HIGH LIGHT

Clinicopathologic analysis of frontotemporal and corticobasal degenerations and PSP

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Abstract—*Objective:* To examine the relationship between early clinical features, pathologies, and biochemistry of the frontotemporal lobar degenerations (FTLDs), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). *Methods:* The authors conducted pathologic reexamination with the most recent immunohistochemistry of all cases diagnosed with FTLD, PSP, and CBD between 1970 and 2004. The authors also reviewed the early clinical features for clinical diagnosis and application of published research criteria. *Results:* Of 127 cases analyzed, 57 had a pathologic diagnosis of FTLD, 49 PSP, and 21 CBD. Of these, 38 were clinically reclassified as frontal variant frontotemporal dementia (FTD), 13 as progressive non-fluent aphasia (PNFA), 21 as CBD-like, 33 as PSP-like, and 13 with frontotemporal dementia with coexisting motor neuron disease (FTD-MND). The authors were unable to classify nine cases. All cases of FTD-MND were tau-negative and had pathologic evidence of motor neuron degeneration. All cases classified as PSP-like or CBD-like had tau-positive pathology. Of the 13 cases with PNFA, PSP and CBD accounted for almost 70% of the cases, while FTD was almost equally divided between tau-positive and tau-negative diseases. *Conclusion:* Frontotemporal lobar degeneration, corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP) have overlapping clinical features. The prediction of tau-positive pathology from a CBD or PSP-like presentation is good, while the frontotemporal dementia (FTD)-motor neuron disease syndrome almost certainly predicts motor neuron degeneration. Surprisingly, PSP and CBD accounted for most cases classified as progressive non-fluent aphasia. Frontal variant FTD is an unpredictable disease in terms of its biochemistry.

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The frontotemporal lobar degenerations (FTLDs), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) have overlapping clinical and pathologic features. Yet, while some authors advocate the term Pick's complex to encompass these neurodegenerative diseases,[1] their immunohistochemical profiles of intracellular inclusions identified by light microscopy can be used to divide them into tau-positive and tau-negative (figure 1).[2] It should be noted that the terms FTLD, PSP, and CBD are being used pathologically with FTLD being used as an umbrella term to represent a spectrum of pathologic entities (see figure 1).[2]

The tau-positive neurodegenerative diseases are characterized by tau-positive inclusions and include PSP,[3] CBD,[4] and three variants of FTLD: Pick disease (PiD),[5] multiple system tauopathy (MST),[6] and frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17).[7] The tau-negative neurodegenerative diseases include four variants of FTLD: FTLD with ubiquitin-only-immunoreactive neuronal changes without motor neuron degeneration (FTLD-U),[8,9] FTLD with motor neuron degeneration (FTLD-MND),[2,10] dementia lacking distinctive histology (DLDH),[11] and neurofilament inclusion body disease (NIBD).[12,13]

While FTLD, PSP, and CBD have relatively distinct clinical features,[14-16] they may overlap,[17] resulting in misdiagnoses.[18-20] Regardless, while predicting pathologic diagnoses is important, it may be more important to be able to predict the underlying biochemical abnormality, with the expectation that future treatment may be aimed at modifying the expression of tau.[21]

A few studies have examined the relationship between clinical features of FTLD and CBD, and

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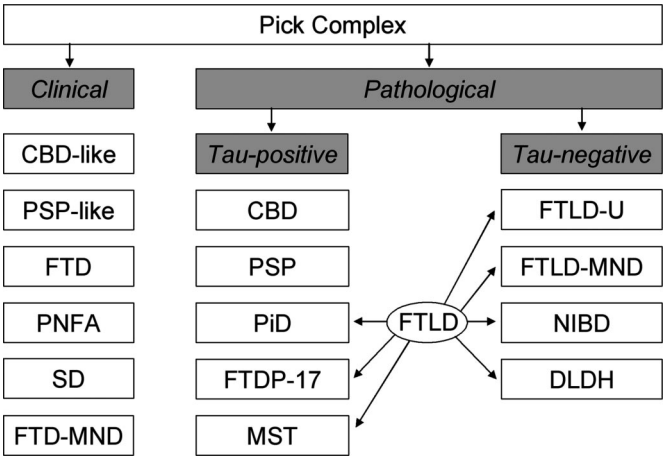

