The clinical and neuroanatomical phenotype of FUS associated frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is genetically and pathologically heterogeneous. Until recently, two main pathological subtypes were recognised, defined by the presence of tau positive or tau negative, ubiquitin positive neuronal inclusions. However, the identification of TDP-43 as a major constituent of ubiquitinated inclusions led to descriptions of a smaller subgroup of patients with ubiquitin positive but TDP-43 negative pathology. Recently, the major constituent of the inclusions in such cases has been identified as FUS (‘fused-in sarcoma’) protein, implicated in RNA processing.1

We retrospectively reviewed all cases ascertained via a tertiary level cognitive disorders clinic between 1992 and 2009 with a clinical diagnosis of FTLD and neuropathological confirmation (post mortem or brain biopsy during life). Five of 100 patients were found to have FUS pathology (FUS1 with neuronal intermediate filament inclusion disease and four other cases with atypical FTLD with ubiquitin-positive inclusions).

CASE REPORTS

FUS1 was previously described as having young onset sporadic Pick’s disease.2 The patient presented with an 18 month history of progressive behavioural change with apathy, social withdrawal, reduced speech and fatuous giggling. The patient had also developed increased difficulty using their hands for everyday tasks. On examination the patient was distractible with impoverished, dysarthric speech and bilateral limb apraxia but no other neurological signs. Neuropsychometry demonstrated executive impairment and dyscalculia but normal naming and visuoperceptual skills. The patient was unable to perform tests of episodic memory. The condition deteriorated over the next 3 months with worsening apathy, development of urinary incontinence and falls. The patient was subsequently lost to follow-up.

FUS2 presented with a 1 year history of progressive personality change with disinhibition, restlessness, loss of initiative, behavioural rigidity, obsessions and increased alcohol consumption. The patient’s mother and maternal grandfather had both died aged in their 50s with dementia dominated by social withdrawal, behavioural rigidity, increased apathy and declining self-care. The patient complained of forgetfulness. Neurological examination was normal. Neuropsychometry demonstrated low normal performance on tests of verbal and non-verbal episodic memory and executive impairment. Over the next year spontaneous speech became sparse and there was increasing apathy with development of incontinence. The patient died 9 years after symptom onset.

FUS3 presented with a 4 year history of progressive behavioural impairment with apathy, depression and declining social withdrawal. The patient was initially assessed there had been episodes of stealing from shops. When initially assessed there was a child-like demeanour with disinhibition, counting rituals and little spontaneous speech. Neurological examination was normal. Neuropsychometry was limited by poor attention and irritability but demonstrated impairments of verbal and non-verbal episodic memory and executive functions with relatively intact naming. Subsequently there was increasing cognitive impairment with mutism and the patient died 11 years after symptom onset. FUS4 presented with a 4 year history of progressive memory impairment and apathy with social withdrawal, behavioural rigidity, increased apathy and declining self-care. In the year prior to assessment there had been episodes of stealing from shops. When initially assessed there was a child-like demeanour with disinhibition, counting rituals and little spontaneous speech. Neurological examination was normal. Neuropsychometry was limited by poor attention and irritability but demonstrated impairments of verbal and non-verbal episodic memory and executive functions with relatively intact naming. Subsequently there was increasing cognitive impairment with mutism and the patient died 11 years after symptom onset.

FUS5 presented with an 18 month history of progressive personality change with declining self-care, social withdrawal, depression, visual hallucinations and occasional auditory hallucinations of voices prompting the patient to commit suicide. The patient developed a sweet tooth and was occasionally inappropriate in public. On examination there was sparse, echolalic speech but no other neurological abnormalities. Neuropsychometry demonstrated only mild executive dysfunction. When reassessed a year later the patient was almost mute with emotional lability and frequent inappropriate behaviours. The patient died 6 years after symptom onset.

IMAGING ANALYSIS

Volumetric T1 weighted brain MRI was available for three patients (FUS1–3). All patients had asymmetrical cerebral atrophy, as evidenced by left/right hemisphere volume ratios (table 1). Caudate volumes were measured in all patients3 and found to be reduced compared with controls, particularly in the hemisphere where cortical atrophy was greater. A voxel based morphometry analysis4 (in comparison with an age matched control group, n=28) showed grey matter atrophy maximally affecting the orbitofrontal cortex, insula, anteromedial temporal lobe, anterior cingulate and caudate (figure 1).

