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Severe Anterograde Amnesia with Extensive Hippocampal Degeneration in a Case of Rapidly Progressive Frontotemporal Dementia

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Abstract

Frontotemporal dementia (FTD) is usually characterized as a spectrum of relatively slowly progressive disorders with largely focal frontal or temporal presentations. The development of clinical and research criteria for discriminating FTD from Alzheimer's disease has relied, in part, on the relative preservation of episodic memory in FTD. We present a patient with FTD who, in addition to the more typical behavioural and language deficits, had a profound anterograde amnesia at the time of diagnosis. Neuroimaging confirmed atrophy of frontal and temporal lobes bilaterally, most marked in the anterior left temporal region. At post-mortem, non-Alzheimer pathology resulting in devastating cell loss was revealed in the hippocampi, as well as in the frontal and temporal cortex, thus providing neuroanatomical corroboration of the episodic memory deficit. Progression of the disease was extraordinarily rapid, with just 2 years between reported onset and time of death. This case demonstrates that the pattern of FTD may include severe anterograde amnesia as a prominent and early consequence of the disease.

Introduction

Frontotemporal dementia (FTD) is the term now generally preferred to describe a spectrum of disorders typically characterized by personality and behavioural changes, and/or by impairments in language production and comprehension (Brun *et al.*, 1994; Neary *et al.*, 1998). The recent discovery of a genetic basis for familial FTD (Basun *et al.*, 1997; Bird, 1998) together with the identification of a range of distinctive non-Alzheimer pathological features (Brun, 1993; Jackson and Lowe, 1996; Goedert *et al.*, 1998) has contributed to the recent burgeoning of interest in FTD, which represents the second commonest cause of dementia in younger people (Knopman *et al*, 1990; Miller *et al.*, 1997; Bird, 1998).

The development of clinical and research criteria for accurately discriminating FTD from other forms of dementia, especially Alzheimer's disease, has been a major focus of attention (Levy *et al.*, 1996; Mendez *et al.*, 1996; Miller *et al.*, 1997). In contrast to Alzheimer's disease, the relative preservation of episodic memory has been regarded as a defining characteristic of FTD, although atrophy of the hippocampal formation has sometimes been noted on imaging (Frisoni *et al.*, 1996) and pathology of medial temporal structures in FTD has also occasionally been described (Snowden *et al.*, 1992; Knopman, 1993).

Neary *et al.* (1998) described three distinct prototypical clinical syndromes in FTD: a bilateral frontal syndrome with altered behaviour and personality; a predominantly left perisylvian syndrome of progressive non-fluent aphasia; and semantic dementia, a predominantly left temporal disorder, comprising a severe naming and comprehension impairment. More recently, Boone *et al.* demonstrated differences in the neuropsychological profiles of FTD patients with predominantly right versus left hypoperfusion on single photon emission computed tomography (SPECT) (Boone *et al.*, 1999).

Amongst patients with semantic dementia, pathology (beyond the early stages) is almost invariably bilateral, but often more extensive on the left than the right (Mummery *et al.*, 2000). The most striking feature from a neuropsychological point of view is loss of content word vocabulary, usually accompanied by a progressive loss of word meaning and semantic knowledge (Snowden *et al.*, 1992; Hodges *et al.*, 1999). Although the anomia often appears to be a direct and commensurate consequence of the comprehension impairment, patients with predominantly left temporal atrophy may suffer from anomia that is disproportionately more severe than the measured semantic deficit (Lambon-

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Ralph *et al.*, 2001). For example, one patient has been reported whose initial unilateral left temporal abnormality produced a profound loss of content word vocabulary coupled with only mildly impaired comprehension (Graham *et al.*, 1995) although the subsequent spread of pathology to the right temporal region in this case was accompanied by eventually severe semantic decline (Graham *et al.*, 2001).

While rapid deterioration has been observed in FTD (Gregory and Hodges, 1996), and particularly in the form of FTD associated with motor neurone disease (Bak and Hodges, 1999), the course of the disease has most often been described as one of gradual evolution, with a mean duration of 7.5 years and a range of 3–17 years (Knopman *et al.*, 1990; Tyrell *et al.*, 1990; Miller *et al.*, 1991; Gustafson, 1993; Kertesz and Munoz, 1997; Schwarz *et al.*, 1998).