Figure 1. Pick complex can be divided into clinical syndromes and pathologic diagnoses which are further subdivided into tau-positive and tau-negative. Corticobasal degeneration (CBD)-like, progressive supranuclear palsy (PSP)-like, frontal variant frontotemporal dementia (FTD), progressive non-fluent aphasia (PNFA), semantic dementia (SD), and frontotemporal dementia with motor neuron disease (FTD-MND) are clinical diagnoses. CBD, PSP, and frontotemporal lobar degeneration (FTLD) are pathologic diagnoses; FTLD can be further subdivided. PiD = Pick disease (+ Pick bodies); FTLD-U = frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes; FTDP-17 = frontotemporal dementia and parkinsonism liked to chromosome 17; DLDH = dementia lacking distinctive histology; NIBD = neurofilament inclusion body disease; MST = multiple system tauopathy.

pathology,[22-24] but this is the first large series reporting on the relationship between clinical features, pathology, and biochemistry of the FTLDs, PSP and CBD.

Methods. We reviewed the Mayo Clinic electronic medical records database to identify all cases evaluated at the Mayo Clinic, Rochester, MN, with an autopsy confirmed diagnosis of FTLD, CBD or PSP, made between January 1970 and December 2004. A subset of these cases has been previously reported.[25,26]

In all cases tissue slides of frontal, temporal, and parietal cortex, hippocampus, basal ganglia, thalamus, cerebellum, pons, midbrain, and medulla were re-reviewed for determination of a histologic diagnosis. In cases in which the pathologic diagnosis was made before 1996, paraffin blocks were re-cut in order to have a full set of tissue slides representative of all the above regions.

All cases had routine stains completed including hematoxylin and eosin, and modified Bielschowsky or Bodian silver.

In addition, immunohistochemistry was performed with a battery of antibodies, including markers of glial pathology: glial fibrillary acid protein for astrocytes (clone GA5, 1:1000; BioGenex, San Ramon, CA) and either CD68 (clone PG-M1, 1:1000; DAKO, Carpinteria, CA) or HLA-DR (LN-3, 1:5; ICN, Costa Mesa, CA) for microglia. Neuronal pathology was studied with antibodies to neurofilament protein (NF-L: clone 2F11, 1:75; DAKO; NF-H: clone SMI-31, 1:2000; Sternberger Monoclonals, Lutherville, MD), ubiquitin (clone Ubi-1 [MAB1510], 1:250; Chemicon, Temecula, CA), alpha-synuclein (clone LB509, 1:200; Zymed, San Francisco, CA, or NACP98, polyclonal antibody, 1:2000; Mayo Clinic Jacksonville, FL), and phospho-tau (CP13: gift from Dr. Peter Davis, Albert Einstein College of Medicine, Bronx, NY, or clone AT8, 1:1000; Innogenetics, Alpharetta, GA).

Neuropathologic classification. In all cases a pathologic diagnosis was made by one of two neuropathologists (J.E.P., D.W.D.) with expertise in the diagnosis of neurodegenerative diseases, according to most recent consensus criteria.[2,27,28] For diagnostic consensus, clinical and pathologic features of difficult cases (n = 9) were reviewed at a bimonthly conference, attended by a movement disorder specialist, neuropathologists, and behavioral neurologists.

A diagnosis of PiD was made if there were neurofilament positive balloon neurons and silver and tau-positive Pick bodies in the cerebral cortex, and subcortical gray structures; CBD by the presence of neurofilament positive ballooned neurons and tau-positive coiled bodies, threads and astrocytic plaques affecting cardinal nuclei; PSP if there were tau-positive globose neurofibrillary tangles, coiled bodies, threads and tufted astrocytes affecting cardinal nuclei; MST by widespread tau-positive globular neuronal and glial inclusions and negative microtubule associated protein tau (MAPT) screening, and FTDP-17 if there was a mutation found in MAPT sequencing.

A diagnosis of FTLD-U was made if there was evidence of neuronal loss, gliosis, and spongiosis predominantly in frontal and temporal cortices, plus ubiquitin-positive, tau and alpha-synuclein negative, abnormal neurites and intraneuronal inclusions in either frontal or temporal cortex, or dentate granule cell layer and an absence of histologic evidence of motor neuron degeneration. A diagnosis of FTLD-MND was made if there was frontotemporal lobar degeneration and motor neuron degeneration, or degeneration of the corticospinal tract. Bunina bodies were sought in all cases and determined as helpful in making a diagnosis of FTLD-MND, but by themselves, they were not sufficient to make this diagnosis. A diagnosis of NIBD was made if there were intraneuronal inclusions that were stained with neurofilament, variably with ubiquitin, but negative for tau and alpha-synuclein. If any such case was identified, additional immunohistochemistry with alpha-internexin (Mab 2E3, 1:2000, Encor Biotechnology USA) was undertaken. In cases with neuronal loss, gliosis, and spongiosis predominantly in frontal and temporal cortices and lacking tau, alpha-synuclein, neurofilament and ubiquitin immunohistochemistry and any evidence of motor neuron degeneration, a diagnosis of DLDH was made.

