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CLINICO-PATHOLOGICAL CORRELATIONS IN FRONTOTEMPORAL DEMENTIA: AN UPDATE ON THE CAMBRIDGE SERIES AND REVIEW OF THE LITERATURE

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SUMMARY

Background The pathological basis of frontotemporal dementia is complex. Few studies have followed large groups prospectively to examine clinico-pathological correlations. Improved prediction is important for planning therapy with the advent of disease-modifying therapies.

Material/ Methods: From a total of 250 brain donors recruited into the Cambridge Brain Bank between 1990 and 2010, 150 had a diagnosis of an FTD variant in life, of whom 132 had sufficient data for inclusion in this study, which examines the correlations between *in vivo* clinical diagnosis and pathology *postmortem*.

Results: Overall 50 patients had FTLD-U, 41 a form of FTLD tau, 33 Alzheimer's disease (AD) and 8 other pathologies. There were numerous clear correlations. Of the 26 with semantic dementia (SD), 19 (73%) had FLTD-U. Patients with progressive nonfluent aphasia (n=26) had mainly tau deposition (43%) or AD (46%). In mixed aphasia (n=8), AD was present in 75%. Patients with FTD complicated by motor neurone disease (FTD-MND) showed FTLD-U in 100%. In behavioural variant FTD (n=40), the pathology was unpredictable and split equally between FTLD-tau and FTLD-U. In corticobasal syndrome (CBS n=19), the majority (58%) had AD pathology and the remainder FTLD-tau.

Conclusions: The underlying pathology in patients diagnosed clinically with FTD is heterogeneous. Clear predictions can be made in SD, FTD-MND (which are FTLD-U related) and to a lesser extent PNFA (which is largely tau related or secondary to AD) but not in bvFTD or CBS. Alzheimer's disease is surprisingly common in patients with progressive nonfluent or mixed aphasia and CBS.

Key words: frontotemporal lobar degeneration, progressive aphasia, semantic dementia, corticobasal syndrome

INTRODUCTION

Frontotemporal dementia (FTD) is the clinical diagnostic label now preferred to describe patients with a range of progressive dementia syndromes associated with focal atrophy of the orbitomesial frontal and anterior temporal lobes (Hodges, 2007). Epidemiological studies suggest that FTD is the second most common cause of young onset dementia after Alzheimer's disease (AD) (Ratnavalli et al*.,* 2002, Rosso et al*.,* 2003). Two independent studies from the UK revealed a prevalence of around 15 cases per 100, 000 population aged 45 to 64 with large confidence intervals (8 to 27), (Ratnavalli et al*.,* 2002).

Unlike AD, both the clinical profile and underlying pathology are heterogeneous in FTD. Two broad clinical presentations are recognised: progressive deterioration in social function and personality, known as behavioural-variant FTD (bvFTD or sometimes simply FTD) and insidious decline in language skills, known as primary progressive aphasia, which can, in turn, be subdivided according to the predominant pattern of language breakdown into progressive nonfluent aphasia (PNFA) and semantic dementia (SD; Grossman, 2010, Hodges and Patterson, 2007, Neary et al*.,* 1998). Patients with PNFA present effortful, nonfluent or distorted spontaneous speech with speech production errors and/or agrammatism (Neary et al*.,* 1998). In SD, speech is fluent and well-articulated, without phonological or syntactic errors, but patients show severe anomia and impaired word comprehension. The linguistic deficit reflects a breakdown in the conceptual knowledge base underlying language comprehension and production (Adlam et al*.,* 2006, Hodges and Patterson, 1996, Hodges et al., 1992, Snowden, 1989).

The syndrome of FTD overlaps with motor neurone disease (MND) both clinically and pathologically, and with a number of the extrapyramidal motor disorders. Around 10% of patients with FTD develop clinical and neurophysiological evidence of MND (Lillo et al*.,* 2010, Lomen-Hoerth et al*.,* 2002) and likewise patients with MND show behavioural and/or language changes, which, in some instances, are severe enough to qualify for a diagnosis of FTD (Lillo et al*.,* in press). In addition to MND, there is substantial overlap between FTD and the corticobasal syndrome (Kertesz et al*.,* 2005). The term corticobasal degeneration (CBD) was introduced to describe patients presenting with extrapyramidal rigidity, dystonia, apraxia and alien limb phenomenon together with cognitive features, notably aphasia and frontal executive dysfunction. Initial pathological reports described a specific form of tau-positive disease resembling classic Pick's disease. Recent series, however, have emphasised the range of pathologies found in patients with clinical CBD and the fact that this form of tau-positive pathology can be found in patients presenting with bvFTD or progressive aphasia. These findings have led to the adoption of the term corticobasal syndrome (CBS), which is used in the present study.

