

# The pathological basis of semantic dementia

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**Semantic dementia is a syndrome of progressive deterioration in semantic memory (knowledge of objects, people, concepts and words). It falls within the clinical spectrum of frontotemporal dementia but its pathology is yet to be studied systematically. This study included 18 consecutive post mortem cases meeting clinical criteria for semantic dementia. Clinic records and diagnostic histopathology were available for all cases; structural neuroimaging, neuropsychology and semi-quantitative histopathology/immunohistochemistry data were analysed where possible. The pathological diagnosis in a clear majority of cases was frontotemporal degeneration with ubiquitin inclusions ( $n = 13$ ). Eleven of these cases had characteristic motor neuron disease-type inclusions in the dentate gyrus and cerebral cortex. Ubiquitin inclusions were found only in the inferior olivary nucleus in the other two, one of which was the only case to show degeneration of motor tracts and also to have shown evidence of motor neuron disease during life. None of the patients had motor symptoms or signs at presentation. A family history of motor neuron disease was documented in one case. Pick body-positive Pick's disease appeared three times. Two cases had Alzheimer's disease and significant coincidental Alzheimer-type pathology was also found in one of the ubiquitin inclusion cases. One of the Alzheimer's disease patients had changes in white matter signal on scanning, whereas all other scans showed cerebral atrophy only. Semi-quantitative assessment of regional neuronal loss found that anterior and inferior temporal regions bore the brunt of disease across all histopathological subtypes, usually on the left side, implicating this region in semantic processing.**

**Keywords:** Alzheimer's disease; frontotemporal dementia; motor neuron disease inclusions; Pick's disease; semantic dementia

**Abbreviations:** CA = cornu ammonis; FTD = frontotemporal dementia; FTD–MND = frontotemporal dementia with motor neuron disease; MMSE = Mini-Mental State Examination; MND = motor neuron disease; MNDID = motor neuron disease inclusion dementia

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## Introduction

The syndrome of semantic dementia is characterized by progressive loss of conceptual knowledge, resulting in anomia, impaired comprehension and speech that is fluent but empty of content (Snowden *et al.*, 1989; Hodges *et al.*, 1992; Bozeat *et al.*, 2000). Word-based tests show clear deficits, but more generalized impairment is apparent when non-verbal tests of object or person knowledge are employed (Bozeat *et al.*, 2000; Thompson *et al.*, 2004). Phonological and syntactic aspects of language are relatively preserved, as are other cognitive domains. On neuroimaging, semantic dementia is associated

with atrophy of the anterior temporal lobe involving particularly polar, anterior parahippocampal and fusiform regions including perirhinal cortex (Chan *et al.*, 2001b; Galton *et al.*, 2001b; Davies *et al.*, 2004). The atrophy is bilateral but typically asymmetric and often more severe on the left.

The study of patients with semantic dementia has provided unique insights into the organization and neural basis of semantic memory as well as the impact of semantic dissolution on other cognitive processes (Garrard and Hodges, 2000; Hodges and Miller, 2001). It is now widely considered to

constitute one of the major clinical variants of frontotemporal dementia (FTD) or frontotemporal lobar degeneration (Neary *et al.*, 1998; McKhann *et al.*, 2001), yet despite an extensive neuropsychological and neuroradiological literature (Hodges *et al.*, 1992; Mummery *et al.*, 2000; Chan *et al.*, 2001*b*; Galton *et al.*, 2001*b*) there have been few reports on the pathological basis of the syndrome; and there has been no systematic immunohistochemical study of consecutive autopsy cases. A review of the published literature revealed 13 case descriptions with neuropathology (Hodges *et al.*, 1998). Features of frontotemporal degeneration were present in all, i.e. focal frontal and/or temporal atrophy with severe cortical neuronal loss in the absence of significant inflammatory or vascular pathology. Microscopy in some cases showed classical tau-containing Pick bodies; others lacked distinctive histopathological features. None had the pathology of Alzheimer's disease. A more recent paper described three semantic dementia patients with inclusions containing the protein ubiquitin, two of which had been reported previously under the rubric of frontotemporal degeneration lacking distinctive histopathological features (Rossor *et al.*, 2000). Such ubiquitin-positive (tau-negative,  $\alpha$ -synuclein-negative) inclusions are typically found in motor neuron disease (MND) or in cases where cognitive-behavioural features of FTD occur with motor neuron signs (FTD–MND) (Hudson, 1981; Wightman *et al.*, 1992). They are also seen in dementia cases, such as those described by Rossor (Rossor *et al.*, 2000), without *in vivo* evidence of MND (Jackson *et al.*, 1996). Such cases may be termed motor neuron disease inclusion dementia (MNDID).

The primary aim of this study was to examine the pathological basis of semantic dementia in a large, unselected series and specifically to test the hypothesis that MND-type pathology might be its predominant cause. A secondary goal, assuming a degree of pathological heterogeneity in the sample, was to evaluate ante mortem data for features potentially useful in predicting pathology. A final purpose, with reference to the *in vivo* neuroanatomical literature on semantic dementia, was to assess the distribution of pathology. Nine of the 18 cases described were reported in the context of a recent large FTD clinico-pathological study (Hodges *et al.*, 2004). Entry criteria for that study (diagnosis within the pathological spectrum of FTD), however, differed and no attempt was made to quantify the distribution of histopathological changes or to examine individual clinical features predictive of pathology in semantic dementia.

## Methods

Cases were obtained from two neuropathological series of dementia patients in Cambridge, England and Sydney, Australia. Both series were collected as a part of multidisciplinary research programmes closely linked to specialist tertiary referral dementia clinics serving similar catchments. The effort at both centres to enrol patients with young onset and atypical dementias into brain donor programmes yielded a 90% success rate for obtaining declarations of intent during life. The provision of on-call services by the brain banks ensured that tissue donation occurred in virtually 100% of these cases. Over a

12-year period (1992–2004), similar numbers of cases were collected at the two centres (Cambridge 156, Sydney 168). The longstanding interest in semantic dementia at Cambridge is reflected in the discrepancy between semantic dementia case numbers at the two centres (Cambridge  $n = 16$ , Sydney  $n = 2$ ).

The research programmes were approved by the Human Ethics Committees of the Universities of Sydney and New South Wales and the Addenbrooke's Hospital Local Research Ethics Committee. Nine of the cases were reported in two recent Sydney–Cambridge clinico-pathological publications (Hodges *et al.*, 2003, 2004). Case 12 was also the subject of a quantitative pathological study (Harasty *et al.*, 1996). Other cases have appeared in a range of clinical and neuropsychological papers (Bozeat *et al.*, 2000; Galton *et al.*, 2001*a, b*; Thompson *et al.*, 2004). Cases 1, 11 and 15 were described in the first paper from Cambridge on semantic dementia (Hodges *et al.*, 1992).

## Clinical features

All cases fulfilled clinical criteria for semantic dementia in accordance with the 1998 international consensus (Neary *et al.*, 1998; McKhann *et al.*, 2001). In brief, all had progressive impairment of the semantic basis of language and evidence of an associative agnosia with sparing of other aspects of cognition.

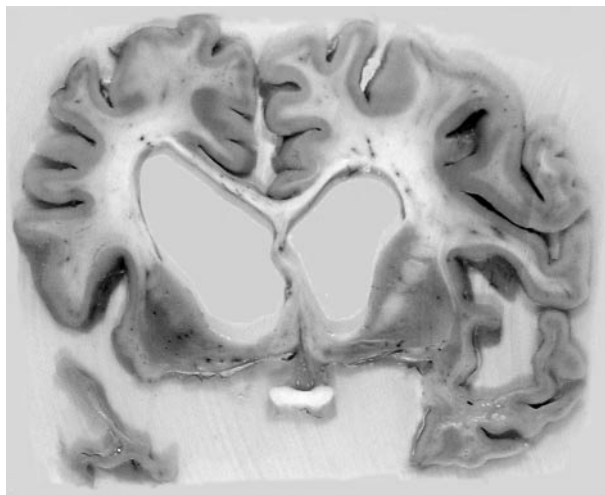
Demographic details and information on symptom duration were available in all cases. A review of the records was undertaken to ascertain the presence or the absence of behavioural and motor symptoms. The conjecture was that these features might point away from Alzheimer pathology or towards MND pathology. MRI scans were available in 10 cases. More recent cases were scanned near the time of presentation; some older cases were scanned later in their clinical course (longest delay from presentation 5.9 years, mean delay 1.8 years).

