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Citation for published version:

Digital Object Identifier (DOI):
10.1002/ana.20203

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Annals of Indian Academy of Neurology

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Clinicopathological Correlates in Frontotemporal Dementia

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The term frontotemporal dementia (FTD) encompasses a range of clinical syndromes that are believed not to map reliably onto the spectrum of recognized pathologies. This study reexamines the relationships between clinical and pathological subtypes of FTD in a large series from two centers (n = 61). Clinical subtypes defined were behavioral variant FTD (n = 26), language variants (semantic dementia, n = 9; and progressive nonfluent aphasia, n = 8), and motor variants (corticobasal degeneration, n = 9; and motor neuron disease, n = 9), although most cases presented with a combination of behavioral and language problems. Unexpectedly, some behavioral cases (n = 5) had marked amnesia at presentation. The pathological subtypes were those with tau-immunopositive inclusions (with Pick bodies, n = 20; or without, n = 11), those with ubiquitin immunopositive inclusions (n = 16), and those lacking distinctive histology (n = 14). Behavioral symptoms and semantic dementia were associated with a range of pathologies. In contrast, other clinical phenotypes had relatively uniform underlying pathologies: motor neuron disease predicted ubiquitinated inclusions, parkinsonism and apraxia predicted corticobasal pathology, and nonfluent aphasia predicted Pick bodies. Therefore, the pathological substrate can be predicted in a significant proportion of FTD patients, which has important implications for studies targeting mechanistic treatments.

Ann Neurol 2004;56:399–406

Frontotemporal dementia (FTD) is the preferred term for the spectrum of non-Alzheimer’s dementias characterized by focal atrophy of frontal and anterior temporal regions. Recent epidemiological studies suggest that FTD is the second commonest cause of dementia in persons younger than 65 years.1 Interest in the disease has increased greatly over the past decade since the identification, in some familial cases, of mutations in the gene for tau protein.2

Definitive diagnosis of FTD requires neuropathological examination, and, to date, few clinicopathological series have been reported.3,4 Unlike other dementia syndromes, notably Alzheimer’s disease (AD), FTD encompasses considerable pathological heterogeneity. Three broad subdivisions have been recognized, depending on the profile of immunohistochemical staining and the pattern of intracellular inclusions.3–8 The first subdivision is cases with tau-positive pathology; these, in turn, comprise several subvariants: those with classic argyrophilic, tau-positive, intraneuronal Pick bodies (Pick’s disease [PiD]); those with tau gene mutations (FTDP-17) and diffuse tau-positive neuronal and astrocytic immunoreactivity; those characterized by tau-positive astrocytic plaques and ballooned achromatic neurons (corticobasal degeneration [CBD]), and those with tau-positive argyrophilic grain disease (AGD). The second and third subdivisions are cases with tau-negative, ubiquitin-positive inclusions in the dentate gyrus and in the brainstem motor nuclei (FTD with motor neuron inclusions [FTD-MND]) and dementia lacking distinctive histology (DLDH).

Two major clinical presentations of FTD have been recognized for some time and appear to depend on the initial locus, but not the type, of neuropathology.9,10 In frontal or behavioral variant (fvFTD), the overwhelming clinical problem is one of progressive personality change including disinhibition, loss of empathy, change in eating patterns, ritualized or stereotypical behavior, and apathy.11 The aphasic variant can be further subdivided into progressive fluent or nonfluent aphasia, the focus of pathology being temporal or frontal (perisylvian), respectively. In the fluent form, there is progressive loss of the knowledge base underlying language, leading many authorities to adopt

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Received Oct 14, 2003, and in revised form Mar 11 and May 26, 2004. Accepted for publication May 26, 2004.

Published online Aug 9, 2004, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20203

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the term *semantic dementia* (SD) to encapsulate this syndrome. The nonfluent form is characterized by breakdown in the phonological and syntactic components of language. It has become increasingly apparent that either behavioral or aphasic symptoms may be associated with motor neuron disease, typically preceding the motor problems. Finally, there is growing awareness of the overlap between the clinical features of CBD (asymmetric parkinsonism, apraxia, myoclonus, etc) and FTD. In summary, five main clinical syndromes have been consistently associated with FTD pathology: fvFTD, SD, progressive nonfluent aphasia (PNFA), FTD-MND, and CBD.