Although there is intense interest in FTD currently, the literature offers surprisingly few studies encompassing detailed neuropsychology, neuroimaging and neuropathology (Liebermann *et al.*, 1998; Schwarz *et al.*, 1998). Here we present such a study of a case that was furthermore remarkable for several reasons: (a) the progression from presentation to time of death was extraordinarily rapid; (b) a profound anterograde amnesia was present early in the course of the disease; and (c) undoubtedly related to (b), the neuropathological evidence revealed extensive atrophy in the hippocampal formation in addition to the more typical changes in the frontal and temporal lobes.

Case report

A 53-year-old right-handed man presented with a history of 10 months' deterioration in cognition and behaviour. His wife reported that he seemed to have forgotten the names of familiar people. At the same time he exhibited a pervasive loss of drive, including failure to complete tasks and loss of libido. He was hyperphagic with daytime somnolence. At presentation (October 1997) he was oriented in time but not place, and his speech was fluent, prosodic and syntactically well structured but almost free of meaningful content. He seemed to understand what was said to him but was profoundly anomic. He denied problems with memory or comprehension but grudgingly admitted word-finding difficulty.

The patient was a non-smoker but had long been in the habit of consuming several pints of beer a day. There was no family history of dementia. The initial neurological examination was unremarkable. He underwent a comprehensive work-up for unusual causes of dementia, including EEG and cerebral spinal fluid (CSF) examination, cardiovascular investigation, full blood count including erythrocyte sedimentation rate (ESR), B12 and folate levels, and an auto-antibody screen, all of which were negative.

Past medical history included a closed head injury sustained in a motor vehicle accident at the age of 14 years. No record of this event was available, but according to the patient's wife there had been a period of coma and he had been hospitalized for several weeks. There was no indication of any learning disability or neurodevelopmental condition prior to this event and, following it, he was thought to have made a complete recovery. Having finished his schooling at the age of 15 years, soon after the accident, he went on to successful employment as a ticketing agent for an airline company for a number of years, before establishing and running a small goods retail business with his wife. At the time of presentation she had taken over many of his responsibilities.

Over the following 12 months his condition deteriorated rapidly. Three months after presentation he was placed in residential care. A month after admission he had become mute, abulic and incontinent. He was unable to recognize people including his wife. Five months following admission, he developed a shuffling gait, fine tremor in both hands and difficulty maintaining balance when standing. He became incapable of feeding himself before he stopped eating altogether. He died 12 months after initial presentation.

Neuroimaging

Sagittal T1, axial fluid-attenuated inversion recovery, fast spin-echo and coronal multiplanar gradient-recalled magnetic resonance imaging sequences were acquired at the time of presentation. The anterior left temporal lobe was moderately atrophic compared with the right, with mild generalized atrophy elsewhere (Fig. 1A). Areas of hyperintensity, most likely representing gliosis, were seen in the deep frontal white matter bilaterally and particularly involving the left hippocampus (Fig. 1B). An area of encephalomalacia was noted in the right occipital lobe (presumably related to the accident at age 14 years described above).

Neuropsychology

An extensive range of neuropsychological tests was administered over several occasions between October and December 1997. These included tests of general intellectual function, language, memory, executive ability and visuospatial function (see Table 1).

The neuropsychological assessment indicated global compromise to cognitive function. Pro-rated full-scale IQ on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was 68, with a verbal IQ of 66 and a performance IQ of 74. Performance on all tasks was below normal but scores on the verbal subtests were the more dramatically impaired.