Most of the cases had been studied extensively from a neuropsychological perspective, with a wide range of standard and experimental tests of semantic function and other aspects of cognition. The core tests performed within one year of presentation in 12 out of the 18 cases consisted of Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975), copy and delayed recall of the Rey-Osterrieth figure (Osterrieth, 1944), the Test for the Reception of Grammar (Bishop, 1989), digit span and letter-based verbal fluency (FAS). Subtests from the Cambridge semantic battery used were category fluency (for animals), naming line drawings, within category word-to-picture matching (Hodges *et al.*, 1992; Hodges and Patterson, 1995) and the picture version of 'Pyramids and Palm Trees', a test of associative semantic knowledge (Howard and Patterson, 1992).

## Pathology

In Sydney, the entire brain was retrieved within 24 h of death and fixed by suspension in 15% buffered formalin for 2 weeks. In Cambridge, different approaches had been adopted over the decade of brain collection. In nine cases, autopsies were performed within 48 h, and the cerebrum bisected with one half fixed in 10% buffered formalin (the left hemisphere in seven out of eight cases) and the other half snap frozen. In the remainder, the cerebrum was whole-fixed in 10% buffered formalin for 1–2 months. The weight of the fresh brain specimen was measured in all cases.

The cerebrum was either embedded in agar and cut into 3 mm coronal slices using a rotary slicer ( $n = 2$  Sydney;  $n = 5$  Cambridge), or hand-cut coronally into 5 mm slices (other Cambridge cases, including all those where only one hemisphere was fixed). Each slice



**Fig. 1** Photograph of coronal brain slice anterior to temporal stem showing frontotemporal atrophy with left temporal emphasis (Case 8).

was photographed (Fig. 1) and printed at  $\times 1$  magnification for the assessment of gross atrophy. Macroscopic atrophy was rated with staging points corresponding to worsening atrophy from 1 to 4 ascribed to each lobar region of the coronal brain slice (i.e. frontal, anterior temporal and posterior temporal) (Broe *et al.*, 2003).

Histopathological diagnostic protocols were standardized between centres for the study. Tissue blocks were taken from the frontal (Brodmann area 6 or 46), temporal (areas 21 and 22), parietal (area 39 or 40), occipital (areas 17 and 18) and anterior cingulate (area 24) cortices, as well as from anterior medial temporal lobe (immediately posterior to the amygdala), hippocampus at the level of the lateral geniculate nucleus, midbrain, pons, medulla oblongata and cerebellum. These were embedded in paraffin and sectioned at 10  $\mu\text{m}$ . Spinal cord sections were, unfortunately, not available. Sections from all regions were stained for routine screening using current diagnostic protocols (Lantos and Papp, 1994; McKeith *et al.*, 1996; Mirra, 1997; Dickson, 1999; Hodges *et al.*, 2004).

A diagnostic category was reached for each case based on the occurrence of specific microscopic lesions. The presence of Alzheimer-type neurofibrillary lesions was quantified by means of the Braak protocol (Braak and Braak, 1991). Other specific lesions sought were Pick bodies, Pick cells, glial tau pathology, cytoplasmic ubiquitin inclusions (MND inclusions), intranuclear ubiquitin inclusions (associated with familial MND), ubiquitinated neurites, neurofilament inclusions and Lewy bodies.

In contrast to the basic diagnostic sections, processed at either centre over several years, sections for semi-quantitative assessment from 12 cases were prepared together in one laboratory (Sydney). Emphasis was placed on staining the histopathological features of frontotemporal degeneration: sections were prepared with haematoxylin and eosin, modified Bielschowsky silver stain, ubiquitin antibodies (Z0458, Dako, Glostrup, Denmark, diluted 1:200), tau antibodies (T5530, Sigma, St Louis, MO, diluted 1:10 000),  $\alpha$ -synuclein antibodies (18-0215, Zymed Laboratories, San Francisco, CA, diluted 1:200) and neurofilament antibodies (2F11, Dako, diluted 1:250, antigen retrieval by microwaving in 0.01M Tris for 10 min). Blocks examined were frontal, temporal, parietal and occipital cortices, anterior medial temporal lobe (anterior CA1, entorhinal cortex

and perirhinal cortex), posterior medial temporal lobe [dentate gyrus, cornu ammonis subdivision 1 (CA1), posterior parahippocampal cortex], midbrain (substantia nigra), pons, medulla oblongata (hypoglossal nucleus) and cerebellum.

The distribution and severity of neuronal loss and inclusion pathology were determined in a semi-quantitative manner using a four-point scale (0 = normal, +++ = most abnormal) (Mirra, 1997). In accordance with the Consortium to Establish a Registry for Alzheimer's Disease protocol, the degree of abnormality in cortical regions, including CA divisions of the hippocampus, was judged by comparison with standard photographs (Mirra, 1997). For circumscribed structures (dentate gyrus and brainstem nuclei), the scale was as follows: 0 = no inclusions, + = 1–2 inclusions per  $\times 100$  power field, ++ = 3–5 inclusions per  $\times 100$  power field, +++ = more than 5 inclusions per  $\times 100$  power field. Neuronal loss was judged visually: 0 = no cell loss, + = mild cell loss (typically, lamina II spongiosis), ++ = definite cell loss across laminae, +++ = devastation of laminar pattern with few neurons remaining. The most severely affected field of each section was selected for quantification.

## Analyses

Data were analysed according to pathological diagnosis. Where numbers allowed, statistical analyses were performed using *t*-tests, with Bonferroni correction when applicable, Wilcoxon signed rank test and Spearman's ranked correlation coefficient. Statistical analyses were performed using the SPSS 10.0 statistical package (SPSS, Chicago, IL) and Microsoft Excel.

## Results

### Clinical features

Demographic and clinical variables are summarized in Tables 1 and 2. The series included 10 men and 8 women. Mean age at symptom onset was 58.3 years (SD 7.0 years) and the mean age at death, 67.7 years (SD 6.6 years). Mean length of illness from symptom onset to death was 9.3 years (SD 4.5 years, range 2.3–19.5). There was an account of a first degree relative with cognitive or behavioural problems in three semantic dementia cases (17%). The brother of one patient (Case 6) had suffered from MND.

General semantic impairment was necessarily present in all cases. Behavioural disturbance was present in eight cases, consisting of disinhibition, apathy, reduced empathy or stereotypic behaviour (Table 1). Motor problems occurred infrequently. No patient had extrapyramidal motor features and none had motor neuron signs at presentation. It should be noted however that, once global dementia supervened, patients were typically not seen in the clinic. Fortuitously, one patient (Case 11) was assessed by a senior neurologist (J. R. Hodges) 6 months before her death at the nursing home where she resided; examination at this time showed no specific motor abnormalities. One patient developed walking difficulty  $\sim 1$  year before death; clinical examination and neurophysiological studies confirmed MND features (Case 10). Another was noted to have dysphagia and dysphonia in the ante mortem period but these were not fully characterized (Case 7).

