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The clinical diagnosis of early-onset dementias: diagnostic accuracy and clinicopathological relationships

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Accuracy of clinical diagnosis of dementia is increasingly important for therapeutic and scientific investigations. In this study, we examine diagnostic accuracy in a consecutive series of 228 patients referred to a specialist early-onset dementia clinic, whose brains were subsequently examined at post-mortem. Diagnosis was based on structured history, neurological examination and neuropsychological assessment, with emphasis on qualitative as well as quantitative aspects of performance. Neuroimaging provided support for but did not alter the clinical diagnosis. We set out the principles that guided diagnosis: (i) time course of illness; (ii) weighting of physical, behavioural and cognitive symptoms and signs; (iii) 'anterior' versus 'posterior' hemisphere character of cognitive change; and (iv) specificity of deficit, paying attention to the differentiation between syndromes of frontotemporal lobar degeneration and focal forms of Alzheimer's disease. Forty-two per cent of the patients had clinical diagnoses of one of the syndromes of frontotemporal lobar degeneration, the high proportion reflecting the research interests of the group. Forty-six per cent were diagnosed with Alzheimer's disease and the remaining patients, dementia with Lewy bodies, Creutzfeldt–Jakob disease, vascular or unclassified dementia. Frontotemporal lobar degeneration was identified with 100% sensitivity and 97% specificity and Alzheimer's disease with 97% sensitivity and 100% specificity. Patients with other pathologies were accurately identified on clinical grounds. Examination of subsyndromes of frontotemporal lobar degeneration showed a relatively predictable relationship between clinical diagnosis and pathological subtype. Whereas the behavioural disorder of frontotemporal dementia was associated with tau, transactive response DNA binding protein 43 and fused-in-sarcoma pathology, cases of frontotemporal dementia with motoneuron disease, semantic dementia and, with one exception, progressive non-fluent aphasia were associated with transactive response DNA binding protein 43 pathology, distinguished by ubiquitin subtyping (types B, C and A, respectively). Clinical diagnoses of progressive apraxia, corticobasal degeneration and progressive supranuclear palsy were, with one exception, associated with Pick, corticobasal and progressive supranuclear palsy subtypes of tau pathology, respectively. Unanticipated findings included Alzheimer pathology in two patients presenting with the behavioural syndrome of frontotemporal dementia and corticobasal pathology in four others with clinical frontotemporal dementia. Notwithstanding such anomalies, which serve as a reminder that there is not an absolute concordance between clinical phenotype and underlying pathology, the findings show that dementias can be distinguished in life with a high

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level of accuracy. Moreover, careful clinical phenotyping allows prediction of histopathological subtype of frontotemporal lobar degeneration. The principles guiding diagnosis provide the foundation for future prospective studies.

Keywords: Alzheimer's disease; frontotemporal dementia; frontotemporal lobar degeneration; neuropathology; progressive aphasia

Abbreviations: FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; MND = motoneuron disease; TDP-43 = transactive response DNA binding protein 43

Introduction

Dementia was traditionally defined as a global impairment in intellectual function, the corollary being that accurate differentiation between the dementias should not be possible in life. In recent years, it has become clear that there are distinct dementia profiles, which reflect the distribution of pathological change within the brain and which, by inference, are predictive of the underlying pathology. For example, dominant problems in memory, combined with problems in word retrieval, perceptuospatial and constructional difficulties, occurring in the context of preserved social skills, strongly suggest Alzheimer's disease (Martin *et al*., 1986; Neary *et al*., 1986; Galton *et al*., 2000). In contrast, breakdown in social behaviour, affect and executive functions, occurring in the context of preserved perceptuospatial skills, favour a diagnosis of frontotemporal dementia (FTD) (Neary *et al*., 1988, 1998, 2005; Miller *et al*., 1991; Perry and Hodges, 2000). These distinct profiles are reflected in the characteristic neuroimaging changes in temporoparietal cortex in Alzheimer's disease (Foster *et al*., 1983; Neary *et al*., 1987; Jagust *et al*., 1988; Minoshima *et al*., 1997; McNeill *et al*., 2007; Rabinovici *et al*., 2007) and in frontal and anterior temporal lobes in FTD (Talbot *et al*., 1995; McNeill *et al*., 2007; Rabinovici *et al*., 2007). In a proportion of patients with frontotemporal dementia, the behavioural and executive disorder are accompanied by physical signs of motoneuron disease (FTD/MND) (Neary *et al*., 1990). No such association is present in Alzheimer's disease.

The behavioural disorder of FTD (behavioural variant FTD) is just one of the prototypical syndromes of frontotemporal lobar degeneration (FTLD), comprising focal syndromes associated with non-Alzheimer pathology. Other prototypical syndromes are semantic dementia, a multimodal disorder of conceptual knowledge associated with bilateral, asymmetric atrophy of the temporal lobes (Snowden *et al*., 1989, 1996; Hodges *et al*., 1992; Neary *et al*., 1998) and progressive non-fluent aphasia (Mesulam, 1982, 2001; Neary *et al*., 1998), a disorder of expressive language associated with left perisylvian atrophy. Progressive aphasia is itself heterogeneous and subtypes of aphasia have been described (Mesulam, 1982, 2001, 2009; Snowden *et al*., 1992; Gorno-Tempini *et al*., 2004; Amici *et al*., 2006). Corticobasal degeneration and progressive supranuclear palsy have also been linked to FTLD by some authors on both clinical and pathological grounds (Kertesz *et al*., 2003, 2005; Paviour *et al*., 2004; Scaravilli *et al*., 2005; Josephs *et al*., 2006*a*; Ling *et al*., 2010).

The existence of distinct cognitive/behavioural syndromes, reflective of different topographical emphases of pathology within the brain, means that a comprehensive analysis of patients' clinical history, cognition and behaviour, together with a full neurological examination, ought to lead to a high degree of confidence in clinical diagnosis. Nevertheless, there persists the view that underlying pathology can be predicted on clinical grounds with only limited accuracy. Published consensus clinical diagnostic criteria [e.g. McKhann *et al*. (1984), Dubois *et al*. (2007) for Alzheimer's disease; McKeith *et al*. (1996) for dementia with Lewy bodies; Zerr *et al*. (2009) for Creutzfeldt–Jakob disease] delineate different levels of diagnostic certainty, 'possible' or 'probable' being permitted for clinically defined cases and 'definite' being reserved for cases with pathological confirmation.

There are a number of factors that may contribute to lack of clinical confidence. The most important is that patients sharing a common pathology are not clinically homogeneous. In Alzheimer's disease, the most common dementia, there are marked phenotypic variations (Neary *et al*., 1986; Martin, 1990; Price *et al*., 1993; Fisher *et al*., 1996, 1999; Galton *et al*., 2000; Alladi *et al*., 2007; Snowden *et al*., 2007*a*; Stopford *et al*., 2007, 2008). In some patients, memory impairment is the dominant presenting characteristic, and may represent a circumscribed yet pervasive disorder over many years before other cognitive changes emerge (Didic *et al*., 1998). Such patients may go on to develop semantic deficits, and are more likely than others to show an emphasis of atrophy on the temporal lobes (Snowden *et al*., 2007*a*). In other patients, symptoms of memory impairment emerge as part of a constellation of cognitive problems, which include problems in language, calculation, perception, spatial and constructional skills. This profile, characteristic of early onset Alzheimer's disease, is associated with functional imaging changes in temporoparietal cortex (Snowden *et al*., 2007*a*; Stopford *et al*., 2008). In a minority of patients with Alzheimer's disease, memory symptoms are minimal or absent at presentation. The dominant presenting symptom may be of problems in language (Pogacar and Williams, 1984; Galton *et al*., 2000), spatial skills (Crystal *et al*., 1982; Ross *et al*., 1996), vision (Hof *et al*., 1990, 1993; Levine *et al*., 1993) or praxis (Green *et al*., 1995). These 'focal' presentations of Alzheimer's disease are particularly problematic for clinicians because memory impairment is traditionally seen as the hallmark of Alzheimer's disease. Indeed, non-amnestic presentations would not fulfil conventional clinical (McKhann *et al*., 1984), or more recent research (Dubois *et al*., 2007), criteria for Alzheimer's disease, so that reliance on such criteria alone would lead to such cases being missed.

