Frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes: broadening the clinical picture to include progressive supranuclear palsy


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Summary

The frontotemporal lobar degenerations (FTLDs) are a group of disorders in which the clinical picture is not necessarily predictive of the underlying neuropathology. The FTLD with ubiquitin-only-immunoreactive neuronal changes (FTLD-U) subtype is pathologically characterized by ubiquitin-positive, tau and α-synuclein-negative neuronal cytoplasmic inclusions in the frontotemporal cortex and hippocampal dentate fascia. When similar pathological changes are accompanied by histological features of motor neuron disease (MND), the term FTLD-MND is used. The latter pathological changes may be found in patients with or without clinical evidence of MND. We retrospectively reviewed the clinical details of three patients with a rapidly progressive, levodopa-unresponsive bradykinetic-rigid syndrome and frontal cognitive impairment. A diagnosis of progressive supranuclear palsy (PSP) had been considered in all three cases at initial presentation. Two of the cases fulfilled clinical diagnostic criteria for PSP, which was the final clinical diagnosis during life. Pathological analysis showed typical histological appearances of FTLD-MND in two cases and of FTLD-U in one case. Semi-quantitative analysis of pathological load seemed to correlate with the clinical phenotype. FTLD-U or FTLD-MND should be considered in the differential diagnosis of progressive frontal dementia with an akinetic rigid syndrome and supranuclear gaze palsy or Steele–Richardson–Olszewski disease.

Keywords: FTLD-U; FTLD-MND; progressive supranuclear palsy; clinico-pathological correlation

Abbreviations: CAA = cerebral amyloid angiopathy; CBD = corticobasal degeneration; DUI = dementia with tau-negative ubiquitin-positive inclusions; EMG = electromyography; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; FTLD-U = FTLD with ubiquitin-only-immunoreactive neuronal changes; FTLD-MND = FTLD with motor neuron disease; FTDP-17 = frontotemporal dementia with parkinsonism linked to chromosome 17; ITSNU = inclusions, tau and α-synuclein-negative, ubiquitinated; MMSE = mini-mental state examination; MND = motor neuron disease; MND-ID = motor neuron disease inclusion body dementia; NINDS-SPSP = National Institute of Neurological Disorders and Stroke–Society for Progressive Supranuclear Palsy; OKN = optokinetic nystagmus; PNFA = progressive non-fluent aphasia; PSP = progressive supranuclear palsy; riMLF = rostral interstitial nucleus of the medial longitudinal fascicle; SD = semantic dementia; WAIS-R = revised Weschler adult intelligence scale

Introduction

The neurodegenerative diseases known as frontotemporal lobar degenerations (FTLDs) have overlapping clinical syndromes and may have a number of different histopathological appearances (Neary et al., 1998; Lowe and Rossor, 2003). The most recent reports quote the prevalence of FTLD as 9.4 per 100 000 at age 60–69 years (Rosso et al., 2003) and FTLD may be as common as Alzheimer’s disease in those under 65 years of age. The three best delineated clinical syndromes are frontotemporal dementia (FTD), progressive non-fluent aphasia (PNFA) and semantic dementia (SD). However, the clinical subtype does not accurately predict the nature of the underlying degenerative disease and, therefore, it has been proposed that these three clinical sub-types be subsumed under the broader term of FTD. Motor neuron disease (MND) is recognized to be associated with FTD (Bak and Hodges, 2001) and the commonest presentation is with ‘frontal’ behavioural disturbance, followed by the emergence of clinical features of MND.

Neuropathological studies have shown that FTD may be associated with a number of different disease entities including Pick’s disease, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) (Mann et al., 1993; Cooper et al., 1995; Lowe and Rossor, 2003), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) (Foster et al., 1997), FTLD otherwise known as dementia lacking distinctive histology (Knopman et al., 1990), FTLD with ubiquitin-only-immunoreactive neuronal changes (FTLD-U), FTLD accompanied by histological features of motor neuron disease (FTLD-MND) (Jackson et al., 1996; Lowe and Rossor, 2003) and neurofilament inclusion body disease (Bigio et al., 2003; Cairns et al., 2003; Josephs et al., 2003). A recent study showed that, in 62% of FTD cases, the underlying neuropathological changes were those of FTLD-U (Josephs et al., 2004).