**Table 1** Summary of demographics, clinical features within 1 year of presentation and diagnostic pathology

Case no.	Demographics			Clinical features			Pathological features			
	Sex	Age at death (years)	Symptom duration (years)	Family history	Early behavioural symptoms	Early motor neuron signs	Diagnosis	Location of ubiquitin inclusions	Motor system pathology	Other features
1	M	63	4.6	–	–	–	MNDID	DG, ION	–	Yes <sup>a</sup>
2	M	67	2.5	Yes <sup>b</sup>	Yes	–	MNDID	DG	Slight <sup>c</sup>	–
3	M	67	9.6	–	–	–	MNDID	DG	–	Yes <sup>d</sup>
4	M	75	8.9	–	Yes	–	MNDID	DG	–	–
5	F	63	9.6	Yes <sup>e</sup>	–	–	MNDID	DG	Slight <sup>c</sup>	–
6	F	67	8.0	Yes <sup>f</sup>	Yes	–	MNDID	DG, ION	Moderate <sup>c</sup>	–
7	F	71	9.3	–	Yes	–	MNDID	DG, ION	–	–
8	M	73	19.5	–	Yes	– <sup>g</sup>	MNDID	DG	–	–
9	F	80	13.3	–	–	–	MNDID	DG, ION	–	–
10	M	61	10.0	Yes <sup>h</sup>	Yes	– <sup>i</sup>	MNDID	ION	Severe <sup>j</sup>	–
11	F	67	14.2	–	–	– <sup>k</sup>	MNDID	DG, ION	–	–
12	F	68	2.3	–	–	–	MNDID	ION	–	–
13	M	70	4.7	–	–	–	MNDID	DG, ION	Slight <sup>c</sup>	–
14	M	50	9.9	–	Yes	–	PiD	–	–	–
15	F	73	7.3	–	Yes	–	PiD	–	–	Yes <sup>a</sup>
16	M	74	15.8	–	–	–	PiD	–	–	–
17	F	63	11.6	–	–	–	AD	–	–	–
18	M	66	6.0	–	–	–	AD	ION	–	Yes <sup>l</sup>

M, male; F, female; MNDID, motor neuron inclusion dementia; PiD, Pick's disease; AD, Alzheimer's disease; DG, dentate gyrus; ION, inferior olivary nucleus; <sup>a</sup>incidental tumour deposit; <sup>b</sup>father had progressive behavioural disturbance in later life attributed to 'strokes'; <sup>c</sup>cell loss in medullary motor nuclei; <sup>d</sup>co-existing Alzheimer pathology; <sup>e</sup>father said to have had multi-infarct dementia; <sup>f</sup>brother died of motor neuron disease; <sup>g</sup>developed prominent dysphagia late in clinical course; <sup>h</sup>father and uncle committed suicide; <sup>i</sup>developed clinical and neurophysiological motor neuron signs late in history; <sup>j</sup>severe degeneration of motor tracts; <sup>k</sup>formal neurological examination performed six months before death; no motor neuron signs found; <sup>l</sup>white matter ischaemia, also evident on MRI.

**Table 2** Clinical data by pathological diagnosis

	Overall	MNDID	Pick's disease	Alzheimer's disease
Sex (M/F)	10/8	7/6	2/1	1/1
Demographics				
Mean age at symptom onset (SD)	58.3 (7.0)	59.5 (5.8)	55.0 (12.8)	55.5 (6.4)
Mean length of history at death (SD)	9.3 (4.5)	9.0 (4.9)	11.0 (4.4)	8.8 (4.0)
Clinical features				
Family history (%)	22	31	0	0
Early behaviour symptoms (%)	44	46	67	0
Early motor symptoms or signs (%)	0	0	0	0
Mean neuropsychological test scores (SD)				
(MNDID = 9, PiD = 1, AD = 2);				
Control cut-off quoted for each				
MMSE (28)	22.1 (5.5)	23 (4.9)	23	17.5 (7.8)
Rey copy (30)	31.5 (4.9)	30.8 (5.5)	34	33.5 (3.6)
Rey recall (4)	11.9 (7.5)	12.2 (6.9)	21.5	5.5 (7.8)
Digits forward (5)	6.4 (1.2)	6.7 (1.2)	6	5.5 (0.7)
Digits backward (3)	4.0 (1.0)	4.2 (1.1)	4	3.0 (0)
TROG (76)	74.3 (5.7)	75.1 (6.0)	78	69 (1.4)
Letter fluency (30)	20.0 (8.1)	21.8 (7.8)	21	11.5 (7.8)
Animal fluency (17)	7.3 (4.0)	7.8 (4.1)	10	3.5 (2.1)
Naming (50)	18.6 (14.8)	17.2 (14.4)	39	14.5 (16.3)
Word-picture (46)	39.1 (8.6)	37 (9.0)	48	44 (1.4)
Picture PPT (49)	41.6 (7.7)	40.6 (8.6)	47	43.5 (3.5)
Age tested (SD)	61 (5.0)	60.3 (5.2)	68	60.5 (2.1)
Symptom duration at test(SD)	4.2 (3.2)	3.3 (2.6)	10	5 (4.2)

M, male; F, female; MMSE, Mini-Mental State Examination; TROG, test of reception of grammar; PPT, Pyramids and Palm Trees; SD, standard deviation; PiD, Pick's disease; AD, Alzheimer's disease.

MRI findings were in keeping with published reports on semantic dementia. All scans showed bilateral frontotemporal lobar atrophy. Temporal atrophy was definitely more marked than frontal atrophy in 5 of the 10 cases, and no case showed worse frontal than temporal atrophy. Six scans showed a left-sided emphasis to the disease, two had right-side predominant atrophy and two had symmetrical appearances. One MRI scan (Case 18) also showed diffuse increase in signal throughout the white matter of both hemispheres in addition to marked left temporal atrophy. No further abnormalities were detected.

Neuropsychological tests scores are given in Table 2. As expected, significant deficits were found in verbal and non-verbal assessments of semantic ability. A mean MMSE (Folstein *et al.*, 1975) score of 22.1 reflected mild to moderate dementia. Visuo-constructional performance and attention [copy of the Rey figure (Osterrieth, 1944) and digit span] were unimpaired but delayed recall of the Rey figure showed mild impairment. Across the series, no significant correlation was found between performance and age, symptom duration or educational level.

### Diagnostic pathology

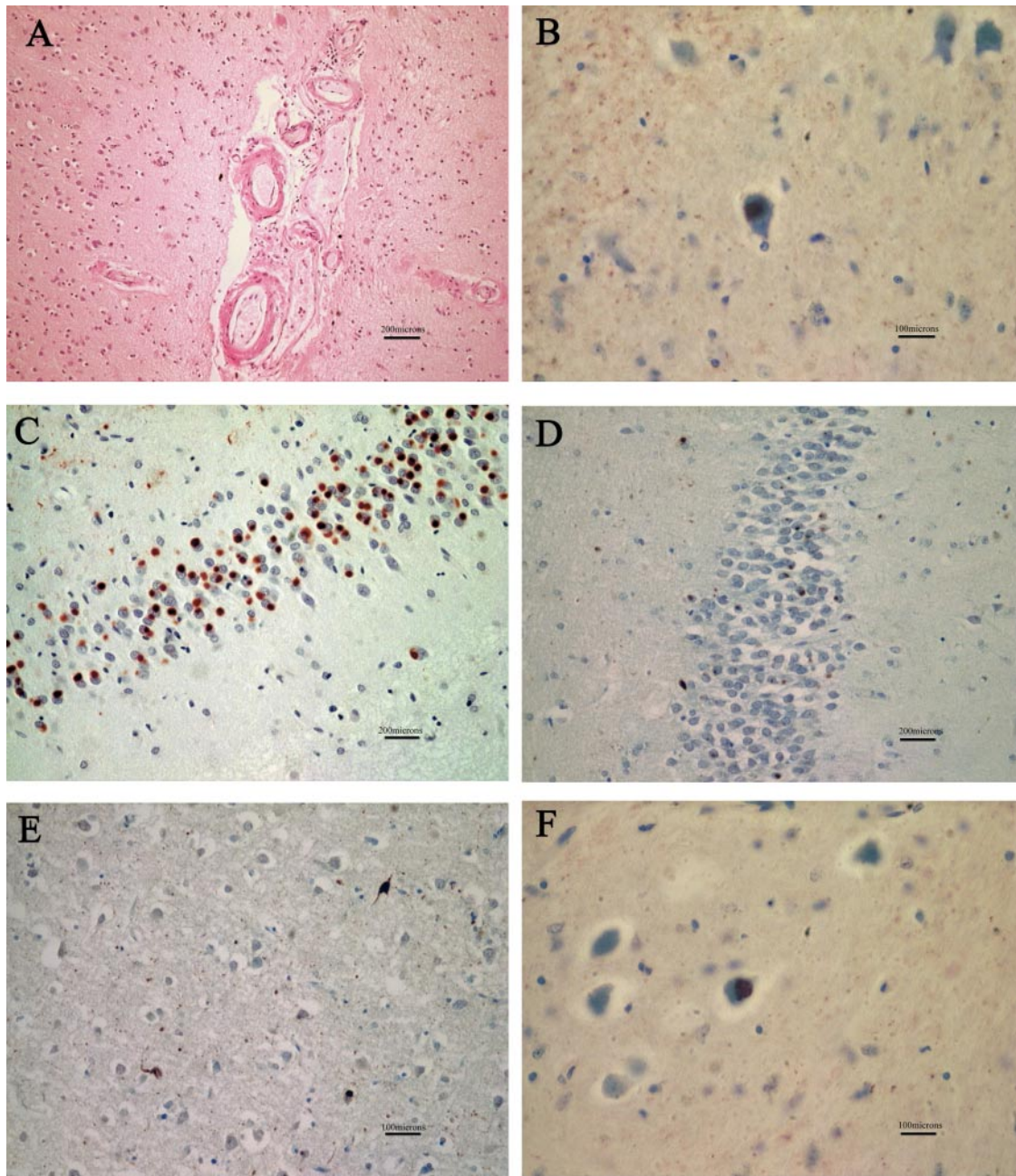
Three pathological diagnoses were represented in the series (Table 1). A total of 16 cases fell within the pathological spectrum of frontotemporal degeneration; 13 had MNDID and 3 had Pick body-positive Pick's disease. Two cases had Alzheimer's disease.

