Focal cortical presentations of Alzheimer’s disease

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To determine the frequency of Alzheimer’s disease (AD) pathology in patients presenting with progressive focal cortical syndromes, notably posterior cortical atrophy (PCA), corticobasal syndrome (CBS), behavioural variant frontotemporal dementia (bvFTD), progressive non-fluent aphasia (PNFA) (or a mixed aphasia) and semantic dementia (SD); and to compare the age of onset, evolution and prognosis in patients with focal cortical presentations of AD versus more typical AD and those with non-AD pathology. From a total of 200 patients with comprehensive prospective clinical and pathological data we selected 120:100 consecutive cases with focal cortical syndromes and 20 with clinically typical AD. Clinical files were reviewed blind to pathological diagnosis. Of the 100 patients with focal syndromes, 34 had AD as the primary pathological diagnosis with the following distribution across clinical subtypes: all 7 of the PCA (100%); 6 of 12 with CBS (50%); 2 of 28 with bvFTD (7.1%); 12 of 26 with PNFA (44.1%); 5 of 7 with mixed aphasia (71.4%) and 2 of 20 with SD (10%). Of 20 with clinically typical AD, 19 had pathological AD. Age at both onset and death was greater in the atypical AD cases than those with non-AD pathology, although survival was equivalent. AD is a much commoner cause of focal cortical syndromes than previously recognised, particularly in PCA, PNFA and CBS, but rarely causes SD or bvFTD. The focal syndrome may remain pure for many years. Patients with atypical AD tend to be older than those with non-AD pathology.

Keywords: Alzheimer’s disease; frontotemporal dementia; posterior cortical atrophy; corticobasal syndrome; progressive aphasia

Abbreviations: PCA = posterior cortical atrophy; CBS = corticobasal syndrome; PNFA = progressive non-fluent aphasia; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; SD = semantic dementia

Introduction

In the absence of an accurate biomarker, the in vivo diagnosis of Alzheimer’s disease (AD), in common with other neurodegenerative disorders, rests very largely on the characterization of the presenting cognitive profile supported by neuroimaging (Nestor et al., 2004; Hodges, 2006). AD is regarded as an essentially amnestic syndrome, whereas frontotemporal dementia (FTD) and corticobasal syndrome (CBS) are the overarching labels for patients with prominent behavioural deficits, aphasia or apraxia (Neary et al., 1998; Hodges and Miller, 2001; Hodges, 2006; Josephs et al., 2006a, b). The gold standard, however, remains neuropathological examination with the demonstration of characteristic histological changes (Blennow et al., 2006). Comprehensive unbiased clinicopathological studies are limited; but recent single, and multi-centre, surveys suggest that AD pathology—in cases presenting with focal syndromes not involving prominent amnesia—may be more common than previously recognised (Forman et al., 2006; Hodges, 2006; von Gunten et al., 2006). Moreover, amnesia may be prominent in pathologically verified FTD, which further clouds the issue (Graham et al., 2005).

In this study, typical AD refers to a pattern characterized by early episodic memory loss followed by various combinations of attention-executive, language and visuospatial impairment, thought to reflect the spread of pathology from the medial temporal lobe to other neocortical areas (Brun and Englund, 1981; Braak and Braak, 1991; Van Hoesen, 1997; Price and Morris, 1999; Tiraboschi et al., 2004; Hodges, 2006). In contrast to this typical profile, there are a growing number of reports of atypical focal cortical presentations of AD. It is well established that most patients with a progressive disturbance of aspects of visuo-perceptual and spatial abilities, often referred to as...
posterior cortical atrophy, have underlying AD pathology (Benson et al., 1988; Hof et al., 1993; Mackenzie-Ross et al., 1996; Hof et al., 1997; Galton et al., 2000; von Gunten et al., 2006). In addition, it is now clear that a proportion of patients with progressive aphasia, of both fluent and non-fluent type, can have AD as the primary pathology (Galton et al., 2000; Knibb et al., 2006; von Gunten et al., 2006). Recently, cases of CBS secondary to AD pathology have also been reported (Boeve et al., 1999; Lleo et al., 2002; Doran et al., 2003). The existence of a frontal presentation is more controversial: patients with familial AD secondary to presenilin 1 mutations may have a behavioural onset (Portet et al., 2003; Mendez and McMurtray, 2006) and there are isolated reports of sporadic AD resembling FTD (Johnson et al., 1999; von Gunten et al., 2006).

