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Parkinsonism and Frontotemporal Dementia: The Clinical Overlap

Alberto J. Espay and
Department of Neurology, Movement Disorders Center, UC Neuroscience Institute, University of Cincinnati, Cincinnati, OH, USA

Irene Litvan
Department of Neurology, Division of Movement Disorders Center, University of Louisville, Louisville, KY, USA. Division of Movement Disorders, Department of Neurology, University of Louisville School of Medicine, Frazier Rehab Neuroscience Institute, 220 Abraham Flexner Way, Suite 1503, Louisville, KY 40202, USA

Irene Litvan: i.litvan@louisville.edu

Abstract

Frontotemporal dementia is commonly associated with parkinsonism in several sporadic (i.e., progressive supranuclear palsy, corticobasal degeneration) and familial neurodegenerative disorders (i.e., frontotemporal dementia associated with parkinsonism and *MAPT* or *progranulin* mutations in chromosome 17). The clinical diagnosis of these disorders may be challenging in view of overlapping clinical features, particularly in speech, language, and behavior. The motor and cognitive phenotypes can be viewed within a spectrum of clinical, pathologic, and genetic disorders with no discrete clinicopathologic correlations but rather lying within a dementia–parkinsonism continuum. Neuroimaging and cerebrospinal fluid analysis can be helpful, but the poor specificity of clinical and imaging features has enormously challenged the development of biological markers that could differentiate these disorders premortem. This gap is critical to bridge in order to allow testing of novel biological therapies that may slow the progression of these proteinopathies.

Keywords

Frontotemporal dementia; Frontotemporal lobar degeneration; Parkinsonism; Corticobasal syndrome; Progressive supranuclear palsy; Corticobasal degeneration

Introduction

Parkinsonism is characterized by the presence of slow (bradykinesia) and/or low-amplitude movements (hypokinesia) associated with either rigidity, tremor at rest, or postural instability. The parkinsonism may precede, coincide, or follow the behavioral or language-predominant cognitive impairments characteristic of frontotemporal dementia (FTD). FTD with parkinsonism are part of a growing number of pathologically and phenotypically

Correspondence to: Irene Litvan, i.litvan@louisville.edu.

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separate frontotemporal lobar degenerations (FTLD). The clinical phenotypes include the "classical" presentation of progressive supranuclear palsy (PSP, Steele–Richardson–Olszewski syndrome), corticobasal syndrome, progressive akinesia and freezing of gait, and a number of additional clinical variants, representing a range of distinct pathologies (Table 1). The underlying pathologies of these phenotypes include PSP, corticobasal degeneration (CBD), Alzheimer's disease (AD), tau-positive neuronal and glial inclusions FTLD (FTDP-tau), and tau-negative but ubiquitin-positive neuronal inclusions that are also TDP-43 positive (FTDP-U or FTDP-TDP; Mackenzie et al. 2009).

PSP and CBD are the most common FTLD-tau motor phenotypes (Mackenzie et al. 2009; Cairns et al. 2007; Kovacs et al. 2008). *MAPT* and *PGRN* mutations may account for up to 40% of inherited cases of FTDP-tau and FTDP-TDP, respectively. FTD with motor neuron disease (MND), a clinical phenotype corresponding to FTDP-TDP pathology (Table 1), may present with rapidly progressive parkinsonism (disease course between 1 and 3 years; Cairns et al. 2007; Josephs et al. 2005).