The two cases of pure Alzheimer's disease had severe tangle deposition (Braak stages V and VI) and both had prominent amyloid angiopathy with occasional microscopic infarcts (Fig. 2A). Neither showed any non-Alzheimer's disease features on microscopy with the exception, in Case 18, of ubiquitin-positive inclusions in the inferior olivary nucleus (Fig. 2B). The three Pick's disease cases had argyrophilic, tau-positive Pick bodies predominantly in the granule cells of the dentate gyrus (Fig. 2C) and occasional ballooned achromatic neurons. In the remaining cases, tau and amyloid-beta pathology was largely absent (median Braak stage I). Tau-containing lesions suggestive of other pathological diagnoses (e.g. cortico-basal degeneration and argyrophilic grain disease) were also absent. Neurofilament immunohistochemistry was negative. No Lewy bodies were found in any case. Case 11 showed two small foci of cystic infarction on the right, one in the lentiform nucleus and the other in the posterior parietal white matter. Evidence of neoplasia was seen in two cases (neither had undergone MRI). Case 1 had a 4 cm left posterior parafalcine meningioma deemed incidental to the cognitive presentation. Case 15 had a small necrotic focus (diameter 1.5 cm) in the left frontal lobe suggestive of metastasis; a diagnosis of metastatic adenocarcinoma had been made ante mortem in this patient. There was microscopic evidence of very modest cerebrovascular changes in 10 cases (enlarged Virchow–Robin spaces with or without arteriosclerosis).

Turning to the largest diagnostic group, the ubiquitin immunohistochemical findings were in keeping with previous descriptions of FTD–MND and MNDID (Jackson *et al.*, 1996; Lowe and Leigh, 2002; Forman *et al.*, 2004). All inclusions were intracytoplasmic and, on the basis of light microscopy appearances, not intranuclear. As expected, most cases were found to have perikaryal inclusions (Fig. 2D) in the cells of dentate gyrus ( $n = 11$ ) and also had ubiquitin-positive neurites ( $n = 8$ ; Fig. 2E).

Although numerically dominant, the ubiquitin-inclusion pathology group was not entirely homogeneous. Two (Cases 10 and 12) lacked inclusions in the dentate gyrus and cortex but were found to have inclusions in the inferior olivary nucleus (Fig. 2F). Inferior olivary inclusions were also found in 6 of the remaining 11 MNDID cases. Morphologically, the dentate inclusions were circumscribed whereas the olivary inclusions had a more agglomerated form. Case 12, previously reported by Harasty (1996), was also notable for showing considerably less cell loss across cortical regions than any of the other seven MNDID cases that underwent semi-quantitative assessment (mild-to-moderate versus severe). Case 10, by contrast, was the only case showing impressive degeneration of motor cortical areas and corticospinal tracts. Both cases were grouped with the 11 typical MNDID. Although the medullary motor nuclei were examined across the series, the only instances of definite cell loss were Cases 6 and 10. Three further MNDID cases had equivocal loss of brainstem motor neurons. Finally, Case 3 was unique in having MND inclusions with focally very severe frontotemporal degeneration together with significant Alzheimer pathology (Braak V). On balance, the severity of the neuronal loss was more consistent with a primary diagnosis of MNDID than Alzheimer's disease.

In addition to the quantitative study of Case 12 (Harasty *et al.*, 1996), two recent clinico-pathological publications included nine of the patients described here (Hodges *et al.*, 2003, 2004). These series reported on cases with pathology from the frontotemporal degeneration spectrum. The current study includes a further seven cases reaching autopsy after 2002 and the two Alzheimer's disease cases. The nine semantic dementia cases previously described consisted of four MNDID cases, three with Pick's disease and two with frontotemporal degeneration lacking distinctive immunohistochemistry. The latter two cases require some explanation as none in the current series were categorized in this way. One was Case 12, who had a paucity of inclusions although the presence of inferior olivary inclusions and widespread ubiquitinated neurites was similar to the appearances of Case 10 (the case with clinical MND). In Case 1, by contrast, there were numerous ubiquitin inclusions visible on the sections through dentate gyrus prepared for this study which simply did not appear in the section stained (by the same protocol) in 1994 which were reviewed in 2002. The remaining cortical blocks in Case 1 were difficult to assess because of ice artefact resulting from an error at the time of autopsy.

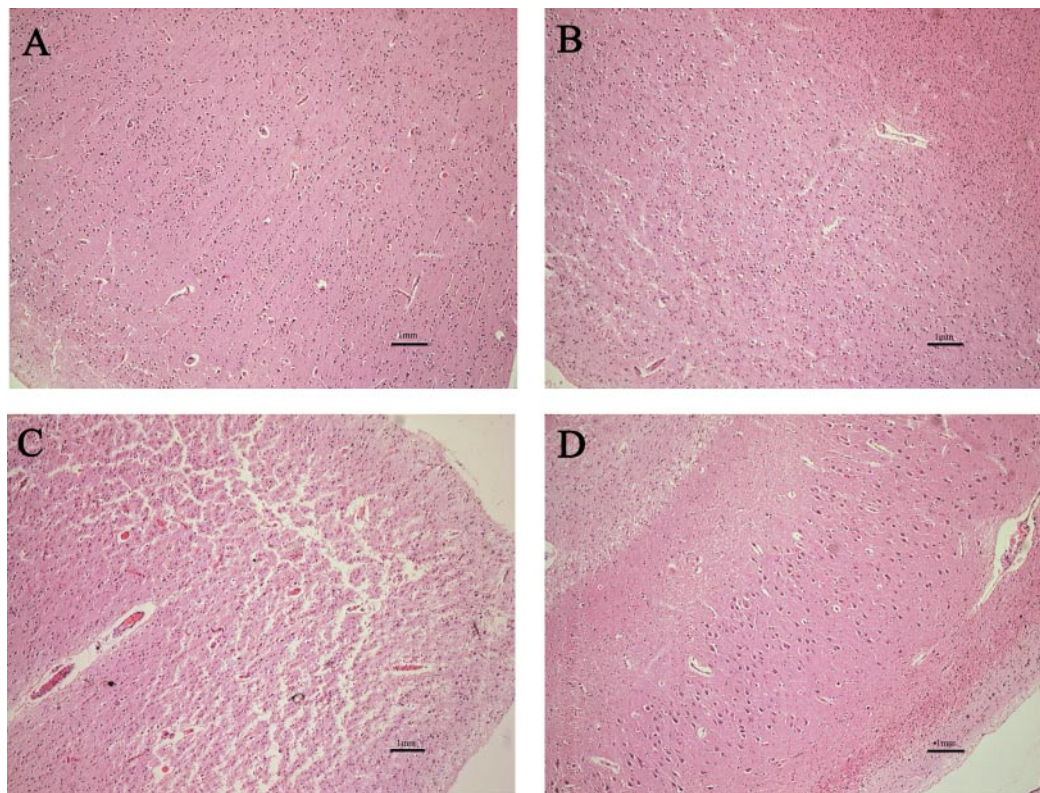


**Fig. 2** Photomicrographs showing diagnostic features. **(A)** (Case 18: haematoxylin and eosin) Congophilic angiopathy and cortical ischaemia. **(B)** (Case 18: ubiquitin immunohistochemistry) Ubiquitin-positive inclusion in the inferior olivary nucleus in Alzheimer's disease. **(C)** (Case 16: tau immunohistochemistry) Pick bodies in the granule cells of the dentate gyrus. **(D)** (Case 5: ubiquitin immunohistochemistry) Perikaryal MND inclusions in the dentate gyrus. **(E)** (Case 5: ubiquitin immunohistochemistry) Ubiquitin-positive neurites in neocortex. **(F)** (Case 5: ubiquitin immunohistochemistry) Ubiquitin-positive inclusion in the inferior olivary nucleus in MNDID.