Several issues remain unresolved. First, the frequency at which focal dementias are secondary to AD pathology has not been established. An earlier case series from Cambridge reported on 13 patients with atypical and typical presentations of AD from a total of 50 patients reaching autopsy but did not attempt to estimate the frequency at which such syndromes are due to AD versus other pathologies (Galton et al., 2000). Second is the related question of whether focal dementia secondary to AD pathology differs from more typical AD, and from focal dementia due to other pathologies, in age of onset, disease duration and survival. FTD is usually associated with an early onset (Ratnavalli et al., 2002; Harvey et al., 2003) and a more rapid progression of disease than in AD (Raskovsky et al., 2005; Roberson et al., 2005). Third, do atypical AD cases remain focal for a short or long time? There has been an assumption that focal cortical syndromes that remain without significant memory impairment are unlikely to be due to AD (Mesulam, 2001). The evolution of deficits requires further systematic study to address this important question. In this large clinicopathological series from a single centre, our aims were

1. To determine the frequency of AD pathology in clinically typical AD versus progressive focal cortical syndromes, notably PCA, CBS, bvFTD, PNFA and SD.
2. To compare the age of onset, evolution and prognosis of patients with focal presentations and more typical AD.

**Methods**

A total of 120 cases with a clinical diagnosis of either (i) typical AD \((n=20)\) or (ii) a focal cortical syndrome \((n=100)\) were selected from 200 consecutive patients seen in the Memory and Cognitive Disorders Clinic at Addenbrooke’s Hospital, Cambridge during the period 1990–2007 on whom detailed clinical, neuropsychological and post-mortem neuropsychopathological data were available. All 120 had been seen by the senior author (JH). Cases with an in vivo diagnosis of an alternative neurodegenerative disease including Progressive Supranuclear Palsy, Huntington’s disease, Dementia with Lewy bodies, fronto-temporal dementia with motor neuron disease were excluded \((n=50)\). Cases were also excluded if they had a non-degenerative diagnosis such as leukodystrophy, tumour or vascular pathology \((n=20)\). A small number with inadequate clinical and neuropsychological data were also excluded \((n=10)\). Typical AD was diagnosed clinically in cases presenting with progressive and predominant amnesia associated with other cognitive deficits. Focal cortical syndromes consisted of one of the following subtypes: progressive aphasia (non-fluent, fluent or mixed), progressive social-dysexecutive syndrome (behavioural variant FTD), posterior cortical atrophy (PCA) or corticobasal syndrome (CBS) (see later for criteria). All cases were classified on the basis of clinical features at first presentation. Over this time period every effort was made to enrol all patients with a focal cortical syndrome into the brain donor programme, with a greater than 90% success rate in brain retrieval post-mortem. Of the 100 focal cortical presentation cases, 30 were included in the earlier combined Cambridge–Sydney series (Hodges et al., 2003, 2004) essentially comprising all of the FTLD pathology cases who died prior to 2002. More typical AD patients were enrolled as part of a longitudinal study of cognition in AD undertaken on a cohort assessed between 1992 and 1995 (Greene et al., 1995; Hodges and Patterson, 1995; Greene et al., 1996; Greene and Hodges, 1996; Lambon-Ralph et al., 2003; Hodges et al., 2006). Pathological diagnoses were all made by the same senior neuropathologist (JHX) who was blind to the clinical information. Although all patients underwent imaging, variable methods were used during the 15-year period which precluded an informative comparison or interpretation of these results. The work was approved by the Cambridge Local Research Ethics Committee. Declarations of intent for post-mortem brain donation were obtained from next of kin with subsequent consent for participation after death.

Clinic records of the 120 patients were reviewed by a researcher blind to pathological diagnosis (SA), looking for a range of cognitive, behavioural and neurological features either reported to be present at onset or recorded at first presentation to the clinic (Table 1). Formal neuropsychological evaluation was conducted in all cases but a wide variety of tasks were used during the study period. Assessments always included tests of episodic and semantic memory, language, visuospatial and executive function. Follow-up data were evaluated for development of new cognitive deficits with time. Since focal cortical syndrome patients did not have memory loss as the first and predominant complaint, particular attention was paid to later development of amnesia.

**Typical AD** (McKhann et al., 1984, 2001)

1. Memory loss as the first and predominant complaint.
2. Associated with at least one of the following—language disorder (e.g. anomia), visuospatial impairment, attentional deficit or apraxia.
3. Neuropsychological evaluation showing deficits in memory and one another cognitive domain.