The existence of 'atypical' variants of Alzheimer's disease highlights the more general point: not all patients with dementia exhibit a 'prototypical' pattern and diagnostic boundaries may be blurred. For example, the language disorder of Alzheimer's disease might potentially be confused with the progressive aphasia of FTLD, the apraxia of Alzheimer's disease with that of corticobasal

degeneration and the semantic disorder of Alzheimer's disease with that of semantic dementia. Even when such known atypical phenotypes are accounted for there are cases where, even with hindsight, the pathology is unexpected. There may not always be a one-to-one correspondence between clinical phenotype and underlying pathology.

Accurate diagnosis of patients in life is increasingly important, both on clinical and scientific grounds. It is a guide to prognosis and a prerequisite for optimal clinical care and management. It is essential for clinical trials: therapies need to be targeted appropriately if their efficacy is to be meaningfully evaluated. It is crucial for genetic studies; advances depend on accurate and refined characterization of the patients from whom DNA is extracted. Heterogeneous cohorts might dilute or obscure potentially significant findings. The importance of precise clinical phenotyping is well illustrated by studies of Alzheimer's disease. Possession of the *APOE* ε4 allele, an established risk factor for Alzheimer's disease, and especially homozygosity at this locus, has been linked particularly to the amnestic phenotype (Snowden *et al*., 2007*a*) and associated with greater hippocampal atrophy (Lehtovirta *et al*., 1995; Hashimoto *et al*., 2001; Gutiérrez-Galve *et al*., 2009). Possession of the *APOE* ε4 allele has been found to occur significantly less often in patients presenting a mixed constellation of symptoms, in whom memory symptoms have moderate prominence (Snowden *et al*., 2007*a*) and significantly less often still in patients with a 'visual' presentation of Alzheimer's disease in whom memory symptoms are minimal or absent (Schott *et al*., 2006; Snowden *et al*., 2007*a*). Understanding the range of potential (genetic) risk factors for Alzheimer's disease and their precise contribution will depend on identification of distinct clinical variants of disease.

The present study outlines the principles that guided differential diagnosis in patients attending a specialist early onset dementia clinic. The study investigates the usefulness of these principles through an examination of the relationship between clinical and pathological diagnoses in a consecutive series of patients who came to post-mortem. Cases where there is agreement between clinical and pathological diagnoses are important because they validate the clinical diagnostic methods. Moreover, they strengthen and refine diagnostic distinctions in 'atypical' cases where clinical boundaries might otherwise be blurred. Cases where there is disagreement between clinical and pathological diagnoses are equally instructive. They may provide pointers to weaknesses in existing diagnostic methods. They may highlight domains in which the correspondence between clinical phenotype and underlying pathology is unpredictable, and may even challenge traditional assumptions regarding the neurobiology of disease. Of particular focus in the present study is the differentiation of the two most common forms of early onset degenerative dementia Alzheimer's disease and FTLD.

Materials and methods

Patient cohort

The cohort consisted of 228 patients (136 males and 92 females), examined clinically between 1983 and 2008 and who came to post-mortem between 1987 and 2009. The criteria for selection were that (i) the patients had received a dementia diagnosis in life in the Cerebral Function Unit, a specialist unit for early onset dementias within the Neuroscience Centre at a Manchester University teaching hospital (formerly Manchester Royal Infirmary, latterly Salford Royal Foundation Trust) and (ii) their brains had been donated post-mortem to the Manchester Brain Bank and full neuropathological examination of brain tissue had been undertaken. Patients with a clinical diagnosis of Huntington's disease were excluded because the diagnosis was verified during life by genetic testing, and therefore not dependent on clinical information alone. Other inherited disorders, such as familial Alzheimer's disease, were not excluded because genetic screening was not part of the diagnostic process. The mean age at onset of symptoms of patients in the study cohort was 57 years [standard deviation (SD) 8], the youthful age reflecting the referral bias of younger people to the Cerebral Function Unit clinics. The mean duration of symptoms at the time of patients' diagnostic assessment was 3 years (SD 2).

The study cohort represent 12% of the patients clinically diagnosed with dementia due to neurodegenerative disease during that same period, but <1% of the patients diagnosed with dementia due to cerebrovascular disease, the bias reflecting the research interests of the group. The pathological series is representative of the clinical series in terms of onset age and duration of symptoms at onset. In the clinical series, of 670 patients with an initial clinical diagnosis of one of the syndromes of FTLD, 14 (2%) have shown no progression of symptoms, resulting in subsequent re-evaluation of diagnosis. No patient clinically diagnosed with Alzheimer's disease has failed to progress.

Diagnostic methods

The clinical diagnosis was based on a detailed clinical history using a structured proforma, full neurological examination and a neuropsychological assessment carried out using the Manchester Neuropsychological Profile, an assessment instrument developed in-house for characterization of different forms of dementia (Thompson *et al*., 2005; Snowden *et al*., 2007*a*; Stopford *et al*., 2008). The clinical history aimed to elicit and characterize cognitive, behavioural and affective as well as physical symptoms. The proforma incorporates questions on language (expression, comprehension, naming, reading and writing), numeracy (recognizing coins, reckoning change), perception (objects and faces), spatial skills (localization, negotiation of environment), activities of daily living (dressing, cooking, self-care, driving, gadget use), memory (recent and past, events, names), executive skills (attention, distractibility, reason and judgement, planning and organization, checking, insight and motivation), affect (sympathy, empathy, depression, anxiety, irritability), behaviour (disinhibition, overeating, food preferences, motor and verbal stereotypies, rituals and routines, abnormal pain response) and arousal (fluctuations, confusion, hallucinations, delusions). The Manchester Neuropsychological Profile complements the historical information in addressing the same range of cognitive domains. It incorporates both published tests [e.g. Visual Object and Space Perception Battery (Warrington and James, 1991) for assessment of object perception and spatial skills] as well as locally developed tasks (e.g. Visual Object Memory, for assessment of immediate and delayed recall and forced-choice visual recognition memory; a brief famous face identification test for assessment of face perception and semantic knowledge). Interpretation takes account of qualitative performance characteristics, such as error types, as well as quantitative test scores in recognition of the fact that there is not a one-to-one correspondence between test and function (Thompson *et al*., 2005), and test scores alone can mask different underlying

reasons for failure. Interpretation follows the principle, moreover, that deficits in one domain can have a secondary impact on performance in another domain so that performance on individual tests needs to be interpreted in context and not in isolation.

Patients underwent magnetic resonance and/or single photon emission tomographic imaging (with the exception of a few early cases). Neuroimaging was typically carried out after the initial clinical diagnosis had been made and had a supportive role. MRI was regarded as particularly important in confirming the presence of suspected vascular disease. In no patient, in the clinicopathological series, was the diagnosis changed as a result of imaging findings.

The majority of patients were followed up after their initial clinical diagnostic assessment, although the number of follow-up reviews varied substantially across the cohort. The clinical diagnoses reported here represent those made following patients' initial assessment, except where a diagnosis of dementia was equivocal at initial presentation (e.g. patients presenting with mild cognitive impairment), and became apparent only on follow-up examination.