### Quantitative pathology

Post mortem coronal brain slice images were available for all except Case 12. Mean post mortem brain weight was 1081 g (SD 178 g). Brain weight correlated negatively with age at death ( $\rho = -0.56$ ,  $P = 0.025$ ) and with stage of frontotemporal atrophy ( $\rho = -0.58$ ,  $P = 0.019$ ) but showed no association with other features. All cases showed atrophy of at least a moderate degree as indicated by stage. In the nine cases where

images of both hemispheres were available for comparison, the left side was consistently more atrophic (median left frontal, anterior temporal and posterior temporal stagings, 2, 3 and 3, respectively; right, 1.5, 2 and 2, respectively). A significant correlation was found between symptom duration and the posterior temporal staging ( $\rho = 0.64$ ,  $P = 0.006$ ) but not between symptom duration and either frontal or anterior temporal stagings. This would be in keeping with very marked anterior temporal



**Fig. 3** Photomicrographs showing severity of neuronal loss across temporal lobe regions, sections also showing occasional Pick cells (Case 15: haematoxylin and eosin). **(A)** Superior temporal gyrus is well preserved, cortical laminae and columns are clearly visible. **(B)** Middle temporal gyrus shows moderately severe cell loss. **(C)** Medial bank of the collateral sulcus shows extremely severe neuronal loss. **(D)** Moderate neuronal loss in CA1.

atrophy occurring even before the time of presentation and progressive atrophy of the adjacent regions as the condition worsens.

Staging scores could not readily be compared across lobes: equivalent numerical staging need not imply equivalent atrophy. As Fig. 1 shows, the scope for tissue loss in the anterior temporal region is less and therefore, any given stage implies less residual brain tissue at this site than would be the case for the frontal and posterior temporal regions. Comparison of relative anterior and posterior temporal stages across disease groups, however, showed more severe disease stage in posterior than anterior temporal regions in both Alzheimer's disease cases. This compares with 1 of the 12 MNDID cases and 1 of the 3 Pick's disease cases and is consistent with the greater posterior than anterior temporal volume loss previously shown in Alzheimer's disease (Chan *et al.*, 2001*a, b*; Davies *et al.*, 2004).

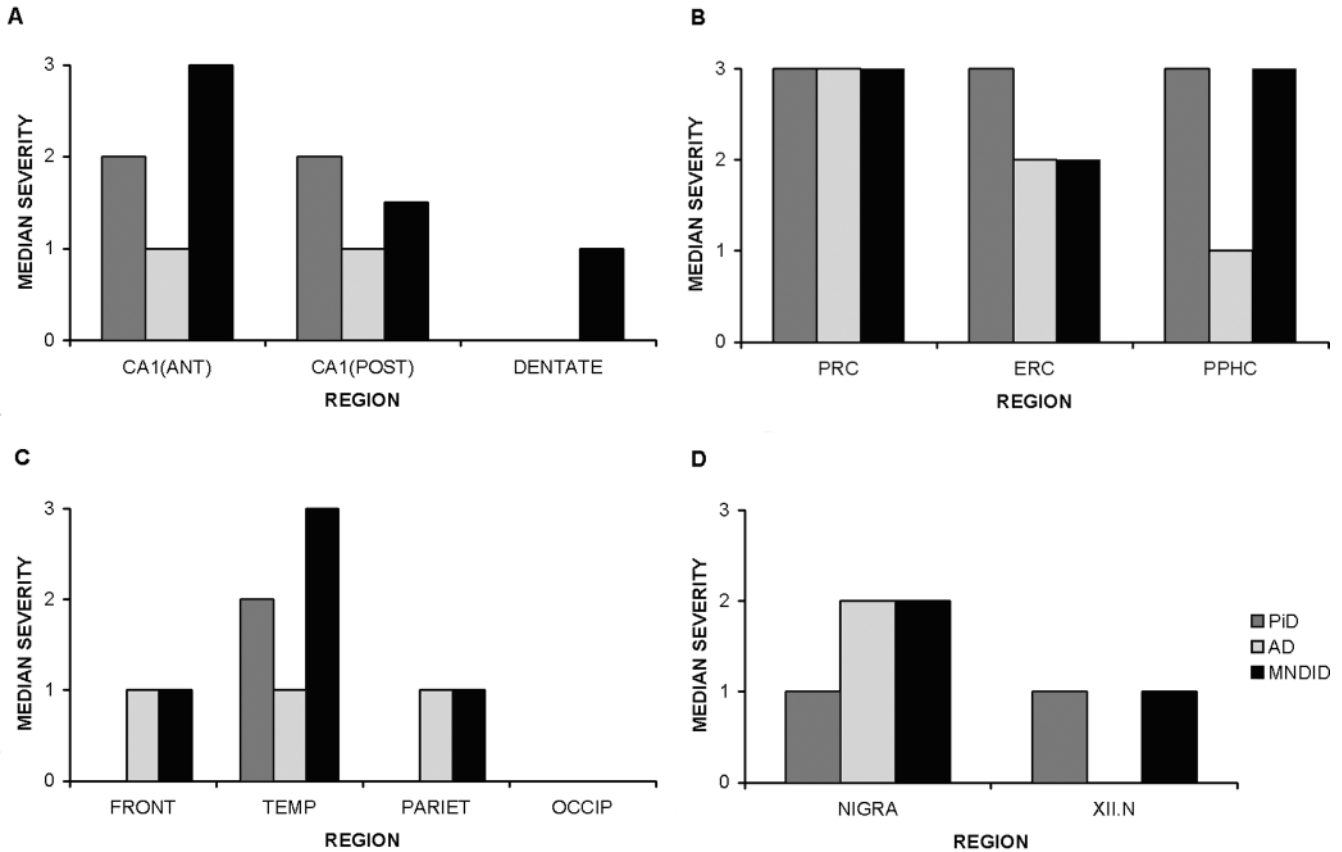
Semi-quantitative assessment of histopathology was performed in 12 semantic dementia cases (8 MNDID, 3 Pick's disease and 1 Alzheimer's disease). The distribution of neuronal inclusions and other histopathological lesions was consistent with recognized patterns for the various disease categories (Jackson *et al.*, 1996; Dickson, 2001). Both Pick bodies and ubiquitin-positive MND-inclusions are known to have a predilection for the hippocampal dentate gyrus, irrespective of clinical syndrome; both types of inclusion

were most numerous in the dentate gyrus in this series. Dentate gyrus neurons, however, were well preserved.

Across the series, the distribution of the microscopic abnormalities confirmed the involvement of the temporal lobe and, in particular, the anteroinferior-medial temporal gyri (Fig. 3). As predicted from recent volumetric MRI studies, the medial temporal cortices showed severe neuronal loss (Davies *et al.*, 2004) with median score of 3 for perirhinal, entorhinal, posterior parahippocampal and anterior CA1 (Fig. 4). The perirhinal cortex achieved the worst rating most consistently (all except Case 12). Across the series, marked cell loss was also evident in other temporal regions, specifically temporal neocortex (median 2.5), amygdala (2) and posterior CA1 (1.5). Outside the temporal lobe, only mild neuronal loss was seen in frontal cortex. This relative preservation of frontal neurons parallels the macroscopic staging; cell loss has previously been shown to correlate with stage (Schofield *et al.*, 2003; Kersaitis *et al.*, 2004). Parietal cortex was largely preserved and no cell loss was apparent in occipital cortex. Brainstem neurons, including those of the medullary motor nuclei, were only mildly reduced in density.