Molecular subclassification. Cases were subclassified as tau-positive if they had a pathologic diagnosis of PSP, CBD, PiD, FTDP-17, or MST. Cases were subclassified as tau-negative if they had a pathologic diagnosis of FTLD-U, FTLD-MND, DLDH, or NIBD.

Clinical classification. The historical medical records were retrospectively reviewed by one of two neurologists (K.A.J., D.S.K.) with expertise in behavioral neurology and movement disorders. Both neurologists were blinded to the pathologic diagnoses since the only identifier used in the review were unique numbers (clinic numbers) for the cases. Furthermore the review of complex cases (n = 9) at the consensus conferences occurred after abstraction of clinical data. The first clinical evaluation and early follow-up evaluation were reviewed to determine the best possible clinical diagnoses. These evaluations were reviewed to determine what the early clinical features of the presenting syndrome were, as documented in the historical records. Disease duration was defined as the difference between the age at first symptom/symptoms onset and the age at death. For purposes of this study, in order to separate the clinical syndromes from the pathologic diagnoses, we choose PSP-like and CBD-like, as clinical terms, to represent the cases in which early clinical features were most suggestive of PSP or CBD. Follow-up evaluations were necessary to determine if the patients treated with levodopa were responsive to treatment. A diagnosis of PSP-like was rendered if the extrapyramidal features were symmetric and there were any combination of early falls, supranuclear gaze palsy, axial more than appendicular rigidity, akinesia, and levodopa unresponsiveness; CBD-like if there were asymmetric extrapyramidal features that were unresponsive to levodopa treatment with or without cortical features (since cortical features may not have been documented). In addition a diagnosis of frontal variant FTD was rendered if the dominant features were executive dysfunction, personality changes, behavioral dyscontrol, lack of empathy, apathy, food preferences (particularly sweet cravings), or obsessive and compulsive behaviors; progressive non-fluent aphasia (PNFA) if aphasia was the predominant feature and was non-fluent with hesitancy and phonetic errors; semantic dementia (SD) if there was loss of verbal semantic knowledge, impaired comprehension, and the presence

Table 1 *Demographics of all cases of pathologic FTLD, CBD, and PSP*

Features	FTLD				PSP	CBD	Total	ANOVA p value
	PiD	FTLD-U	FTLD-MND	Others				
N	12	21	18	6	49	21	127	–
M/F	4/8	11/10	13/5	3/3	30/19	11/10	72/55	0.4
Age at symptom onset, y (SD)	60.0 (8.7)	61.3 (11.2)	51.9 (11.4)	53.8 (14.3)	69.4 (9.1)	63.9 (7.2)	63.1 (11.4)	<0.001
Duration of illness, y (SD)	10.2 (3.2)	8.3 (3.2)	2.3 (1.4)	6.8 (2.4)	7.0 (2.8)	7.0 (3.0)	6.8 (3.4)	<0.001

FTLD = frontotemporal lobar degeneration; CBD = corticobasal degeneration; PSP = progressive supranuclear palsy; ANOVA = analysis of variance; PiD = Pick disease; FTLD-U = frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes; FTLD-MND = frontotemporal lobar degeneration with motor neuron degeneration; others = multiple system tauopathy (n = 2) + neurofilament inclusion body disease (n = 1) + frontotemporal dementia and parkinsonism linked to chromosome 17 (n = 3).

of semantic paraphasias. Cases in which there were mixed clinical features of dementia and motor neuron disease, specifically bulbar symptoms, considerable muscle atrophy, prominent and diffuse fasciculations, or electromyographic evidence of motor neuron disease, were given a clinical diagnosis of FTD-MND. Cases that could not be classified as PSP-like, CBD-like, FTD, FTD-MND, PNFA, or SD, because of significant episodic memory loss, excellent levodopa responsive parkinsonism, or they did not have features particularly suggestive of a diagnosis of PSP, CBD, or FTLD, were labeled as not classifiable.

