease Research Center at University of California Los Angeles.

The authors have no duality or conflicts of interest to declare.

milder involvement. A subsequent large multicenter study that reviewed the demographic and clinical features of 37 aFTLD-U cases confirmed the clinical description and concluded that the phenotype was sufficiently consistent and unique to allow for the prediction of underlying aFTLD-U pathology (8).

In this report, we describe 2 cases of aFTLD-U which broaden the phenotype to include later age of onset, milder behavioral abnormalities, early memory and language impairment, and a relatively restricted neuropathology.

## MATERIALS AND METHODS

### Cases

Cases were initially identified by reviewing the Neuropathology archives in the Departments of Pathology at the University of British Columbia and University of California Los Angeles. Dementia clinic notes from the respective Divisions of Neurology were then reviewed.

### Immunohistochemistry

IHC was performed on 5-μm-thick sections of formalin-fixed, paraffin-embedded tissue using the Ventana BenchMark XT automated staining system (Ventana, Tucson, AZ) with heat pretreatment and developed with aminoethylcarbizole (AEC). The primary antibodies employed recognized ubiquitin (1:500, Dako, Glostrup, Denmark), FUS (1:1000, Sigma-Aldrich, St. Louis, MO), TAF-15 (1:200, Bethyl Laboratories, Montgomery, Texas), EWS (Bethyl Laboratories, 1:200), hyperphosphorylated tau (AT-8, 1:2000, Innogenetics, Ghent, Belgium), Aβ (1:100, Dako), TDP-43 (1:1000, ProteinTech Group, Rosemont, IL), α-synuclein (1:10 000, Zymed, South San Francisco, CA), α-internexin (1:500, Zymed), nonphosphorylated neurofilament (1:2000, Dako), and phosphorylated neurofilament (1:8000, Sternberger SMI 31, BioLegend, San Diego, CA).

## RESULTS

### Case 1

This previously healthy man was first noted to have subtle behavioral changes at the age of 68 when he began to show obsessive behaviors. Over the next 3 years his mood, personality and behavior progressively deteriorated. He became apathetic, withdrawn, neglected personal hygiene, developed rigid eating habits with a craving for sweets, motor restlessness and disordered sleep patterns. Despite previously being described as shy, he developed new inappropriate and impulsive behaviors. There was no family history of dementia or psychiatric illness.

When first assessed at age 71, he scored 29/30 on the MMSE and 88/100 on the 3MS. He exhibited impaired executive function and judgment, with preserved memory. Motor function was intact. MRI revealed mild bilateral frontal and temporal lobe atrophy. A provisional diagnosis of bvFTD was made.

His behavior continued to deteriorate with increasing restlessness, impulsivity and inappropriate actions; however, he did not demonstrate any aggressive or antisocial behavior. He spent the final year of his life in a nursing home where he was noted to develop memory loss, mild dysarthria, dysphagia, and gait difficulty. He ultimately regressed to a child-like state before dying at the age of 73, 5 years after symptom onset.

At autopsy, the 1350-g brain showed mild, diffuse cerebral atrophy. Microscopic examination demonstrated severe loss of neurons from the CA1 sector of the hippocampus and subiculum (hippocampal sclerosis), but only mild chronic neurodegenerative changes in the frontal and temporal neocortex and substantia nigra (Table). No specific pathological changes were appreciated on standard hematoxylin and eosin stain or Bielschowsky silver method; specifically, there were no basophilic inclusion bodies or hyaline conglomerate neuronal inclusions. IHC for ubiquitin, FUS, TAF-15, and EWS all showed similar pathology, with TAF-15 being the most sensitive (Fig. 1A–C). Small oval or crescentic NCI and filamentous NII were numerous in the dentate granule layer of the hippocampus, but only present in small numbers in the neocortex and cingulate gyrus. The basal ganglia and substantia nigra were mildly involved; whereas, most other subcortical regions were spared. Specifically, the hypoglossal nucleus had a normal neuronal population with only a single TAF-15-ir NCI while the cerebellum was not affected. No other significant pathological changes were demonstrated with other IHC, including those that recognize neuronal intermediate filaments.

### Case 2

This woman began to develop memory loss and behavioral changes around age 60. She often appeared to be confused and became apathetic, developed a blunt affect, poor insight, irritability, hypersexuality, impulsivity, and started overeating. In her early sixties, she started to develop expressive language difficulties. There was no family history of dementia.