Differential diagnosis

Separation between forms of dementia followed the general algorithm outlined in Fig. 1, attention being given to (i) the evolution and course of illness; (ii) the relative salience of cognitive, behavioural and physical symptoms and signs; (iii) the pattern of cognitive deficits; and (iv) the degree of selectivity of those deficits. The first two dimensions are relatively non-controversial. An insidious onset and progressive course is a key feature of degenerative brain disease. The speed of evolution of symptoms is a crucial consideration in distinguishing Creutzfeldt–Jakob disease from degenerative disorders such as Alzheimer's disease. The relative weighting and character of neurological symptoms and signs is also highly informative. It helps to define movement disorders such as progressive supranuclear palsy and corticobasal degeneration, and aids the distinction been 'cortical' dementias, typically associated with physical well-being and 'subcortical' dementias, associated with prominent neurological symptoms and signs. For example, both behavioural variant FTD and subcortical white matter vascular disease may give rise to frontal-type behavioural change and executive impairments, yet patients with behavioural variant FTD are typically physically well (except when associated with MND), whereas patients with small vessel vascular disease typically have a history of vascular risk factors and exhibit neurological signs such as dysarthria, weakness and ataxia. The severity of parkinsonism as a presenting feature helps to distinguish dementia with Lewy bodies from Alzheimer's disease. It is recognized, however, that patients with Lewy body dementia may not exhibit all characteristics outlined in published guidelines (McKeith *et al*., 2005). The presence of a fluctuating mental state, incoherence in line of thought and intrusion and interference errors as described previously (Doubleday *et al*., 2002), helped to distinguish dementia with Lewy bodies rather than Alzheimer's disease even in the absence of overt parkinsonism.

Differentiation between Alzheimer's disease and frontotemporal lobar degeneration

Of particular importance in the context of the present study, in view of their high prevalence, is the differentiation between the 'cortical' dementias of Alzheimer's disease and FTLD-related syndromes. Two

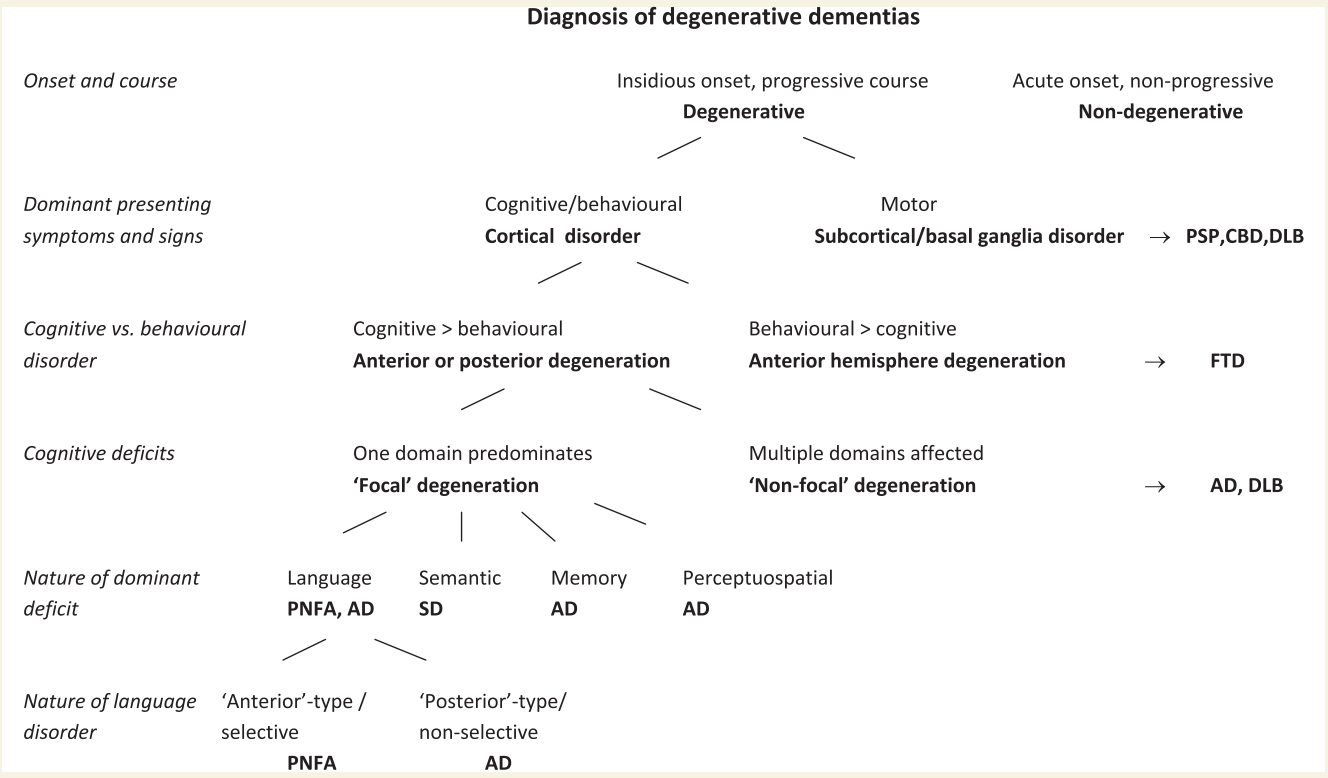

Figure 1 Algorithm for diagnosis of degenerative dementias. AD = Alzheimer's disease; CBD = corticobasal degeneration; DLB = dementia with Lewy bodies; PNFA = progressive supranuclear palsy; PSP = progressive supranuclear palsy; SD = semantic dementia.

guiding principles underlay their differentiation. First, it was assumed that Alzheimer's disease is predominantly a disorder of medial temporal lobes and posterior cerebral hemispheres whereas the syndromes of FTLD predominantly affect the anterior cerebral hemispheres. Although Alzheimer's disease may involve frontal lobe function, it was presumed that this is in the context of medial temporal/posterior hemisphere deficits. Thus, a profile of neuropsychological symptoms and signs that emphasized loss of function of medial temporal lobes/posterior hemispheres (e.g. amnesia/visuospatial impairment) would point to Alzheimer's disease, whereas a profile emphasizing frontal lobe dysfunction (e.g. personality change, altered affect and executive test performance indicating 'frontal' features: perseveration, rule violation, concreteness, inability to shift mental set) would point to FTLD. It should be emphasized here that poor performance *per se* on executive tests was regarded as non-contributory. Such tests are cognitively demanding, can be failed for multiple reasons and are sensitive to breakdown in all forms of dementia, hence the diagnostic importance of 'qualitative' frontal features.

The second guiding principle underpinning differentiation was the assumption that FTLD affects functional systems in a more selective (albeit potentially more profound) way than Alzheimer's disease. Thus, it was presumed that in 'focal' presentations of Alzheimer's disease, close examination may reveal subtle deficits in other cognitive domains. Moreover, within an affected domain (e.g. language), the impairment in Alzheimer's disease would be more likely than in FTLD to cut across functional system boundaries (e.g. phonology, orthography, syntax, semantics). In contrast, in FTLD, it may affect functional systems in a strikingly discrete way (e.g. impaired semantics with preserved phonology and syntax, dissociated access to phonology and orthography, agrammatism with relative preservation of word semantics). This feature of 'specificity of functional deficit' has particular relevance for the differentiation of progressive language disorders, but is relevant to the differentiation of progressive apraxic disorders.

Table 1 shows the specific symptoms and signs regarded as characteristic of Alzheimer's disease. Patients who exhibited a constellation of such symptoms and signs would fulfil conventional clinical diagnostic criteria for Alzheimer's disease (McKhann *et al*., 1984), and their diagnosis is relatively non-problematic. The importance of Table 1 is that it guides recognition of 'focal' Alzheimer presentations, which would not fulfil conventional criteria. The assumption was made that focal presentations fall within the same domains found in typical Alzheimer's disease and share similar characteristics, reflecting medial temporal/posterior cortical dysfunction. Thus, people with relatively circumscribed memory loss were classified as Alzheimer's disease (amnestic type) provided that the memory loss was of sufficient severity to affect functional independence and to be clearly pathological (patients were disoriented, showed impaired recognition memory as well as recall and there was loss of information over a delay). Such patients would fulfil recent research criteria for Alzheimer's disease (Dubois *et al*., 2007).