Although the clinical, neuropsychological, and radiological features of these syndromes have been described in detail, several issues remain unresolved. First, the proportion of FTD cases, defined by the gold standard of neuropathology, conforming to the discrete clinical categories is not known. Second, the degree to which clinical and pathological FTD subforms co-occur is unclear. Third, with relevance for in vivo diagnosis, analysis of the clinical features in FTD by pathological subform has not been attempted previously. Such issues are likely to become increasingly important as therapies targeting cellular pathology emerge. Their elucidation requires the study of many cases, possible only with cross-center collaboration.

This study aims to examine presenting clinical features of a large series of pathologically proven FTD and to identify any in vivo features that may assist in diagnosing a particular pathological subform of FTD.

**Subjects and Methods**

Cases were selected from two neuropathological series of patients with dementia in Sydney, Australia, and Cambridge, England. Both series were collected as part of multidisciplinary research programs closely linked to specialist tertiary referral dementia clinics. In both centers, every attempt was made to enroll patients with dementia into the brain donor program with a 90% success rate in obtaining “declarations of intent” for brain tissue donation in life. Over a 10-year period (January 1992–2002), similar numbers of cases were collected at the two centers (Sydney, 125; Cambridge, 105). The research programs were approved by the Human Ethics Committees of the Universities of Sydney and New South Wales and the Addenbrooke’s Hospital Local Ethics Committee.

In Sydney, the entire brain was fixed by suspension in 15% buffered formalin for two weeks. In Cambridge, autopsies were performed within 48 hours, and the cerebrum was bisected with the left half fixed in formalin and the right half frozen. The cerebrum was either embedded in agar and cut into 3mm-thick coronal slices using a rotary slicer (Sydney) or hand cut coronally in 5mm slices (Cambridge).

Despite differences in whole-brain handling between the centers, histopathological methods have been standardized for this study. In both centers, tissue samples were taken from the frontal (Brodmann area 9), temporal (area 20), parietal (area 39), occipital (areas 17 and 18), and anterior cingulate (area 24) cortices, as well as from the hippocampus at the level of the lateral geniculate nucleus, amygdala, anterior and posterior basal ganglia (including the basal forebrain), thalamus, hypothalamus, midbrain, pons, medulla oblongata, and cerebellum. Sections from all regions were stained for immunohistochemistry was performed using antibodies against ubiquitin (Z0458 diluted 1:200; Dako, Glostrup, Denmark), tau (T5530 diluted 1:10,000; Sigma, St. Louis, MO, or mAb 11.57 courtesy of Laboratory of Molecular Biology, Cambridge, UK), and α-synuclein (18–0215, Zymed Laboratories, San Francisco, CA; or SA3400 diluted 1:200, Affiniti Research Products, Mamhead, Exeter, UK). Cases were excluded if they met pathological criteria for AD or dementia with Lewy bodies or had macroscopic infarction or significant subcortical pathologies, such as multiple system atrophy or progressive supranuclear palsy.

**Neuropathological Classification**

All cases were classified according to the presence or absence of immunoreactive inclusions or staining patterns into two broad categories (tau-positive cases and tau-negative cases, see definitions below). Interrater reliability studies were undertaken on 22 cases using percentage agreement (sensitivity) and weighted kappa statistics to determine the level of diagnostic agreement.

Tau-positive cases included (1) cases with classic PiD (Fig 1A) defined on the basis of silver- and tau-positive Pick bodies in the cerebral cortex, amygdala, or hippocampus; and (2) cases with tau-positive pathology but lacking classic Pick bodies. These cases fell into two subgroups: (1) CBD (see Fig 1B, C) characterized by the presence of cortical achromatic ballooned neurons, tau-positive glia, threads, and astrocytic plaques; and (2) AGD (see Fig 1D) characterized by numerous tau-positive argyrophilic grains and coiled bodies in the hippocampus and neocortex.

Tau-negative cases included (1) FTD-MND cases (see Fig 1E, F) characterized by ubiquitin-positive, tau-negative inclusions in brainstem motor nuclei and/or hippocampus; and (2) cases lacking any of the above distinctive features with neuronal loss, gliosis, and vacuolation in frontal and/or temporal cortices, but no silver, tau, or ubiquitin-positive intraneuronal inclusions or pathology (DLDH, see Fig 1G).