A striking frontal lobe syndrome disrupted performance on many tasks. The patient was able to recite the alphabet but was incapable of the alternation required to execute Part B of the Trail Making Test. He was prone to utilization behaviour, and to perseveration, so that on naming tasks the same word or phrase might reappear in his attempts to name several objects. For example, having responded 'two-storey

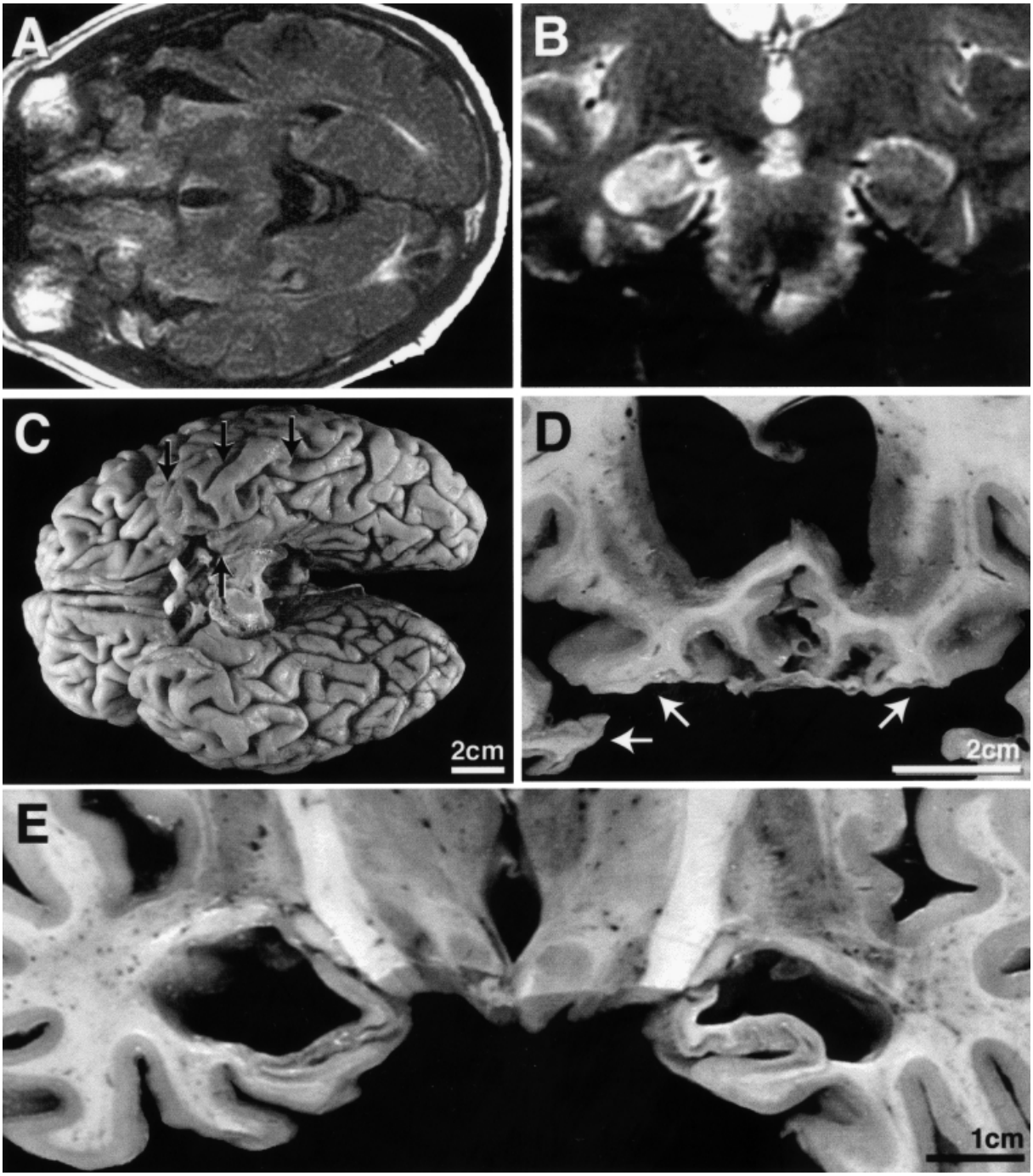

Fig. 1. Macroscopic brain changes. (A) Magnetic resonance imaging (MRI) scan of a horizontal section through the orbits. There is significant atrophy of the anterior left temporal lobe compared with the right, and areas of hyperintensity in the deep frontal white matter. An area of encephalomalacia can be seen in the right occipital lobe. (B) MRI scan of a coronal section through the anterior thalamus and hippocampus. There is atrophy of the left temporal lobe compared with the right, and significantly enhanced hyperintensity of the left hippocampus compared with all other brain structures. (C) Undersurface of the brain after removal of the brainstem and cerebellum. Atrophy of the left inferior temporal gyrus and uncus can be seen (arrows). (D) Anterior brain slice showing enlarged ventricles, atrophic head of caudate (left worse than right), and separation of the cortical lamina in the anterior temporal pole and orbital cortices (arrows). (E) Slice through the anterior hippocampal formation showing significant degeneration, enlargement of the lateral horns and necrosis of the pyramidal cell layer (left worse than right). The closely associated entorhinal and fusiform gyri were also atrophic.

house' to the picture of a house, he named a subsequent picture of a camel as 'two-storey camel'.

Unsurprisingly, in the context of such poor spoken production, story recall was very poor; but the patient's visual memory was also clearly impaired. Immediate recall of the visual reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) placed him at the sixth percentile, while he was unable to recall any of the items following a delay and denied having seen the cards previously. Recall of the Rey Complex Figure (RCF) was also very impoverished. On the