Patients with 'visual' symptoms were classified as Alzheimer's disease ('visual' or posterior cortical atrophy type), if the history and neuropsychological findings demonstrated perceptual and/or spatial impairments, as outlined in Table 1. Object agnosia was of the apperceptive rather than associative type, evidenced by (i) particular difficulty for degraded and fragmented stimuli; (ii) visually based errors; (iii) responses based on local elements rather than global configuration; (iv) inability to copy; and (v) preserved conceptual understanding of objects. The dominant feature of most patients with 'visual' presentations of Alzheimer's disease is spatial impairment, reflecting parietal atrophy, hence the emphasis on spatial function in the clinical history and assessment. Patients presenting with a predominant limb apraxia were diagnosed with Alzheimer's disease (apraxic type) provided that this was in the context of evident spatial impairments: gestures were spatially degraded in terms of their internal configuration and position in space; copies of line drawings showed loss of spatial configuration; performance was impaired on spatial tasks with minimal motor demands (e.g. spatial subtests of Visual Object and Space Perception Battery). The finding of additional subtle problems in memory, span, word retrieval and calculation, as shown in Table 1, reinforced the Alzheimer's disease diagnosis. Asymmetry of apraxia pointed to a need for caution in diagnosing Alzheimer's disease, and raised the possibility of the prototypical asymmetrical apraxic disorder corticobasal degeneration. Nevertheless, it did not categorically exclude an Alzheimer diagnosis. Patients were diagnosed with Alzheimer's disease provided that the asymmetrical apraxia occurred in the context of characteristics, such as spatial impairment, outlined above.

Patients presenting with an expressive language disorder were diagnosed as Alzheimer's disease (language type), if the features of the language disorder were consistent with those in Table 1: hesitant, halting delivery, word retrieval difficulties, loss of train of thought indicative of reduced verbal short-term memory, difficulties in writing and spelling, problems following left–right commands. The diagnosis too was influenced by a relative lack of specificity of the psycholinguistic deficits. Thus, the finding of a general reduction in complexity of grammatical sentence structure in spontaneous speech, sporadic phonological errors particularly on repetition tasks and occasional semantic errors in naming would be regarded as in keeping with Alzheimer's disease because these features suggest that the degenerative process cuts across psycholinguistic systems. The additional presence of calculation impairments and subtle deficits in perceptuospatial and constructional skills and memory reinforced the Alzheimer's disease diagnosis because it pointed both to relative lack of specificity of deficit and the 'posterior' character of the disorder. Patients' general demeanour of preserved social skills, insightfulness and concern supported the Alzheimer's disease diagnosis, because it was in keeping with a 'posterior' rather than 'anterior' hemisphere degenerative process. Language disorders with a more 'frontal' quality, such as effortful speech production, speech apraxia and agrammatism, as well as echolalia, concrete responses and verbal stereotypies, were regarded as contrary to an Alzheimer's disease diagnosis and in keeping with FTLD (Table 2).

Perhaps the biggest diagnostic conundrum arises in patients presenting with an apparently circumscribed anomia. Again, the degree of selectivity and specificity influenced diagnosis. Patients were diagnosed with suspected Alzheimer's disease if the naming impairment was identified as a relatively non-specific problem in lexical retrieval. In contrast, if neuropsychological analysis indicated a highly selective breakdown in a particular psycholinguistic functional system [e.g. profoundly impaired word semantics in the context of preserved speech fluency, phonology and syntax; dissociated access to phonological and orthographic word forms, so that the patient names in one modality but not the other (e.g. Snowden *et al*., 2003)], it was attributed to FTLD (Table 2). In the case of evident semantic loss, the disorder was ascribed to Alzheimer's disease if the semantic impairment occurred in the context of non-semantic language deficits or a classical amnesia with impaired autobiographical memory. If it represented a severe, isolated disorder then it was ascribed to FTLD.

Table 2 highlights the key characteristics influencing the diagnosis of prototypical syndromes of FTLD. In keeping with clinical criteria (Neary *et al*., 1998), the core determining feature of behavioural variant FTD was character and behavioural change. Particular emphasis was placed in the history on affective change (blunting, fatuousness, loss of empathy), social inappropriateness, repetitive behaviours, dietary changes and reduced pain response, since these dimensions have been

Table 1 Characteristic symptoms and signs of Alzheimer's disease

Symptoms obtained from clinical history	On assessment
Memory	
Poor recent/day to day memory	Disorientation in time and place
Better memory for remote than recent past	Impaired recall and recognition memory
Repetitive in conversation	Loses information over a delay
Mislays objects	Consistent performance
Would get lost if unaccompanied	Impaired working memory—reduced digit and word span, patient loses track of test instructions
Language	
Difficulty finding words	Conversational speech hesitant and halting, with unfinished sentences
Difficulty remembering people's names	Word retrieval difficulty
Loses train of thought in conversation	Impaired repetition, with phonemic errors
Difficulty following group conversation	Impaired sentence comprehension
Reads less	Difficulty following multi-stage commands
Difficulty writing, producing a signature	Problems with left/right (spatial) commands Reading consistent with conversational speech Impaired writing and spelling
Calculation	
No longer deals with bills, household accounts	Impaired mental and written arithmetic—especially subtractions involving holding and manipulating numbers, carrying across columns
Difficulty reckoning change	
Perception, spatial skills, praxis	
Slow to locate and/or identify objects ('doesn't see things in front of them')	Impaired object perception for degraded stimuli/unusual views
Difficulty remembering locations of objects ('puts things in wrong place')	Visually based errors on perceptual tasks
Disoriented in familiar environment	Slow to localize stimuli in visual field
Difficulty negotiating stairs (judging depth)	Impaired space perception
Car accidents suggesting poor spatial judgement (e.g. hitting parked car)	Loss of spatial configuration of drawings
Difficulty executing manual tasks with spatial demands (folding clothes, dressing, laying table)	Spatially impaired reproduction of hand postures
	Impaired gestural praxis (spatial configuration and position in space)
Executive skills	
Difficulty working out use of gadgets (e.g. washing machine, TV remote control)	Poor executive test performance. Patient 'overloaded' by complex tasks
Difficulty organizing household affairs	
Difficulty grasping complex ideas	
Behaviour	
More irritable	Socially appropriate. Preserved social facade
More anxious	Anxious/low mood depending on insight
Less confident—takes a 'back seat' in social groups	
Physical status	
Minimal physical symptoms	Few signs—mild akinesia and rigidity
Slowing—usually mid-course	Myoclonus, impaired tactile localization

demonstrated to be strong discriminators between behavioural variant FTD, Alzheimer's disease and vascular dementia (Bathgate *et al*., 2001). Neuropsychological assessment looked for 'frontal' qualitative characteristics of performance in the absence of primary deficits in 'posterior' hemisphere functions. A distinction was made between patients with behavioural variant FTD with and without physical signs of MND/amyotrophic lateral sclerosis (behavioural variant FTD versus FTD/MND).