### Prediction of diagnostic pathology

Demographic data were generally unhelpful in differentiating pathological subgroups (Table 2); sex ratios were similar



**Fig. 4** Median severity of neuronal loss across brain regions by pathological subtype (Pick's disease,  $n = 3$ ; Alzheimer's disease  $n = 1$ ; MNDID;  $n = 8$ ). (A) Hippocampal subregions. (B) Parahippocampal gyrus subregions. (C) Neocortical regions. (D) Brainstem regions.

across pathological subgroups, as were the mean ages and rate of progression (length of history). The broad symptom categories evaluated were also of limited value. Behavioural symptoms occurred in 6 of the 13 MNDID cases, 2 of the 3 Pick's disease cases but neither of the Alzheimer's disease cases. Case 10, in whom clinical signs of MND were documented several years after presentation, did go onto a post mortem diagnosis of MNDID. Case 7, in whom late bulbar symptoms were described, also had MNDID. Conversely, Case 11, who had no MND features even in the immediate ante mortem period, also had MND-type pathology. Family history was positive only in MNDID: two of the four consisted of non-specific cognitive impairment in later life (relatives of Cases 2 and 5). In Case 10, both father and uncle had committed suicide in mid-life. In Case 6, the patient's brother had succumbed to MND (without apparent dementia); furthermore, cell loss from the medullary motor nuclei in Case 6 was second only to that seen in Case 10.

A further symptom that arose within a year of death in one of the Alzheimer's disease cases (Case 18) consisted of unusual visual fixation behaviour. This abnormality was not fully characterized but had similarities to the simultanagnosia seen in Balint's syndrome together with problems of low level visual perception. The occurrence of this visuo-spatial deficit in one of the two Alzheimer's disease cases, rather

than in any of those with frontotemporal degeneration, is consistent with the consensus that visuo-spatial problems rarely occur in FTD (Neary *et al.*, 1998; Hodges *et al.*, 2004). Case 18 was also the only instance of white matter change; the scan appearances were presumably a consequence of the prominent amyloid angiopathy later demonstrated on microscopy. There was a suggestion that the Alzheimer's disease cases had more diffuse atrophy affecting posterior as well as anterior regions, in keeping with the post mortem posterior staging data. All cases with symmetrical or predominantly right-sided frontotemporal atrophy on scanning went on to a diagnosis of MNDID.

Of the 12 patients in whom formal neuropsychological testing had been performed, only one had Pick's disease and this patient's high scores must be set against a high pre-morbid level of function. The lower mean MMSE (Folstein *et al.*, 1975) score in the Alzheimer's disease group may reflect more diffuse impairment in that group, greater sensitivity of the MMSE to Alzheimer's disease or greater symptom severity in the two Alzheimer's disease cases. Name production (picture naming, category fluency) was somewhat more impaired than comprehension (word-picture matching, Pyramids and Palm Trees) in the Alzheimer's disease cases in comparison with those having frontotemporal degeneration (Chertkow and Bub, 1990; Greene and Hodges, 1996).



## Discussion

### Pathological diagnosis

This study demonstrates that the pathological lesion most commonly associated with the clinical syndrome of semantic dementia is the ubiquitin-positive, tau-negative intraneuronal inclusion characteristic of MND (Jackson *et al.*, 1996). MND inclusions in the dentate gyrus were the defining pathology in 11 of the 18 consecutive cases in the series. Two further cases, including the only semantic dementia case to date with documented clinical MND, showed widespread ubiquitinated neurites and ubiquitin-positive inclusions in the inferior olivary nucleus without dentate gyrus inclusions.

Much less common than ubiquitin pathology was classical Pick's disease, found in three cases. No further frontotemporal degeneration subtypes were present; no semantic dementia cases had corticobasal degeneration pathology, argyrophilic grain disease or neurofilament inclusions (Braak and Braak, 1998; Dickson, 1999; Cairns *et al.*, 2003).

Unexpectedly, two semantic dementia cases had the pathology of Alzheimer's disease; one MNDID case also had significant co-existing Alzheimer pathology. Alzheimer's disease pathology has not previously been reported in semantic dementia. However, Alzheimer's disease is very common (Bachman *et al.*, 1993) and semantic difficulties often follow the early episodic memory impairment in the natural history of Alzheimer's disease (Hodges and Patterson, 1995). Atypical cases of Alzheimer's disease are also well documented. Galton described nine such cases, two of whom had fluent progressive aphasia reminiscent of semantic dementia, although the presence of day-to-day memory difficulties and other cognitive deficits at presentation meant that neither had been categorized as semantic dementia (Galton *et al.*, 2000). The absence of Alzheimer's disease pathology from the semantic dementia literature may reflect publication bias as the finding goes against conventional understanding that the terms semantic dementia and temporal variant FTD are synonymous. Descriptions of the semantic dementia syndrome, however, are also absent from the vast literature on clinical presentations of Alzheimer's disease, suggesting that such cases are indeed very few. In addition, it could be argued that one of the two Alzheimer's disease cases here (Case 18) might have been excluded, because of the prominent white matter abnormalities on MRI although current criteria for semantic dementia do not mandate the presence of focal temporal lobe atrophy or the absence of other pathology (Neary *et al.*, 1998; McKhann *et al.*, 2001). Removal of Case 18 would give a series of 17 cases with the characteristic temporal atrophy and leave Alzheimer's disease as an even more rare cause of the syndrome (1 of 17 versus 2 of 18).

### Relationship between pathology in MND and semantic dementia

Clinical descriptions of MND (or amyotrophic lateral sclerosis) have traditionally emphasized the motor features. Even in the nineteenth century, however, there were accounts

of personality changes in MND (Bak and Hodges, 2004), and a subset of patients with frank dementia has more recently been recognized (Neary *et al.*, 1990; Lomen-Hoerth *et al.*, 2002). The dementia typically consists of behavioural and language deficits of the type seen in FTD, hence the designation FTD–MND. There is also increasing awareness of the very high frequency of subtle behavioural and/or linguistic deficits among 'classical' MND cases (Rakowicz and Hodges, 1998; Lomen-Hoerth *et al.*, 2003). Furthermore, post mortem findings in dementia cases without clinical evidence of MND have been noted to show inclusions characteristic of MND, hence MNDID (Jackson *et al.*, 1996). Clinical assessment of these patients in the ante mortem period has generally been rather limited and the possibility that some might have had subtle MND features cannot be discounted. Crucially, however, MNDID specimens often show histopathological sparing of motor structures.

Classical pathological descriptions of 'motor' MND describe a shrunken, atrophic spinal cord with reduced numbers of myelinated fibres in the ventral roots and degeneration of cortico-spinal tracts (Lowe and Leigh, 2002). Ubiquitin-positive 'MND inclusions', corresponding to earlier descriptions of hyaline bodies represent a frequent and specific histopathological finding (Lowe and Leigh, 2002; Kovari *et al.*, 2004). They are found in lower motor neurons (often displaying a skein-like conformation), cortical motor neurons and granule cells of the dentate gyrus (often more spherical in form). Intranuclear ubiquitin inclusions have also been described in familial cases (Woulfe *et al.*, 2001; Mackenzie and Feldman, 2004).

All ubiquitin-immunopositive pathology cases listed in this semantic dementia series manifested intracytoplasmic, perikaryal not intranuclear, inclusions. In two cases, inclusions were not identified at the most typical location, namely the dentate gyrus. Both, however, along with six of the cases with dentate gyrus inclusions had inclusions in the inferior olivary nucleus of the medulla oblongata. The significance of these lesions is uncertain. It has been suggested that olivary deposits are non-specific, and possibly a feature of normal ageing (Dickson *et al.*, 1990; Kato *et al.*, 1990), a point reinforced by their presence in one of the Alzheimer's disease cases here. It is notable, however, that one of the two cases in which olivary deposits were the only perikaryal inclusions detected was also the only case with clinically proven MND. Although certainly not a specific marker in pathological diagnosis, olivary inclusions detected in the absence of more definite abnormalities may be a sensitive marker of MND-type pathology. By analogy, in the wider pathological spectrum of FTD, olivary inclusions positive for neurofilament (and ubiquitin) have been described (Cairns *et al.*, 2003).

Ubiquitin is a protein involved in non-lysosomal degradation of abnormal and short-lived proteins (Bossy-Wetzel *et al.*, 2004). It conjugates protein aggregates in each of the major neurodegenerative diseases and ubiquitin immunostaining can be found in the brains of elderly persons without overt

cognitive impairment (Garcia Gil *et al.*, 2001; Kimura *et al.*, 2002). The question, therefore, arises of whether the ubiquitin inclusions seen in semantic dementia are appropriately designated MND inclusions. The occurrence of the semantic dementia inclusions in the dentate gyrus, their morphology and their immunohistochemical properties all suggest that the designation is justified. Three positive observations from the cases here also affirm the point: (i) the MNDID patient with a family history of ‘motor’ MND; (ii) the MNDID case in whom clinical MND was documented and (iii) motor system pathology in 5 of the 13 MNDID cases. Crucially, all these pointers to the semantic dementia/MND link arose only in cases with ubiquitin inclusions and not with Pick’s disease or Alzheimer’s disease.