**Progressive aphasia** (Mesulam et al., 2003; Knibb et al., 2006)

1. The primary complaint, and the predominant feature on clinical assessment, was of gradual-onset language disturbance.
Table 1 Definition of clinical features extracted from patient files

1. Amnesia; forgetting events and/or conversations; repetitive questioning and/or misplacing objects; deficit confirmed by episodic memory tests.
2. Aphasia; word finding difficulty, reduced speech output, anomia, semantic or phonetic paraphasias, impaired comprehension or repetition, dyslexia and dysgraphia.
3. Visuospatial deficits; spatial disorientation, impaired visuconstruction or visuoperception on neuropsychological tests, hemineglect, Balint’s syndrome (optic ataxia, visual disorientation, simultagnosia), visual failure not due to primary ocular disease.
5. Dyscalculia, dysgraphia, alexia, as prominent features.
6. Frontal behavioural symptoms; changes in personality and social behavior, specifically apathy, disinhibition, stereotyped behaviors, alterations in food preference, and poor self-care.
7. Other neuropsychiatric features; delusions, hallucinations, agitation and depression.
8. Motor signs; extrapyramidal features that include rigidity, bradykinesia, tremors and postural instability, myoclonus, bulbar involvement, early urinary incontinence, gait disorder.

(2) Activities of daily living were not affected by any deficit other than language disturbance (for example, episodic memory impairment or visuospatial impairment).

Progressive non-fluent aphasia (PNFA) was diagnosed in the presence of effortful or distorted speech output with phonological and/or syntactic errors. Semantic dementia (SD) was defined as fluent speech, marked anomia, impaired word comprehension and deficits in non-verbal semantic association tasks (Adlam et al., 2006). Patients with features not typical of non-fluent aphasia or semantic dementia or with some features of each were considered to have mixed aphasia.

Behavioural variant FTD (Neary et al., 1998; Rahman et al., 1999; Torralva et al., 2007)

(1) Change in personality and social behaviour as the first and prominent symptom, notably apathy, reduced empathy, disinhibition, stereotypic behaviours, alterations in food preference and poor self-care.
(2) Diagnosis supported by the presence of dysexecutive symptoms.
(3) Mild or later onset of memory loss.

Corticobasal syndrome (Litvan et al., 1997)

(1) Asymmetric apraxia and extrapyramidal syndrome (rigidity, bradykinesia, tremor).
(2) Cortical involvement suggested by alien limb phenomena, cortical sensory loss, hemisensory neglect, visuo-spatial deficits or myoclonus.

Posterior cortical atrophy (McMonagle et al., 2006)

(1) Presentation with progressive visual or visuospatial impairment in the absence of ophthalmologic impairment.
(2) Evidence of complex visual disorder on examination: elements of Balint’s syndrome, visual agnosia, dressing apraxia or environmental disorientation.
(3) Proportionately less memory loss or reduced verbal fluency.

PCA patients were further divided into three broad subgroups:
(1) Biparietal syndrome: apraxia, visuospatial problems, agraphia, Balint’s syndrome with preserved basic perceptual abilities, object recognition and reading.
(2) Occipitotemporal syndrome: alexia, apperceptive agnosia and/or prosopagnosia.
(3) Visual variant: primary visual failure and impairment of basic perceptual abilities.

Pathological criteria
Autopsies were performed within 48 h, and the cerebrum was bisected with the left half fixed in formalin and the right half frozen. Tissue samples were taken from the frontal (Brodman area 9), temporal (area 20), parietal (area 39), occipital (areas 17 and 18) and anterior cingulate (area 24) cortices, as well as from the hippocampus at the level of the lateral geniculate nucleus, amygdala, anterior and posterior basal ganglia (including the basal forebrain), thalamus, hypothalamus, midbrain, pons, medulla oblongata and cerebellum. Sections from all regions were stained for routine screening using currently recommended diagnostic protocols for AD (Mirra et al., 1997; Knibb et al., 2006). Non-AD pathologies were diagnosed according to standard criteria used in previous clinicopathologic studies (Galton et al., 2000) as follows: frontotemporal lobar degeneration (FTLD) with either tau-positive, tau-negative or ubiquitin-positive inclusions (FTLD-U), corticobasal degeneration (Hodges et al., 2004), dementia with Lewy bodies (McKeith et al., 1996; Knibb et al., 2006), progressive supranuclear palsy (Dickson, 1999; Knibb et al., 2006). Standard stains used included haematoxylin and eosin, Congo red, and the modified Bielschowsky silver stain. Immunohistochemistry was performed using antibodies against ubiquitin (Z0458 diluted 1:200; Dako, Glostrup, Denmark), tau (T5530 diluted 1:10 000; Sigma, St Louis, MO or mAb 11.57 courtesy of Laboratory of Molecular Biology, Cambridge, UK), βA4 peptide (M872 DAKO UK, diluted 1:50 using ABC format with 5 min pre-treatment in formic acid) and synuclein (18-0215, Zymed Laboratories, San Francisco, CA; or SA3400 diluted 1:200, Affiniti Research Products, Mamhead, Exeter, UK). A diagnosis of AD was made only in cases reaching Braak stage 4 or greater (Braak and Braak, 1991) and required the presence of both neuritic plaques and neurofibrillary tangles with involvement of the isocortex.