Inherited FTLD-tau is associated with frontotemporal dementia and parkinsonism linked to chromosome 17 and *MAPT* gene mutations (FTDP-17T/*MAPT*; Hutton et al. 1998). Inherited FTLD-TDP comprises FTDP associated with progranulin (*PGRN*) gene mutations (FTDP-17U/*PGRN*; Baker et al. 2006), as well as Perry syndrome associated with *dynactin 1* mutations (Farrer et al. 2009), inclusion body myopathy with Paget's disease of the bone and frontotemporal dementia, associated with *valosin-containing protein* (*VCP*) gene mutations (Watts et al. 2004), and familial amyotrophic lateral sclerosis associated with *TAR DNA-binding protein-43* (*TARDBP*) gene mutations (Rutherford et al. 2008). Parkinsonism has not been reported as a feature of the latter two. Mutations in either *MAPT* or *PGRN* account for 2–10% of all cases and 10–20% of familial cases (Rohrer et al. 2009). Parkinsonism in carriers of mutations in chromatin modifying protein 2B (FTD-3/*CHMP2B*) and fused in sarcoma (ALS-FTD/*FUS*), which more often causes amyotrophic lateral sclerosis (ALS) and psychosis, is very rare and has therefore not been well characterized.

Clinical Features

The classical PSP phenotype is characterized by a symmetric distribution of parkinsonian deficits, whereas asymmetry is characteristic of the corticobasal syndrome (CBS; Table 1). Early frontal executive disturbances and apathy are typically observed early in PSP, which overlaps with other FTDs (Yatabe et al. 2011). Similarly, while early vertical supranuclear palsy is typical of PSP, it can be seen in CBD. However, vertical supranuclear gaze palsy precedes the development of horizontal gaze palsy in PSP, whereas both horizontal and vertical supranuclear gaze palsy tend to occur simultaneously in CBD, typically preceded by an increase in saccade latency rather than a decrease in speed as well as some degree of ocular motor apraxia (Vidailhet et al. 1994; Rivaud-Pechoux et al. 2000). Greatly diminished blink rate and eyelid "apraxia," a difficulty or slowness when opening or closing the eyelids, accompanied by compensatory elevation of the eyebrows and frontalis muscle overactivity, probably indicative of focal dystonia (Krack and Marion 1994), are also more common in PSP but potentially overlapping with pathology-proven CBD.

Major overlapping clinical deficits between PSP, CBD, and other FTDs are speech, swallowing, and language disorders (Fig. 1). PSP patients typically develop a hypokinetic–spastic dysarthria, but language impairments may also occur in the form of (fluent or nonfluent) aphasia with perseveration and anomia (Esmonde et al. 1996; Josephs and Duffy 2008). Prominent early or severe (especially nonfluent) aphasia and swallowing difficulties may also be present in CBS cases due to CBD pathology. Apraxia of speech, in particular, is strongly associated with underlying tau pathology (FTLD-Tau, CBD, and PSP) (Josephs et

al. 2006a). Some clinical features may favor a specific tauopathy over another in the appropriate premortem clinical scenario. Clinicopathologic case series suggest that speech impairments in the form of isolated dysarthria favor a diagnosis of PSP but in the form of nonfluent aphasia or speech/orobuccal apraxia predict CBD (Table 2; Graham et al. 2003; Ozsancak et al. 2004).

The bulk of these observations suggest that most phenotypes are in general poorly predictive of the underlying pathology (Josephs et al. 2006b). CBS can include a diverse, non-CBD range of neuropathologies including PSP and most notably AD (Shelley et al. 2009), particularly when episodic memory complaints are prominent (see Bradley Boeve's, "The multiple phenotypes of corticobasal syndrome and corticobasal degeneration," this issue). Conversely, although the classical PSP phenotype predicts underlying PSP pathology more often than other pathologies (Josephs et al. 2006b), it can also be the expression of CBD (Table 2; Ling et al. 2010; Kouri et al. 2011). Minor deviations from the classical PSP phenotype may indicate an alternative diagnosis. For instance, patients with FTDP-17T/*MAPT* (+16 mutation) may present with a PSP phenotype at a younger age (40s) and without falls within the first year from symptom onset (Morris et al. 2003).