Table 1. Results of neuropsychological investigation. The figures in parentheses, following the test name, indicate the maximum scores

General intellectual function	
WAIS-R (Wechsler, 1981)—Age-scaled scores	
Digit span	6
Vocabulary	1
Arithmetic	5
Similarities	2
Picture completion	5
Block design	6
Digit symbol substitution	4
Full-scale IQ	68
Verbal IQ	66
Performance IQ	74
Memory	
Logical memory (WMS-R) (Wechsler, 1987)	
Immediate	3
Delayed	0
Visual reproduction (WMS-R) (Wechsler, 1987)	
Immediate	20
Delayed	0
Rey Figure—30′ delayed recall (36)	2
RMT (Warrington, 1984)—faces (50)	32
Language	
Naming	
BNT (60)	14 (54.5 ± 5.2)
Semantic battery (Hodges *et al.*, 1992) (48)	13 (43.6 ± 2.3)
Test of naming (Graham *et al.*, 1994) (106)	17 (98.1 ± 4.5)
Comprehension	
PPT—word version (Howard and Patterson, 1992) (52)	42 (51.1 ± 1.1)
PALPA spoken word–picture match (Kay *et al*., 1992) (40)	35 (38.9 ± 2.2)
Picture sort (Hodges *et al.*, 1992)	
Level 1 (48)	48 (48 ± 0.21)
Level 2 (48)	41 (47.2 ± 0.9)
Level 3 (72)	65 (68.8 ± 1.9)
Test of comprehension (word–picture match) (Graham *et al.*, 1994) (106)	95 (105.3 ± 0.9)
TROG (Bishop, 1989) (80)	70 (78.8 ± 1.8)
Repetition	
PALPA syllable length repetition (24)	24
PALPA sentence repetition (18)	18
Face recognition	
Benton Facial Recognition Test (Benton *et al.*, 1994) (54)	32
Famous faces (16)	
Recognized as familiar	10
Named	0
Executive function	
Trail Making Test (Reitan and Wolfson, 1985)	
Part A	77″
Part B abandoned, incomplete, after 3′40″–	
Stroop Test—colour naming too unstable to proceed	
Phonemic fluency (FAS)	3
Visuospatial function	
Rey figure copy (36)	26
JLO (Benton *et al.*, 1994) (30)	16

WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised; RMT, Recognition Memory Test; BNT, Boston Naming Test; PPT, Pyramids and Palm Trees; PALPA, Psycholinguistic Assessment of Language Processing in Aphasia; TROG, Test for the Reception of Grammar; JLO, Judgement of Line Orientation.
Mean ± standard deviation for age-matched controls are shown in parentheses after the patient's scores on naming and comprehension tests.

Recognition Memory Test (RMT) for faces he scored below the fifth percentile. Thus, even on memory tests that did not require verbal output, performance was severely impaired.