Results
Clinically typical AD
Of the 20 patients selected with clinical features typical for AD in life, 19 had pathological confirmation of AD and one had a diagnosis of FTD with ubiquitin-positive inclusions [as previously reported (Graham et al., 2005)].

Focal cortical syndromes
Of the 100 patients with focal cortical syndromes, AD was the primary pathological diagnosis in just over a third (34 of 100, 34%): of these 34, 19 presented with progressive aphasia, two with behavioural variant FTD, 6 with CBS and 7 with PCA (Fig. 1). Specifically with regard to the 53 patients with progressive aphasia, AD pathology was
found in 19 (36%) including 12 of 26 with PNFA (46%), 2 of 20 with SD (10%) and 5 of 7 with mixed aphasia (71%). Of 28 with bvFTD only 2 (7.1%) had AD pathology. A half of those with CBS had AD pathology (6 of 12, 50%) while all seven cases (100%) with PCA were found to have AD pathology. None of the progressive aphasia or CBS or PCA patients with AD pathology had evidence of classic corticobasal type pathology or concurrent cortical Lewy body inclusions.

The remaining 66 cases had one of the pathological variants of FTLD, as shown in Table 2. In line with our earlier report concerning a smaller combined Cambridge–Sydney series (Hodges et al., 2003, 2004), the PNFA patients had predominant tau-positive pathology with two showing classic corticobasal degeneration and three Pick body positive, four had progressive supranuclear palsy and tangle-only dementia (AD type but without amyloid plaques). Only 4 of the 26 had FTD-U. In contrast, the vast majority of the semantic dementia patients (14 of 20; 70%) had ubiquitin positive inclusions (FTLD-U). The mixed aphasia group (n=7) had predominantly AD pathology (5 of 7): the remaining two cases were brothers with a unique combination of tau-positive and α synuclein positive inclusions (Yancopoulou et al., 2005). The bvFTD showed the widest spectrum of pathologies: 16 had tau-positive forms of FTLD (nine classic Pick bodies, four corticobasal degeneration, two familial tauopathies and one PSP), 6 had FTDL-U and 4 lacked any distinctive inclusion pathology. All 12 CBS patients had either AD (6; 50%) or classic corticobasal tau-positive pathology (6; 50%).

**Survival**

Table 3 compares the demographic profile, disease course and survival of patients with pathologically confirmed typical AD (n=19), focal AD (n=34) and focal dementias due to non-AD pathology (n=66). Patients with focal dementias due to AD were significantly (P<0.05) older than those non-AD pathology at presentation (68.4 versus 62.8 years) and at death (73.5 versus 67.3 years P<0.05). Average survival from presentation was 5 years in both groups with an overall disease duration from symptom onset of 9.7 years versus 8.1 years in the AD versus non-AD groups. Age at onset, presentation and death was virtually identical in the typical and atypical AD groups. Kaplan Meier survival analysis failed to reveal significant differences in median survival between the typical AD, focal AD and non-AD groups suggesting that prognosis is equivalent.

**Clinical characteristics of focal cortical syndromes**

**Progressive aphasia (Table 4)**

Of the 19 cases with progressive aphasia secondary to AD pathology, 12 fulfilled criteria for PNFA, 2 for SD and 5 had a mixed aphasia syndrome. Only one had prominent behavioural symptoms, one had apraxia and two had visuospatial problems on neuropsychological examination. On follow-up, 10 of the 19 subsequently developed with a unique combination of tau-positive and α synuclein positive inclusions (Yancopoulou et al., 2005). The bvFTD showed the widest spectrum of pathologies: 16 had tau-positive forms of FTLD (nine classic Pick bodies, four corticobasal degeneration, two familial tauopathies and one PSP), 6 had FTDL-U and 4 lacked any distinctive inclusion pathology. All 12 CBS patients had either AD (6; 50%) or classic corticobasal tau-positive pathology (6; 50%).