Neurological examination at this time showed impaired memory, attention, executive function and language, with scores of 15/30 on the MMSE and 51/100 on the 3MS. There was no motor dysfunction. Her symptoms progressed with more aggressive and repetitive behaviors and her language de-

**TABLE.** Summary of Pathological Findings and Comparison With Previous [a]FTLD-U Reports

| | Case 1 | | Case 2 | | aFTLD-U* | |
|---|---|---|---|---|---|---|
| | deg. | FET-ir | deg. | FET-ir | deg. | FET-ir |
| Neocortex | + | + | ++ | + | +++ | ++ |
| HC-CA1/sub | +++ | + | +++ | – | +++ | ++ |
| HC-dentate | – | +++ | – | +++ | – | +++ |
| Basal ganglia | – | + | +++ | +++ | +++ | + |
| Substantia nigra | + | + | ++ | na | +++ | + |

[a]FTLD-U, atypical frontotemporal lobar degeneration with ubiquitin positive inclusions; CA1, cornu ammonis; deg., degeneration; FET-ir, immunoreactive for FET proteins; HC, hippocampus; na, not available; sub, subiculum.

Semiquantitative grading: –, none; +, mild/few; ++, moderate; +++, severe/abundant.

*Based on previous reports (5, 6).

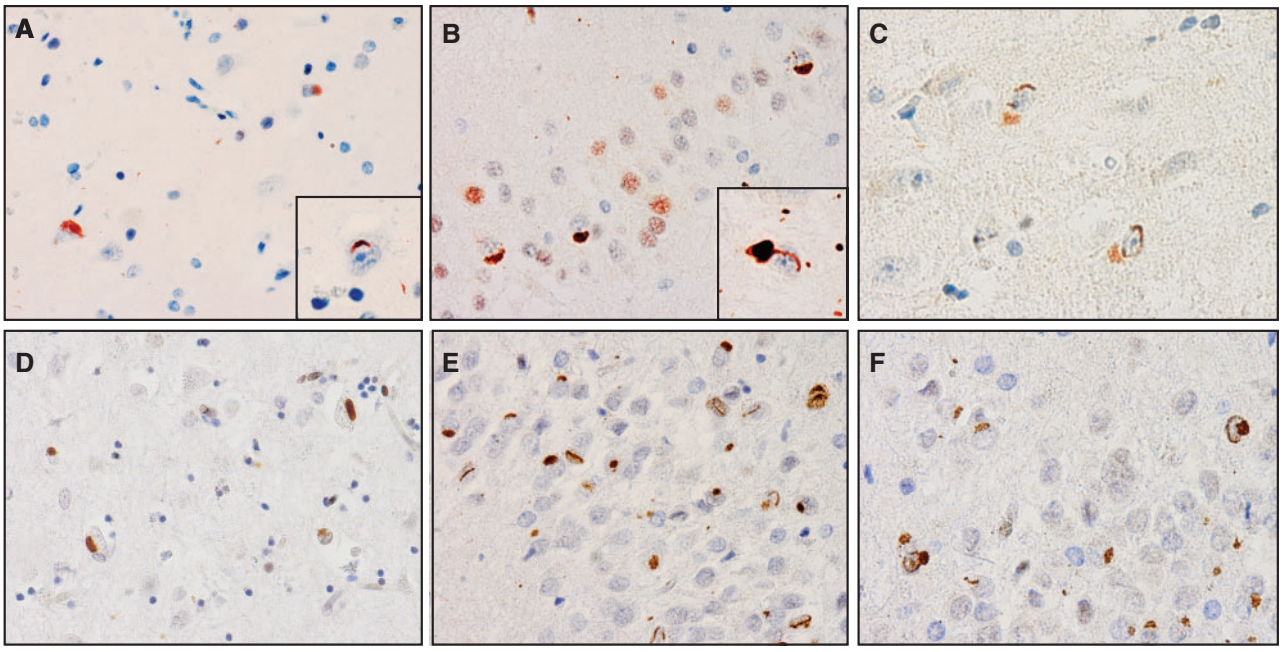


**FIGURE 1.** FET-immunoreactive pathology. Case 1 demonstrated neuronal inclusions that were immunoreactive (-ir) for all of the FET proteins, including fused in sarcoma **(**FUS, **A)**, TATA-binding protein-associated factor 15 **(**TAF-15, **B)**, and Ewing's sarcoma **(**EWS, **C)**. Neuronal cytoplasmic inclusion (NCI) and neuronal intranuclear inclusions (NII) **(**insets in **A** and **B)** were abundant in the dentate granule layer of the hippocampus (HC) **(B)**, but infrequent in the cerebral neocortex, cingulate **(A)**, HC region CA1 **(C)**, and subcortical regions. Case 2 demonstrated infrequent NCI in the neocortex **(D)** and abundant NCI and NII in the HC dentate granule cells **(E, F)** that were immunoreactive for FUS **(D, E)** and TAF-15 **(F)**. Immunohistochemistry for FUS **(A, D, E)**, TAF-15 **(B, F)**, and EWS **(C).**

teriorated to eventual mutism. She died 6 years after disease onset.