Contrasting patterns of aphasia and the contrasting life expectancy, however, draw a distinction between semantic dementia and FTD–MND. The aphasia of FTD–MND is typically non-fluent in character (Bak *et al.*, 2001; Lomen-Hoerth *et al.*, 2002; Bak and Hodges, 2004), whilst semantic dementia is a syndrome of fluent aphasia. Furthermore, FTD–MND is known to be associated with a markedly reduced life expectancy in comparison with other clinical FTD subtypes, including semantic dementia (Hodges *et al.*, 2003). Here, the MNDID cases had the same life expectancy as those with Pick’s disease or Alzheimer’s disease; their average illness duration of 10 years is considerably longer than reported in classical MND. These disparities, however, may be explicable in terms of differing sites of pathology rather than distinct pathogenetic processes. The temporal lobe focus of atrophy in semantic dementia entails relative sparing of inferior frontal regions with crucial roles in speech output and in non-linguistic (vital) bulbar functions typically impaired in FTD–MND. Interestingly, the clinical MND case in this series had symptoms and signs in a spinal rather than bulbar distribution, the latter being more typical of FTD–MND. This may be a further reflection of inferior frontal regions being affected late in semantic dementia.

### Regional pathology

Imaging studies consistently demonstrate anterior and inferior temporal lobe involvement in semantic dementia (Mummery *et al.*, 2000; Chan *et al.*, 2001*b*; Davies *et al.*, 2004). Recent reports following cerebral infarction, surgery and herpes encephalitis have also implicated the inferior temporal lobe in semantic processing (Schmolck *et al.*, 2002; Tyler *et al.*, 2002; Sharp *et al.*, 2004). Furthermore, some authors argue that deficits analogous to the object-knowledge impairments of semantic dementia occur when non-human primates undergo experimental lesions at corresponding locations (Murray and Richmond, 2001). Formal quantitative histopathological studies in semantic dementia that include neuronal densities are few, a single case report suggested posterior temporal neuronal loss although only certain regions had undergone stereological assessment (Harasty *et al.*, 1996). Semi-quantitative neuronal density data in

this study, however, confirm the anteroinferomedial temporal focus for semantic dementia pathology predicted by the wider literature. Specifically, the area most consistently achieving the worst rating for neuronal loss was the perirhinal cortex, occupying the inferior temporal pole, anterior parahippocampal gyrus and fusiform gyrus. Temporal neocortex was marginally better preserved. Anterior hippocampal regions were worse affected than posterior, also as predicted from *in vivo* imaging (Chan *et al.*, 2001*a, b*; Davies *et al.*, 2004).

The data on the density of inclusion pathology proved more difficult to interpret, partly because of the confounding effect of the severe neuronal loss. Distribution of lesions was in keeping with the recognized patterns in the specific diseases. Although the neuronal loss at a given brain location intuitively suggests loss of function (Harasty *et al.*, 1996), the same is not necessarily true of abnormal deposits, as shown by the poor correlation between beta-amyloid deposits and cognition in Alzheimer’s disease (Braak *et al.*, 1989). MND inclusions and Pick bodies both occur in the granule cells of the dentate gyrus without obvious reduction in cell numbers. Furthermore, there is no model that implicates the dentate gyrus in semantic function.

### Predicting pathological diagnosis in life

Although this is the largest pathological series of semantic dementia reported to date, categories numbering 13 (MNDID), 3 (Pick’s disease) and 2 (Alzheimer’s disease) are too small for statistical comparison. Despite this, provisional comments on diagnosis are warranted. The case with a family history of MND, for instance, should have been placed in the MNDID category at presentation. Similarly, the emergence of classical MND signs clearly pointed to MND pathology.

Early behavioural symptoms were found in cases only with frontotemporal degeneration (6 of the 13 MNDID and 2 of the 3 Pick’s disease) and not in cases with Alzheimer’s disease pathology. Behavioural disturbance with semantic impairment might, therefore, point away from a diagnosis of Alzheimer’s disease. Some time after presentation, one Alzheimer’s disease patient (Case 18) developed visuo-spatial impairment, a symptom that did not arise in any frontotemporal degeneration case in this series and that features among FTD exclusion criteria (Neary *et al.*, 1998; Hodges *et al.*, 2004). Age did not differ between the Alzheimer’s disease and other cases despite the fact that Alzheimer’s disease typically occurs in an older age group (Bachman *et al.*, 1993; Harvey, 2001).

Implications of the white matter abnormalities on scanning in one of the Alzheimer’s disease cases have already been discussed. The anterior temporal atrophy also seemed less striking than the posterior in Alzheimer’s disease, consistent with the post mortem staging data and with other *in vivo* findings in clinically probable Alzheimer’s disease (Chan *et al.*, 2001*b*; Davies *et al.*, 2004).

## Conclusions

Neurological symptoms and signs follow the anatomy of damage and consistently the site of greatest damage in semantic dementia is the anteroinferomedial temporal lobe. Although progressive damage at this site may be caused by a variety of pathological processes, the commonest by far is MNDID. It may be inferred that the anteroinferior temporal region forms a site of predilection for MND-type pathology. Reasons why a given disease process might strike motor, semantic or other brain regions to varying degrees in individual cases are, of course, unknown.

A major goal in the field is to find therapy that targets the mechanism of disease. In turn, this demands early and accurate predication of pathology. Already, riluzole produces modest benefits in 'motor' MND and it is possible that these effects might translate to semantic dementia cases with MND pathology. This dataset alone indicates that blanket prediction of MNDID in all semantic dementia cases would be reasonably accurate (72%). Examining the wider clinical spectrum of FTD we may arrive at a potentially useful, though not absolute, dichotomy. Semantic dementia cases and FTD–MND cases (Hodges *et al.*, 2004) could together form a large grouping with a high likelihood of ubiquitin-positive, tau-negative pathology. The remainder, consisting of behavioural variant FTD cases and non-fluent FTD cases without MND signs would form a group more likely to have tau-based pathology.