![Spectrum of focal cortical syndromes secondary to AD pathology](image-url)

**Fig. 1** Spectrum of focal cortical syndromes secondary to AD pathology (n=29).

### Table 2 Distribution of pathologies according to clinical diagnosis

<table>
<thead>
<tr>
<th>FTLD Subtypes</th>
<th>Progressive Aphasia</th>
<th>bvFTD</th>
<th>CBS</th>
<th>PCA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PNFA</td>
<td>Semantic Dementia</td>
<td>Mixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tau-positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic Pick bodies</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Familial</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>5a</td>
<td>0</td>
<td>2b</td>
<td>1c</td>
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<tr>
<td><strong>Tau-negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ubiquitin-positive</td>
<td>4</td>
<td>14</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Alzheimer's Disease</strong></td>
<td>12</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>26</td>
<td>20</td>
<td>7</td>
<td>28</td>
<td>12</td>
</tr>
</tbody>
</table>

a1 tangle only dementia, 4 PSP; b1 familial cases with α synuclein and tau pathology; cPSP. DLDH = Dementia lacking distinctive histology.
prominent memory loss after 2 to 8 years (mean 4.5 years) from the onset of aphasia. The remaining nine patients retained a pattern of remarkably pure aphasia at least to the stage at which they were no longer able to attend the clinic. The clinical profiles of many of these patients have been previously reported (Knibb et al., 2006). The mixed cases were of particular interest. There was considerable heterogeneity, but of the five with AD pathology, two resembled semantic dementia but with additional phonological deficits (see Galton et al., 2000). Three conformed to what has been referred to as logopenic aphasia with reduced speech output and anomia and impaired sentence repetition, but without phonological errors (Gorno-Tempini et al., 2004). The two non-AD cases were brothers with mixed semantic and phonological deficits extensively documented by Croot et al. (1999) and later shown to have a unique neuropathological profile characterized by both tau and α-synuclein inclusions (Yancopoulou et al., 2005).

**Behavioural variant FTD**

In two AD patients the history was dominated by behavioural symptoms. Both presented with disinhibition, apathy and personality change, one had a prominent dys-executive syndrome. Both developed memory symptoms between 1 and 3 years after onset. There was a degree of aphasia at presentation in both although behavioural changes predominated.

**Illustrative bvFTD case with AD pathology.** A 56-year-old woman had become argumentative, garrulous and disinhibited for 2 years. One year later her practical skills, including cooking and dressmaking, declined. At the memory clinic in 1991, she was found to have prominent perseveration, utilization behaviour, impulsivity, confabulation and forgetfulness. There were marked deficits on a range of frontal executive tests. Language skills were preserved. She scored 13/30 on the MMSE. A clinical diagnosis of bvFTD was made. Assessment 2 years later showed severe anomia, poor language comprehension, impaired day-to-day memory and deficits on visuoperceptual tasks. She died at the age of 66 years, 10 years after disease onset.

**Corticobasal syndrome (Table 5)**

All six patients with AD pathology and CBS presented with severe asymmetric upper limb apraxia and extrapyramidal features. Three had alien limb phenomenon and myoclonus. All had a degree of generalized cognitive impairment characterized by mild memory loss and four had prominent visuospatial problems (visuoconstructive and constructive impairment in two, visuoconstructive and hemineglect in two).

**Illustrative CBS case with AD pathology.** A 70-year-old woman presented in 1995 with 3 years of difficulty in control of her right arm, causing problems with writing and dressing. One year later memory problems and word finding deficits appeared. Cognitive examination showed dyspraxia, dyscalculia, severe dysgraphia, mild word finding difficulty and poor executive function. Physical examination revealed slow saccades, myoclonic finger jerks, rigidity, alien hand phenomena and a tendency for the arms to adopt awkward positions while walking. Her MMSE was 15/30 and ACE 51/100. CT scan showed generalized cerebral atrophy. A diagnosis of CBD was made. During the next 2 years, she developed complete loss of function of both hands and progressive memory impairment. Her last assessment in 1998 was dominated by severe bilateral apraxia. She died aged 79 years, 9 years post onset.

**Posterior cortical atrophy (Table 6)**

Of the seven patients with PCA, all of whom had AD pathology, two had progressive visual failure and five had biparietal syndrome. Six of seven patients developed memory impairment 1–3 years (mean 2 years) after onset of visuospatial symptoms. On follow-up, six patients became severely amnesic, four developed aphasia while none demonstrated prominent behavioural symptoms.

