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**, Combined FUS+ Basophilic Inclusion Body Disease and Atypical Tauopathy  
Presenting with an ALS/MND-plus Phenotype**

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## **Abstract**

**Aims:** Amyotrophic lateral sclerosis / motor neurone disease (ALS/MND) is characterised by the presence of inclusions containing TDP-43 within motor neurones. In rare cases, ALS/MND may be associated with inclusions containing other proteins, such as fused in sarcoma (FUS), whilst motor system pathology may rarely be a feature of other neurodegenerative disorders. We here have investigated the association of FUS and tau pathology.

**Methods:** We report a case with an ALS/MND-plus clinical syndrome which pathologically demonstrated both FUS pathology and an atypical tauopathy.

**Results:** Clinical motor involvement was predominantly upper motor neurone, and was accompanied by extrapyramidal features and sensory involvement, but with only minimal cognitive impairment. The presentation was sporadic and gene mutation screening was negative. Post-mortem study demonstrated inclusions positive for FUS, including basophilic inclusion bodies. This was associated with 4R-tauopathy, largely as non-fibrillary diffuse phospho-tau in neurones, with granulovacuolar degeneration in a more restricted distribution. Double-staining revealed that neurones contained both types of protein pathology.

**Conclusion:** FUS-positive basophilic inclusion body disease is a rare cause of ALS/MND, but in this case was associated with an unusual atypical tauopathy. The coexistence of two such rare neuropathologies raises the question of a pathogenic interaction.

Key words: motor neurone disease, amyotrophic lateral sclerosis, fused in sarcoma, basophilic inclusion body disease, atypical tauopathy.

## Introduction

Amyotrophic lateral sclerosis / motor neurone disease (ALS/MND) is characterised, in most cases, by neuronal protein aggregates that contain phosphorylated TDP-43, associated with nuclear mislocalisation. The ALS variant of motor neurone disease is characterised by upper and lower motor neurone involvement. Extramotor pathology can be seen, particularly in frontal cortex and hippocampus, and TDP-43 pathology may be seen in glia as well as neurones [1]. Motor system degeneration may however, rarely be associated with other neurodegenerative disorders and protein deposition.

Fused in sarcoma (FUS), also known as translated in sarcoma, may form inclusions in rare cases of familial ALS/MND type 6 [2, 3]. These inclusions do not contain TDP-43 or tau. FUS inclusions also characterise a subset of frontotemporal lobar degenerations (FTLD-FUS), which includes three entities; atypical FTLD with ubiquitinated inclusions, basophilic inclusion body disease (BIBD) and neuronal intermediate filament inclusion disease (NIFID) [4]. In contrast to ALS/MND-FUS, these FUS-associated frontotemporal dementias are not usually associated with *FUS* mutation, and the inclusions contain other proteins (e.g. transportin-1, and, in the case of NIFID,  $\alpha$ -internexin). Given these differences between ALS/MND-FUS and FTLD-FUS, it is unclear whether they are part of a disease spectrum.

Tau pathology has also been described in association with ALS/MND, although tau deposition is not a feature of the typical inclusions of ALS/MND-TDP. Abnormal neuronal and glial tau phosphorylation has been suggested in the ALS/MND spectrum [5, 6] but, other studies have found that this is mostly low-Braak stage Alzheimer's type pathology and have not confirmed glial tau pathology [7]. A lack of predilection for enhanced tauopathy in FTLD-TDP, and of TDP-43 in FTLD-tau, suggests a lack of direct interaction [8].

Motor cortical degeneration, with upper motor neurone signs, may rarely be a feature of primary and secondary tauopathies, although usually in the context of other more typical dominant signs. Both progressive supranuclear palsy and corticobasal degeneration may demonstrate motor cortex involvement and corticospinal tract degeneration [9, 10], whilst globular glial tauopathy, also a 4-repeat tauopathy, may present with motor neurone disease plus dementia, and associated with atrophy of the precentral gyrus [11, 12]. Alzheimer's disease may also rarely demonstrate corticospinal tract involvement, particularly familial cases associated with presenilin-1 mutations, and is associated with A $\beta$  deposited as cotton wool plaques [13].

Here we report an unusual sporadic case with an ALS/MND-plus clinical phenotype and with complex neurodegeneration, combining both FUS pathology and an atypical tauopathy. This co-occurrence of two unusual pathologies, with dual pathology in the same neurones, would seem an unlikely coincidence and suggests that, in some FUS cases and in selected neuroanatomical areas, there may be a pathogenic interaction between FUS and tau.