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## References

- Bachman DL, Wolf PA, Linn RT, et al. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. *Neurology* 1993; 43: 515–9.
- Bak TH, Hodges JR. The effects of motor neurone disease on language: further evidence. *Brain Lang* 2004; 89: 354–61.
- Bak TH, O'Donovan DG, Xuereb JH, Boniface S, Hodges JR. Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease-dementia-aphasia syndrome. *Brain* 2001; 124: 103–20.
- Bishop DVM. Test for the reception of grammar. London: Medical Research Council; 1989.
- Bossy-Wetzell E, Schwarzenbacher R, Lipton SA. Molecular pathways to neurodegeneration. *Nat Med* 2004; 10 (Suppl): S2–9.
- Bozeat S, Lambon Ralph MA, Patterson K, Garrard P, Hodges JR. Non-verbal semantic impairment in semantic dementia. *Neuropsychologia* 2000; 38: 1207–15.
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol (Berl)* 1991; 82: 239–59.
- Braak H, Braak E. Argyrophilic grain disease: frequency of occurrence in different age categories and neuropathological diagnostic criteria. *J Neural Transm* 1998; 105: 801–19.
- Braak H, Braak E, Ohm T, Bohl J. Alzheimer's disease: mismatch between amyloid plaques and neuritic plaques. *Neurosci Lett* 1989; 103: 24–8.
- Broe M, Hodges JR, Schofield E, Shepherd CE, Kril JJ, Halliday GM. Staging disease severity in pathologically confirmed cases of frontotemporal dementia. *Neurology* 2003; 60: 1005–11.
- Cairns NJ, Perry RH, Jaros E, et al. Patients with a novel neurofilamentopathy: dementia with neurofilament inclusions. *Neurosci Lett* 2003; 341: 177–80.
- Chan D, Fox NC, Jenkins R, Scahill RI, Crum WR, Rossor MN. Rates of global and regional cerebral atrophy in Alzheimer's disease and frontotemporal dementia. *Neurology* 2001a; 57: 1756–63.
- Chan D, Fox NC, Scahill RI, et al. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Ann Neurol* 2001b; 49: 433–42.
- Chertkow H, Bub D. Semantic memory loss in dementia of Alzheimer's type. What do various measures measure? *Brain* 1990; 113: 397–417.
- Davies RR, Graham KS, Xuereb JH, Williams GB, Hodges JR. The human perirhinal cortex and semantic memory. *Eur J Neurosci* 2004; 20: 2441–6.
- Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. *J Neurol* 1999; 246 (Suppl 2): II6–15.
- Dickson DW. Neuropathology of Pick's disease. *Neurology* 2001; 56: S16–20.
- Dickson DW, Wertkin A, Kress Y, Ksiezak-Reding H, Yen SH. Ubiquitin immunoreactive structures in normal human brains. Distribution and developmental aspects. *Lab Invest* 1990; 63: 87–99.
- Folstein MF, Folstein SE, McHugh PR. 'Mini mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–98.
- Forman MS, Trojanowski JQ, Lee VM-Y. Hereditary tauopathies and idiopathic frontotemporal dementias. In: Trojanowski JQ, editor. *The neuropathology of dementia*. Cambridge: Cambridge University Press; 2004. p. 257–88.
- Galton CJ, Patterson K, Xuereb JH, Hodges JR. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. *Brain* 2000; 123: 484–98.
- Galton CJ, Gomez-Anson B, Antoun N, et al. Temporal lobe rating scale: application to Alzheimer's disease and frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2001a; 70: 165–73.
- Galton CJ, Patterson K, Graham K, et al. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology* 2001b; 57: 216–25.
- Garcia Gil ML, Moran MA, Gomez-Ramos P. Ubiquitinated granular structures and initial neurofibrillary changes in the human brain. *J Neurol Sci* 2001; 192: 27–34.
- Garrard P, Hodges JR. Semantic dementia: clinical, radiological and pathological perspectives. *J Neurol* 2000; 247: 409–22.
- Greene JD, Hodges JR. Identification of famous faces and famous names in early Alzheimer's disease. Relationship to anterograde episodic and general semantic memory. *Brain* 1996; 119: 111–28.
- Harasty JA, Halliday GM, Code C, Brooks WS. Quantification of cortical atrophy in a case of progressive fluent aphasia. *Brain* 1996; 119: 181–90.
- Harvey RJ. Epidemiology of presenile dementias. In: Hodges JR, editor. *Early-onset dementia*. Oxford, UK: Oxford University Press; 2001. p. 1–22.
- Hodges JR, Patterson K. Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia* 1995; 33: 441–59.
- Hodges JR, Miller BL. Frontotemporal dementia (Pick's disease). In: Hodges JR, editor. *Early-onset dementia*. Oxford: Oxford University Press; 2001. p. 284–303.
- Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain* 1992; 115: 1783–806.
- Hodges JR, Garrard P, Patterson K. Semantic dementia. In: Munoz DG, editor. *Pick's disease and Pick complex*. New York: Wiley-Liss Inc.; 1998. p. 83–104.
- Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia. *Neurology* 2003; 61: 349–54.

- Hodges JR, Davies RR, Xuereb JH, et al. Clinicopathological correlates in frontotemporal dementia. *Ann Neurol* 2004; 56: 399–406.
- Howard D, Patterson K. *Pyramids and palm trees: a test of semantic access from pictures and words*. Suffolk: Thames Valley Test Company; 1992.
- Hudson AJ. Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other neurological disorders: a review. *Brain* 1981; 104: 217–47.
- Jackson M, Lennox G, Lowe J. Motor neurone disease-inclusion dementia. *Neurodegeneration* 1996; 5: 339–50.
- Kato S, Hirano A, Suenaga T, Yen SH. Ubiquitinated eosinophilic granules in the inferior olivary nucleus. *Neuropathol Appl Neurobiol* 1990; 16: 135–9.
- Kersaitis C, Halliday GM, Kril JJ. Regional and cellular pathology in frontotemporal dementia: relationship to stage of disease in cases with and without Pick bodies. *Acta Neuropathol (Berl)* 2004; 108: 515–23.
- Kimura T, Fujise N, Ono T, et al. Identification of an aging-related spherical inclusion in the human brain. *Pathol Int* 2002; 52: 636–42.
- Kovari E, Gold G, Giannakopoulos P, Bouras C. Cortical ubiquitin-positive inclusions in frontotemporal dementia without motor neuron disease: a quantitative immunocytochemical study. *Acta Neuropathol (Berl)* 2004; 108: 207–12.
- Lantos PL, Papp MI. Cellular pathology of multiple system atrophy: a review. *J Neurol Neurosurg Psychiatry* 1994; 57: 129–33.
- Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* 2002; 59: 1077–9.
- Lomen-Hoerth C, Murphy J, Langmore S, Kramer JH, Olney RK, Miller B. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 2003; 60: 1094–7.
- Lowe JS, Leigh N. Disorders of movement and system degenerations. In: Lantos PL, editor. *Greenfield's neuropathology*. Vol. 2. London: Arnold; 2002. p. 325–430.
- Mackenzie IR, Feldman H. Neuronal intranuclear inclusions distinguish familial FTD-MND type from sporadic cases. *Dement Geriatr Cogn Disord* 2004; 17: 333–6.
- McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996; 47: 1113–24.
- McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* 2001; 58: 1803–9.
- Mirra SS. The CERAD neuropathology protocol and consensus recommendations for the postmortem diagnosis of Alzheimer's disease: a commentary. *Neurobiol Aging* 1997; 18: S91–4.
- Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. *Ann Neurol* 2000; 47: 36–45.
- Murray EA, Richmond BJ. Role of perirhinal cortex in object perception, memory, and associations. *Curr Opin Neurobiol* 2001; 11: 188–93.
- Neary D, Snowden JS, Mann DM, Northen B, Goulding PJ, Macdermott N. Frontal lobe dementia and motor neuron disease. *J Neurol Neurosurg Psychiatry* 1990; 53: 23–32.
- Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998; 51: 1546–54.
- Osterrieth PA. Le test de copie d'une figure complexe: contribution à l'étude de la perception et de la mémoire. *Arch Psychol* 1944; 30: 205–20.
- Rakowicz WP, Hodges JR. Dementia and aphasia in motor neuron disease: an underrecognised association? *J Neurol Neurosurg Psychiatry* 1998; 65: 881–9.
- Rossor MN, Revesz T, Lantos PL, Warrington EK. Semantic dementia with ubiquitin-positive tau-negative inclusion bodies. *Brain* 2000; 123: 267–76.
- Schmolck H, Kensinger EA, Corkin S, Squire LR. Semantic knowledge in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. *Hippocampus* 2002; 12: 520–33.
- Schofield E, Kersaitis C, Shepherd CE, Kril JJ, Halliday GM. Severity of gliosis in Pick's disease and frontotemporal lobar degeneration: tau-positive glia differentiate these disorders. *Brain* 2003; 126: 827–40.
- Sharp DJ, Scott SK, Wise RJ. Retrieving meaning after temporal lobe infarction: the role of the basal language area. *Ann Neurol* 2004; 56: 836–46.
- Snowden JS, Goulding PJ, Neary D. Semantic dementia: a form of circumscribed cerebral atrophy. *Behav Neurol* 1989; 2: 167–82.
- Thompson SA, Graham KS, Williams G, Patterson K, Kapur N, Hodges JR. Dissociating person-specific from general semantic knowledge: roles of the left and right temporal lobes. *Neuropsychologia* 2004; 42: 359–70.
- Tyler LK, deMornay-Davies P, Anokhina R, Longworth C, Randall B, Marslen-Wilson WD. Dissociations in processing past tense morphology: neuropathology and behavioral studies. *J Cogn Neurosci* 2002; 14: 79–94.
- Wightman G, Anderson VE, Martin J, et al. Hippocampal and neocortical ubiquitin-immunoreactive inclusions in amyotrophic lateral sclerosis with dementia. *Neurosci Lett* 1992; 139: 269–74.
- Woulfe J, Kertesz A, Munoz DG. Frontotemporal dementia with ubiquitinated cytoplasmic and intranuclear inclusions. *Acta Neuropathol (Berl)* 2001; 102: 94–102.