**Discussion**

Several insights emerge from this large clinicopathological study of typical AD and focal cortical syndromes. The most significant is that a high proportion (i.e. just over a third) of focal cortical dementia syndromes are associated with
### Table 4 Summary of clinical features of progressive aphasia cases with AD pathology

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age of onset</th>
<th>Duration of symptoms at presentation (years)</th>
<th>Total duration of symptoms (years)</th>
<th>Clinical syndrome at presentation</th>
<th>Amnesia</th>
<th>Apraxia</th>
<th>Visuospatial</th>
<th>Frontal behavior</th>
<th>Duration of followup (years)</th>
<th>Deficits on follow up within three years of presentation</th>
<th>Onset of amnesia after aphasia (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>4</td>
<td>8</td>
<td>PNFA</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>3</td>
<td>None</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>2</td>
<td>6</td>
<td>PNFA</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>2</td>
<td>None</td>
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<td>PNFA</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>6</td>
<td>Apraxia</td>
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<td>PNFA</td>
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<td>N</td>
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<td>Disinhibition, Apraxia</td>
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<td>PNFA</td>
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<td>Amnesia</td>
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<td>PNFA</td>
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<td>Y</td>
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<td>Apraxia, Amnesia, Visuospatial</td>
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<td>8</td>
<td>PNFA</td>
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<td>N</td>
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<td>N</td>
<td>Y</td>
<td>Y</td>
<td>4</td>
<td>Amnesia</td>
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</tbody>
</table>

Asymmetrical = Y; N = no. Visuospatial problems detected only on neuropsychological assessment.

### Table 5 Summary of clinical features of CBS with AD pathology

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age of onset</th>
<th>Duration at presentation (years)</th>
<th>Total duration at presentation (years)</th>
<th>Asymmetric apraxia</th>
<th>Extra pyramidal features</th>
<th>Visuospatial deficits</th>
<th>Gerstmann's syndrome</th>
<th>Amnesia</th>
<th>Aphasia</th>
<th>Frontal Behavior</th>
<th>Deficits on follow up within three years of presentation</th>
<th>Onset of amnesia after apraxia (years)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>5</td>
<td>5</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>3</td>
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<tr>
<td>2</td>
<td>81</td>
<td>10</td>
<td>13</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
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<td>3</td>
<td>9</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Cortical sensory loss</td>
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<td>60</td>
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<td>3</td>
<td>Y</td>
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<td>N</td>
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<td>N</td>
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<tr>
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<td>3</td>
<td>10</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Behavioural</td>
<td>0</td>
</tr>
</tbody>
</table>

Y = yes; N = no.
AD pathology, with the association strongest for PCA. A surprisingly high proportion, a half, of those with CBS and with progressive non-fluent aphasia also had AD pathology. Patients with behavioural variant FTD and SD only rarely (one-tenth in our series) demonstrated AD pathology. Another major finding was the late onset, or absence, of significant amnesia even in advanced stages, suggesting sparing of the medial temporal lobe by AD pathology until very late. Survival of patients with typical AD did not differ from those with focal dementias with AD pathology, although cases with non-AD pathology were significantly younger at presentation and diagnosis. Survival in the atypical AD cases and the non-AD cases was very similar (9.7 versus 8.1 years from reported symptom onset). All of the focal AD patients had advanced Alzheimer pathology (at least Braak stage 4) and lacked other explanatory neuropathological changes. In this series, a diagnosis of clinically typical AD almost always predicted AD pathology.

Increased interest in the clinical manifestations of neurodegenerative disorders over the past decade has led to the realization that focal dementia syndromes represent a much higher proportion of cases than previously recognized. For instance, two epidemiological studies showed that FTD was the second most common form of dementia in the age group less than 65 years (Ratnavalli et al., 2002; Harvey et al., 2003). In a large clinic-based series from Japan involving 330 dementia patients, 13% were diagnosed in life as FTD (Ikeda et al., 2004). The unique clinical features of each of the focal cortical syndromes clearly reflect the locus of pathology and not necessarily its histological nature. The assumption, so far, has been that clinical variants of FTD (bvFTD, SD and PNFA) and CBS are generally not due to AD pathology, although studies correlating clinical diagnosis and pathology in focal dementias have been few and have consisted mainly of either single case reports or relatively small series with particular cortical syndromes (Boeve et al., 1999; Galton et al., 2000; Knibb et al., 2006; von Gunten et al., 2006). Taking neuropathology as a starting point, Forman et al. (2006) compared 90 cases with a pathological diagnosis of FTLD and 24 additional cases with a clinical diagnosis of FTD but with alternative pathology including 19 with AD: of these 19 cases approximately half had a language presentation. Our findings concur with those of Forman et al. Since the present study was longitudinal in nature, with 200 consecutive autopsies, including 100 with focal cortical dementias, evaluated over a period of 17 years in a single centre, the high frequency of AD pathology in this group (one-third) assumes considerable significance.