Language testing revealed a profound anomia accompanied by only modestly impaired semantic knowledge (see Table 1). When unable to name an object he was often able to pantomime the action (e.g. blow a whistle). Sometimes his responses were circumlocutory, and often sufficiently descriptive to indicate that he recognized the object (e.g. doll – 'that's a, is that just a little play fella that's been playing'). At other times the responses were less indicative of correct object identification (e.g. plug – 'that's just the governor that sticks in with the front things'). Single-word misnamings were generally semantic (e.g. 'lettuce' for 'carrot'), but sometimes they seemed to comprise a combination of semantic and visual confusion (e.g. button – 'it's just a just the one of the wheels pulled out of the drawers').

Comprehension was much less affected than naming. Although he managed to name successfully only 13 of 48 items from the semantic memory battery (Hodges *et al.*, 1992), he was able to sort 41 of the same 48 pictures into categories (land animals, birds, water creatures, for living things; household items, vehicles, musical instruments, for man-made artefacts). This is called level 2 sorting in the semantic battery, level 1 corresponding to sorting in terms of broad domain (living versus man-made), on which he obtained a perfect score. Even more impressively and in contrast to a number of reported cases of this syndrome (e.g. Hodges *et al.,* 1994; Hodges and Patterson, 1995), this patient achieved a very creditable score of 65/72 in sorting at the third, attribute, level (e.g. fierce/not fierce for animals; electrical/non-electrical for household items). He made only five errors on word–picture matching of the 48 items. Similarly, on the Graham *et al.* (1994) test of naming, reading and comprehension, he was able to name only 17 of 106 items but could match 95 of 106 words to pictures (five alternatives). Repetition of single words and sentences was excellent, but phonological transposition errors were detected in his repetition of short lists of unrelated words. For instance, 'armour, lips, neck' reproduced as 'armour, nips, leck' (see Patterson *et al.*, 1994 for a study of this phenomenon in three cases of semantic dementia).

He recognized as familiar 10/16 faces, but was able to name none of them. Of the familiar faces, he was able to offer only a vague statement as to who the person might be. For instance, of John F. Kennedy, he said 'one of the best people that's ever been, I've got the name and everything, it's all here'.

Neuropathology

The brain was collected at brain-only autopsy and placed in 15% buffered formalin for 2 weeks. After fixation, the whole brain was examined macroscopically prior to sectioning of the cerebrum in the coronal plan at 3 mm intervals using a rotary slicer. Bilateral samples were taken of the orbital and superior frontal, anterior cingulate, superior parietal, polar, medial, inferior and superior temporal, and occipital cortices, and from the hippocampus, amygdala, anterior and posterior basal ganglia, midbrain, pons and medulla oblongata for

paraffin tissue processing. Ten micron sections were cut and stained with haematoxylin and eosin, haematoxylin and congo red, the modified Bielschowsky silver stain, and immunohistochemistry for tau II (T5530, Sigma, St Louis, MO, USA, diluted 1:10 000, cresyl violet counterstain), β-amyloid (a gift from Professor Colin Masters, diluted 1:500), ubiquitin (Z0458, Dako, Denmark, diluted 1:200, cresyl violet counterstain), and glial fibrillary acidic protein (Z334, Dako, diluted 1:750, luxol fast blue counterstain) with peroxidase visualization as previously described (Halliday *et al.*, 1995).

Macroscopically there was marked atrophy of the anterior temporal poles bilaterally with the left side more affected than the right (Fig. 1C). Examination after sectioning revealed gross destruction of the temporal and frontal orbital cortices (Fig. 1D, E). The grey matter tissue was separated along a horizontal band parallel to the cortical surface (Fig. 1D, E). There was severe atrophy of the underlying caudate nucleus and putamen (Fig. 1D) with marked enlargement of all ventricles. Within the medial temporal lobe the amygdala and hippocampus were extremely atrophic, especially on the left (Fig. 1E). There was similar destruction of the hippocampal pyramidal layer (Fig. 1E) which was of normal appearance only in the right posterior hippocampus. Additional atrophy of the left superior temporal gyrus and some widening of the frontal sulci were observed.