In addition to the clinical classification criteria described above, we also applied published diagnostic criteria for the clinical syndromes,[14,17,29] paying special attention to both inclusion and exclusion criteria, to determine if they made any difference in terms of predicting the underlying pathology.

Clinical subclassification. In addition, some cases were also subclassified clinically as tauopathy and non-tauopathy. All cases with a given clinical diagnosis of PSP-like or CBD-like were classified as tauopathy, while cases with a clinical diagnosis of FTD-MND were classified as non-tauopathy. This classification is based on previous studies suggesting that these three syndromes have relatively specific biochemical correlation.[19,22] Cases with a clinical diagnosis of FTD, PNFA, SD, or those not classifiable were not subclassified, since these syndromes do not necessarily suggest tau-positive or tau-negative biochemistry.[22]

Statistical analysis. Statistical analyses were performed utilizing the JMP computer software (JMP Software, version 5.1.2; SAS Institute Inc., Cary, NC) with significance set at $p < 0.05$. Analysis of variance (ANOVA) was used to compare the mean ages at onset, and survival times, between the different pathologic groups. If significance was found, the Tukey-Kramer test was used to compare all pairs of groups. Sex ratios were compared using a χ^2 test.

Results. *Neuropathologic classification.* For the years specified, 1970–2004, we found 127 cases that met our inclusion and exclusion criteria. These cases were classified pathologically as the following: PSP (n = 49); CBD (n = 21); FTLD-U (n = 21); FTLD-MND (n = 18); PiD (n = 12); and others (n = 6). Among the cases classified as others, there were two with a diagnosis of sporadic MST, three with FTDP-17, and one with NIBD. There were no cases with a diagnosis of DLDH. The demographics of these 127 cases broken down by pathologic diagnosis are shown in table 1. ANOVA revealed group differences for age at disease onset ($p < 0.001$) and survival ($p < 0.001$). The Tukey-Kramer analysis showed that the age at onset for the FTLD-MND group was significantly different from the FTLD-U, CBD, and PSP groups, and that the age at onset of the PSP group was significantly different from the FTLD-U and other groups. The survival times were also significantly different between the FTLD-MND group and the five other groups, between PiD and PSP, and between PiD and CBD. There was no sex difference between groups ($p = 0.4$).

Molecular subclassification. Eighty-seven cases were classified as tau-positive (PSP + CBD + PiD + MST + FTDP-17) and 40 cases as tau-negative (FTLD-U + FTLD-MND + NIBD). Tau negative cases were younger at onset ($p < 0.001$), and had shorter disease duration ($p = 0.003$). There was no sex difference between the groups ($p = 0.6$). Table 2 shows the demographics of cases classified based on molecular biochemistry.

Clinical classification. We were able to clinically classify all but nine cases. Thirty-eight cases were clinically classified as FTD, 13 as FTD-MND, 13 as PNFA, 21 as CBD-like, and 33 as PSP-like. We did not have any cases with a SD syndrome. The median time from symptom onset to the first evaluation in the whole group was 1 year (range 0 to 8), for the FTD group 2 years (0 to 8), for

Table 2 *Demographics of tau-positive vs tau-negative cases*

Features	Tau-positive	Tau-negative	Total	ANOVA p value
N	87	40	127	–
M/F	48/39	24/16	72/55	0.6
Age at symptom onset, y (SD)	66.2 (9.9)	56.8 (12.0)	63.1 (11.4)	<0.001
Duration of illness, y (SD)	7.4 (3.0)	5.5 (3.9)	6.8 (3.4)	0.003

Tau-positive = progressive supranuclear palsy + corticobasal degeneration + Pick disease + multiple system tauopathy + frontotemporal dementia and parkinsonism linked to chromosome 17.

Tau-negative = frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes+ frontotemporal lobar degeneration with motor neuron degeneration + neurofilament inclusion body disease.

ANOVA = analysis of variance.

Table 3 *Syndromic correlation to histologic diagnosis*

	FTLD						
Clinical syndrome	PiD	FTLD-U	FTLD-MND	Others	PSP	CBD	Total
FTD	9	16	5	4	2	2	38
FTD-MND	0	0	13	0	0	0	13
PNFA	1	3	0	0	5	4	13
CBD-like	1	0	0	0	10	10	21
PSP-like	0	0	0	0	30	3	33
Not able to diagnose	1	2	0	2	2	2	9
N	12	21	18	6	49	21	127

FTLD = frontotemporal lobar degeneration; PSP = progressive supranuclear palsy; CBD = corticobasal degeneration; PiD = Pick disease; FTLD-U = frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes; FTLD-MND = frontotemporal lobar degeneration with motor neuron degeneration; others = multiple system tauopathy (n = 2) + neurofilament inclusion body disease (n = 1) + frontotemporal dementia and parkinsonism linked to chromosome 17 (n = 3); FTD = frontal variant frontotemporal dementia; FTD-MND = frontotemporal dementia with motor neuron disease; PNFA = progressive non-fluent aphasia.