## Clinical Features

A 43 year old man presented with a 12 month history of dexterity problems predominantly affecting his right hand, associated with mild weakness and episodic paraesthesia in the right hand and forearm, with mildly reduced sensation. His mother developed Alzheimer's disease at age 75 years but there was no other family history of neurological disease. Over the following 2-years he had increasing difficulty with the use of his hands, and reported wasting of the right, first dorsal interosseous muscle. Electrophysiology, MRI scan of the brain and cervical spine with gadolinium, lumbar puncture, anti-neuronal antibodies and EEG remained normal. However, a SPECT (single-photon emission computerized tomography) scan demonstrated bilateral multifocal hypoperfusion, both cortical and deep, and a DAT (dopamine transporters) scan showed decreased uptake. The patient was given a trial of baclofen and then levodopa with no discernible benefit. By two years after initial presentation, the right upper limb weakness had progressed, and walking balance was impaired, causing stumbling and falls. He reported widespread muscle twitching, and episodic, short-lived sharp pains in limbs. Although he reported some cognitive slowing, on bedside examination cognitive function was preserved, speech was clear, and he had a normal gait. He had severe weakness of the right upper limb with milder changes affecting the left upper limb. The lower limbs were normal in tone and power. Reflexes were brisk throughout, but the plantar responses were flexor. No definite sensory or cerebellar signs were elicited. EMG now showed chronic denervation and ongoing reinnervation in 3 regions, with normal nerve conduction studies. However no active denervation was seen.

The following year the patient developed dramatic mirror movements. A trial of ropinirole gave no discernible benefit. Progressive deterioration in the strength of upper and lower limbs continued, spasticity became a problem and his speech became dysarthric. He also developed bradykinesia, loss of coordination and impaired proprioception, and he described himself at times as unaware of his body position. He had difficulty with sequencing of actions and became emotionally labile. He also developed urinary frequency and urgency. Non-invasive ventilation was introduced due to a reduction in forced vital capacity and symptomatic hypercapnia. A re-trial of dopaminergic medication was unsuccessful. An FDG-PET scan was performed (approximately 4yrs after presentation) and a 'stripe sign' of hypometabolic activity in the primary motor cortices (PMC) was seen. Progressive weakness in all muscle groups, including the bulbar muscles, continued, necessitating a gastrostomy tube insertion, and the patient died 11 years after symptom onset.

Genotyping was performed by Sheffield Diagnostic Genetics Service for ALS and dementia related gene panels (Supplementary table 1). The genes screened were all negative for mutation, including *FUS*, *MAPT*, and *C9ORF72*.

## Neuropathology

Consent was obtained for a post mortem examination limited to brain and spinal cord, with donation of tissue to the Sheffield Brain Bank. Following transfer to our institution, the brain and spinal cord were removed with a post mortem interval (PMI) of approximately 96hr. A portion of cerebellum was flash frozen in liquid nitrogen for storage at -80 °C. The brain and cord were fixed in formalin prior to dissection; hemi-brain slices were not flash frozen according to the usual brain bank protocols because of the extended PMI. The brain, weighing 1455g, showed moderate atrophy of the motor cortex, with mild atrophy of primary sensory cortex and superior parietal lobe (Figure 1A,B). The corpus callosum was thinned in the mid-cerebrum and the medullary pyramids were atrophic and grey.

Microscopical examination of haematoxylin and eosin stained sections revealed spongiosis of the motor cortex with pallor of underlying white matter (Figure 1C-D). Many pyramidal neurones contained ovoid, circumscribed, basophilic inclusion bodies, in some cases associated with vacuoles containing dot-like profiles suggestive of granulovacuolar degeneration (GVD) (Figure 1E-F). The basophilic inclusions immunolabelled with antibodies to FUS (Novus Biologicals polyclonal rabbit antibody NB100-2599, 1:100, pressure cooker antigen retrieval pH9 Menarini super buffer), which also showed neuronal cytoplasmic labelling, and ring-like fibrillary structures (Figure 2A,B).