Over the past decade, there have been enormous advances in our understanding of the pathology and molecular basis of FTD (Mackenzie et al*.,* 2010). The pathologies in patients with FTD are classified on the basis of the pattern of

protein accumulation and are referred to collectively as frontotemporal lobar degeneration (FTLD) (Cairns et al*.,* 2007). At *postmortem,* cases share, by definition, bilateral frontotemporal atrophy with neuronal loss, microvacuolation and a variable degree of astrocytic gliosis. A fundamental dichotomy is into those with and without inclusions of the microtubular binding protein tau (FTLD-tau) (Mackenzie et al*.,* 2010). Tau positive cases include the subset with mutations of the microtubule associated phosphoprotein tau (*MAPT*) gene, patients with Pick bodies, corticobasal degeneration and argyrophilic grain disease (Mackenzie et al*.,* 2010). The majority of the remaining cases are tau negative but ubiquitin positive (FTLD-U). A landmark discovery in 2006 was that TAR DNA binding protein or TDP-43 was the main protein component of the ubiquitinated inclusions found in the majority of cases with FTLD-U (Neumann et al*.,* 2006). A minority of cases (around 5 to 10%) are both tau and TDP-43 negative (Mackenzie et al*.,* 2008). Very recently, inclusions of FUS, fused in sarcoma protein, have been found in many of these cases (FTLD-FUS) (Mackenzie et al*.,* 2010, Neumann, 2009). A small proportion of cases have either no inclusions (FTLD-ni) or show ubiquitin inclusions that are TDP-43 and FUS negative (FTLD-UPS) (Mackenzie et al*.,* 2010), suggesting that additional protein abnormalities will be found in FTLD.

To complicate things further, it has become apparent that a proportion of patients with a clinical label of FTD or CBS show Alzheimer's pathology at *postmortem*. Initial reports were of patients with PNFA, but subsequent single-case reports and series have shown that all the clinical syndromes (perhaps with the exception of FTD-MND) can be associated, to some degree, with AD pathology (Alladi et al*.,* 2007, Deramecourt et al*.,* 2010, Galton et al*.,* 2000, Josephs et al*.,* 2008, Mesulam et al*.,* 2008).

With the advent of drugs aimed at modifying the underlying pathology in the dementias (Boxer and Boeve, 2007, Mendez, 2009), it has become increasingly important to identify the pathology *in vivo*. Clinico-pathological studies are therefore vital for establishing the correlation between clinical phenotype and pathology. Such studies can be divided into two types. The first, which hail from centers with extensive pathology databases, such as that at the Mayo Clinic (Josephs et al*.,* 2006(a), Josephs et al*.,* 2006 (b), Josephs et al*.,* 2008, Knopman et al*.,* 2005) and the University of Pennsylvania (Forman et al*.,* 2006) and Manchester (Shi et al*.,* 2005, Snowden et al*.,* 2007), ascertain cases based upon the pathological diagnosis, then examine retrospectively the clinical diagnosis. Such studies are clearly important in terms of establishing the range and pattern of clinical diagnoses associated with particular FTD pathologies, but take no account of patients with a clinical diagnosis of FTD who show alternative pathologies, such as AD. The second form of study ascertains cases based upon their *in vivo* diagnosis and relates this to the profile of pathological changes, giving a potentially more representative picture of the spectrum of changes found in given clinical syndromes. Such studies have typically focused on a particular syndrome, such as semantic dementia (Davies et al*.,* 2005, Hodges et al*.,* 2010), progressive aphasia more broadly (Deramecourt et al*.,* 2010, Grossman, 2010, Knibb et al*.,* 2006,

Table 1. Acquisition of brains by the Cambridge Brain Bank as part of the dementia programme (1990-2010)

5-year epochs	Brain donations
1990-1994	19
1995-1999	51
2000-2004	96
2005-2009	84 (includes 7 in 2010)
Total	236

Mesulam et al., 2008), CBS (Shelley et al., 2009) or FTD with MND (Bak & Hodges, 2004, Lillo et al., 2010, Lillo & Hodges, 2009). Very few studies have considered the entire spectrum of FTD. Notable exceptions are the study by Kertesz et al. (Kertesz et al., 2005) that included 60 patients presenting from Canada, and one from Cambridge (Alladi et al., 2007), which analyzed the pathological findings in 100 patients with a focal dementia syndrome. This paper provides an update on the correlation between clinical syndromes and pathology in the Cambridge series and reviews the published literature.