FTD-MND 1 year (0 to 4), for PNFA 2 years (0 to 7), for CBD-like 1 year (0 to 6), and for PSP-like 1 year (0 to 5).

Clinicopathologic correlations. Clinicopathologic correlation is shown in table 3. The most common pathologic diagnosis in cases of FTD was FTLD-U, occurring in almost half, followed by PiD.

All cases with a clinical diagnosis of FTD-MND were found to have FTLD-MND on pathology.

The cases classified as PNFA had heterogeneous pathology with PSP and CBD accounting for almost 70% of the cases.

In cases with a clinical diagnosis of CBD-like, 50% had pathologically proven CBD and the other 50% PSP. However, unlike cases with a clinical diagnosis of CBD-like, over 90% of the cases with a clinical diagnosis of PSP-like had a pathologic diagnosis of PSP.

Of the cases pathologically diagnosed as PiD, 75% were clinically classified as FTD. Similarly, 76% of pathologically diagnosed FTLD-U cases presented with the FTD syndrome. Of the cases pathologically diagnosed as FTLD-MND 72% were clinically classified as FTD-MND, the rest as FTD. And, in the cases of pathologically confirmed PSP, 61% were clinically classified as PSP-like, while only 50% of pathologically diagnosed CBD had a CBD-like presentation.

Clinical classification and subclassification vs molecular subclassification. The associations between clinical syndromes and biochemical classification are shown in table 4. In the cases classified as FTD, 42% were tau-positive and 58% were tau-negative. Of those given clinical diagnoses of PNFA 77% were tau-positive and 23% tau-negative. Sixty cases were not subclassified as tauopathy or non-tauopathy, of which slightly more than half were tau-positive. All cases clinically subclassified as tauopathy (PSP-like + CBD-like) were tau-positive and all non-tauopathy cases (FTD-MND) were tau-negative.

Applying research criteria. In all 127 cases we applied published research criteria for the clinical syndromes associated with FTLD, PSP, and CBD.[14,17,29] The results are shown in table 5. Thirty-two of the 38 cases of FTD met research criteria for FTLD.[14] All 13 cases of FTD-MND and all 13 cases of PNFA also met research criteria.[14] For cases with a clinical diagnosis of CBD-like, 62% satisfied research criteria for CBD[17] while 79% of the cases of PSP-like met research criteria for PSP.[29]

Of the cases of FTD that met research criteria for FTLD,[14] the pathologic diagnoses were heterogeneous with FTLD-U accounting for 50%. Six cases with a diagnosis of FTD did not meet research criteria due to the presence of noted early mild episodic memory loss. Of these, PiD accounted for 50%. Eight cases of CBD-like did not meet proposed criteria. Of these, however, CBD was the most common pathology accounting for 63%. Surprisingly, of the ones that did meet research criteria for CBD, 62% did not have CBD, but instead PSP. Twenty-six cases classified as PSP-like satisfied research criteria for a diagnosis of PSP. Of these, 92% had PSP on pathology, the rest CBD.

Discussion. In this study we found that clinical features of the FTLDs, CBD, and PSP significantly

Table 4 *Syndromic correlation to biochemical classification*

Clinical syndrome	Tau-positive	Tau-negative	Total
Tauopathy (CBD-like + PSP-like)	54	0	54
Non-tauopathy (FTD-MND)	0	13	13
Did not subclassify	33	27	60
Total	87	40	127
FTD	16	22	38
FTD-MND	0	13	13
PNFA	10	3	13
CBD-like	21	0	21
PSP-like	33	0	33
Not able to diagnose	7	2	9
Total	87	40	127

CBD = corticobasal degeneration; PSP = progressive supranuclear palsy; FTD = frontal variant frontotemporal dementia; FTD-MND = frontotemporal dementia with motor neuron disease; PNFA = progressive non-fluent aphasia.