The two best understood forms of autosomal dominant FTDP exhibit broad though overlapping differences (Table 3). Parkinsonism in FTDP linked to chromosome 17 with tau pathology (FTDP-17T/*MAPT*) is typically tremorless and may exhibit early but rarely sustained response to levodopa (Tsuboi et al. 2002). It also tends to develop at a younger age, about a decade earlier, than in FTDP linked to chromosome 17 but with ubiquitin and TDP-43-positive pathology (FTDP-17U/*PGRN*) (Boeve and Hutton 2008). A number of *MAPT* mutations have been reported among those with early (N279K, delN296, S305S, +11) (Soliveri et al. 2003; Pastor et al. 2001; Wszolek et al. 2001; Skoglund et al. 2008) or late (P301S, N296H, +3, +12, +14, +16; Baba et al. 2007; Iseki et al. 2001; Rohrer et al. 2011) parkinsonism associated with FTLDP-17T/*MAPT*, with a picture most often resembling PSP. Similarly, several mutations in *PGRN* have been reported among those with parkinsonism associated with FTDP-17U/*PGRN*, with a phenotype most often suggestive of CBS, with or without language abnormalities (c.26C>A, g.2988_2989delCA, P439_R440fsX6, IVS1+1 G–>A, +1, +11; Wider et al. 2008; Gabryelewicz et al. 2010; Boeve et al. 2006). Psychiatric symptoms and language impairment, particularly in the form of progressive nonfluent aphasia (PNFA), are more common among patients with *PGRN* mutations (see Fujioka and Wszolek, this issue).

Hypoventilation, slowness of vertical saccades, and weight loss can be features of Perry syndrome. Unlike CBD and PSP, Perry syndrome patients can be strikingly levodopa responsive and demonstrate axial and craniocervical L-dopa-induced dyskinesia (Newsway et al. 2010). Finally, FTD and parkinsonim may even be due to α-synuclein pathology; thus, disorders such as Parkinson's disease dementia, dementia with Lewy bodies, and multiple system atrophy may be misdiag-nosed as FTD, decreasing the power of finding relevant biomarkers in clinically defined cohorts.

Laboratory Studies

Lacking validated biomarkers, only postmortem pathology can definitively ascertain the diagnosis. A neurological examination yielding features suggestive of the classical PSP phenotype or even CBS is reasonably predictive of tau-positive pathology. Brain MRI may assist in delineating a pattern of regional atrophy that involves the dorsolateral or inferior frontal, anterolateral temporal, and parietal regions disproportionate to other brain regions. CBD is associated with asymmetric atrophy in dorsal prefrontal and perirolandic cortex, corpus callosum, striatum, and brainstem (Kouri et al. 2011; Lee et al. 2011). PSP is

associated with atrophy of the midbrain, which yields the image of a “hummingbird or a standing king penguin” in a midsagittal view on brain MRI (Groschel et al. 2006).

Magnetic resonance spectroscopy may demonstrate reduced *N*-acetylaspartate (NAA)/creatine–phosphocreatine (Cre) ratio in the brainstem, centrum semiovale, frontal and precentral cortex, and reduced NAA/Choline (Cho) in the lentiform nucleus in PSP patients compared to controls, whereas CBS patients have reduced NAA/Cre in the centrum semiovale and reduced NAA/Cho in the lentiform nucleus and parietal cortex compared to controls (Tedeschi et al. 1997). This technique is not helpful in distinguishing PSP from CBS or from FTD and is currently not recommended for application in individual patients. Patterns of regional glucose metabolism using ^{18}F-Fluorodeoxyglucose PET scans have been shown to be helpful in identifying CBS and PSP cases, but the technique is not widely available, and further validation studies are needed (Eckert et al. 2005). Such is also the case for reduction in PET measures of striatal dopamine D_2 receptor density using ^{76}Br-bromospiperone or ^{11}C-raclopride (Baron et al. 1986; Brooks et al. 1992).

Unlike the symmetric pattern of frontotemporal brain atrophy of patients with FTDP-17T/*MAPT*, patients with FTDP-17U/*PGRN* show asymmetric frontotemporal *and* parietal atrophy (Rohrer et al. 2010; Kelley et al. 2009). Caudate atrophy tends to be more common in patients with FTDP-17T/*MAPT* (Kim et al. 2007) and ALS-FTD/*FUS* compared to other genetic FTLDs (Josephs et al. 2010). Currently, mutation type and pathology trump clinical phenotypes in predicting the topographical distribution of atrophy (Whitwell et al. 2010). Transcranial sonography is reported to distinguish between PSP and CBS, but at present, there are no studies in which the diagnosis made with imaging has been compared to pathology.