THE CAMBRIDGE BRAIN DONOR PROGRAMME

The brain donor programme in Cambridge began in 1990 with an attempt to enrol patients with neurodegenerative disorders, particularly forms of FTD, presenting to the memory Clinic who had participated in a range of studies of cognitive disorders. In the early years, the clinic and team were small. Recruitment into the brain bank was accordingly slow, but increased markedly following the establishment of two specialist clinics: the Early Onset Dementia and the Disorders of Movement and Cognition. These clinics were attended by the nurse coordinator of the Cambridge Brain Bank, Angela O'Sullivan, who counselled patients and acted as the liaison officer until her retirement in 2007. After 1997, as part of a 10-year MRC funded programme, we aimed to enrol all of the patients with focal and atypical dementia syndromes attending the clinic. Once a declaration of intent was obtained from the families of our patients, we had a greater than 90% success for donation after death due to the provision of a 24 hour on-call system and close liaison with regional nursing homes.

In the first five years (1990-December 1994), we had only19 deaths, although several were patients with FTD, so we were able to publish initial observations within a few years of establishing the programme (Esmonde et al., 1996, Greene et al., 1996). As shown in Table 1, a marked increase in donations took place during the late 1990s, and, for the past decade, the brain bank has been processing between 15 and 20 brains per annum. At the time of writing this review, we had just reached 250 brains. Of the 250, 150 had received a diagnosis in life of one of the forms of FTD, including FTD-MND, and CBS. A further 30 had been

diagnosed with PSP and 40 with typical Alzheimer's disease, often of young onset. The remainder have a wide range of more unusual disorders.

Each brain was examined by the same senior neuropathologist (John H. Xuereb) without access to the clinical information. The histological and immunohistochemical methods used have evolved considerably over the years since the inception of the programme and have been detailed previously (Alladi et al*.,* 2007, Knibb et al*.,* 2006, Lillo et al*.,* 2010). Briefly, AD pathology was diagnosed in cases reaching Braak stage 4 or greater and with presence of both neuritic plaques and neurofibrillary tangles, and with involvement of the isocortex. FTD-spectrum pathologies were divided into three subgroups according to immunohistochemical criteria. The first was a tau-positive group that included classic Pick's disease, CBD, and progressive supranuclear palsy (PSP). Second was tau negative but ubiquitin positive FTD. We are currently in the process of screening FTLD-U cases for the presence of the newly discovered proteins TDP 43 and FUS. To date, all of the FTLD-U cases have been positive for TDP 43. The third group was tau-negative and TDP 43-negative (dementia lacking distinctive histology, DLDH).

DIAGNOSES IN LIFE

Establishing clinical phenotype to pathology correlations in FTD is particularly complex, as the clinical spectrum evolves with time and patients often have mixed syndromes even at presentation. For the purposes of this review, I have taken the diagnosis at the time of presentation to the clinic. Of 150 patients initially diagnosed with the FTD spectrum, 18 had limited clinical information, and had typically presented in the early years of the programme and at an advanced stage. The clinical diagnoses of the remaining 132 are shown in Table 2.

Patients with progressive aphasia were classified as semantic dementia (SD), progressive nonfluent aphasia (PNFA) or mixed. In SD, the main presenting pattern was either (i) progressive deterioration of both expressive and receptive vocabulary in the context of relatively fluent and phonologically correct speech production, together with impaired performance on tests of nonverbal semantic knowledge - the classic profile associated with left-predominant temporal lobe atrophy (Hodges & Patterson, 2007, Hodges et al*.,* 1992) or (ii) progressive impairment in recognition of people of a cross-modal type affecting identification from faces and names, a profile which typifies those with right-predominant atrophy (Thompson et al*.,* 2003). Structural imaging by MRI revealed focal atrophy in one or both anterior temporal lobes.