In the past, different terminologies have been used for the occurrence of ubiquitin-positive, tau and α-synuclein-negative inclusions in the context of sporadic and familial FTD. These include motor neuron disease inclusion dementia (MND-ID) (Jackson et al., 1996), familial frontotemporal dementia with ubiquitin-positive, tau-negative inclusion bodies (inclusions, tau and α-synuclein-negative, ubiquini- nated or ITSNU) (Kertesz et al., 2000), and dementia with tau-negative ubiquitin-positive inclusions (DUI) (Rossor et al., 2000). Most recently the terms FTLD-U and FTLDMND have been adopted (Lowe and Rossor, 2003) and this terminology will be used in this study.

Cases of FTLD-U are neuropathologically characterized by ubiquitin-positive, tau and α-synuclein-negative inclusions, similar to those described in cases of MND with associated dementia. Such inclusions are present in the frontal and temporal cortices and in hippocampal dentate granule cells. Neuritic processes immunoreactive for ubiquitin may also be present. Cases with additional pathological features of MND in the brainstem and spinal cord, with or without clinically documented features of MND, have been described and are classified pathologically as FTLD-MND (Holton et al., 2002; Lowe and Rossor, 2003).

The classical clinical presentation of PSP (Steele–Richardson–Olszewski disease) is with early gait disturbance, postural instability and backward falls. Other early features include frontotemporal behavioural and cognitive changes, slurring of speech, visual symptoms and slowness beginning after the age of 40 years and usually in the seventh and eighth decades of life (Steele et al., 1964; Lees, 1987). In typical cases there is vertical supranuclear gaze palsy with the earliest neuro-ophthalmological finding being slowed vertical saccades (Stell and Bronstein, 1994). Supranuclear limitation of downgaze leading to falls downstairs and ‘the dirty tie syndrome’ are characteristic. Other features supporting the diagnosis are frontalis overactivity, tonic inhibition of levator palpebrae (apraxia of eyelid opening), pseudobulbar palsy, severe axial rigidity with an upright posture and neck extension and frontal executive dysfunction. PSP is un-responsive to levodopa and progresses relentlessly with a mean duration from onset to death of around 6 years. The characteristic neuropathological changes are tau-positive neurofibrillary tangles, neuropil threads, tufted astrocytes and oligodendrogial coiled bodies in structures including the midbrain, cerebellum and basal ganglia as well as pre-motor and motor cortical areas (Hauw et al., 1994; Daniel et al., 1995; Litvan et al., 1996; Verny et al., 1996). In the normal adult human brain, tau is present as six different isoforms, generated by alternative splicing of exons 2 and 3 in the N-terminal region and the presence of either three or four repeated (3R and 4R) microtubule-binding domains encoded by exon 10 of the tau gene. In PSP, tau deposits largely consist of 4R isoforms (Morris et al., 1999; de Silva et al., 2003). Most individuals with typical PSP are homozygous for an intronic polymorphism (A0) (Conrad et al., 1997). This allele is linked to other polymorphic alleles on the tau gene, defining the H1 haplotype, and there is a strong association between clinically typical PSP and H1 homozygosity (Baker et al., 1999).

There is a widening spectrum of clinical phenotypes documented in PSP and pathologically confirmed cases without an eye movement disorder have been described (Daniel et al., 1995; Revesz et al., 1996; Morris et al., 2002). A number of other neurodegenerative and vascular pathologies have been associated with a clinical picture of PSP including diffuse cerebrovascular disease (Winikates and Jankovic, 1994; Josephs et al., 2002), cerebral amyloid angiopathy with MND (Weeks et al., 2003), CBD (Litvan et al., 1997), FTDP-17 (Morris et al., 2003; Soliveri et al., 2003), subcortical gliosis with prion protein deposition (Will et al., 1988; Revesz et al., 1995) and diffuse Lewy body disease (Fearnley et al., 1991; de Bruin et al., 1992; Nakashima et al., 2003). Midbrain tumours (Silbert et al., 1993), Whipple’s disease (Averbuch-Heller et al., 1999), neuro-syphilis
(Murialdo et al., 2000) and neuroleptics (Campdelacreu et al., 2004) are other rare causes of a similar clinical picture.

We describe three cases in which the combination of a bradykinetic-rigid syndrome and frontal cognitive impairment resulted in a diagnosis of PSP being considered during the disease course and in two cases it was the final clinical diagnosis. Neuropathological examination revealed histological appearances of FTLD-U in one case and FTLD-MND in two cases indicating that a syndrome closely resembling PSP may be seen as part of the clinical presentation of these pathological disorders.