Table 5 *Clinical and pathologic diagnosis vs research criteria*

	Neary criteria FTLD	Boeve criteria CBD	Litvan criteria PSP	Comments regarding pathologic diagnoses in cases that fit research criteria	Comments regarding pathologic diagnoses in cases that do not fit research criteria
Clinical syndromes					
FTD (n = 38)	32	0	0	CBD (2), FTLD-MND (5), FTLD-U (16), others (2), PiD (6), PSP (1)	PSP (1), PiD (3), others (2)
FTD-MND (n = 13)	13	0	0	FTLD-MND (13)	
PNFA (n = 13)	13	0	0	PSP (5), CBD (4), FTLD-U (3), PiD (1)	
CBD-like (n = 21)	0	13	0	CBD (5), PSP (8)	CBD (5), PSP (2), PiD (1)
PSP-like (n = 33)	0	0	26	PSP (24), CBD (2)	PSP (6), CBD (1)
Pathologic diagnoses					
PiD (n = 12)	7	0	0		
FTLD-U (n = 21)	19	0	0		
FTLD-MND (n = 18)	18	0	0		
Others (n = 6)	2	0	0		
PSP (n = 49)	6	8	24		
CBD (n = 21)	6	6	2		

FTLD = frontotemporal lobar degeneration; CBD = corticobasal degeneration; PSP = progressive supranuclear palsy; FTD = frontal variant frontotemporal dementia; FTLD-MND = frontotemporal lobar degeneration with motor neuron degeneration; PiD = Pick disease; FTLD-U frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes; others = multiple system tauopathy (n = 2) + neurofilament inclusion body disease (n = 1) + frontotemporal dementia and parkinsonism linked to chromosome 17; FTD-MND = frontotemporal dementia with motor neuron disease; PNFA = progressive non-fluent aphasia.

overlap and may represent different points on a single disease spectrum.[30]

The proposal that the FTLDs, CBD, and PSP may represent different points on a single disease spectrum is furthermore substantiated by genetic studies that have revealed pathologically confirmed cases of PSP, CBD, and FTLD with mutations from a single gene (MAPT).[7,31-35] Therefore, the concept of Pick's complex[1] to encompass the clinicopathologic spectrum of these diseases may be useful.

We found no significant sex difference between the different pathologies. However, we found that cases with FTLD-MND, FTDP-17, NIBD, and MST present at a younger age, almost a decade younger than those with PiD, FTLD-U, PSP, and CBD. Cases with FTLD-MND also had a very short survival, with disease duration on average 2 to 3 years, similar to that of amyotrophic lateral sclerosis (ALS).[36] This is to be expected, since the motor neuron degeneration and other pathologic findings in FTLD-MND are similar to those in ALS where survival is about 3 years.[37] After pathologic reexamination, we did not have any cases of DLDH, unlike a recent clinicopathologic series.[22] Our finding, however, is similar to three recent publications on pathologic subclassification of the FTLD from three separate brain banks showing that most, if not all, cases of DLDH can now be reclassified with ubiquitin immunohistochemistry as FTLD-U and FTLD-MND.[8,38,39]

When we subclassified the cases into tau-positive vs tau-negative, we found that tau-negative cases were significantly younger at onset with shorter disease duration. These differences were being driven predominantly by the cases of FTLD-MND with significantly younger age at onset and shortened survival time.[26] In addition, however, patients with PSP have disease onset significantly older than the patients with FTLD-U, and among the tau-positive diseases, patients with PiD survive significantly longer than patients with PSP and CBD. While the reason for this has not been systematically studied, we speculate that the difference is due to the fact that patients with PiD have less brainstem pathology than CBD and PSP, late in the disease course, less bulbar symptoms, and are therefore less likely to choke, aspirate, and die.

We were able to clinically classify all but nine cases into one of five recognizable clinical syndromes: PSP-like, CBD-like, FTD, FTD-MND, and PNFA. We did not have any cases that were classified as SD. This study demonstrates that when a clinical diagnosis of FTD-MND is made, FTLD-MND is almost certainly the diagnosis. This suggests that when there are mixed clinical features of FTD, and upper motor neuron disease (weakness, clonus, Babinski sign, or hyperreflexia) or lower motor neuron disease (weakness, muscle atrophy, or fasciculations), one can almost certainly predict the underlying pathology. While we demonstrate that the most common pathology underlying the FTD syndrome is FTLD-U, we also show that PSP and CBD pathologies can also underlie this clinical syndrome and, therefore, both should be considered in the differential diagnosis of the FTD presentation.