Turning to individual cortical syndromes, our findings support a growing literature suggesting that progressive aphasia is probably the commonest atypical presentation of AD and that a higher proportion of cases have AD pathology than previously recognized (Forman et al., 2006; Knibb et al., 2006; von Gunten et al., 2006). Among

### Table 6 Summary of clinical features of posterior cortical atrophy with AD pathology

<table>
<thead>
<tr>
<th>Onset of amnesia after visuospatial symptoms (years)</th>
<th>Deficits on follow up within three years of presentation</th>
<th>Clinical syndrome</th>
<th>Total duration (years)</th>
<th>Age of onset (years)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>n.a.</td>
<td>53</td>
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<tr>
<td>2</td>
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<td>-</td>
<td>n.a.</td>
<td>53</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>n.a.</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>n.a.</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>n.a.</td>
<td>53</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>n.a.</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>n.a.</td>
<td>53</td>
</tr>
</tbody>
</table>

Y = yes, N = no, NT = not tested.
the aphasia subtypes, PNFA accounted for the majority of AD cases. In a few cases, unusual mixed aphasia appeared to be a clinical clue suggestive of AD pathology. Some of these cases conform to what has been termed logopenic progressive aphasia (Gorno-Tempini et al., 2004) which has been previously suggested to be associated with AD pathology. Further work is required to establish premorbid markers of different pathologies. In terms of the spectrum of FTLD pathologies present in the progressive aphasic cases, the findings support our earlier work from Cambridge and Sydney which took as a starting point a positive pathological diagnosis and looked back at the diagnosis. It should be noted that 30 of 100 cases from the present series were included in the joint Cambridge–Sydney initiative study (Hodges et al., 2003, 2004). Patients with PNFA had a very high rate of tau-positive pathology with either AD (46%), classic Pick body FTD (11%), corticobasal degeneration (7%) or PSP (15%). Only 4 of the 26 cases (15%) had FTLD-U. Clinical features that might discriminate between underlying pathologies were explored in detail by Knibb et al. (2006) who found the AD cases to be older, but no other distinguishing factors. Apraxia of speech has been suggested to be a marker of non-AD forms of tauopathy in PNFA (Josephs et al., 2006a, b). We were not able to explore this hypothesis since our patients were not assessed for this specific language output disorder, many having presented to the clinic before we routinely evaluated motor speech. Earlier work has established that, by contrast to PNFA, semantic dementia is very predictably associated with FTLD-U type pathology, but without the intraneuronal Lentiform inclusions that characterize familial ubiquitinopa-thies (Davies et al., 2005). In this series of 20 cases, 14 (70%) had FTLD-U. Interestingly, although semantic memory problems are prominent in AD, semantic dementia as a focal manifestation of AD appears to be very rare. The occasional case with AD or Pick body positive FTLD pathology appears clinically indistinguishable from those with FTLD-U.

The concept of frontal variant AD has been somewhat controversial. Prominent and early behavioural problems and executive dysfunction in AD have occasionally been reported giving rise to the label of frontal variant AD (Johnson et al., 1999; von Gunten et al., 2006). In these cases, however, frontal involvement typically occurred on the background of an otherwise typical amnestic syndrome. In our series, bvFTD secondary to AD pathology was present in 2 of 28 cases coming to autopsy (7%). While none of them had amnesia at onset, in both diffuse cognitive dysfunction developed within 3 years of symptom onset. Our findings are thus compatible with the existence of a behavioural variant of AD, but in contrast to patients with non-AD pathology, the disease process does not appear to remain restricted to the frontal lobes for very long. The other 26 cases had a wide spectrum of FTLD pathologies with a slight preponderence of tau-positive cases (nine classic Pick body inclusions, four corticobasal degeneration and two familial tauopathies) compared to tau-negative (six FTLD-U and four lacking distinctive histopathology). As in a prior study, there were no clear markers which distinguished subgroups (Hodges et al., 2003, 2004) but further longitudinal analysis of bvFTD cases is required to establish markers of AD versus other pathology.