If available, PIB PET imaging may help confirm if the CBS is due to a focal form of AD. Similarly, cerebrospinal fluid (CSF) levels of beta amyloid and tau may help differentiate AD from the other disorders. Of potentially more immediate use is the measurement of CSF tau 33 kDa/55 kDa ratio by immunoprecipitation and Western blot analysis. This ratio is significantly lower in PSP compared to other neurodegenerative disorders, including the other four-repeat tauopathy, CBD (Borroni et al. 2008). This CSF tau ratio, which represents truncated tau production and selectively affects brainstem neuron susceptibility, would need to be validated in other FTD cohorts to refine its role as a biomarker of the PSP variant of FTLD.

Measurement of serum progranulin using a commercial ELISA has been recently suggested as a cost-effective means of predicting *PGRN* mutations (Schofield et al. 2010). Four patients with *PGRN* mutations confirmed on DNA testing (2/17 behavioral FTD, 2/8 CBS) had abnormally low serum progranulin levels. The sensitivity and specificity of this test remain to be determined. Additional potential biological markers are sorely needed.

Genetic Investigations

Only in cases where there is strong family history or when age at onset is less than 50 years are commercially available genetic tests recommended. Most cases of FTLD associated with parkinsonism are tauopathies, and therefore, *MAPT* mutations are recommended as first step in genetic investigations (Goldman et al. 2011). When the presentation includes CBS with PNFA (especially if there is asymmetric parietal atrophy identifiable on brain MRI), *PGRN* mutations may be pursued first (Guerreiro et al. 2008; Spina et al. 2007). Additional clinical scenarios may be considered to refine the sequence of additional genetic testing if no *MAPT* or *PGRN* mutations are found (Goldman et al. 2011). The presence of MND should discourage testing for either of these genes. Together, the known FTLD genes explain less than 50% of the familial cases, suggesting that additional genes await discovery. Currently,

commercially available genetic testing in the USA and Europe is limited to *MAPT*, *PGRN*, *VCP*, and *TARDBP* (the latter two are not recommended in the setting of FTD with parkinsonism).

There is a genetic susceptibility to PSP and MAPT conferred by tau H1 haplotype. More recently, vascular endothelial growth factor haplotypes have been reported to increase risk of FTD, CBS, and PSP (Borroni et al. 2010). Investigation of haplotypes are not currently recommended as part of the diagnostic work up of individual patients.

Conclusions

The overlapping clinical and pathological features render clinicians at a disadvantage in diagnosing and counseling patients with a variety of parkinsonian disorders associated with FTD. The multiplicity of phenotypes that can arise within the same tau- and ubiquitin-based pathologies (or even within the same MAPT and PGRN genotypes), the delay in the presentation of telltale signs, the large gap in our knowledge on the genetic contribution of over half of FTLDs, and the lack of validated biological markers are substantial obstacles on the road ahead. Nevertheless, when carefully characterized, clinical features can be helpful in steering the diagnostic work up and refining the probable ante-mortem diagnosis of these disorders. It is hoped that needed diagnostic markers be soon developed so properly diagnosed patients can be included in novel therapeutic trials that could decrease specific protein aggregation and slow disease progression.