**Case reports**

The clinical features in all three cases are summarized in Table 1.

**Case 1**

A 75-year-old man presented with unsteadiness and a short episode of confusion. He had complained of tinnitus for 10 years, which was thought to be due to anti-tuberculous therapy as a young man. An MRI of the brain was normal. His unsteadiness progressed, he became depressed and developed difficulty with word finding, concentration and short-term memory. Two of his four children had a tremor and his brother and mother had been diagnosed with Parkinson’s disease. Neurological referral was made at the age of 78 years following two falls. On examination he had a mini-mental state examination (MMSE) score of 29 out of 30 (Folstein et al., 1975), decreased speech production, hypomimia, bradykinesia and cogwheel rigidity at the wrists with no resting tremor. Neck movements were reduced, the right plantar was extensor and he had impaired postural reflexes. Repeat MRI brain scanning revealed white matter signal change suggestive of small vessel disease. Levodopa challenge resulted in mild improvement but this was not sustained with continued therapy and a diagnosis of ‘atypical parkinsonism’ was made.

One year later he had a markedly reduced blink rate, blepharospasm and bilateral Babinski signs. Eye movement examination revealed slow jerky pursuits and slow,
hypometric vertical saccades. He developed marked frontal release signs with increasing cognitive blunting, scoring only 16 out of 30 on a repeat MMSE. He died of bronchopneumonia 5 years after the disease onset, with a final clinical diagnosis of PSP.

Neuropsychology: Case 1

The patient was assessed on the revised Weschler adult intelligence scale (WAIS-R) (Warrington et al., 1986) on two occasions, 7 months apart. Verbal and performance IQs were 100 and 116, and 93 and 98, respectively. There was a decline in the verbal and visual versions of the short recognition memory test (Warrington, 1984) (21 out of 25 to 19 out of 25 verbal and 23 out of 25 to 21 out of 25 visual). Spontaneous speech was slow and lacked fluency, with evidence of word finding difficulties, but the graded naming test result was static (23 out of 30, previously 22 out of 30) (McKenna and Warrington, 1983). Visual perceptual functions remained satisfactory as measured on object decision (19 out of 20, previously 20 out of 20) and cube analysis (9 out of 10, previously 8 out of 10). Tests of frontal executive function were severely impaired. He was only able to give two solutions on the Weigl sorting test (Weigl, 1927) and interpretation of proverbs demonstrated concrete thinking. Cognitive estimates (Shallice and Evans, 1978) were abnormal and word fluency (Spren and Strauss, 1998) was severely reduced (2 in 60 s, previously 4). There was marked slowness of thought throughout the testing.

Case 2

A 49-year-old right-handed lady presented after losing her job because of elementary and uncharacteristic mistakes. Over the next 6 months her reactions became slowed and her gait laboured. She occasionally behaved aggressively towards her husband and complained that her right eye was closing of its own accord. Over the next 6 months, she developed difficulty swallowing and became incontinent of urine without concern. MRI scanning showed enlargement of the lateral, third and fourth ventricles. Visual evoked potentials, CSF analysis and EEG were normal. Within 12 months of symptom onset she developed falls, her speech was increasingly slurred and she exhibited disinhibited, hypersexual behaviour.

Examination demonstrated mild confusion, a frozen face, inappropriate laughter and jocularity and poor concentration. She had a positive glabellar tap, bilateral grasp reflexes, a brisk jaw jerk, impaired postural reflexes and severe dysarthria. Her gait was slow and unsteady and she had a combination of extrapyramidal and pyramidal increased tone in the arms and legs with axial rigidity. Detailed neuro-ophthalmological examination revealed vertical supranuclear gaze palsy, slow horizontal saccades and reduced smooth pursuits. Low amplitude optokinetic nystagmus (OKN) was preserved in all directions. Coordination was normal. Routine biochemical and haematological investigations were normal including repeat CSF analysis, EMG and nerve conduction studies, serum copper and caeruloplasmin. Cardiovascular autonomic function tests, including a cold pressor test and blood pressure responses during isometric exercise were normal. There was no improvement with levodopa. She deteriorated cognitively, had increasing falls and died from bronchopneumonia 5 years after disease onset. The final clinical diagnosis was PSP.