**Clinical Classification**

A retrospective review of the full medical records was conducted by one of two behavioral neurologists with expertise in the dementias (Sydney, J.R.H.; Cambridge, R.D.D.), who were unaware of the pathological diagnosis and had not been involved in the patients’ management. Particular attention was paid to the first clinical assessment and diagnosis, the date of diagnosis, and onset of symptoms as reported by the family (there was a discrepancy of up to 10 years). We reviewed all charts looking for clinical features characteristic of one of the clinical variants of FTD at presentation, or within 6 months of it: (1) changes in personality and social...
behavior, specifically apathy, disinhibition, stereotypic behaviors, alterations in food preference, and poor self-care; (2) dysexecutive features, specifically poor planning, forethought, reasoning, or organization; (3) disorders of language and communication, including features of SD (fluent speech with marked anomia and impaired word comprehension) or non-fluent aphasia (disrupted speech output with phonological and/or syntactic errors); (4) extrapyramidal motor signs, notably rigidity, akinesia, or apraxia; (5) features of bulbar or spinal motor neuron disease. Special note was also made of
features regarded as uncharacteristic of FTD including (1) prominent complaints of poor memory; (2) psychotic symptoms (hallucinations or delusions); and (3) visuospatial features such as topographical disorientation.

Family history was regarded as positive if a first-degree relative had suffered from a disorder within the FTD spectrum.

Based on the five main clinical syndromes outlined in the introduction, we classified cases into those with fvFTD, SD, and PNFA according to the consensus criteria. Patients were classified as FTD-MND if they presented with behavioral changes and developed bulbar symptoms accompanied by fasciculation within 12 months. Patients were classified as CBD if their main symptoms included limb apraxia, gait disturbance, or parkinsonism.24 Of note was a small subgroup (n = 5) that could not be accommodated within this classification, all presenting with severe memory loss. As all subsequently developed behavioral changes, they were grouped with the fvFTD cases (further discussion below).

Statistical Analysis
Statview (Abacus, Berkeley, CA) was used to calculate all statistical analyses. Means and standard deviations were calculated for all variables, and a p value of less than 0.05 was considered the level of significance.

Results
Reliability of Pathological Diagnosis
Interrater reliability of pathological diagnosis among the FTD subtypes compared with other common dementia syndromes has not been tested previously. To test the reliability of diagnosis across centers, we selected 22 cases: 18 FTD cases included in the study (8 from Sydney, 10 from Cambridge) and 4 cases not in the study (excluded because of other tau-positive dementia syndromes, 2 from Sydney, 2 from Cambridge; 3 with AD, 1 with progressive supranuclear palsy). The percentage agreement for a diagnosis of tau-positive FTD (N = 8) was 100% and for tau-negative FTD (N = 10) was 100%. Incorporating excluded cases in the analysis gave near perfect diagnostic agreement across all cases (κ = 0.92). Of the 61 FTD cases included in the study, 31 had tau-positive inclusions (20 PiD, 9 CBD, 2 AGD) and 30 were tau-negative (16 FTD-MND, 14 DLDH).

Basic demographics for the 61 cases, divided according to pathological subtype, are shown in Table 1. The mean age at symptom onset, diagnosis, and death for the total group were 58.5 (± 7.7), 61.5 (± 7.6), and 65.6 (± 8.7), respectively. In view of the relatively low numbers in the individual subgroups, we compared those with and without tau-positive pathology. The tau-positive group were consistently older at all time points, with significant differences in their age at diagnosis (64.3 ± 6.8 vs 58.6 ± 7.3; t[df59] = 3.14, p < 0.01) and death (69.4 ± 8.1 vs 61.7 ± 7.6, t[df59] = 3.8, p < 0.001). The difference at symptom onset (60.3 ± 7.3 vs 56.6 ± 7.9, t[df59] = 1.8, p = 0.06) failed to reach significance. Table 1 shows that this age trend was maintained across each of the pathological subtypes.

A breakdown of the age at diagnosis according to pathological subgroup is shown in Figure 2. Of note is the fact that 39 (64%) presented younger than age 65 years. The majority were between 50 and 69 (84%), but six patients (10%) were older than 70 years at diagnosis. The total group contained a preponderance of men (36) over woman (25). Comparison of the tau-positive and tau-negative cases showed almost exactly the same ratios of men to women: positive 18 to 13 and negative 17 to 13. Overall, 20 of the 61 patients had a positive family history (33%); these were distributed evenly across pathological subtypes (see Table 1).