The corticobasal syndrome (CBS) is now known to demonstrate considerable pathologic heterogeneity (Boeve et al., 1999; Mathuranath et al., 2000). Our findings confirm a strong association between CBS and AD pathology. Clinical manifestations of CBS due to AD pathology in our series ranged from typical asymmetric apraxia, extrapyramidal syndrome and late cognitive impairment to a disorder characterized by severe cognitive dysfunction with apraxia and extrapyramidal features. Further work is required to determine in vivo markers of AD pathology in CBS.

Posterior cortical atrophy (PCA) is now a well-recognized focal dementia syndrome which appears to be nearly always due to AD pathology (Benson et al., 1988; Hof et al., 1993; Mackenzie-Ross et al., 1996; Hof et al., 1997; Galton et al., 2000; von Gunten et al., 2006). In our series, all seven cases with PCA had AD pathology and other pathologies, notably cortical Lewy bodies and cortico-basal changes, were absent. Presentation as biparietal syndrome was more common than primary visual failure. All seven cases had normal or only mildly impaired memory at presentation. Additionally, there was relative preservation of behaviour and language. This suggests that AD pathology remains restricted to the posterior regions of the brain with sparing of temporal and frontal lobes till late in the disease. Another interesting finding was the overlap of cognitive features between PCA and CBS. Both syndromes are characterized by apraxia and prominent visuospatial features: visual neglect, optic ataxia and Gerstmann’s syndrome (Mendez, 2004; Bak et al., 2005, 2006). Case descriptions of clinical CBD with AD pathology also have supported this clinical overlap (Boeve et al., 1999; Lleo et al., 2002; Doran et al., 2003). Involvement of parietal cortex asymmetrically in both clinical variants is the likely explanation for the difficulty in clinically distinguishing CBS from PCA in certain cases.

Our study has significant implications for early diagnosis of AD at the stage of mild cognitive impairment (MCI). The original concept of MCI arose from the assumption that amnesia is the prominent early feature of AD (Petersen et al., 1999, 2001a, b) although the label has been extended to patients with so-called non-amnestic MCI (Gautier et al., 2006). Our study confirms that non-amnestic presentations of AD occur more often than previously recognized (Boeve et al., 1999; Galton et al., 2000; Mendez, 2004; Knibb et al., 2006). Wider inclusion criteria for MCI and longitudinal follow-up of patients with non-amnestic MCI will reveal whether it is possible to make a diagnosis of focal atypical AD at a preclinical stage.

Certain limitations surface in this study. First, our study does not address the actual prevalence or incidence
of atypical AD due to the specialist clinic-based nature of the sample. Future community-based clinicopathological studies that include both typical and focal dementias are required to establish how common focal AD is in the population. Secondly, the lack of uniform imaging data precluded us from determining whether focal AD is associated with characteristic patterns of brain atrophy. It remains to be established whether imaging data is complementary to clinical features in making a more accurate ante-mortem diagnosis. It seems unlikely that structural imaging will discriminate between pathologies since symptoms reflect the location of disease regardless of the exact histological type, although it is possible that more systematic evaluation of the medical temporal lobes can provide clues as to the presence of underlying AD pathology (Likeman et al., 2005). In contrast, modern functional imaging such as the amyloid binding ligand PIB (Klunk et al., 2004; Engler et al., 2006) or CSF markers of tau and β amyloid (Clark et al., 2003) are much more likely to discrimination pathologies in vivo. Thirdly, the sample of typical AD cases in our series was relatively small and it is likely that alternative pathologies would be found in a larger sample of clinically diagnosed AD particularly of older onset. Our findings apply to younger patients presenting to a specialist clinic.

In conclusion, a clinical diagnosis of typical AD of relatively younger onset appears to be almost always concurrent with AD pathology, but the converse is not true. AD pathology is frequently found in patients with atypical cortical syndromes, suggesting that diagnosis of AD needs to be considered even in patients who present with focal dementia without significant memory loss, especially in cases with PCA, CBS and PNFA. The development of more specific biomarkers is needed to improve in vivo diagnosis of the pathological substrate in such cases. A great degree of heterogeneity in clinical presentations of AD exists and memory can be spared even into advanced stages of disease. Our findings have implications for understanding the relationship between type of pathology and clinical dementia syndromes, as well as for early diagnosis and treatment.

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Focal cortical Alzheimer’s


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