PNFA was defined as insidious onset, gradually progressive loss of language fluency characterised by effortful, distorted speech output, often with prominent phonetic or phonological errors in spontaneous speech or on single word repetition, often accompanied by syntactic errors (e.g. agrammatic use of tenses, omission or misuse of closed-class words) but with preservation of single word comprehension (Knibb et al*.,* 2006). In the mixed cases there were those that were unclassified and had features that overlapped with SD and PNFA. Some of

the patients labelled as PNFA or mixed would undoubtedly be classified now as logopenic progressive aphasics (LPA), but this syndrome was not fully elucidated until 2008 (Gorno-Tempini et al*.,* 2008). The distinction between PNFA and LPA depends upon qualitative assessment of speech output and performance on tests of sentence repetition that were not regularly performed. I will return to this topic in the discussion. All patients included in the language groups showed preservation of basic activities of daily living at the time of assessment and performed well on bedside tests of cognitive ability which are not language dependent.

Behavioural variant FTD was the label given to patients presenting with insidious onset and progressive changes in social behaviour and personality, typically dominated by disinhibition and/or apathy together with stereotyped behaviours, loss of empathy, changes in eating pattern and satiety and dysexecutive symptoms. Some patients in the bvFTD category had concurrent language symptoms, but behavioural changes dominated the clinical picture.

Patients with FTD-MND typically presented with behavioural and/or language features but within 2 years of initial presentation developed features of MND usually with prominent bulbar symptoms (Bak et al*.,* 2001, Lillo et al*.,* 2010).

Corticobasal syndrome was diagnosed in patients presenting with progressive limb apraxia accompanied by focal cortical symptoms (typically nonfluent speech or dysgraphia) and extrapyramidal motor features (Graham et al*.,* 2003, Shelley et al*.,* 2009).

CLINICOPATHOLOGICAL CORRELATIONS (Table 2)

The correspondence between clinical syndrome and pathology was complex, with no simple one-to-one relationship except in the cases of FTD-MND. In this group, all 13 cases (100%) had FTLD-U pathology. The next most consistent re-

Table 2. Clinico-pathological correlations in the 132 prospectively studied cases

	FTLD-U	FTLD-tau Pick body	FTLD-tau CBD	FTD-Tau other	PSP	AD	Other	**Total**
PNFA	3	4	4	0	3	12	0	26
SD	19	4	0	0	0	3	0	26
PA mixed	0	0	0	0	0	6	2*	8
bvFTD	14	9	5	4	0	3	5**	40
FTD-MND	13	0	0	0	0	0	0	13
CBS	1	0	6	0	0	11	1***	19
Totals	50	17	15	4	3	33	8	132

* Two brothers with combined α-synuclein and tau pathology 46.
** Four FTLD-ni and one subcortical gliosis
*** Unsuspected glioma

lationship was found in patients with SD: of the 26 SD cases, 19 (73%) had FTD-U deposition (confirmed to be TDP positive in 13 of 13 examined (see Hodges et al*.,* 2010); a further 4 cases (15.5%) had FTLD-tau with Pick bodies, and in the remaining three cases (11.5%) Alzheimer's pathology was found. In PNFA, the converse relationship was found: of the 26 cases, only 3 (11.5%) had FTLD-U with TDP deposition in all three, while 11 (42.3%) had a form of FTLD-tau, and 12 (46%) had AD pathology. Of the 8 with mixed aphasia, 6 (75%) had AD, while two brothers had a very unusual pathology with FTLD-tau and synuclein positive inclusions (Yancopoulou et al*.,* 2005). CBS was also strongly associated with AD pathology: of the 19 cases, 11 (58%) had AD, and only 6 (31.5%) had the classic FTLD-tau, CBD type; 1 case had FTLD-U and 1 an unsuspected low grade tumor.

The pathology in those with bvFTD, the largest single clinical group, was also highly heterogeneous. Of 40 bvFTD patients, 18 (45%) had a form of FTLD-tau pathology, including 9 with classic Pick bodies, 5 with CBD, 3 with the pathology associated with *MAPT* mutation with diffuse tau staining, and 1 atypical tauopathy. Among the other cases, 14 (35%) had FTLD-U and 3 (7.5%) had AD, 2 of those with significant vascular pathology. Of the 5 remaining cases, 4 (10%) had FTLD lacking ubiquitin and tau inclusions (FTLD-ni) and 1 case had a diffuse subcortical gliosis.

Looked at in terms of pathology, the most common finding was FTLD-U (n=50), and these cases presented with bvFTD, SD or FTD-MND. Taking the FTLD-tau group as a whole (n=41), these cases most often presented with bvFTD, PNFA or CBS. Patients with AD (n=33) masquerading as a form of FTD had either PNFA, mixed aphasia or CBS, rarely SD or bvFTD and never FTD-MND.