DISCUSSION

All patients presented with a progressive behavioural syndrome fitting criteria for behavioural variant frontotemporal dementia5 with variable age at onset (range 27–51 years; mean 41.8 years) and clinical disease duration (range 5.5–11.3 years; mean 8.4 years). Cognitive impairment (mainly affecting executive and episodic memory functions) developed in all cases but was initially relatively minor in relation to behavioural dysfunction in three patients: Mini-Mental State Examination may therefore be normal early in the disease and assessment of behavioural symptoms is important. Only one patient (FUS1, the patient with neuronal intermediate filament inclusion disease) developed abnormal neurological signs (dysarthria and apraxia) during the period of follow-up. A neuroimaging analysis in three cases revealed asymmetrical cerebral atrophy chiefly affecting the orbitofrontal, insula and anterior temporal cortices, anterior cingulate and caudate.

The clinical features of our cases are similar to those previously described in association with FUS pathology.1 3 6 Age of disease onset in those previous cases varied from 28 to 65 years and disease duration ranged from 5 to 15 years. All patients developed progressive behavioural decline frequently characterised by apathy, social withdrawal and adynamia leading to mutism. Delusions and hallucinations prompted initial diagnosis of a psychosis in some cases. Cognitive impairment and (in some cases) extrapyramidal features supervened later in the course of the illness.

FUS mutations have been identified as an uncommon cause of apparently ‘sporadic’ FTLD.7 However, despite an autosomal dominant pattern family history in FUS2 here, no FUS mutations were identified, suggesting that FUS pathology in this family is due either to an undiscovered FUS mutation or a mutation in another unidentified gene.

The neuroimaging features in this series provide an anatomical substrate for the behavioural phenotype of FUS associated FTLD. Frontoinsular cortex and anterior cingulate are likely to constitute a functional network mediating complex social behaviours. Involvement of the anterior cingulate and caudate suggests a basis for the development of apathy in FUS associated FTLD: these structures are optimally located to integrate frontal cortical (executive) and limbic (affective) processing. Atrophy of the caudate nucleus has emerged here and in previous studies of FUS cases as a signal of frontosubcortical network damage.5

Further work in larger cohorts with detailed correlation of FUS associated FTLD...
in relation to other FTLD pathologies is needed to corroborate these findings and establish the extent to which they may reflect an underlying molecular specificity.

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Table 1 Summary of FUS (‘fused-in sarcoma’) cases: clinical, neuropsychological and MRI data

<table>
<thead>
<tr>
<th>FUS1</th>
<th>FUS2*</th>
<th>FUS3</th>
<th>FUS4</th>
<th>FUS5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>27</td>
<td>44</td>
<td>51</td>
<td>40</td>
</tr>
<tr>
<td>Total disease duration (years)</td>
<td>Not known</td>
<td>7.4</td>
<td>9.4</td>
<td>11.3</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Apathy, mutism, giggling</td>
<td>Disinhibition, apathy, obsessi</td>
<td>Apathy, forgetfulness</td>
<td>Apathy, sweet tooth, child-like</td>
</tr>
<tr>
<td>Family history</td>
<td>Nil</td>
<td>Mother and maternal grandfather had dementia (mother FUS positive pathology)</td>
<td>Father had a diagnosis of multiple sclerosis—died aged 55</td>
<td>Nil</td>
</tr>
<tr>
<td>Mini-Mental State Examination score (/30)</td>
<td>22</td>
<td>29</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>Dysarthria, limb apraxia</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Volumetric brain MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration at scan (years)</td>
<td>2.3</td>
<td>1.3</td>
<td>2.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Whole brain volume (as % of total intracranial volume)</td>
<td>64.0</td>
<td>68.4</td>
<td>64.0</td>
<td>N/A</td>
</tr>
<tr>
<td>Left/right hemisphere volume ratio</td>
<td>1.05</td>
<td>0.98</td>
<td>1.04</td>
<td>N/A</td>
</tr>
<tr>
<td>Left caudate volume (% of control mean)</td>
<td>98.6</td>
<td>60.3</td>
<td>91.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Right caudate volume (% of control mean)</td>
<td>71.8</td>
<td>61.3</td>
<td>73.2</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Verbal and performance IQ were measured using the Wechsler Adult Intelligence Scale-Revised. All patients were UK born and spoke English as a first language.

*Positive family history (FUS pathology in parent).
†Patient refused further testing.
N/A, not available; NT, not tested; VOSP, visual object and space perception battery.

Figure 1 Voxel based morphometry analysis on grey matter regions in the FUS (‘fused-in sarcoma’) group relative to healthy controls. Statistical parametric maps (SPMs) have been thresholded at p < 0.001 after false discovery rate correction over the whole brain volume and rendered on a study specific average group T1 weighted MRI template image in DARTEL space. The colour bar (lower right) indicates the t score. Left (L) and right (R) markers are shown for ease of reference.
UK. JW has received research support from the Wellcome Trust (Intermediate Clinical Fellowship).

Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the National Hospital for Neurology and Neurosurgery local ethics committee.

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