A surprising finding was the pathologic heterogeneity in the cases with PNFA. Unlike in prior series, the most common pathology underlying cases of PNFA was PSP, followed by CBD. We suspect that this is due to the relatively loose criteria for the diagnosis of PNFA which often include cases of progressive anomia (non-semantic type) and progressive apraxia of speech.[40,41] We have recently published four of these five cases with PSP pathology and suggest that the presence of apraxia of speech, a motor planning or programming abnormality, as a dominant or co-dominant feature to the aphasia may be a clue to predicting PSP pathology.[42,43] Cases of CBD presenting as PNFA have also been reported.[44,45] Further work is needed on this subgroup of patients to determine if refining clinical diagnostic criteria for PNFA may better be able to predict pathology.

The majority of cases diagnosed as PSP-like had PSP at pathology. In two recent publications approximately 76% and 78% of PSP-like cases were confirmed to have PSP at autopsy.[19,20] In this series 91% of the cases diagnosed as PSP were confirmed to have PSP at autopsy. We suspect however that this increased frequency may be a bias of the study design, since other neurodegenerative diseases, for example Lewy body disease, multiple system atrophy, and AD, causes of the PSP-like syndrome,[19] were not included in this study. However, when we reviewed the initial diagnoses given by the evaluating clinicians we found that 23 had been clinically diagnosed as PSP, of which 21 (91%) had autopsy-confirmed PSP. Unlike PSP, however, where the PSP-like syndrome was suggestive of PSP pathology, the pathologic diagnoses in the CBD-like cases were divided equally among PSP and CBD. When we reviewed the clinical features of the cases classified as CBD-like, we were unable to find any features that were helpful in predicting PSP from CBD.

We also applied published criteria to the CBD-like and PSP-like syndromes. The majority of cases with the PSP-like syndrome satisfied research criteria for PSP, while 62% of the cases with a CBD-like syndrome satisfied research criteria for CBD. Some cases did not meet criteria for CBD because early examination did not reveal or report cortical sensory signs. With disease progression, however, the majority of cases categorized as CBD-like would have met CBD criteria.[17] These findings emphasize that unlike in the PSP-like syndrome, pathologic diagnosis in the CBD-like syndrome is heterogenous,[18] and confirm that PSP can present with a CBD-like syndrome.[46,47] Furthermore, we did not include cases of AD or Creutzfeldt-Jakob disease, which can have a CBD-like presentation.[18] The data suggest that the CBD-like presentation is simply nonspecific.

It is worth mentioning that even though all cases with a clinical diagnosis of FTD-MND had a pathologic diagnosis of FTLD-MND, not all cases diagnosed as FTLD-MND had been classified as FTD-MND. Five cases were classified as FTD. The explanation for this is currently being evaluated but it is possible that in FTLD-MND, when dementia is present, either preclinical motor neuron disease exists, or that identification of very early features of motor neuron disease is difficult.

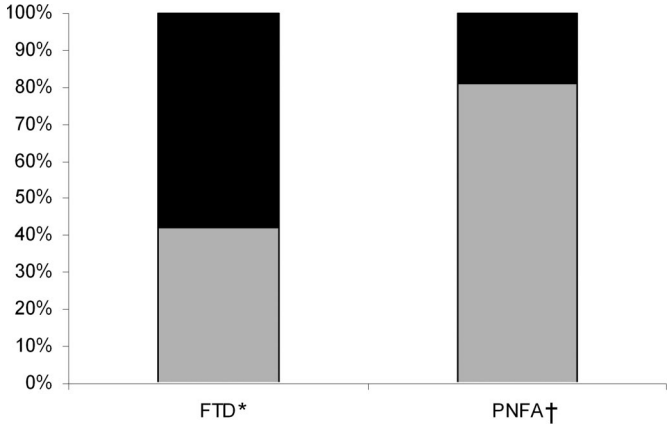

*Figure 2. The percentage of published cases of frontal variant frontotemporal dementia and progressive nonfluent aphasia with tau-negative (■) vs tau-positive (□) pathology. *Current study + reference 22 + reference 8. †Current study + reference 22.*

While predicting pathologic diagnosis is helpful, especially for prognosis, it may be that in neurodegeneration, predicting the biochemical abnormality may become equally important because attempts to develop therapies are underway to try to modify the expression of soluble tau.[22] Therefore, being able to predict the underlying biochemical abnormality will become important for the application of such treatment in the near future. As we have already discussed, in cases of FTD-MND, a non-tauopathy, predicting the pathology of FTLD-MND is very good. When cases of CBD-like and PSP-like are lumped under the rubric of tauopathy, predicting tau-positive biochemistry was better than predicting the pathology from either syndrome. Further analysis is needed to address the issue of sensitivity and specificity with the inclusion of all the neurodegenerative diseases.