There was a large, soft depression on the external surface of the right occipital lobe with destruction of the cortex around the depression and complete loss of the underlying white matter.

On microscopic examination, multiple regions of the cerebral cortex showed severe neuronal loss and gliosis with virtually no plaques or inclusions. There was almost complete cell loss and loss of lamination and prominent neuronophagia in the temporal pole (Fig. 2A) whereas the superior temporal gyrus was relatively spared (Fig. 2B). Broca's area showed moderate cell loss especially in layers V and VI (Fig. 2C). The hippocampus showed massive loss of the CA1–4 and dentate gyrus (Fig. 2D) and there was virtually total cell loss in the entorhinal cortex (Fig. 2E). Only some of the subiculum remained. There was also substantial cell loss in the amygdala. Within the basal ganglia there was severe cell loss in the caudate nucleus (Fig. 2F) and to a lesser extent in the putamen. Ubiquitin-positive but tau- and silver-negative neurites were found in the regions of neurodegeneration (Fig. 2G). Some rare swollen neurones (Fig. 2H) were seen in cortical regions. There were significant hyaline changes to many of the vessels in the regions of atrophy, associated with prominent cribiform change. β-amyloid immunohistochemistry was negative. The brainstem showed severe depigmentation and cell loss in the midbrain substantia nigra and pontine locus coereleus, but no Lewy body formation.

Discussion

Although FTD is usually characterized by a predominance of either frontal or temporal features at onset (Neary *et al.*, 1998), it can present with both frontal and temporal features in the earliest stages, as demonstrated in this case. The onset here was marked by anomia and by behavioural changes, both of which progressed relentlessly throughout the swift course of the disease. While some authors have noted that progression can be quite rapid (Gregory and Hodges, 1996), most reports suggest that FTD progresses relatively slowly. The rate of deterioration in this patient was remarkable, with less than 12 months elapsing between the onset of symptoms and diagnosis, and only a further 12 months to the time of death.

In FTD, episodic memory is usually said to be relatively spared (Brun *et al.*, 1994; Neary *et al.*, 1998), especially in tests of autobiographical memory for events of recent (1–2 years) occurrence (Graham and Hodges, 1997; Graham *et al.*, 1999). Complaints of poor memory and under-performance on tests of episodic memory are usually attributed to the secondary effects of frontal lobe dysfunction rather than primary degeneration of hippocampal and related structures (Neary *et al.*, 1998). Our patient unequivocally had poor anterograde memory at presentation. The impression gained at the time of testing was of a primary deficit of episodic memory, and not simply poor strategic retrieval. This hypothesis was confirmed at post-mortem by the finding of a devastating loss of hippocampal tissue. Thus, while episodic memory loss may not typify patients with FTD, the presence of this feature should not be regarded as pathognomonic of Alzheimer's disease. Both the neuropsychology at presentation and the neuropathological findings reported here demonstrate that medial, as well as lateral, temporal structures can be vulnerable to the degenerative changes associated with FTD.

Unlike many patients with FTD, our patient showed features of both orbitofrontal dysfunction (changes in social conduct, loss of drive) and semantic dementia (severe anomia with predominantly semantic errors, in combination with a mild but measurable deficit of word and picture comprehension) (Hodges *et al.*, 1992; Snowden *et al.*, 1992). The pattern of linguistic change—disproportionately marked anomia compared with comprehension—mirrored the pattern of temporal lobe atrophy, involving the left much more than the right side. A recent study of a number of cases of semantic dementia demonstrated that those with greater left- than right-sided involvement show a level of naming impairment which exceeds that expected based on their semantic breakdown (Lambon-Ralph *et al.*, 2001).