Neuropsychology: Case 2

Formal neuropsychological assessment was performed once during the illness but was hampered by anarthria and marked distractibility. WAIS assessment provided a performance IQ of 84. She scored poorly on non-verbal reasoning tests (advanced progressive matrices, 3 out of 12 correct). She scored 27 out of 30 on a recognition memory test involving coloured matrices and 19 out of 20 on the fragmented letters test of perception, counting 9 out of 10 dots correctly. With written answers, she was able to name 11 out of 12 objects correctly from their descriptions. She failed the Weigl sorting test, finding only one solution (colour). In summary, she had frontal executive dysfunction and memory functions were slightly impaired, with no localizing or lateralizing features.

Case 3

A 60-year-old man presented with an 18-month history of problems with grip in his dominant (right) hand. He had been emotionally labile for 12 months with increased irritability and for 6 months he complained of poor balance and several falls as well as slow, slurred speech, difficulty with handwriting and mild word-finding difficulties. He had been treated for hypertension and drank 20 units of alcohol weekly. On examination, he had upper limb bradykinesia, worse on the right than the left and marked extrapyramidal dysarthrophonia. There was no tremor, rigidity, dyspraxia or abnormality of eye movements. The early falls in the context of a brady-kinetic-rigid syndrome raised the possibility of PSP.

After 4 months he was still able to work but had developed, emotional lability with loss of motivation, more frequent falls, micrographia, increasing dysarthria and occasional dysphagia for liquids. His MMSE was 22 out of 30. He had normal eye movements, bilateral palmo-mental reflexes, brisk reflexes and fasciculations in all four limbs, but not his tongue. Routine biochemical and haematological investigations, auto-immune screen and CSF examination were normal. Detailed nerve conduction studies and EMG on three occasions, including sampling of the tongue, revealed no evidence of chronic partial denervation. A levodopa challenge was negative and there was no evidence of cardiovascular autonomic failure. MRI brain scanning on two occasions was normal. An atypical neurodegenerative
motor neuron disease with extrapyramidal and cognitive features was diagnosed. He continued to deteriorate with progressively impaired mobility and rigidity and died 4 years after the disease onset.

Neuropsychology: Case 3

Neuropsychological testing demonstrated a national adult reading test (NART) IQ of 110 (Nelson, 1982) and verbal IQ on the WAIS-R of 102 suggesting a slight decline. On a recognition memory test for faces he scored 45 out of 50 and for words 45 out of 50. On a graded difficulty object naming test, he scored 25 out of 30 and 18 out of 20 on the object decision test of visual perception. Verbal fluency was weak (F, A and S = 29 in 60 s), but on other tests such as the Wisconsin card sorting test (Heaton, 1981) and cognitive estimates he performed satisfactorily. On the digit symbol test of speed and attention, he was slow, scoring 24 in 90 s.

Application of the National Institute of Neurological Disorders and Stroke–Society for Progressive Supranuclear Palsy (NINDS-SPSP) clinical diagnostic criteria for PSP in these three cases, provides a diagnosis of clinically probable PSP in Case 1 and clinically definite PSP in Case 2 (Litvan et al., 2003). The presence of widespread fasciculations in the third case excludes a clinical diagnosis of PSP.

Methods

Neuropathological procedure

Consent for post-mortem examination and research was obtained in accordance with routine Queen Square Brain Bank procedures. Each brain was divided with a midline sagittal incision and one half brain was fixed in 10% buffered formalin for a minimum of 4 weeks. The other half was frozen and stored at −80°C. Fixed half brains were sliced in the coronal plane and tissue blocks selected. Following processing and paraffin wax embedding, 7 μm sections were cut and stained with routine methods including haematoxylin and eosin, luxol fast blue/cresyl violet and Bielschowsky’s silver impregnation. Immunohistochemical staining was performed using a standard avidin–biotin complex protocol utilizing the following antibodies as described previously (Josephs et al., 2003): NF cocktail (ICN Pharmaceuticals); ubiquitin (DAKO); tau (DAKO); tau (AT8; Autogen Bioclear); glial fibrillary acidic protein (DAKO); Aβ (DAKO); α-synuclein (Autogen Bioclear). Antibody binding sites were visualized using the chromogen diaminobenzidine.