Semantic dementia was diagnosed only if the semantic impairment was a striking yet relatively isolated disorder. Attention was paid to the disparity between performance on tasks requiring object identity or semantics (impaired) and those tapping basic perceptual and spatial skills (preserved). Performance on formal tests of verbal memory was regarded as non-contributory since performance can be affected secondary to the semantic disorder. However, patients should demonstrate an absence of significant amnesia by means of their ability to provide a good autobiographical account, orientation in time or preserved visual recognition memory. Behavioural alterations prevalent in semantic dementia (Snowden *et al*., 2001), such as obsessive preoccupation with a limited range of activities and concern for time reinforced the diagnosis. The presence of non-fluent, effortful production precluded a diagnosis of semantic dementia, as did the presence of phonological errors in conversational speech and naming. Semantic impairment occurring in the context of frank 'frontal' behavioural

Table 2 Key characteristics of principal FTLD syndromes

Symptoms obtained from clinical history	On assessment
Behavioural variant FTD	
Character change	Abnormal affect—flattened, unconcerned, fatuous
Breakdown in social behaviour, loss of empathy	Social disinhibition and/or apathy
Neglect of self-care and responsibilities Repetitive behaviours (motor mannerisms, verbal stereotypies, hoarding, wandering, rituals and routines) Dietary change (gluttony, sweet food preference) Altered response to pain Impaired application to and persistence on tasks Poor judgement	'Frontal' performance features: economy of effort, impulsivity, lack of checking, inattention, concreteness, lack of adherence to task goal, poor organization, sequencing and set shifting, perseveration, echolalia, verbal and motor stereotypies. Open-ended task performance (e.g. free recall, verbal fluency) worse than closed tasks (e.g. recognition, confrontation naming)
	Physical signs limited (e.g. grasp reflexes) or amyotrophic lateral sclerosis
Semantic dementia	
Difficulty 'remembering' words	Fluent, effortless speech production
Uses wrong words, asks what words mean	Prominent naming disorder, with semantic errors. No benefit from phonemic cues. No differences between spoken and written naming Impaired word comprehension
Difficulty recognizing faces (e.g. acquaintances) and things (e.g. fruit in supermarket)	Impaired recognition of famous faces and names
	Preserved perception, except when object identity (semantics) involved
No problems with spatial tasks—getting dressed, finding way, locating objects	Preserved spatial skills Good autobiographical memory
	Physically well or (rarely) amyotrophic lateral sclerosis
Enjoys puzzles/word and number games/quiz programmes	Demeanour—may be time bound, pedantic, preoccupied with theme (e.g. loss of driving licence)
Narrowed behavioural repertoire	
Preference for routine, clockwatches	
Progressive non-fluent aphasia	
Difficulty in expressive language	Non-fluent production, anomia, agrammatism, speech apraxia, phonological impairment
Memory problems limited to 'verbal' memory'—e.g. remembering what has been told	Psycholinguistic performance dissociations e.g. spoken versus written naming; imageable versus non-imageable word reading
No spatial symptoms	Limb apraxia without spatial impairment
High degree of functional independence	Physically well or asymmetric limb rigidity, rarely amyotrophic lateral sclerosis

change and executive impairments was classified as FTD rather than semantic dementia.

Aside from the prototypical syndromes outlined in Table 2, a classification of 'progressive apraxia' was also adopted to designate patients presenting with prominent, circumscribed buccofacial or limb apraxia in the absence of notable asymmetry and with minimal parkinsonism (Dick *et al*., 1989). We separated these patients from those with asymmetric 'basal' signs of parkinsonism and 'cortical' signs of apraxia in keeping with corticobasal degeneration (Litvan *et al*., 2003; Zadikoff and Lang, 2005) on the assumption that the progressive apraxic syndrome was likely to have a different functional and neurobiological substrate to that of corticobasal degeneration.

Diagnoses were all made prospectively. The general approach and certain principles underpinning diagnosis, such as the importance of 'anterior' versus 'posterior' hemisphere symptomatology in distinguishing FTLD and Alzheimer's disease was consistent throughout. We distinguished 'frontal-type' dementia from Alzheimer's disease, on clinical grounds, several years before Lund-Manchester (1994) criteria were published. Nevertheless, there has inevitably been an evolution and refinement of diagnostic principles with advancing knowledge of the field, for example, in the identification of dementia with Lewy bodies. Recognition of the importance of 'specificity of deficit' in distinguishing focal Alzheimer's disease from FTLD has come from experience of longitudinal follow-up of patients.

Neuropathological methods

Brains were obtained at post-mortem and fixed for variable periods up to 12 months before documentation of external appearances and cutting into coronal sections for reporting of macroscopic changes and preparation of tissue blocks for histological inspection. Usually, one hemi-brain was fixed (most commonly the left side) except in those instances where asymmetric clinical signs had been present (e.g. progressive non-fluent aphasia, corticobasal degeneration, progressive apraxia) in which case the whole of the brain was fixed (apart from a few selected blocks that were dissected fresh and frozen for genetic or biochemical analyses). Representative fixed tissue blocks were cut from 14 standardized regions of brain to include all major cortical, subcortical, midbrain and brainstem regions, and cerebellum and spinal cord (where available), and processed routinely into paraffin wax. When the whole brain was fixed, representative blocks from both left and right cerebral hemispheres and subcortical regions were taken. Sections were cut at a thickness of 6 μm and stained with haematoxylin–eosin, and immunostained for phosphorylated tau

[mouse monoclonal antibody AT8 (Innogenetics) 1:750 or rabbit polyclonal tau antibody (Sigma) 1:200], amyloid β protein [4G8 mouse monoclonal antibody (Covance Research Products Inc.) 1:3000], transactive response DNA binding protein 43 (TDP-43) [rabbit polyclonal antibody (10782-2-AP, Proteintech) 1:1000], fused-in-sarcoma (FUS) protein [rabbit polyclonal antibody HPA-008784 (Sigma) 1:200], α-internexin [rabbit polyclonal antibody (Abcam) 1:200], α-synuclein [mouse monoclonal antibody NCL-L-ASYN (Novocastra, Leica Biosystems) 1:40], GFAP [rabbit polyclonal antibody (Sigma) 1:750] or ubiquitin [rabbit polyclonal antibody Z0458 (Dako Cytomation) 1:750] employing a standard ABC Elite kit (Vector) with diaminobenzidene as chromagen.

Cases were examined both prospectively and retrospectively, following new developments, for the presence of neuritic plaques and neurofibrillary tangles (in frontal, temporal, cingulate, entorhinal, inferior parietal and occipital cortex, hippocampus and amygdale, locus caeruleus, substantia nigra and cerebellum), Lewy bodies (in cerebral cortex, limbic regions, substantia nigra and locus caeruleus) and TDP-43 immunoreactive intracytoplasmic and intranuclear inclusions and neurites in frontal and temporal cortex (to include entorhinal cortex, hippocampus and amygdala). Cases with FTLD were also examined for FUS intracytoplasmic and intranuclear inclusions in temporal cortex (to include hippocampus and amygdala). Cases of clinically suspected Creutzfeldt–Jakob disease were investigated for prion disease. Cases of clinically suspected FTLD ascertained between 1987 and 2003 were also investigated for prion disease as part of a UK national Creutzfeldt–Jakob disease surveillance screen of 'atypical dementias' funded by the Department of Health and coordinated by the National Creutzfeldt–Jakob disease Surveillance Unit, Edinburgh. For this, 6-μm wax sections of frontal, temporal, cingulate, parietal and occipital cortex, hippocampus and amygdala, basal ganglia and thalamus, and cerebellum and brainstem were immunostained for prion protein using KG9 antibody following 5 min pretreatment with 100% formic acid (Fraser *et al*., 2003). For all cases, cerebrovascular lesions (small vessel disease, amyloid angiopathy) associated with lacunae, microhaemorrhages or white matter loss or more discrete regions of macroinfarction were ascertained by macroscopic observation and microscopic examination of haematoxylin–eosin and Luxol fast blue stained sections.

