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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, obsessiveness and increased alcohol consumption. The patient's mother and maternal grandfather had both died aged in their 50s with dementia dominated by behavioural symptoms. The mother had FUS positive pathology at post mortem. Neurological examination was normal. Neuropsychometry demonstrated normal performance in a number of domains. Over the following year, increasing disinhibition and obsessiveness was exhibited with development of food fads and episodic memory impairment. The patient died 7 years after symptom onset. No mutations were identified in the FUS gene despite screening all exons.

FUS3 presented with a 4 year history of progressive behavioural impairment with apathy, decreased motivation 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.

FUS4 presented with a 4 year history of progressive memory impairment and apathy with social withdrawal, behavioural rigidity, increased alcohol use 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 patients[3] and found to be reduced compared with controls, particularly in the hemisphere where cortical atrophy was greater. A voxel based morphometry analysis[3] (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 dementia[4] 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

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

	FUS1	FUS2*		FUS3	FUS4	FUS5
Age at onset (years)	27	44		51	40	47
Total disease duration (years)	Not known	7.4		9.4	11.3	5.5
Clinical presentation	Apathy, mutism, giggling	Disinhibition, apathy, obsessionality		Apathy, forgetfulness	Apathy, sweet tooth, child-like	Depression, hallucinations, sweet tooth, emotional lability, mutism, echolalia
Family history	Nil	Mother and maternal grandfather had dementia (mother FUS positive pathology)		Father had a diagnosis of multiple sclerosis—died aged 55	Nil	Nil
Mini-Mental State Examination score (/30)	22	29		29	16	28
Neurological examination	Dysarthria, limb apraxia	Normal		Normal	Normal	Normal
Neuropsychometry						
Duration at assessment (years)	2.3	1.3	2.6	5.4	4.8	1.9
Verbal IQ	Unable	98	84	98	73	78
Performance IQ	Unable	121	101	101	74	85
Recognition memory test for words (/50)	Unable	45	30	40	Unable	48
Recognition memory test for faces (/50)	Unable	42	19	38	Unable	43
Graded naming test (/30)	18	27	19	20	15	20
VOSP incomplete letters (/20)	20	19	20	20	NT	18
Modified Wisconsin sorting test/Weigl test	Fail	Pass	†	Fail	NT	Pass
Volumetric brain MRI						
Duration at scan (years)	2.5	1.5		5.6	N/A	N/A
Whole brain volume (as % of total intracranial volume)	64.0	68.4		64.0	N/A	N/A
Left/right hemisphere volume ratio	1.05	0.98		1.04	N/A	N/A
Left caudate volume (% of control mean)	98.6	60.3		91.2	N/A	N/A
Right caudate volume (% of control mean)	71.8	61.3		73.2	N/A	N/A

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.

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 5 6] Age of disease onset in those previous cases varied from 28 to 65 years and disease duration ranged from 3 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,

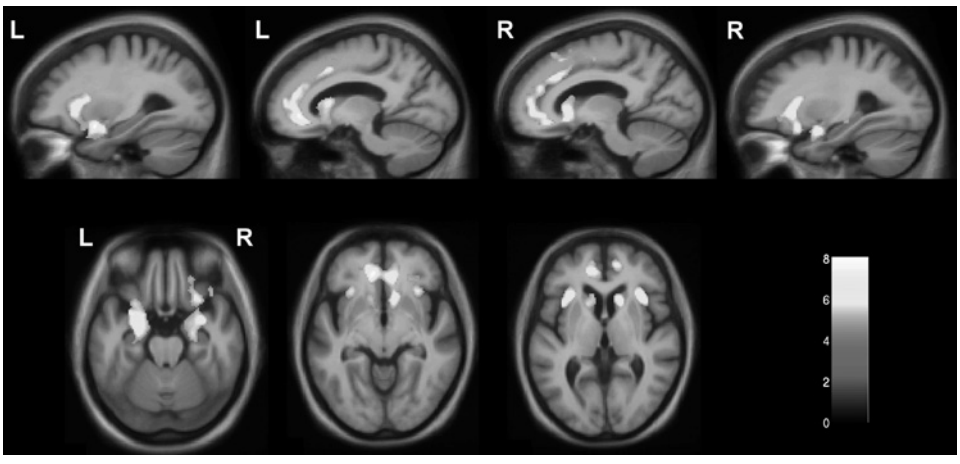

Figure 1 Voxel based morphometry analysis on grey matter regions in the FUS ('fused-in sarcoma') group relative to healthy controls. Statistical parametric maps (SPMs) have been thresholded at $p<0.001$ after false discovery rate correction over the whole brain volume and rendered on a study specific 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.