Clinical Details, Classification, and In Vivo Diagnoses
Analysis of the presenting clinical features showed that the commonest symptom overall was change in personality or social conduct, present in 55 (90%) of cases. Dysexecutive and language-related symptoms were also very common, occurring in 54% and 56% of cases, respectively. Surprisingly, reports of memory impairment also were reported in most cases (57%) and, in a small subgroup (n = 5, 8%), represented the dominant presenting symptom. This group developed behavioral changes over 1 to 4 years of follow-up, but these fea-
Features of visuospatial or perceptual impairment such as misreaching for objects, spatial disorientation, or perceptual alterations were strikingly absent in the cohort. The fact that most patients had a combination of symptoms made it impossible to categorize on a straightforward inclusion-exclusion basis. Instead, consideration of the dominant symptom(s) was required. The clinical files were reviewed again with this in mind. The largest subgroup comprised those with predominant behavioral changes (fvFTD = 26, 42.6%). This subgroup included the five patients in whom amnesia had been the dominant symptom at presentation (see below). Nine patients (14.75%) fulfilled diagnostic criteria for SD; eight (13.1%) had PNFA. In both SD and PNFA subgroups, behavioral features were relatively minor and consisted mainly of apathy in PNFA and stereotypic behaviors in SD. Nine (14.75%) were classified as FTD-MND and nine (14.75%) as CBD. Most of FTD-MND and CBD patients had mixed behavioral-dysexecutive-aphasic symptoms (Table 2). Apart from the CBD group, extrapyramidal signs were unusual at presentation.

Because all cases had been evaluated in specialist centers, we were interested in their clinician's in vivo diagnoses. All patients exhibiting classic features of SD and PNFA had been diagnosed in life with progressive aphasia. All nine with FTD-MND also received diagnosis as such within 12 months of presentation, although they initially had mixed behavioral/language symptoms and only subsequently developed bulbar and upper limb signs of MND. Of the nine patients in the CBD category, just three had been diagnosed with CBD in life. Three had been considered to have FTD or AD with unusually pronounced motor features. Falls and gait instability were prominent, leading to a diagnosis of progressive supranuclear palsy in the remaining three. Only five had marked apraxia at presentation, with mild apraxia in an additional three. Of the 26 remaining fvFTD cases, 21 had received a diagnosis of fvFTD. Of particular interest is the subgroup of five patients in whom amnesia was the presenting symptom. In two cases, memory loss was accompanied at presentation by apathy but no other behavioral changes, and two had prominent dysexecutive symptoms. In one, memory loss was isolated. In these five cases, local specialist teams (understandably) diagnosed AD and two had entered anticholinesterase drug trials. All five later developed behavioral features, and, in three, the diagnosis was later revised to fvFTD.

**Clinicopathological Correlations**

Comparison of pathological and clinical subtypes is shown in Table 3. Considered in terms of the clinical syndrome at presentation, clear trends emerge in three of the five clinical groups. Of those with a clinical diagnosis of FTD-MND, all nine (100%) had ubiquitin-positive FTD-MND pathology. Of the nine patients with clinical CBD, seven (77.7%) had all of the pathological hallmarks of CBD, one had ubiquitin-positive (FTD-MND) pathology, and one had AGD. Most patients with PNFA (six of eight; 75%) had tau-positive PiD. In contrast, the pathology in fvFTD and SD was unpredictable. Of the 26 fvFTD patients, 14 (54%) had tau-positive and 12 (46%) tau-negative pathology (see Table 3). A comparison of the age at diagnosis and at death of the tau-positive and tau-negative fvFTD confirmed that those with tau-positive pathology were significantly older at the time of diagnosis (53.7 ± 7.2 vs 61.7 ± 6.0, t[df24] = 3.2, p < 0.01) and at death (59.4 ± 7.1 vs 69.3 ± 6.9, t[df24] = 3.5, p < 0.01). The subgroup of five cases with amnesia also had varied pathology (one ubiquitin-positive, two DLDH, and two PiD).