DISCUSSION

This series of 132 FTD spectrum patients with postmortem pathology is by far the largest reported yet. The findings confirm and extend the earlier reports. The first comprehensive series published in 2004 concerned 60 patients, half from Cambridge and half from Sydney (Hodges et al*.,* 2004). At the time of analysis (2002), there had been only 100 brain donations in Cambridge, with a similar number in Sydney. A number of conclusions were cautiously suggested, given the relatively small numbers in each subgroup: patients with a clinical diagnosis of SD all had FTLD-U (this was before the era of TDP) as did those with FTD-MND; those with PNFA had a range of pathologies, most commonly FTLD-tau or AD; bvFTD was associated equally with FTD-U and FTLD-tau, and CBS was associated with either FTLD-tau or AD. Subsequent reports from Cambridge described the pathological finding in cohorts of patients with specific syndromes, notably SD (Davies et al*.,* 2005, Hodges et al*.,* 2010), PNFA (Knibb et al*.,* 2009, Xiong et al*.,* 2010), FTD-MND (Bak et al*.,* 2001, Lillo et al*.,* 2010) and CBS (Shelley et al*.,* 2009). A more comprehensive study looked more specifically at the prevalence of AD pathology in 100 patients presenting with focal dementia syndromes (Alladi et al*.,* 2007). This review presents an update that essentially confirms in a larger cohort the findings of earlier studies.

Of the clinical variants of FTD, SD represents the most clinically and pathologically coherent; patients typically complain of "loss of memory for words" and show severe anomia with an evolving and characteristic pattern of semantic errors. Word repetition is spared in the presence of marked impairment in comprehension of meaning. The cognitive deficits and the implications for understanding the organization of semantic memory have been extensively documented (Patterson et al*.,* 2007). The imaging findings in SD are consistent across cases, with atrophy of the anterior temporal lobe centered upon the temporal pole and anterior fusiform gyrus (Davies et al*.,* 2009, Galton et al*.,* 2001, Mion et al*.,* 2010). Pathologically, the majority of our patients (73%) exhibited FTLD-U with TDP positive inclusions in 13 of 13 cases so far available for re-straining of sections. A minority, however, had either FTLD-tau (15.5%) or AD (11.5%). Other groups have likewise reported a strong association between SD and tau negative forms of FTLD (Godbolt et al*.,* 2005, Kertesz et al*.,* 2005, Snowden et al*.,* 2007). For instance, Snowden et al. (2007) found that 9 of 9 SD had FTLD-U, typically characterized by dystrophic neurites and an absence of neuronal cytoplasmic inclusions or intranuclear inclusions (Mackenzie type 2) (Mackenzie et al*.,* 2010). There seems to be little clinical difference between those with FTLD-U and other pathologies in terms of presenting symptoms, age of onset or progression (Hodges et al*.,* 2010), although a recent quantitative MRI study, using VBM, that included a subgroup of 8 of the SD patients reported here (5 with FTLD-U and 3 with AD) suggested that those with AD have a distinctive atrophy pattern and lack the signature anterior temporal degeneration seen in cases with FTLD-U (Pereira et al*.,* 2009).

As in prior studies, patients with the nonfluent form of progressive aphasia had heterogeneous pathology that spanned the spectrum of FTLD as well as AD. In the Cambridge clinic, established in 1990, patients with progressive aphasia other than SD were classified prospectively as PNFA (n = 26) or mixed (n = 8). Considering these non–SD cases together, AD was largest single underlying pathology and was found in 12 (46%) of the PNFA and 6 (75%) of the mixed cases. FTLD-U was rare and was the diagnosis on only 3 patients, all with PNFA. The remainder had a range of tau positive FTLD, including classic Pick body pathology (n = 4), CBD (n = 4) and PSP type pathology (n = 3). The sub-classification of patients with nonfluent aphasia remains a vexed issue. There have been many attempts to develop satisfactory nosology, with a recent consensus regarding the existence of a coherent subgroup labeled LPA. These patients appear to have distinct clinical features, atrophy distribution and underlying pathology (Gorno-Tempini et al*.,* 2008, Gorno-Tempini et al*.,* 2011, Grossman, 2010). At a clinical level, LPA patients are anomic and show frequent word finding pauses that slow their speech output, and may make phonological errors. These patients, however, lack apraxia of speech and agrammatism, which are now regarded as the hallmarks of true PNFA. A characteristic feature is their marked reduction in word span with difficulty repeating sentences, which contrasts with their relatively preserved single-word repetition. Syntactic comprehension is impaired, although this is likely to reflect the reduced word span rather than true syntactic impairment (Mesulam et al*.,* 2009).