Diagnosis

A diagnosis of FTLD-U was made on finding ubiquitin-positive, tau and α-synuclein-negative, abnormal neurites and/or neuronal intra-cytoplasmic inclusions in either the hippocampal dentate granule cell layer and/or the frontal or temporal cortex in the absence of pathological evidence of MND. The diagnosis of FTLD-MND was made when the above findings were associated with histological features of MND, including axonal loss in the pyramidal tracts, neuronal loss in the brainstem motor nuclei or spinal cord anterior horns and/or characteristic ubiquitin-positive cytoplasmic neuronal inclusions in motor neurons.

Semiquantitative analysis

Neocortical microvacuolation, caudate atrophy, axonal loss in the brainstem and spinal cord pyramidal tracts and neuronal loss in the caudate, putamen, substantia nigra, locus coeruleus, XIIth nerve nucleus and spinal cord anterior horns were assessed and graded on a four-point scale in which 0 = unaffected; + = mildly affected; ++ = moderately affected and +++ = severely affected.

Using ubiquitin immunohistochemistry the number of ubiquitinated intraneuronal inclusions in the frontal and temporal neocortices, dentate fascia, caudate, putamen, subthalamic nucleus, IIIrd nerve nuclear complex, pons, XIIth nerve nucleus, dentate nucleus, and anterior horn motor neurons and also the number of ubiquitin-positive neurites in the frontal and temporal neocortices were graded in a similar manner, whereby 0 = absent; + = a small number of inclusions/neurites; ++ = moderate numbers of inclusions/neurites and +++ = frequent inclusions/neurites.

Results

Macroscopic findings

The brain from Case 1 weighed 1360 g. The external surface and cut surfaces of the cerebral hemisphere and cerebellum
were normal. Pigmentation of the substantia nigra was reduced and the remaining brainstem was unremarkable.

In Case 2 the brain weight was 780 g. There was severe cortical atrophy with widening of the sulci and ‘knife-edge’ gyri affecting the frontal and temporal lobes, while the parieto-occipital regions were spared. Slicing the cerebral hemisphere revealed marked dilatation of the lateral ventricle and thinning of the cortical ribbon in the frontal and temporal lobes with reduction in bulk of the underlying white matter. The hippocampus and caudate nucleus were severely atrophic and the latter was discoloured throughout its extent (Fig. 1). The putamen, globus pallidus, thalamus and subthalamic nucleus showed less severe reduction in bulk. There was marked pallor of the substantia nigra. The cerebral peduncles, pontine base and medullary pyramids were reduced in bulk. The cerebellum was unremarkable. In the spinal cord grey discolouration of the lateral columns was noted.

Case 3 (brain weight 1415 g) showed no evidence of cortical atrophy and coronal slices of the cerebral hemisphere revealed no abnormalities. The middle and lateral parts of the substantia nigra were pale, as was the locus coeruleus. The brainstem and cerebellum were otherwise normal.

**Microscopic findings**

All three cases showed similar features and these will be described together with exceptional findings reported separately. The semiquantitative analysis of the histological features is summarized in Table 2.

All cases showed a variable degree of microvacuolation in layer 2 of the frontal and temporal neocortices which was most marked in the frontal lobe of Case 2. Immunohistochemical staining for ubiquitin revealed small numbers of neuronal cytoplasmic inclusions in cortical neurons in the upper laminae of the frontal neocortex in all cases and in the temporal neocortex in Case 1 (Fig. 2B). Such inclusions were negative using immunohistochemical staining for tau, α-synuclein and neurofilaments with the exception of scanty inclusions in Case 2 which were neurofilament-positive. Occasional comma-shaped ubiquitin-positive neurites were also observed in the frontal neocortex in Cases 1 and 3 and in the temporal cortex in Case 1 (Fig. 2B, inset). The hippocampal dentate fascia contained ubiquitin-immunoreactive neuronal cytoplasmic inclusions in Cases 1 and 2 (Fig. 2A).

Scanty ubiquitinated neuronal cytoplasmic inclusions were observed in the XIIth nerve nucleus in Case 3 only, although there was marked neuronal loss in this structure in Case 2, while in Case 1 it was unaffected. There was severe myelin pallor and axonal depletion in the brainstem pyramidal tracts in Case 2, while in Cases 1 and 3 they were unaffected. Examination of the spinal cord in Case 2, which was the only case in which the cord was available, showed myelin pallor in the lateral columns and depletion of anterior horn cells in the cervical and thoracic regions, with small numbers