**Discussion**

Most of the cases assessed in this survey of clinical and pathological FTD subtypes presented with symptoms recognized as falling within the FTD spectrum. A few (n = 5) had isolated amnesia and thus resembled early AD; the greater number, however, were notable for manifesting combined behavioral, dysexecutive, and language-related symptoms. The occurrence of combined features in so many cases tends to undermine current classifications based on inclusion-exclusion checklists: patients may meet criteria for more than one FTD variant. A heuristic approach, based on the dominant symptom type in an individual patient, may be more appropriate. For example, in this survey, cases were readily identified as either SD or PNFA, although most had concomitant behavioral symptoms. In the literature, whereas earlier reports focused on neurolinguistic and cognitive features in SD and PNFA,
recent surveys have shown a high prevalence of behavioral changes, particularly in SD.\(^\text{11,25}\) Nonetheless, in arguing against a clinical classification where behavioral and aphasic variants of FTD are mutually exclusive, the observed continuum of symptoms emphasizes the coherence of the FTD concept.

A key finding was that, in many situations, the pathological features of FTD can be predicted in life. Thus, all patients with the syndrome of FTD-MND in life had ubiquitin-positive FTD-MND pathology at postmortem examination.\(^\text{26-28}\) Similarly, when clinical criteria for CBD had been fulfilled, tau-positive CBD pathology was overwhelmingly likely. A novel finding was that patients with PNFA tended to have tau-positive PiD pathology. In contrast, the syndrome of SD often was associated with tau-negative pathology. Interestingly, four of the SD patients had ubiquitin-positive FTD-MND inclusions, although clinical features of MND had not been evident in life.\(^\text{29}\) The pathology of fvFTD was unpredictable; approximately equal numbers were tau-positive (14) and tau-negative (12).

Patients classified from review of the case notes as having CBD had all presented with prominent motor features (apraxia and/or akinetic-rigid syndrome), but only three cases were diagnosed with CBD in life. Marked behavioral and cognitive symptoms led to a diagnosis of fvFTD in two and AD in one patient, although the unusual degree of motor disturbance had been documented. Falls and/or abnormalities of extraocular movements led to a diagnosis of progressive supranuclear palsy in three others. It should be recalled, however, that recruitment into the Cambridge and Sydney brain banks started in the early 1990s, when the syndrome of CBD was less well recognized, still less its nonmotor features.\(^\text{30,31}\) CBD pathology was present in seven of these nine patients (78%) with one each having FTD-MND and DLDH. This degree of pathological heterogeneity has been reported previously.\(^\text{32}\)

Although the clinical features of AGD have not been fully elucidated, there is evidence to support the inclusion of AGD as a tauopathy based on its clinical, pathological, and biochemical profile.\(^\text{33-36}\) Some patients demonstrate clinical and pathological features (atrophy, neuronal loss, astrocytosis, and cortical microvacuolar change) consistent with FTD.\(^\text{33,37}\) This is most commonly restricted to the temporal lobe,\(^\text{38}\) but similar changes have been found diffusely.\(^\text{37}\) In addition, AGD has been shown to coexist with CBD and other tauopathies with 41% of CBD and 19% of PSP having AGD.\(^\text{34}\) In our series, one patient with argyrophilic grains clinically had classic fvFTD, whereas the other had features of CBD with some behavioral changes, but without the pathological features of CBD.

Of considerable interest, the clinical syndromes of CBD and PNFA both were associated with tau-positive pathology. Recent clinical studies emphasize the clini-

### Table 2. Distribution of Presenting Symptoms by Clinical Classification

<table>
<thead>
<tr>
<th>Symptom</th>
<th>fvFTD</th>
<th>SD</th>
<th>PNFA</th>
<th>FTD-MND</th>
<th>CBD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior</td>
<td>26</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>61</td>
</tr>
<tr>
<td>Dysexecutive</td>
<td>21</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>55</td>
</tr>
<tr>
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<td>0</td>
<td>9</td>
<td>7</td>
<td>33</td>
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<td>Aphasia</td>
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<td>9</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>Extrapyramidal</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>MND</td>
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<td>0</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\)Predominant feature in five cases (see text).

fvFTD = frontal or behavioral variant of frontotemporal dementia; SD = semantic dementia; PNFA = progressive nonfluent aphasia; FTD-MND = FTD with motor neuron inclusions; CBD = corticobasal degeneration.