Diagnosis (with subtyping where appropriate) was made using standardized neuropathological consensus criteria: Alzheimer's disease (Braak and Braak, 1991; Mirra *et al*., 1991), dementia with Lewy bodies (McKeith *et al*., 1996), FTLD (Mackenzie *et al*., 2009, 2010), corticobasal degeneration (Dickson *et al*., 2002), progressive supranuclear palsy (Litvan *et al*., 2003), Creutzfeldt–Jakob disease (Budka *et al*., 1995). To qualify for a diagnosis of Alzheimer's disease, a CERAD plaque threshold of Grade C was adopted and Braak stage of 5 or 6. Comorbidies were noted but were not ascribed a secondary diagnosis unless the extent of involvement of such pathological changes met accepted consensus criteria for the relevant disorder.

Results

Clinical diagnoses

A relatively high percentage of the cohort (42%) had a clinical diagnosis of one of the forms of FTLD (behavioural variant FTD, semantic dementia and progressive non-fluent aphasia) or a syndrome presumed to be related to FTLD (corticobasal degeneration and progressive supranuclear palsy), reflecting the interest of the Manchester group in focal degenerative dementias. A clinical diagnosis of Alzheimer's disease accounted for 105 (46%) cases, which included eight patients presenting with a severe circumscribed amnesia, five with progressive language disorder, four with visual impairment and one with apraxia. A clinical diagnosis of dementia with Lewy bodies, Creutzfeldt–Jakob disease, vascular and unclassified dementia together accounted for 12% of the cases.

Patients with FTLD and related syndromes did not differ from patients with Alzheimer's disease in terms of their age at onset of symptoms or duration of symptoms at the time of diagnostic assessment. The patients with Alzheimer's disease had a mean onset age of 56 years (SD 7, range 35–71) and patients with FTLD a mean onset of 57 years (SD 9, range 21–72). Estimated duration of illness at diagnostic assessment was 3 years (SD 2) in both FTLD and Alzheimer's disease. Patients with dementia with Lewy bodies were older [mean onset age 66 years (SD 7)] and their duration of symptoms at referral was somewhat shorter [mean 2 years (SD 1)].

Accuracy of diagnosis: frontotemporal lobar degeneration, Alzheimer's disease, dementia with Lewy bodies, Creutzfeldt–Jakob disease and cerebrovascular dementia

The relationship between clinical and pathological diagnoses is shown in Table 3. There was an overall 97% agreement. Sensitivity and specificity of clinical diagnoses were calculated in accordance with Kukull *et al*. (1990) and Holmes *et al*. (1999). FTLD was identified with 100% sensitivity (no patient with pathologically confirmed FTLD had a non-FTLD-related clinical diagnosis) and 97% specificity (four patients with suspected FTLD had an alternative pathological diagnosis). Investigation for prion disease was negative in all cases.

Accuracy of clinical diagnosis of Alzheimer's disease was made with 97% sensitivity (four patients with pathologically confirmed

Table 3 Clinical-pathological relationships from Manchester brain bank

	Pathological diagnosis						
	FTLD[a]	AD	DLB	CJD	CVD	Other	Total
FTLD[b]	92	2			1	1	96
Clinical diagnosis							
AD		105					105
DLB		1	17			1	19
CJD				3			3
CVD					2		2
Other		1				3	3
Total	92	108	17	3	3	5	228

a: Used here to include the spectrum of pathological subtypes of FTLD as defined by Mackenzie *et al*. (2009).
b: Used here to include the spectrum of clinical syndromes incorporated within the umbrella of or linked to FTLD.
AD = Alzheimer's disease, CJD = Creutzfeldt–Jakob disease;
CVD = cerebrovascular dementia; DLB = dementia with Lewy bodies.

Alzheimer's disease had an alternative clinical diagnosis during life) and 100% specificity (a clinical diagnosis of Alzheimer's disease was never made in error). Fifteen per cent of the patients with a clinical diagnosis of Alzheimer's disease were immunopositive for TDP-43. In most cases, TDP-43 immunopositivity was restricted to medial temporal lobe structures (including amygdala, hippocampus, entorhinal cortex and fusiform gyrus); it rarely had more widespread temporal and frontal neocortical involvement. Accuracy of clinical diagnosis of dementia with Lewy bodies was made with 100% sensitivity. However, two patients with that clinical diagnosis had other pathologies (see below). For Creutzfeldt–Jakob disease, the clinical diagnosis corresponded with the pathological diagnosis in all cases.

Among the 228 patients, there were seven misdiagnoses (see case histories in Supplementary material). Two patients (Cases 1 and 2), who presented with a frontal lobe syndrome and were diagnosed as behavioural variant FTD had Alzheimer's disease pathology, whereas Case 3 had subcortical vascular disease. A patient (Case 4) whose speech apraxia was attributed to FTLD had mixed Alzheimer's disease, Lewy body and vascular pathology. One patient with clinical dementia with Lewy bodies (Case 5) had Alzheimer's disease pathology whereas another (Case 6) had mixed Alzheimer and vascular pathology. One patient (Case 7), who presented with an unusual cerebellar syndrome, accompanied by frontal features had Alzheimer's disease pathology.

Clinical–pathological relationships within frontotemporal lobar degeneration-related disorders

Pathological subtypes of FTLD were classified in accordance with the nomenclature proposed by Mackenzie *et al*. (2009, 2010, 2011). Data from 85% of the cases have been incorporated into a recent multi-centre review (Josephs *et al*., 2011). A clinical diagnosis of behavioural variant FTD was associated with the spectrum of pathological subtypes of FTLD (Table 4). A diagnosis of FTD/MND, in contrast, was invariably associated with tau negative histopathology. Moreover, in FTD/MND, the FTLD-TDP pathology was of the same subtype: type B according to a harmonized classification system (Mackenzie *et al*., 2011). This corresponds to type 3 according to the numerical classification system of Mackenzie *et al*. (2006) and type 2 according to the classification of Sampathu *et al*. (2006). A clinical diagnosis of semantic dementia was linked in all cases to FTLD-TDP pathology, and the pathological subtype was, in all but one case, type C. Type C corresponds to type 2, in the classification system of Mackenzie *et al*. (2006), and type 1 according to Sampathu *et al*. (2006). Progressive non-fluent aphasia was linked to FTLD-TDP pathology in all but one case, the FTLD-TDP subtype being type A, which corresponds to type 1 according to Mackenzie *et al*. (2006) and type 3 according to Sampathu *et al*. (2006). A clinical diagnosis of primary progressive apraxia was made in three cases. Each showed FTLD-tau pathology of Pick type. A clinical diagnosis of corticobasal degeneration was made in seven cases and all but one showed corticobasal degeneration pathology. A diagnosis of progressive supranuclear palsy was made in six cases, each being associated with progressive supranuclear palsy pathology.

The FTLD pathological findings in this series typically follow a consistent and predictable pattern. Nevertheless, there were a few findings that did not accord with prediction. One patient classified as behavioural variant FTD showed the subtype of FTLD-TDP pathology (type C) normally linked to semantic dementia. That patient was one of the earliest of the pathological series, diagnosed in the 1980s prior to the characterization of semantic dementia. He was seen only late in his illness when behavioural problems dominated the clinical picture, hence the diagnosis of behavioural variant FTD. However, behaviours had a 'temporal' flavour (obsessive behaviours, pica) and there was historical evidence of early problems in naming and 'memory' in additional to obsessionality. Post-mortem examination showed predominant temporal lobe atrophy. Therefore, it is highly likely that he had semantic impairment. One patient with semantic dementia showed an unclassifiable form of FTLD-TDP pathology. Pathological

Table 4 Clinicopathological relationships in FTLD

	Pathological phenotype											
	TDP-43				FTLD-FUS	FTLD-ni	FTLD tau					Total
Subtype	TypeA	Type B	Type C	Uncl			(FTDP-17)	PiD	CBD	PSP	Uncl	
Clinical diagnosis												
bvFTD	10	10	1		3	1	13[a]	9	4		1	52
FTD/MND		6				1						7
SD			8	1								9
PNFA	6	1						1				8
PAX								3				3
CBD	1								6			7
PSP										6		6
Total	17	17	9	1	3	2	13	13	10	6	1	92