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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Virtual reality assessment for visuospatial neglect: importance of a dynamic task

Visuospatial neglect is a common consequence of damage to the right hemisphere in humans; it has been defined as a deficit in orienting towards, responding to and reporting stimuli that appear contralaterally to the side of the brain damage.[1] Assessment of unilateral neglect relies on a battery of quantitative and standardised tests,[2] with pencil and paper tests like the Bell test and behavioural tests, notably the Catherine Bergego Scale (CBS). Virtual reality (VR) has many qualities that give it rehabilitative potential for people with intellectual disabilities, both as an assessment and an intervention. It can provide a safe setting in which to practice skills that might carry too many risks in the real world. VR based tasks have been devised for assessment and rehabilitation of executive dysfunction, memory impairments, spatial ability impairments, attention deficits (see Rose and colleagues[3] for a review) and visual neglect (see Tsirlin and colleagues[4] for a review).

In this prospective study, right brain damaged patients and matched controls were assessed for visuospatial neglect with the use of a head mounted display VR system in a VR task close to everyday life with a virtual town through which the patient navigates. We aim to verify the applicability and interest of VR assessment of visuospatial neglect and navigation. Patients were consecutively included in a rehabilitation unit; eligible patients had a history of unilateral right brain vascular injury. Age and sex matched controls were included. MRI analysis was proposed following a standardised protocol, described elsewhere.[5] Neglect was assessed using the Bell test and the CBS. All subjects and controls received one session of virtual navigation. Patients were equipped with a head mounted display coupled with an electromagnetic sensor system and immersed in a virtual town in which they could move forward via a mouse click. Subjects sat on a swivel chair and had to turn on their own vertical axis in order to change their point of view and direction in the virtual town. Their task was to locate a main target (swings in a park) as well as counting bus stops along the way: the town had 13 bus stops, six on one side and seven on the other side of the street. Each time the subject passed a bus stop, the investigator would note whether it was reported or not, and its location considering the subject's orientation (right or left of the subject). Patients and matched controls were compared using the sign test for the number of omissions and ability to find the swings. All patients gave informed consent to participate in this study.

Nine patients (table 1), five men, were included, with a mean age of 50 years (range 28–67). Matched controls for age and sex were included. Patients had sustained a right hemispheric cerebrovascular accident, seven of them ischaemic, in the months or years preceding assessment (mean time since onset 16 months). Six patients were included in the MRI analysis; three had haemorrhage and three had stroke. Five presented with signs of visuospatial neglect based on the CBS scale. Superimposition of the regions of interest to the anatomical automatic labelling template of the SPM5 package and the white matter fasciculi[6] showed that the only structure which overlapped lesions of all six patients was the right inferior fronto-occipital fasciculus. The degree of intersection of the right inferior fronto-occipital fasciculus and the stroke lesions ranged from 23% to 76% (figure 1). Six patients presented with severe hemiplegia without any spontaneous movement in the upper limbs. Two patients showed no sign of spatial neglect considering their results on the two standardised tests (Bell test and CBS). Three patients presented with moderate visuospatial neglect. Four patients presented with severe visuospatial neglect.

Based on the VR assessment, patients omitted significantly more bus stops than their matched controls (Sign test $p<0.01$). The difference between patients and controls was also significant for left minus right omissions (Sign test $p<0.05$). Patients omitted significantly more left than right bus stops while the difference did not reach significance for the controls. Only four of nine patients found the swings while all controls did. However, patients and controls took the same time to find them. Intervention from the carer was never necessary for the controls while two patients needed help to disentangle them from a corner of a street in the virtual town.

Real and virtual tests had concordant results only for three patients: two patients who needed help in the virtual reality task showed severe neglect in the standardised tests. The third patient who exhibited visuospatial neglect on both the Bell test and the CBS showed visuospatial neglect in the VR task by omitting more left bus stops than the controls.