Of relevance to the current study is the association between LPA and underlying AD pathology, which was first suggested by Gorno-Tempini et al. in their landmark 2004 paper on the three variants of progressive aphasia (Gorno-Tempini et al*.,* 2004); *postmortem* confirmation of these cases, however, was limited. A study of 23 patients with primary progressive aphasia (Mesulam et al*.,* 2008) found that 7 (64%) of 11 patients classified as LPA, presumably on the basis of a retrospective analysis of speech samples and test data, had AD pathology, while others showed FTLD-tau (n = 1) or FTLD-U (n = 3). Deramecourt et al. (2010) have likewise re-classified their patients using recent criteria into six categories. Their one patient with LPA had AD pathology, as did two with progressive jargon aphasia, while AD was not found in any of the other 4 categories, notably SD, progressive anathria or agrammatic progressive aphasia. A major advance in the quest for biomarkers has been the advent of the amyloid binding ligand PiB that is potentially capable of detecting AD pathology (Klunk et al*.,* 2004, Rowe et al*.,* 2007). Application to patients with progressive aphasia is in its infancy, but Rabinovici et al. (2008) reported positive PiB binding in all 4 patients with LPA, compared to only 1 of 6 with PNFA and 1of 5 with SD.

It has been claimed that patients with true PNFA rarely have AD. The Mayo group has emphasized the association between apraxia of speech (sometimes referred to as a motor speech disorder) and FTLD tau pathology, which they have typically found to be of PSP type or CBD (Josephs et al*.,* 2006(a)). In keeping with this, Deramecourt et al. (2010) found that all 5 of their progressive anarthric patients showed FTLD tau based pathology. They further reported that their patients often developed CBS as the disorder progressed. They also stated that progressive anarthria and apraxia of speech are likely to represent different designations for the same entity. By contrast to the work on apraxia of speech in primary progressive aphasia, other groups have stressed the centrality of the disorder of syntax as the key deficit producing a nonfluent syndrome (Grossman, 2010, Gunawardena et al*.,* 2010, Turner et al*.,* 1996), and in many cases agrammatism and deficits in the motor aspects of speech coexist (Knibb et al*.,* 2009). Using agrammatism as the defining feature of PNFA, Mesulam et al. (2008) reported that 4 of 4 patients had underlying FTLD-tau. Similarly Grossman has reported a predominance of FTLD-tau with occasional AD cases among the agrammatics (Grossman, 2010). A series recently reported (Deramecourt et al*.,* 2010) is at odds with this, in that 6 of 6 agrammatic progressive aphasics had FTLD-U (TDP positive); the fact that 4 of the 6 had progranulin gene mutations suggests a very unusual sample with a cluster of familial cases presenting as PNFA. The questions of the defining features of PNFA, its separation from LPA and the ability of particular features to predict pathology remain topics of very active investigation. The distinction between PNFA and LPA hinges on the finding of a motor speech disorder and/or agrammatism in PNFA versus impaired sentence repetition and the absence of a motor speech deficit or agrammatism in LPA (Gorno-Tempini et al*.,* 2011).

Some of these issues will hopefully be clarified with the advent of operationalised criteria, which have recently been agreed by an international consensus group (op.cit.).

Of note is the impairment in sentence comprehension in both disorders but due to different underlying mechanisms. Unfortunately, speech samples are not available in many of the older Cambridge cases to make a qualitative assessment, and sentence repetition tasks were not routinely performed. A number of the cases classified at the time as PNFA may have had what we would now call LPA, but this is unlikely to account for all of the AD positive cases. More recent cases included in our PET study (Nestor et al*.,* 2003), who showed predominately anterior insula hypometabolism, underwent thorough investigation and conformed to the pattern of PNFA rather than LPA. Several of the patients who underwent PET imaging have died and have pathology reported here that confirms the presence of AD. Similarly, the recent quantitative MRI study (Pereira et al*.,* 2009), discussed above in the context of SD, included 3 of the 4 PNFA cases with FTLD pathology, whose VBM showed left insula/frontal opercular atrophy. It appears, therefore, that although LPA is emerging as an important variant of primary progressive aphasia, typically associated with AD, some patients with true PNFA also appear to have AD as the underlying pathology.