At autopsy, the 1010-g brain showed moderately severe, symmetric frontotemporal atrophy and severe hippocampal atrophy. On microscopic examination, there was moderate chronic degeneration of the frontal and temporal neocortex, severe hippocampal sclerosis and degeneration of the basal ganglia, and moderate loss of neurons in the substantia nigra (Table). There were no basophilic inclusion bodies or hyaline conglomerate neuronal inclusions. IHC for ubiquitin, FUS and TAF-15 demonstrated abundant NCI and NII in dentate granule cells of the hippocampus, but only infrequent inclusions in the neocortex (Fig. 1D–F). FUS-ir and TAF-15-ir NCI were also abundant in the basal ganglia. The only other pathologic change demonstrated was the presence of rare tau-ir neuropil threads and neurofibrillary tangles in the entorhinal cortex (Braak stage I/VI) and moderate numbers of diffuse senile plaques (but no neuritic plaques).

## DISCUSSION

The most common forms of FTLD (subtypes of FTLD-tau and FTLD-TDP) show significant clinical overlap, often making it difficult to accurately predict a patient's underlying pathology (1, 2). In contrast, aFTLD-U is often regarded as having such an unusual and consistent phenotype as to allow for antemortem diagnosis with a high degree of accuracy (8, 9). The 2 cases we report here are somewhat exceptional. Although both had FUS/FET-ir pathological changes that were consistent with the aFTLD-U subtype of FTLD-FUS (4), in the absence of any other significant neuropathology that might have influenced their phenotypes, both had a number of clinical features that diverged from those typically ascribed to aFTLD-U.

One of the most characteristic features of aFTLD-U is the early age of symptom onset. In the single large series reported to date, the mean age of onset was 41 ± 9 years (8), and in the original 2 case series which provided more detailed clinical information, only one of the 15 patients presented after age 50 (5, 6). In contrast, the ages at which our patients first developed symptoms (seventh decade) were significantly older and much more similar to that reported for sporadic FTD in general (mean = 60 years) (1).

The presentation of aFTLD-U is typically characterized by severe psychobehavioral abnormalities which are often initially ascribed to an underlying psychiatric disorder, until their progressive nature becomes apparent (5, 6). Moreover, the antisocial, aggressive behavior is often so severe as to necessitate early institutionalization. In contrast, both our patients had a more subtle presentation and, although both displayed a number of inappropriate behaviors, neither displayed significant aggression.

In addition, aFTLD-U is notable for a low prevalence of aphasia, memory problems and motor features (5, 6, 8, 9). One of our patients had prominent early memory loss and developed an expressive language disorder which progressed to mutism (Case 2). Our other patient (Case 1) also developed

memory loss, as well as some motor symptoms, although these only appeared late in the disease course.

Although the pathological features of our cases were diagnostic of aFTLD-U, the somewhat milder severity may correlate with the later, more subtle clinical onset (Table). Case 1, which had a particularly late onset, had only mild cerebral atrophy and much less degeneration of the neocortex and subcortical regions than is usual. In addition, both our cases had much less abundant FET-ir pathology in the neocortex compared with other pathological reports of aFTLD-U. Pathological correlations for the unusual positive clinical features in our cases are more difficult to determine. The language dysfunction in Case 2 was likely related to the chronic degeneration found in the left temporal lobe; however, this was no more severe than what was seen in the frontal lobes or what has been reported in other aFTLD-U cases without aphasia (3, 5, 6). In Case 1, there was no significant pathology found in the lower brainstem or cerebellum to explain the motor features and the parietal lobes were not sufficiently involved to cause apraxia. Unfortunately, the spinal cord was not available for examination.

Another recent case report described a patient with pathologically proven aFTLD-U associated with atypical clinical features, with some similarities to our cases (10). Onset at age 59 included significant memory and cognitive impairment which was followed by a semantic language dysfunction. Although he did display changes in personality and behavior, he did not become aggressive. Additional features of this case, which differed from ours, were rapid decline leading to death in <3 years and more severe and more widespread FUS-ir pathology than our cases.

Onset in early to midadult life is one of the most characteristic features of aFTLD-U (5, 6, 8). In other molecular subtypes of FTD and other common causes of dementia, rare mutations and minor polymorphic variants have been identified that protect against disease (11–14). While it is logical to hypothesize that inheritance of some uncommon genetic variant may be responsible for the less severe neurodegeneration and delayed onset in our cases, not enough is currently known about the molecular pathomechanisms underlying aFTLD-U to speculate further (15).

In summary, the 2 cases we present broaden the clinical spectrum associated with aFTLD-U pathology to include later age at onset, more subtle behavioral changes and more prominent cognitive, memory, language, and motor dysfunction. This indicates that although the phenotype that is most often associated with aFTLD-U may be a highly specific indicator of that pathology, it is not entirely sensitive. In addition, neuropathologists should be aware that, particularly in clinically atypical cases, the pathological changes may be fairly mild and not readily appreciated unless sensitive detection methods (e.g. TAF-15 IHC) are employed.

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