Inclusions labelled with immunohistochemistry to P62 (BD Bioscience monoclonal 1:400 high pH retrieval Dako autostainer), which also labelled circumscribed inclusions in pyramidal neurones and ring-like reactivity in neurons in layer 2 (Figure 2C), corresponding to areas with frequent FUS positivity. The inclusions did not show argyrophilia with the Gallyas method (Figure 2D). AT8 immunostaining (Thermo Scientific monoclonal 1:800, no antigen retrieval Dako autostainer) identified diffuse granular positivity in pyramidal neurones and labelled granulovacuolar degeneration and numerous neuropil threads. AT8+ neurons were most conspicuous in the deeper cortex. Neurofibrillary tangles were not observed and AT8 did not label the basophilic inclusions. No tau-positive glial inclusions were seen. Immunohistochemistry to 4R-tau (Millipore monoclonal antibody 05-804 clone 1E1/A6, 1:3000 with pressure cooker antigen retrieval) labelled tau in some of the neurons and neuropil threads, whilst immunohistochemistry to 3R tau (Millipore monoclonal antibody 05-803, clone 8E61C11, KMnO<sub>4</sub> bleach followed by incubation 1:800 4C for 2 days with pressure cooker antigen retrieval) was negative (Figure 2E-I). The distribution of staining is shown in Supplementary table 2. Notably AT8 immunoreactivity showed a more restricted neuroanatomical distribution than p62 or FUS.

Double immunostaining for FUS and AT8 was performed on motor cortex. Following pressure cooker antigen retrieval at pH6, FUS was stained first using a polymer kit at 1:100 with DAB (giving a brown reaction product), followed by AT8 at 1:200 with a standard ABC kit with vector VIP (giving a blue/purple reaction product). This demonstrated co-existence of these protein pathologies in some neurons (Figure 3A-B, Suppl Figure 1). Small samples (2-3mm) of formalin-fixed tissue from motor cortex were sub-dissected, subsequently fixed in glutaraldehyde and processed for electron microscopy. Ultrastructural examination revealed circumscribed inclusions, which contained polyribosomes arranged in an apparent linear-helical pattern (Figure 3C-D). Lipofuscin and autophagic vacuoles were also noted. However, no filamentous structures were identified in the inclusions and no limiting membrane was detected, although state of preservation linked to the PMI and suboptimal fixation (for ultrastructure) may have limited detection of some structures.

The medullary pyramids were atrophic and there was loss of lower motor neurones from the hypoglossal nucleus and anterior horns of the spinal cord, especially at cervical levels (Figure 4A-D). Neither Bunina bodies nor hyaline conglomerate inclusions were identified. CD68, an indirect marker of long tract degeneration [14], was upregulated in the lateral corticospinal tracts of the cord. FUS/p62 positive inclusions were identified in lower motor neurones. There were no TDP-43-positive inclusions, nor mislocalisation, and no  $\alpha$ -synuclein inclusions in either upper or lower motor neurones. No amyloid- $\beta$  pathology was detected.

Extramotor pathology was also present (Figure 4E-I). Milder pathology, with an occasional balloon neuron, was observed in primary sensory cortex. Prefrontal association cortex (BA8/9) showed only focal layer 2 spongiosis. The substantia nigra revealed moderate cell loss with pigment incontinence. Immunohistochemistry revealed inclusions in primary sensory cortex, with only occasional inclusions in prefrontal cortex. Sparse AT8+ tangles in

entorhinal cortex probably represented age-associated Braak stage I neurofibrillary pathology. However, many GVD-like inclusions were observed in CA1 pyramidal layer neurones. Inclusions were observed in caudate and putamen. P62/FUS+ inclusions were present in the dentate nucleus of the cerebellum; these were AT8-negative and there was no grumose degeneration. White matter did not show inclusions and no glial tau pathology was identified in either grey or white matter structures.

## Discussion

We report a complex case of neurodegenerative disease with combined protein pathology, presenting primarily with a sporadic ALS/MND phenotype, with pathological involvement of motor cortex and lower motor neurones, but with extramotor pathology, most notably in sensory cortex. The case was characterised by both FUS pathology with basophilic inclusion body formation, combined with an atypical non-fibrillar 4R tauopathy, and an absence of pathogenic mutations.

There was ante-mortem diagnostic uncertainty due to clinical features not easily defined by one neurodegenerative disorder, and investigations demonstrating cortical and subcortical involvement. The clinical differential diagnosis was of atypical primary lateral sclerosis (PLS) and corticobasal degeneration (CBD). PLS is a motor neurone disease with only upper motor neurone (UMN) degeneration and corticobasal degeneration is an extrapyramidal motor disorder without significant weakness. This patient had UMN-pattern weakness with only a hint of muscle wasting to suggest LMN involvement and EMG showed evidence of chronic denervation without active denervation and without the spontaneous muscle activity seen with LMN loss. PET scan showed a primary motor cortex hypometabolic stripe that can be seen in PLS, but not exclusively so [15, 16]. He had mild sequencing problems in addition to bradykinesia, reduced coordination, mirror movements and rigidity. Extra-pyramidal signs are recognised in motor neuron disease and it can be difficult to distinguish between UMN spasticity and rigidity of extra-pyramidal origin. The patient was prescribed baclofen but without complete relief of symptoms. He had an abnormal SPECT and DAT scan but without response to dopaminergic therapy. Extramotor involvement was present with paraesthesia and reduced proprioception. He had a subjective mild cognitive deficit but certainly not overt fronto-temporal dementia (FTD) that can be seen with either ALS/MND or tauopathy, nor did he have the cognitive problems seen with CBD.