In confirmation of several previous studies (Knopman *et al.*, 1990; Brun *et al.*, 1994) and a meta-analysis of 13 cases (Hodges *et al.*, 1998), the autopsy results revealed devastating cell loss with no specific characteristic features. More striking was the extent of the pathology, involving both frontal and temporal lobes with both medial and lateral structures affected. In addition to the characteristic cortical degeneration, in this case subcortical changes were just as dramatic. In particular, both the hippocampus and the basal

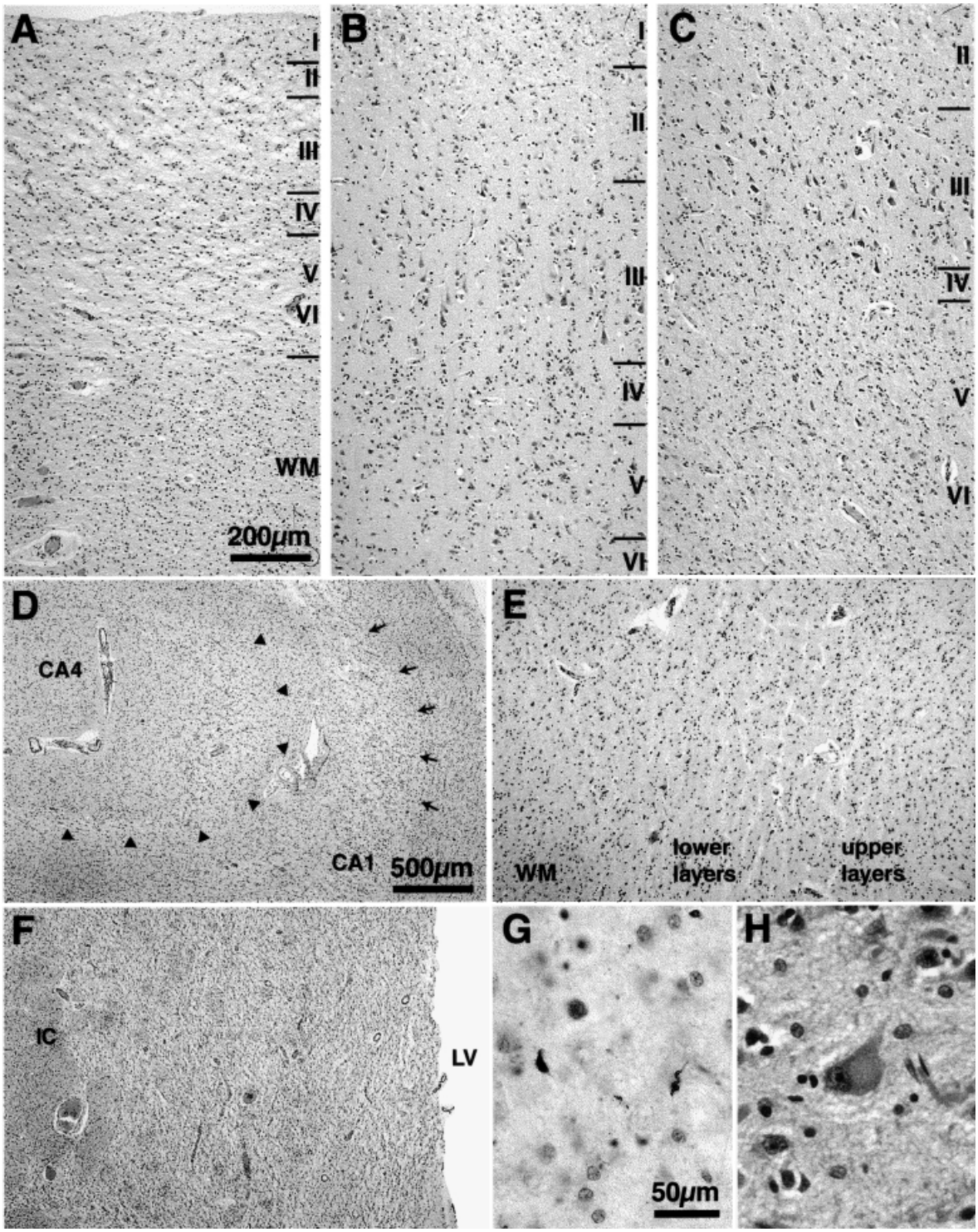

Fig. 2. Representative photomicrographs showing the degree of neurodegeneration. (A)–(F) and (H) are photographs of haematoxylin and eosin stained tissue sections. (G) is a section stained immunohistochemically for ubiquitin. Cortical layers and the white matter (WM) are indicated. LV, lateral ventricle. Scale in (A) is equivalent for (B), (C) and (E). Scale in (D) is equivalent for (F). Scale in (G) is equivalent for (H). (A) No pyramidal neurones were observed in cortical sections of the anterior temporal pole. (B) The superior temporal cortex was relatively spared with large pyramidal neurones evident in layers III and V. However, spongiosis evident in layer I indicates some neurodegeneration in this region. (C) Broca's area showed gliosis and a marked reduction in the density of pyramidal neurones evident in layers V and VI. Pyramidal neurones in layers II and III were small and hyperchromatic. (D) There was complete destruction of both the dentate gyrus (region indicated by arrowheads) and the CA1 region (indicated by arrows) of the hippocampus in most of the section samples. The loss of neurones is indicated by a rarefraction rather than a glial scar. The CA4 region in the hilus of the dentate gyrus is also indicated. (E) Similar to the anterior temporal pole, no pyramidal neurones were observed in cortical sections of the entorhinal cortex with lamination patterns obscured. (F) The tissue of the anterior caudate nucleus resembled the surrounding white matter tracts (internal capsule indicated, IC) because of the absence of neurones in the region. (G) The only intracellular pathology observed in the regions of neurodegeneration was ubiquitin-positive neurites. (H) Occasional swollen cortical neurones were found in the regions of atrophy.

ganglia, especially the caudate nucleus and substantia nigra, were extensively affected.

Summary