### Table 3. Correspondence between Clinical and Pathological Classification

<table>
<thead>
<tr>
<th></th>
<th>PiD</th>
<th>Tau-positive</th>
<th>Non-PiD</th>
<th>FTD-MND</th>
<th>DLDH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>fvFTD</td>
<td>11</td>
<td>3</td>
<td>—</td>
<td>2</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>PNFA</td>
<td>6</td>
<td>1</td>
<td>—</td>
<td>9</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>FTD-MND</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>—</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>CBD</td>
<td>—</td>
<td>7</td>
<td>—</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>11</td>
<td>16</td>
<td>14</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

PiD = Pick's disease; FTD-MND = frontotemporal dementia, with motor neuron inclusions; DLDH = dementia lacking distinctive histology; fvFTD = frontal or behavioral variant of FTD; SD = semantic dementia; PNFA = progressive nonfluent aphasia; CBD = corticobasal degeneration.
cal overlap between these syndromes. \textsuperscript{39} Many patients with CBD develop progressive language output disorder with prominent dysgraphia. \textsuperscript{40} Similarly, patients with PNFA may develop apraxic difficulties. \textsuperscript{40} Previous neuropathological studies in PNFA have emphasized the lack of distinctive histopathology in most cases. Indeed, Snowden and colleagues\textsuperscript{42} state, “all cases of progressive aphasia in our series have been associated with microvacuolar change, rather than tau-positive inclusion pathology.” In a review of primary progressive aphasia (PPA), Mesulam\textsuperscript{42} asserted that the single most common pathological process associated with PPA is focal degeneration characterized by neuronal loss, gliosis, and mild spongiform changes within superficial cortical layers, referred to as “dementia lacking distinctive histological features.” Typical tau-positive argyrophilic Pick bodies was said to occur in 20% of cases. Direct comparisons are difficult, however, because of differing terminologies: Mesulam’s term, PPA, corresponds most closely to PNFA but may be applied to some SD-like cases. A major problem is that most cases were reported before the explosion of interest in the molecular neuropathology of FTD and the widespread use of immunohistochemical staining methods.

One surprising finding was the older age, both at diagnosis and at death, of the tau-positive cases. Those with tau-positive pathology were, on average, 10 years older than those with tau-negative pathology. A parallel study of the same patient group has shown that survival is also significantly longer in these tau-positive cases.\textsuperscript{8} This finding has implications for understanding the neurobiological basis of FTD and suggests that tau-positive pathology may be related to a slower rate of cell death.

Another unexpected finding was the very high prevalence of memory symptoms reported by family members. Close scrutiny of the FTD literature, however, suggests that our finding of severe amnesia as an initial feature is not without precedent. For instance, a case study of a Japanese patient with a novel tau gene mutation described an onset with amnesia and disorientation without personality change.\textsuperscript{43} Two of six PiD cases reported recently by Tsuchiya and colleagues\textsuperscript{44} presented with amnesia and received clinical diagnoses of AD. A recent clinicopathological study of FTD also emphasized the high frequency of memory complaints.\textsuperscript{5} Similarly, an analysis of presenting symptoms in 44 patients with FTD (10 with pathological verification) showed that memory loss was the commonest initial symptom (62%) as reported by caregivers in response to the question, “what was the first symptom of the illness?” In contrast, 29% reported speech disturbance and 35% personality change as the first symptom.\textsuperscript{45} In AD, memory loss is almost always reported as the first symptom. The consensus report on FTD include early severe amnesia among the exclusion criteria.\textsuperscript{9} Other features regarded as excluding FTD,\textsuperscript{9} notably visuospatial and perceptual symptoms, were indeed absent in our series, confirming the functional integrity of posterior brain regions early in the course of the disease.

In summary, patients with tau-positive pathology tend to be older than those without tau pathology. In fvFTD, pathology is unpredictable. In addition to the established pathological correlates in the motor variants of FTD, FTD-MND with tau-negative FTD-MND inclusions and CBD with tau-positive pathology lacking Pick bodies, we have found that patients with PNFA tended to have pathological PiD. The study establishes that the pathological substrate can be predicted for a significant proportion of FTD cases: this has important implications for studies targeting mechanistic treatments.

This work was supported by the Wellcome Trust (Clinical Training Fellowship, 066511/Z/01/Z, R.R.D.), the Medical Research Council (Programme Grant, G9724461, J.R.H.), and the National Health and Medical Research Council of Australia (Project Grant, 301964, 157212, J.J.K., G.M.H.).

We thank all the families for their support and generous donation of brain tissue, Drs H. Creasey and T. Broe for providing clinical details, the laboratory staff at Prince of Wales Medical Research Institute for laboratory assistance, and H. Cartwright for the figure work. A. O’Sullivan and R. Hills provided invaluable help in obtaining and processing brain tissue; K. Dawson and L. McDonald supported the families.

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