Pathological classification according to Mackenzie *et al*. (2009, 2010); TDP-43 subtyping according to Mackenzie *et al*. (2011).
a: In 3 of the 14 FTDP-17 cases, no MAPT mutations were identified.
bvFTD = behavioural variant FTD; CBD = corticobasal degeneration; FUS = intermediate filament; ni = no inclusions; PAX = progressive apraxia; PiD = Pick's disease; PNFA = progressive non-fluent aphasia; PSP = progressive supranuclear palsy; Uncl = unclassified.

changes were sparse and the long neuritic profiles normally found in semantic dementia were not evident. The presence of neuronal cytoplasmic inclusions and short neuritic profiles bore some resemblance to type A pathology (see Supplementary material for image of the TDP-43 pathology). That patient exhibited the prototypical multi-modal semantic impairment of semantic dementia and speech remained fluent and garrulous until late-stage disease. The only 'atypical' clinical feature was that she had right-predominant temporal atrophy and face and object recognition impairments were early presenting features. Screening for progranulin mutations was negative. Four patients with a clinical diagnosis of behavioural variant FTD had corticobasal degeneration pathology. These cases are noteworthy because the clinical presentation in each case was of a frontal lobe syndrome. Three patients were physically well, whereas the fourth showed neurological signs of progressive supranuclear palsy in the context of a frank frontal lobe syndrome. During the time that they were followed up, there was no evidence of apraxia, and parkinsonism was minimal or absent. One of these patients had been seen only 3 months prior to his death. A further patient presented with apraxia and was thought, at initial referral, to have corticobasal degeneration, yet showed FTLD-TDP pathology. He subsequently developed aphasia and was found to have a mutation in the progranulin gene (Baker *et al*., 2006).

Discussion

The clinical differentiation between forms of dementia placed emphasis on clinical history, complementary neuropsychological findings and neurological examination. Dimensions of crucial importance in making a diagnosis were the nature and time course of evolution of symptoms, the relative weighting of physical, cognitive and behavioural symptoms and signs, and the precise characteristics of cognitive change. Focal presentations of Alzheimer's disease and FTLD were distinguished on the basis of the posterior/anterior hemisphere character and degree of functional specificity of the deficit.

There was a strong concordance between clinical diagnosis at the time of patients' initial referral and ultimate pathological diagnoses, largely validating the principles that guided diagnosis. The findings provide confirmation that pathological diagnosis can be predicted on clinical grounds with a high degree of accuracy. This is important for treatment studies that are designed to target a specific disease. It is crucial too for laboratory studies of disease causation that depend on accurate characterization of patients who donate blood samples for genetic analysis.

In this series, there was, in particular, a relatively clear separation between forms of FTLD and the more common disorder of Alzheimer's disease. No patient with clinically diagnosed Alzheimer's disease had FTLD pathology (0%) and only two patients with clinical FTLD or related disorder had Alzheimer's disease pathology (2%), both presenting with a frontal lobe syndrome. No patient with clinically diagnosed progressive non-fluent aphasia, semantic dementia or corticobasal degeneration had the pathology of Alzheimer's disease (0%). Such clear separation is not a universal finding, there being wide variation across studies. Knopman *et al*. (2005) reported that, in a pathological series of 34 cases with FTLD, three (9%) had been clinically diagnosed with Alzheimer's disease. Forman *et al*. (2006) reported that 17% of the patients with clinically diagnosed FTLD had Alzheimer's disease pathology. In a study of 23 patients with progressive non-fluent aphasia and 15 patients with semantic dementia (Knibb *et al*., 2006), ~30% of each group (12/38) had Alzheimer pathology. Alladi *et al*. (2007) found 12 of 26 patients with progressive non-fluent aphasia (44%) to have pathology of Alzheimer's disease. These same authors reported that 6 of 12 patients with corticobasal syndrome (50%) had Alzheimer pathology. Hu *et al*. (2009), Shelley *et al*. (2009) and Okazaki *et al*. (2010) have also described patients with a clinical diagnosis of corticobasal degeneration, showing Alzheimer's disease pathology.

A number of factors are likely to contribute to differences in the degree of agreement between clinical and pathological diagnoses across published studies.

The present cohort was relatively youthful, so was *a priori* less vulnerable to the mixed pathologies that are associated with more elderly populations (Holmes *et al*., 1999; Jellinger, 2006; Brunnström and Englund, 2009) and which inevitably complicate clinical diagnosis. Indeed, the pathological series comprised a substantially higher proportion of cases with FTLD than found in community-based pathological series (Brunnström *et al*., 2009). Although this reflects, in part, the research interests of the Manchester team it also reflects the referral bias to the dementia clinic of relatively youthful patients.

Patients were tertiary referrals, mainly from neurologists or psychiatrists, and had established cognitive/behavioural impairment at the time of their initial referral. Diagnosis is inevitably less problematic than in general memory clinics where many people have mild or questionable cognitive impairment at initial assessment.

The patients were all studied in a single centre, in a multidisciplinary setting in which comprehensive neuropsychological assessment forms an integral part of the patients' diagnostic work-up. In large epidemiological series where brains are obtained from a variety of sources, the clinical information about patients' dementia may be relatively limited and formal neuropsychological evaluation unavailable.

A factor of crucial importance to diagnostic accuracy is the recognition that the most common form of dementia, Alzheimer's disease, is not clinically uniform. Although memory impairment is most often the dominant presenting symptom, this is not invariably the case. Patients may present with relatively circumscribed disorders of language (Pogacar and Williams, 1984; Galton *et al*., 2000), perception or spatial skills (Crystal *et al*., 1982; Hof *et al*., 1990, 1993; Levine *et al*., 1993; Ross *et al*., 1996; Snowden *et al*., 1996) or praxis (Green *et al*., 1995) and as such would not fulfil currently accepted or proposed revised diagnostic criteria for Alzheimer's disease (McKhann *et al*., 1984; Dubois *et al*., 2007). In our own centre, in a consecutive clinical series of 523 patients clinically diagnosed with Alzheimer's disease, 25% of the patients had 'focal' clinical presentations (Snowden *et al*., 2007*a*).

In the current pathological series of 105 cases with Alzheimer's disease, five patients presented with a progressive language disorder that remained as the dominant problem throughout the

disease course, four presented with visual disturbance (posterior cortical atrophy) and one with limb apraxia. In each of these cases, the clinical diagnosis during life was of Alzheimer's disease, their clinical presentations being referred to as 'language', 'visual' or 'praxic' presentations of Alzheimer's disease. In each case the 'posterior hemisphere' characteristics of the patients' neuropsychological symptoms and, in cases of language and praxic impairments, low relative specificity of functional deficit favoured a diagnosis of Alzheimer's disease over FTLD. In terms of current nomenclature, the aphasic Alzheimer patients would be classified as having a 'logopenic' form of aphasia (Gorno-Tempini *et al*., 2008).

The separation on clinical grounds between 'language' and 'praxic' presentations of Alzheimer's disease and the non-Alzheimer syndromes of progressive non-fluent aphasia and corticobasal degeneration, respectively, clearly contribute to the high concordance between clinical diagnosis and pathology in the present study. However, such separation is not the norm. The designation 'progressive aphasia' is commonly applied in a broad, descriptive sense to denote a selective disorder of language occurring in association with circumscribed cerebral degeneration, without the implication of a specific underlying pathology. As such, it inevitably encompasses both FTLD and Alzheimer pathologies. Similarly, 'corticobasal syndrome' is applied loosely to patients displaying a progressive apraxia, and inevitably includes patients with the apraxic form of Alzheimer's disease (Alladi *et al*., 2007; Hu *et al*., 2009; Shelley *et al*., 2009; Okazaki *et al*., 2010). More refined subtyping of progressive aphasias has begun to separate out variants that are more likely to be associated with FTLD and Alzheimer's disease pathology, respectively (Mesulam *et al*., 2008; Rabinovici *et al*., 2008; Deramecourt *et al*., 2010). The 'logopenic' form of aphasia, characterized by word retrieval pauses, is most commonly associated with Alzheimer's disease. Nevertheless, the classification 'logopenic aphasia' also encompasses the anomia of patients with progranulin mutations and FTLD-TDP pathology (Snowden *et al*., 2003, 2007*b*; Rohrer *et al*., 2010). Moreover, the designation of progressive aphasia as an overarching clinical descriptor without implied pathological substrate remains.