<table>
<thead>
<tr>
<th>Feature</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tr>
<td>Frontal cortex microvacuolation</td>
<td>++</td>
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<tr>
<td>Frontal cortex ubiquitinated neurites</td>
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<td>Frontal cortex ubiquitinated inclusions</td>
<td>++</td>
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<td>Temporal cortex microvacuolation</td>
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<td>Temporal cortex ubiquitinated neurites</td>
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<td>Temporal cortex ubiquitinated inclusions</td>
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<td>Dentate fascia ubiquitinated inclusions</td>
<td>++++</td>
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<td>Brainstem pyramidal tract axonal loss</td>
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<td>XII nerve nucleus neuronal loss</td>
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<td>Spinal cord pyramidal tract axonal loss</td>
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N/A = Not available for examination; 0 = unaffected; + = mildly affected or a small number of inclusions/neurites; ++ = moderately affected or a moderate number of inclusions/neurites; +++ = severely affected or frequent inclusions/neurites.
of chromatolytic neurons, axonal swellings and ubiquitin-positive skein-like intraneuronal inclusions (Fig. 2C).

Only limited evaluation of the nuclei involved in the control of eye movements was possible as many areas were not available for examination. In Case 2 basophilic neuronal inclusions were found in the IIIrd nerve nucleus motor neurons as described below. This nucleus appeared to be unaffected in Case 1 and could not be examined in Case 3.

In all three cases small numbers of skein-like ubiquitin-positive skein-like intraneuronal inclusions (Fig. 2D). Small numbers of ubiquitin-positive inclusions similar to those described in the neocortex and dentate fascia were found in small striatal neurons (Fig. 2E). The subthalamic nucleus was affected in Cases 2 and 3. In Case 2 there was severe gliosis with relative neuronal preservation although a proportion of neurons contained ubiquitinated basophilic inclusions. Case 3 showed no significant neuronal loss, although ubiquitinated inclusions were observed. The substantia nigra showed mild neuronal loss in Cases 1 and 3 and severe neuronal loss with small numbers of ubiquitin-positive neuronal inclusions in Case 2. The nuclei of the pontine base were unaffected in Cases 1 and 3, although small numbers of neurons in Case 2 contained basophilic inclusions some of which were ubiquitin-positive. Similarly the dentate nucleus was affected in Case 2 only, in which it was found to contain scanty basophilic inclusions, although no inclusions were seen using ubiquitin immunohistochemistry.

Case 2 showed several features not found in either of the other cases. In addition to the neocortical and dentate fascia pathology described above, there was severe neuronal loss and gliosis of the caudate nucleus and substantia nigra, while the putamen, globus pallidus and locus coeruleus were less severely affected. Well-defined basophilic neuronal cytoplasmic inclusions, a proportion of which were also ubiquitin-positive, were identified in a number of regions including the caudate, putamen, globus pallidus, subthalamic nucleus, substantia nigra, midbrain periaqueductal grey matter, IIIrd nerve motor neurons, Edinger–Westphal nucleus, pontine tegmentum, pontine base, reticular formation of the medulla and dentate nucleus (Fig. 2F).

Both Cases 2 and 3 had a minor degree of pathological ageing with scanty tau-positive neurofibrillary tangles in the hippocampal formation, neocortex, substantia nigra and locus coeruleus but no glial tau pathology. No Aβ deposits were found and staining for α-synuclein revealed no brainstem or cortical Lewy bodies or glial cytoplasmic inclusions in any of the cases.
Discussion

Behavioural change and/or progressive language dysfunction forms the basis of the clinical picture in the majority of cases of FTD. The concept that the entities of FTLD-U and FTLD-MND form the basis of FTD in a proportion of cases has emerged over the last few years (Jackson et al., 1996; Lowe and Rossor, 2003). The underlying aetiology of FTLD-U and FTLD-MND is unknown but around 15% of cases are familial (Gunnarsson et al., 1991; Kertesz et al., 2000) and some of the latter have been associated with intranuclear ubiquitin-positive inclusions in addition to cytoplasmic inclusions (Mackenzie and Feldman, 2003a).

Ubiquitinated inclusions have been reported in the hippocampal dentate fascia in demented and non-demented patients with MND, although in cases with MND and dementia, a greater frequency of neocortical ubiquitin pathology was found (Wilson et al., 2001; Kawashima et al., 2001; Mackenzie and Feldman, 2003b). Cognitive impairment may be underestimated in MND if patients are not adequately assessed late in the disease course and as many as one-third may have cognitive impairment reaching research criteria for FTLD (Lomen-Hoerth et al., 2003). Conversely, FTD cases presenting to dementia clinics are likely to have marked cognitive impairment and the clinical features of MND may be underestimated (Lomen-Hoerth et al., 2002).