We have presented an unusual case of FTD, which was remarkable for a number of features. Unlike most previous FTD cases, this patient presented with marked episodic memory loss in the earliest stages of the disease, in addition to the more typical features of impaired language and behavioural change. Again, unlike most other reported cases, both frontal and temporal features were prominent at the outset. The case was much more rapidly progressive than has usually been described in FTD. The autopsy revealed cell loss not only in the usual distribution in the frontal and anterolateral temporal lobes but also, and just as marked, in the hippocampus and basal ganglia. The neuropsychology, imaging and neuropathology of this case represent a significant contribution to the full characterization of the clinical phenotype in FTD.

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Severe anterograde amnesia with extensive hippocampal degeneration in a case of rapidly progressive frontotemporal dementia

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Abstract
Frontotemporal dementia (FTD) is usually characterized as a spectrum of relatively slowly progressive disorders with largely focal frontal or temporal presentations. The development of clinical and research criteria for discriminating FTD from Alzheimer's disease has relied, in part, on the relative preservation of episodic memory in FTD. We present a patient with FTD who, in addition to the more typical behavioural and language deficits, had a profound anterograde amnesia at the time of diagnosis. Neuroimaging confirmed atrophy of frontal and temporal lobes bilaterally, most marked in the anterior left temporal region. At post-mortem, non-Alzheimer pathology resulting in devastating cell loss was revealed in the hippocampi, as well as in the frontal and temporal cortex, thus providing neuroanatomical corroboration of the episodic memory deficit. Progression of the disease was extraordinarily rapid, with just 2 years between reported onset and time of death. This case demonstrates that the pattern of FTD may include severe anterograde amnesia as a prominent and early consequence of the disease.

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Primary diagnosis of interest
Frontotemporal dementia

Author's designation of case
None

Key theoretical issue
- Anterograde amnesia in frontotemporal dementia

Key words: frontotemporal dementia

Scan, EEG and related measures
MRI

Standardized assessment
Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale-Revised, Rey figure, Warrington Recognition Memory Test, Boston Naming, Pyramids and Palm Trees, Test for Reception of Grammar, Psycholinguistic Assessment of Language Processing in Aphasia spoken word–picture matching, Benton Facial Recognition Test, Trail Making Test, Stroop Test, verbal fluency (FAS)

Other assessment
Semantic battery, test of comprehension

Lesion location
- Atrophy of frontal and anterior temporal lobes bilaterally, left more than right; atrophy of left amygdala and hippocampus

Lesion type
Neurodegenerative

Language
English