FUS was present in basophilic, and other neuronal inclusions, suggestive of BIBD. ALS/MND-FUS is usually associated with *FUS* mutation [2, 3] and, although UMN features are present, this disorder typically has a LMN pattern [17]. Our case, in contrast, demonstrated severe involvement of the motor cortex with UMN weakness, whilst CD68 staining demonstrated evidence of corticospinal tract degeneration. Furthermore, our case appeared to be sporadic and extensive genetic testing revealed no evidence of a mutation.

Electron microscopy demonstrated that the inclusions contain organellar structures containing polyribosomes. Polyribosomes associated with a central filament are described in the BIBD inclusions. This appearance is consistent with that, although a central filament was not conspicuous. These structures also resemble helical polyribosomes, an unusual ribosomal formation described in various cell types, including intestinal cells of rat fetus, muscle cells of *Rana pipiens* embryo, follicular cells and oocytes of rat ovary, various cells in culture, certain non-mammalian cell types [18] and in mammalian cells may be associated with decreased translation [19, 20].

In addition, there was an unusual atypical tauopathy, characterised by diffuse deposits, neuropil threads and GVD. Although present in brain areas affected by the p62 and FUS inclusions, it had a restricted distribution to motor cortex and hippocampus, the latter containing pyramidal neurons in which GVD can typically form. Ultrastructural examination demonstrated that the neuronal inclusions do not contain fibrillary structures as may be seen in other tauopathies, including PSP and CBD [21]. Thus both light and electron microscopic studies suggest that the tau is non-fibrillar. Glial tau was not a conspicuous feature. Immunohistochemistry suggests that this belongs to the 4R-tauopathy group, although we were not able to confirm this with western blotting as suitable frozen tissue was not

available. TDP-43 pathology was not present as a co-pathology. This tauopathy demonstrates unique features that do not fit with existing diagnostic categories. Corticospinal degeneration may be a feature of several tauopathies, although it is seldom a dominant feature. CBD and PSP may occasionally demonstrate corticospinal tract degeneration and long tract signs reminiscent of primary lateral sclerosis [9, 10]. This case also had some subtle extrapyramidal features clinically and degeneration of the substantia nigra pathologically. Given the pattern of atrophy, with superior parietal and sensory cortex involvement, as well as motor involvement, a particular nosological question is whether the tau pathology falls within the spectrum of CBD. Immunohistochemical positivity for 4R tau supports a relationship. However, although occasional balloon neurons were seen, other features of the pathology of this case were not typical of those described for CBD, PSP or other reported tauopathies [22]. These included the presence of conspicuous GVD. Grumose degeneration of the cerebellar dentate nucleus and neurofibrillary tangles were not features and neither astrocytic plaques nor oligodendroglial tau inclusions were seen. Globular glial tauopathy is an emerging 4-repeat tauopathy, distinguished by characteristic globular oligodendroglial inclusions, that can present with an ALS/MND phenotype, [11]. Globular glial 4-repeat tau, associated with TDP43 pathology has been reported in association with an ALS/MND and FTD phenotype [23]. Our case lacked the glial tau pathology characteristic of these disorders. Fronto-temporal lobar degeneration with tau positive inclusions (FTLD-tau) may also rarely have pyramidal signs particularly when associated with particular tau-gene (*MAPT*) mutations, such as K317M [24]. However, only sparse tau pathology was observed in frontal cortex in *this* case, which did not have an FTLD pathological phenotype, nor an FTD clinical phenotype, and there was no *MAPT* mutation.