The cases we describe differ slightly in their clinical presentations. Case 2 presented with rapidly worsening frontal behavioural problems and formal neuropsychological examination demonstrated significant frontal executive dysfunction. Pathological examination confirmed severe frontal cortical changes. The combination of severely slowed information processing and marked early executive dysfunction are characteristic of PSP and have been suggested to help in differentiating it from some other degenerative dementias (Albert et al., 1974; Litvan, 1994). Despite this, features of ‘cortical dementia’ such as dynamic aphasia have been occasionally reported in PSP (Esmonde et al., 1996). In contrast, cortical dementia with dysphasia, meeting Neary criteria for semantic dementia is well recognized in FTLD-U (Rossor et al., 2000) relating specifically to regional cortical atrophy. In the cases in whom the term MND-ID was originally coined, the cognitive impairment described indicates prominent frontal behavioural changes, similar to two of our cases, as well as word finding difficulties (Jackson et al., 1996).

Applying the NINDS-SPSP clinical diagnostic criteria for PSP retrospectively to these cases provides a diagnosis of clinically probable PSP in Case 1 and clinically definite PSP in Case 2 (Litvan et al., 2003). The early postural instability and falls in the context of frontal executive dysfunction with bradykinesia and rigidity meant that PSP was considered in Case 3, but the development of fasciculations and the absence of gaze palsy, excluded it as the final clinical diagnosis. None of the clinical exclusion criteria for PSP, which include features indicating an alternative diagnosis such as an alien limb, cortical sensory loss or early autonomic failure, were present in Cases 1 or 2. Even the most rigorous clinical diagnostic criteria can be expected to have limitations, especially in the face of the increasing phenotypic variation of rare diseases such as FTLD-U and FTLD-MND.

All three of our cases exhibited bradykinesia and rigidity and had variable degrees of neuronal loss in the substantia nigra. Extrapyramidal signs are recognized in MND with or without dementia and MND may be regarded as a multisystem degenerative disease. A number of studies have described cell loss in the substantia nigra in MND and FTLD-MND, sometimes in association with ubiquitin-positive intraneuronal inclusions of either skein or Lewy body-like type (Jackson et al., 1996; Machida et al., 1999; Su et al., 1999; Al Sarraj et al., 2002; Sudo et al., 2002; Mackenzie and Feldman, 2004). Studies describing the co-existence of Lewy bodies in the substantia nigra and pathological changes of MND are rare and should be interpreted with caution without α-synuclein immunohistochemistry to confirm the nature of the inclusions (Williams et al., 1995; Qureshi et al., 1996).

Neuronal loss in the neostriatum has also been described in MND and FTLD-MND (Holton et al., 2002; Sudo et al., 2002) and may be associated with ubiquitin-positive inclusions in the cytoplasm of small neurons (Kawashima et al., 2001; Wakabayashi et al., 2001; Mackenzie and Feldman, 2004). These inclusions should be distinguished from the skein-like inclusions found in large neurons of the striatum in association with normal ageing (Kawashima et al., 2000). Each of our cases had both disease-associated ubiquitin-positive inclusions in the small neurons of the striatum and also the skein-like inclusions described in ageing. The striatum was very severely affected in Case 2 of our series with severe neuronal loss and gliosis in the caudate nucleus, while the putamen and globus pallidus were less severely affected. In these areas, a proportion of neurons contained basophilic cytoplasmic inclusions, at least some of which displayed weak ubiquitin immunoreactivity. Similar inclusions were also found in brainstem structures including the substantia nigra and IIId nerve nucleus. Basophilic inclusions of this type have previously been described in FTLD-MND (Holton et al., 2002) and MND (Oda et al., 1978; Kusaka et al., 1993; Sasaki et al., 2001; Hilton and McLean, 2002). Involvement of the subthalamic nucleus has been reported in a small number of MND patients (Hudson, 1981; Gray et al., 1985; Bergmann et al., 1993; Sudo et al., 2002) and we found severe gliosis with moderate numbers of ubiquitinated inclusions in Case 2, while a small number of ubiquitinated inclusions was seen in Case 3.