The two syndromes in which predicting biochemistry was difficult were PNFA and FTD. We compared the results from our series with results from another recent large clinicopathologic study,[18] and the findings were similar, suggesting that tau positive pathology is more frequently the pathology that underlies the syndrome of PNFA. Since both studies were large clinicopathologic series we combined the results showing that 80% of PNFA cases were tau-positive (figure 2). Predicting whether the underlying biochemical abnormality of FTD will be tau-positive or tau-negative was even more difficult. Figure 2 shows that of 93 pathologically confirmed cases, from three different large pathologic series, a little more than half were tau negative. Applying research criteria[14] to our 38 cases also made little difference. Thirty-two of our 38 cases of FTD fulfilled research criteria for FTLD, as episodic memory loss

was noted in the other six. Of these 32, 66% were tau negative. Therefore, overall, the data suggest that in FTD, only a slightly greater chance exits that the biochemical abnormality will be tau-negative. There are obvious limitations however to combining these data since in two series the data collected was retrospective while the other was prospective. Regardless, the findings from all three series were similar.

The strengths of this study are the large number of autopsy confirmed cases and pathologic reexamination with the most recent immunohistochemical stains and techniques. Weaknesses include the fact that the cases were not all prospectively studied, there may have been referral biases as to which cases end up being autopsied, and not all cases with the CBD-like syndrome had examination documentation of the absence of cortical signs, for example, stereognosis and graphesthesia.

This study demonstrates that the FTLDs, PSP, and CBD have overlapping clinical features. However, some syndromes are better correlated with specific pathologies than others. Predicting biochemistry seems better than predicting specific pathologies. In preparation for future treatment of many of these neurodegenerative diseases, further studies, clinicopathologic as well ones utilizing biomarker techniques, will be needed to improve diagnostic sensitivity.

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Trigeminal neuralgia due to pontine infarction

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An 85-year-old man with diabetes mellitus suddenly developed dysesthesia over the left side of the face, which persisted for a few months and then disappeared. Two years later, he experienced intermittent lancinating pain in the territory of the maxillary branch of the left trigeminal nerve triggered by brushing teeth and chewing. Neurologic examination disclosed slightly diminished superficial sensation in the territory of the maxillary branch of the left trigeminal nerve. MRI revealed a tiny wedge-shaped lesion in the pontine base consistent with an old infarction, which has affected the intramedullary portion of the left trigeminal root (figure). Pontine infarction is believed to cause trigeminal neuralgia,[1,2] and this case documents a clear relationship between the trigeminal root entry zone lesion and trigeminal neuralgia.

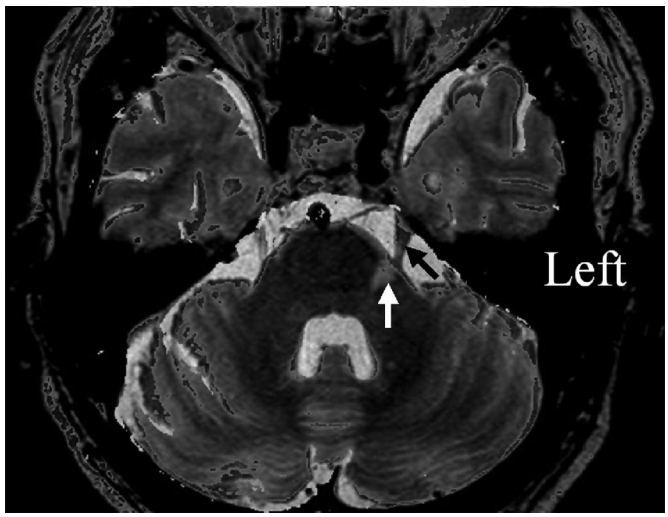

Figure. T2-weighted MRI superimposed on a three-dimensional constructive interference in the steady state image revealing a tiny wedge-shaped lesion in the pontine base consistent with an old infarction (white arrow), which has affected the intramedullary portion of the left trigeminal root. Black arrow indicates the left trigeminal nerve.

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Trigeminal neuralgia due to pontine infarction

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