BIBD is a rare disease and FUS inclusions are negative for tau. FTLD-FUS of the NIFID subtype has been reported in association with a progressive supranuclear palsy pattern of tau [25], but this does not resemble the tauopathy of this case. The coexistence of BIBD with an atypical tauopathy involving similar brain areas suggests a pathogenic relationship, and double staining showed co-pathology in pyramidal neurons. A notable feature of this case is the presence of GVD. Motor cortex is an unusual site for this pathology, although pyramidal layer of hippocampus is a typical site, These tau-containing structures may be related to macroautophagy [26], and disturbance of protein homeostasis and autophagy may be a common feature of neurodegenerative disorders. ALS/MND-associated mutant FUS has been shown to impair autophagy [27]. Furthermore, tau mRNA is a splicing target of FUS [28]. These suggest mechanisms by which FUS pathology may be a driver of tau pathology, so that the presence of these two unusual pathologies may be pathogenically linked in this case. However, the tau pathology here has a more restricted distribution than FUS, so that additional cellular factors may determine whether the pathologies are co-expressed. Whilst these findings may suggest a pathogenic interaction, they do not provide proof, and further cell biological studies and detailed studies of tau mRNA and protein may be warranted in FUS-pathology cases, even those without overt phospho-tau deposition.

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## **Author Contributions**

SBW carried out the neuropathological evaluation and wrote the manuscript except for the clinical sections. NSV wrote the clinical case description and the clinical section in the discussion. BEW carried out the electron microscopy and contributed to their interpretation. JRH and PGI contributed to the neuropathological interpretation. DJF carried out the double-staining immunohistochemistry and KS carried out the tau isoform immunohistochemistry. PJS oversaw the clinical management of the case and contributed to the clinicopathological interpretation. RW carried out additional double-staining immunofluorescence studies. All of the authors contributed to the final draft of the manuscript.

## **Conflict of Interest**

The authors declare that they have no conflict of interest.

## Figure Legends

**Figure 1: Motor Cortex Pathology.** A. Following stripping of the leptomeninges, atrophy is noted in the precentral gyrus (1). Mild atrophy is also apparent in the post-central gyrus (2) and superior parietal lobule (3). B. Coronal slice at the level of the lateral geniculate nuclei, showing bilateral atrophy of motor cortex (arrows). C. Low power view of motor cortex showing atrophy and spongiosis. D. Immunohistochemistry for GFAP demonstrates gliosis. E. Pyramidal neurone in motor cortex showing granulovacuolar degeneration (arrow). F. Basophilic inclusion within a neurone (arrow). Magnification bars: C 1000µm, D 500µm, E, F 10µm

**Figure 2: Immunohistochemical Findings in Motor Cortex.** A, B. FUS labels compact neuronal inclusions in pyramidal neurones (arrows). A ring-like inclusion is also seen in B (open arrow). Note variable nuclear staining. C. Labelling of inclusions in layer 2 for p62. D. Gallyas preparation showing lack of argyrophilia of a compact inclusion (arrow). E. Immunohistochemistry with the AT8 antibody to phospho-tau demonstrating extensive deposition in motor cortex. F. AT8 labels diffuse tau in neurones (arrows) and numerous neuropil threads. G. Immunohistochemistry to 3R tau does not label inclusions. H. Immunohistochemistry to 4R tau labels some neurones and (I.) neuropil threads. Magnification bars: A 1000µm, B, E 500µm, C, D, F 10µm, G 100µm, H,I 50µm

**Figure 3 Detail of inclusions in motor cortex.** A-B Double immunostaining for FUS (brown) and AT8 (purple). Neurites are AT8+, compact inclusions contain FUS. Fine granular positivity for AT8 and GVD are seen in neurones that also contain FUS (arrows), but some FUS positive neurones do not contain tau pathology (open arrow, B). Inset (B) shows an enlarged image of a neurone with more diffuse tau positive (purple) on a diffuse brown FUS+ background. Mag bars 50µm. D: Ultrastructural examination reveals circumscribed cytoplasmic inclusions. Mag bar 1000nm. E. Higher power view reveals helical polyribosome structures but no filamentous structures. Mag bar 200nm.

**Figure 4: Lower motor neurone and extramotor pathology.** A. Low power view of cervical cord showing neuronal loss from the anterior horns. B. CD68 immunohistochemistry revealing microglial up-regulation in the lateral corticospinal tract of the cord. C. FUS+ve inclusions in anterior horn motor neurones (arrow). D. TDP-43 immunohistochemistry reveals no inclusions and normal nuclear localisation. E. Spongiosis of primary sensory cortex. F. Neuronal loss and pigmentary incontinence in the substantia nigra. G. AT8+ inclusions in the CA1 region of the hippocampus. H. Basophilic inclusion in dentate neurone of the cerebellum (arrow). I. Inclusions in cerebellar dentate, labelled with immunohistochemistry to FUS. Magnification bars: A 500µm, B, DF, 100µm, C,G, I 50µm, H 10µm.

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