The presence of slowed vertical saccades and vertical supranuclear gaze palsy are the features that resulted in a clinical diagnosis of PSP in two of our cases. In Case 2 where OKN was evaluated, it was preserved in all directions, while in typical PSP, testing OKN should result in a tonic drift of the eyes in the direction of the slow phase (Dix et al., 1971). The supranuclear control of eye movements depends on the integrity of cortical regions and subcortical nuclei such as the
basal ganglia as well as the pontine and mesencephalic reticular formation, the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and other mesencephalic nuclei. The omnipause neurons in the nucleus raphe interpositus gate activity of burst neurons for vertical saccades (Bhidayasiri et al., 2001) and in PSP, the density of tau-positive pathology in this nucleus correlates with the presence or absence of supranuclear gaze palsy (Revesz et al., 1996). Unfortunately, neither the riMLF nor the nucleus raphe interpositus were available for examination in any of our cases. Gaze palsies have been documented in MND (Mizutani et al., 1992; Okuda et al., 1992; Okamoto et al., 1993), although it is not clear from these studies whether pathological changes were apparent in the brainstem structures known to be involved in the supranuclear control of eye movements. This issue has been addressed in a study in which cell loss in the riMLF was demonstrated in two cases of MND (Averbuch-Heller et al., 1998). Involvement of the IIrN, IVth and VIth cranial nerve nuclei is well described in MND, particularly in advanced cases (Harvey et al., 1979; Mizutani et al., 1992; Okamoto et al., 1993; Komachi et al., 1994; Yuki et al., 1995). In our series, the IIrN nerve nucleus in Case 2 contained ubiquitin-positive inclusions but it was unaffected in Case 1 and was unavailable for study in Case 3.

Although Case 3 in our series had extensive, clinically evident fasciculations, there was no evidence of motor unit denervation on EMG. The spinal cord was not available but ubiquitin-positive inclusions in the hypoglossal nucleus confirmed the pathological diagnosis of FTLD-MND. The EMG undertaken in Case 2, 3 years prior to death, did not reveal changes suggestive of MND. FTLD-MND was the neuropathological diagnosis in this case based on the finding of degeneration in the pyramidal tracts, cell loss in the Xth cranial nerve nucleus and anterior horn of the spinal cord with ubiquitin-positive immunoreactive neuronal inclusions in the latter. In the series of cases of FTLD-U published by Jackson and colleagues, which was limited by the absence of spinal cord for neuropathological examination, no patients had pyramidal signs, although two cases would now be considered to represent FTLD-MND as there was pathological involvement of the nucleus ambiguus (Jackson et al., 1996).

In a recent report, a fulminant PSP-like syndrome was attributed to cerebral amyloid angiopathy (CAA) and changes of FTLD-MND. Although there was mild cell loss in the substantia nigra other brainstem structures were regarded as normal and there was no CAA in these areas. It seems likely that the bradykinesia, rigidity and supranuclear gaze palsy documented in the case described is attributable to FTLD-MND rather than CAA and thus that case is similar to those which we present (Weeks et al., 2003).

In all neurodegenerative diseases, it is not necessarily the type of pathology present, but the rate of degeneration and the regional distribution that determines the clinical phenotype. The patients in our series of pathologically verified FTLD-U and FTLD-MND presented with cognitive decline and an akinetic rigid picture with supranuclear gaze palsy in two cases. FTLD-U has also been reported as presenting with marked asymmetry distinguished by limb rigidity, bradykinesia, dystonia, an alien limb phenomenon and a pre-morbid diagnosis of CBD (Grimes et al., 1999). This demonstrates that, in these conditions, the predominant clinical features can be extrapyramidal with bradykinesia, rigidity and falls as well as the more commonly documented frontal dysexecutive syndrome. The occurrence of ubiquitin-positive inclusions and cell loss in the caudate nucleus, putamen, globus pallidus (Case 2), subthalamic nucleus (Cases 2 and 3) and substantia nigra (all cases) helps to explain the clinical phenotype. This would suggest that, as with tau in CBD and PSP and also with α-synuclein in dementia with Lewy bodies and Parkinson’s disease, FTLD-U and FTLD-MND may present with a predominantly cortical or subcortical flavour. Neurologists should add FTLD-U and FTLD-MND to the list of conditions that can cause a progressive akinetic rigid syndrome or mimic PSP and this diagnosis should be considered particularly when the illness is rapidly progressive or fasciculations are evident on clinical examination.

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