In the present pathological series, there was a relatively predictable relationship between clinical syndrome and subtype of FTLD pathology. As anticipated, all cases of FTD–MND and pure semantic dementia had tau-negative pathology, whereas clinical cases of progressive apraxia, corticobasal degeneration and progressive supranuclear palsy had, with one exception, tau positive pathology. FTD-MND, semantic dementia and progressive non-fluent aphasia further segregated on the basis of subtype of ubiquitin pathology: progressive non-fluent aphasia (type A), FTD-MND (type B), semantic dementia (type C). Progressive apraxia, corticobasal degeneration and progressive supranuclear palsy cases segregated on the basis of subtype of tau pathology, showing Pick-type, corticobasal degeneration and progressive supranuclear palsy pathology, respectively, as defined by Cairns *et al*. (2007) and Mackenzie *et al*. (2009).

The clinical distinction between primary progressive apraxia and corticobasal degeneration is worthy of comment. We separated them *a priori* on clinical grounds on the assumption that the relatively pure symmetric 'cortical' apraxia of progressive apraxia would be likely to have a different neurobiological substrate from that of clinical corticobasal degeneration, characterized by asymmetric 'basal' signs of parkinsonism and 'cortical' signs of apraxia. It is of interest, therefore, that each of the three cases clinically designated as primary progressive apraxia showed Pick's pathology whereas the cases clinically diagnosed with corticobasal degeneration had corticobasal degeneneration pathology. It is noteworthy too that the apraxic patient, diagnosed with Alzheimer's disease on the basis of evidence of spatial impairment, proved to have Alzheimer's disease. Our findings point to the existence of three distinct apraxic syndromes, each associated with a different pathology: (i) primary progressive apraxia, a pure, symmetrical apraxia linked to Pick's pathology; (ii) corticobasal syndrome, an asymmetric apraxia combined with parkinsonism and associated with corticobasal degeneration pathology; and (iii) apraxic variant Alzheimer's disease, apraxia with spatial deficits and associated with Alzheimer pathology. The amalgamation of these syndromes under the generic label of corticobasal syndrome risks hindering progress in the understanding of progressive apraxia.

The link between apraxia and tau (Pick-type) pathology has relevance too for the classification of language disorders. In the present series, all but one patient with progressive non-fluent aphasia had FTLD-TDP pathology. These patients had anomia but no speech apraxia, whereas the remaining patient with FTD-tau (Pick type) pathology had speech apraxia, in keeping with findings of Josephs *et al*. (2006*b*). Phenotypic differences in the nature of patients' aphasia are likely to account for the variable distribution in tau and non-tau pathologies found in other clinicopathological series of progressive non-fluent aphasia (see Grossman, 2010 for review).

The presence in a proportion of Alzheimer cases of TDP-43 immunoreactive changes within medial temporal lobe structures (amygdala hippocampus, entorhinal cortex and fusiform gyrus) is in keeping with other reports (Amador-Ortiz *et al*., 2007; Hu *et al*., 2008; Uryu *et al*., 2008, Arai *et al*., 2009). However, 15% prevalence found here is substantially lower than previously reported figures. The disparity may reflect the more youthful age of the present cohort. Our own data suggest an association between TDP-43 pathology in Alzheimer's disease and advancing age. The influence of age on TDP-43 pathology has also been observed in healthy elderly adults (Geser *et al*., 2010).

The high degree of concordance between clinical syndrome and pathological subtype reinforces earlier findings (Snowden *et al*., 2007*c*) and is in accordance with other reports (Josephs *et al*., 2009). They challenge traditional assumptions that clinical syndromes of FTLD are indicative solely of the topographical distribution of pathological change in the brain and cannot predict underlying histopathology. The findings show that careful clinical phenotyping of patients can predict pathology with a high degree of precision.

There are, nevertheless, some caveats. Two patients presenting with a focal frontal lobe syndrome had Alzheimer's disease. This was not anticipated on the basis of the anterior/posterior guiding principle, but it confirms previous findings that Alzheimer's disease may, very rarely, present as a focal frontal lobe syndrome

(Johnson *et al*., 1999). One patient presenting with a familial cerebellar syndrome also had Alzheimer's disease. One patient with an insidiously progressive and circumscribed behavioural disorder had cerebrovascular dementia, despite absence of physical symptoms and signs.

In line with findings of others (Llado *et al*., 2008; Josephs *et al*., 2009) behavioural variant FTD was associated with the spectrum of FTLD pathologies, pointing to the need for more refined characterization of frontal behavioural syndromes. Evidence for a distinct behavioural variant FTD phenotype in FUS cases (Snowden *et al*., 2011) suggests that such behavioural subtyping is likely to be fruitful. One patient with semantic dementia in this series showed an unclassifiable pathology without clear evidence of the long neurites normally associated with semantic dementia. The pathology bore some resemblance to type A, which is usually associated with behavioural variant FTD or progressive non-fluent aphasia (Josephs *et al*., 2011) and linked to progranulin mutations (Pickering-Brown *et al*., 2008). The patient with semantic dementia was only unusual with respect to her right-predominant presentation. This provides an insufficient explanation for the lack of definitive pathology: another patient with semantic dementia in this series presented similarly with face recognition impairment and right temporal atrophy, yet showed the expected type C FTLD-TDP pathology. Four patients with behavioural variant FTD had corticobasal degeneration pathology, an association reported previously, albeit rarely (Litvan *et al*., 1999; Hassan *et al*., 2010). As found in another series (Ling *et al*., 2010), one patient with corticobasal degeneration pathology exhibited neurological features of progressive supranuclear palsy. One patient with clinical corticobasal degeneration, like others (Tartaglia *et al*., 2011), had TDP-43 (type A) pathology. Such occasional unanticipated findings serve as a cautionary reminder that the correspondence between clinical phenotype and pathology is not absolute.

Limitations of the present study should be noted. Patients represent a selected group, the predominance of neurodegenerative over vascular pathology and the high relative proportion of FTLD cases reflecting the interests of the research team. The patients are not, therefore, representative of the general population of people with dementia. In terms of 'focal' presentations, the number of patients presenting with language impairments is small (nine semantic dementia, eight progressive non-fluent aphasia, five Alzheimer's disease). Whether the proposed guiding principles for distinguishing FTLD and Alzheimer language disorders pertain over a much larger patient cohort needs to be determined in larger prospective studies. Nevertheless, there is little reason for assuming that the general levels of diagnostic accuracy reported here are misleading: efforts to obtain post-mortem confirmation of diagnosis are greater with respect to patients who have unusual clinical presentations for whom the diagnosis may be uncertain, than for patients with 'standard' presentations in whom the diagnosis is unequivocal.

In conclusion, the high correspondence between clinical and pathological diagnoses shows that it is possible to distinguish forms of dementia on clinical grounds with a high degree of accuracy. The findings appear to validate diagnostic methods. Nevertheless, if the principles guiding dementia diagnosis are to have general value, their utility needs to be examined prospectively in independent cohorts of dementia patients.

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Supplementary material

Supplementary material is available at *Brain* online.

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