Around 10% of patients presenting with FTD develop frank motor features of MND, typically within two years of the onset of the behavioural and/or language symptoms, although a higher proportion may have more subtle features of MND (review in Burrell & Hodges, 2010). Their progression is rapid, and psychotic features are unusually common (Lillo et al*.,* in press). The present series included 13 such cases, all of whom showed FTLD-U when examined *postmortem,* confirmed as TDP positive subjects, in whom samples are available for staining (Lillo et al*.,* in press). This finding is in keeping with the literature, which finds a strong association between FTLD-TDP and this clinical syndrome (Mackenzie et al*.,* 2010). For instance, Snowden et al. (2007) reported that all 8 of their FTD-MND cases showed FTLD-U with numerous neuronal cytoplasmic inclusions in both the superficial and deep cortical layers, which contrasted with the pattern of FTLD-U staining found in SD.

The largest single group in our study was those with bvFTD. Pathologically based studies have typically shown that bvFTD is by far the commonest presenting clinical syndrome (Forman et al., 2006, Josephs et al*.,* 2006(a), Josephs et al*.,* 2006 (b), Knopman et al*.,* 2005, Snowden et al*.,* 2007), whereas clinically driven studies have a more even split between language and behavioural presentations (Alladi et al*.,* 2007, Kertesz et al*.,* 2005). A number of conclusions can be reached. It is very rare for bvFTD patients to have AD pathology. In our series there were 3 such cases, although 2 also had extensive vascular pathology. In Kertesz's series, (Kertesz et al*.,* 2005), 32 of 60 patients presented with bvFTD, 2 of whom had AD, 1 with concurrent Lewy body disease. Considering the majority of cases who have FTLD spectrum pathology, there is an approximate 50-50 split between those with FTLD-U and FTLD-tau pathology. In our earlier series,

there were no obvious predictors of pathology (Alladi et al*.,* 2007), but Hu et al. (2007) compared 24 patients with FTLD-tau and 26 FTLD-U cases with a suggestion of greater executive dysfunction in the tau group and behavioural dysregulation in the FTLD-U group.

The pathological basis of the final syndrome under consideration, CBS, is perhaps the most contentious. Our series suggests a predominance of AD, which was found in 11 of the 19 cases, with the remainder having mainly FTLD-tau with a pattern of classic CBD. A recent study from London reported the pathological findings in 21 patients with a clinical diagnosis of CBS seen over a 20-year period, and found classic tau positive CBD in only 5 cases, with the majority having either AD, PSP or other non-tau pathologies (Ling et al*.,* 2010). Similarly, of 19 with a pathological diagnosis of CBD, only 5 had received a clinical diagnosis of CBS, leading the authors to question the validity of the concept of corticobasal degeneration. Other pathologically driven studies have shown a closer association between pathological CBD and the clinical syndrome of CBS, but such studies suffer bias, since the primary inclusion criteria exclude patients with AD and other non-FTLD pathologies (Josephs et al*.,* 2006(a), Josephs et al*.,* 2006 (b), Snowden et al*.,* 2007). An earlier study based on a subset of the Cambridge CBS patients in whom comprehensive data were available suggested that those with AD pathology had greater memory impairment, whereas early behavioural changes, non-fluent aphasia and orobuccal apraxia predicted CBD (Shelley et al*.,* 2009). These findings await prospective validation.

In conclusion, in this study of 132 prospectively studied FTD spectrum patients from a single centre, a quarter had AD pathology, nearly all of whom presented with either PNFA or CBS. Indeed, 11 of our 19 CBS patients showed AD pathology. A proportion of the PNFA patients are likely to have what would now be characterized as LPA, but the imaging evidence suggests that at least some have true PNFA. Of PNFA patients without AD, FTLD-tau was more common than FTLD-U, which is rarely found in PNFA cases. By contrast SD is largely a FTLD-TDP associated disease. Patients with FTD-MND all showed FTLD-TDP. In the commonest clinical variant, bvFTD, the pathology is unpredictable, with an even split between FTLD-tau and FTLD-U. We are in the process of re-staining all of the FTLD-U cases for the presence of TDP, and in TDP negative cases plan to look for FUS pathology. This may yield further insights into the clinico-pathological correlations in this fascinating but complex spectrum.

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