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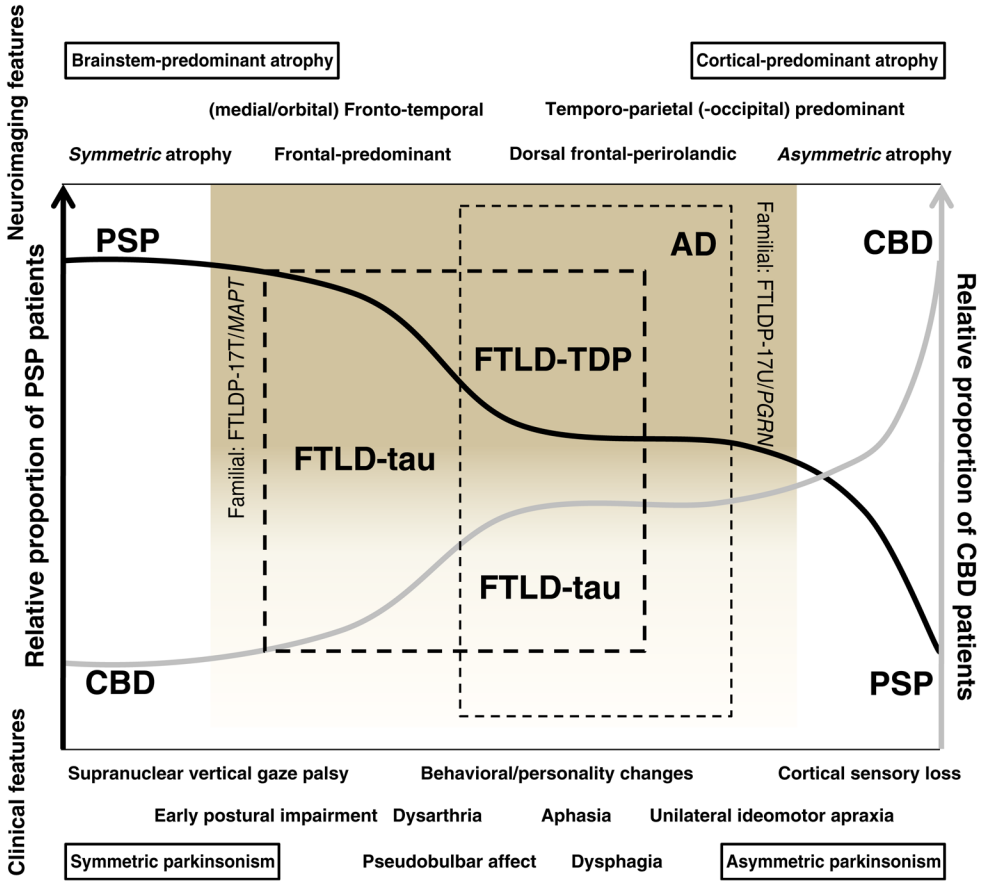

Fig. 1.

The overlap between PSP, CBD, and FTLD. The diagnostic certainty of PSP (*black line*) and CBD (*gray line*) varies depending on the relative presence or absence of clinical (*bottom*) and neuroimaging features (*upper*), and can be diagrammatically represented as belonging to a clinicopathologic spectrum. The "classical" clinical presentation of PSP (early falls, supranuclear vertical gaze palsy) can occur in a small proportion of patients with pathology-proven CBD (*leftmost end* of the proposed spectrum). Less characteristic presentations, or with co-occurrence of behavioral or personality changes or bulbar/pseudobulbar features may fall within the spectrum of FTLD, most often FTLD-tau (*thick hashed line*). Conversely, the typical phenotype of CBD (unilateral ideomotor apraxia, cortical sensory loss) can be present in a small proportion of patients with pathology proven PSP (*right end of the diagram*) or, particularly if behavioral or language abnormalities coexist, in patients with such pathologies as AD (the most common non-CBD etiology in CBS; *thin hashed line*), FTLD-tau, or FTLD-TDP. Neuroimaging patterns in the *left end* of the diagrammatic spectrum tend to show brainstem-predominant (PSP) and symmetric atrophy (FTLD-tau), whereas in the *right end* of the spectrum tend to show asymmetric (FTLD-TPD, particularly due to *PGRN* mutations) and posterior predominant patterns of atrophy (in particular, the posterior cortical atrophy pattern is a feature of some forms of CBD and AD). As a caveat, however, no pattern of atrophy can reliably distinguish FTLD-tau from FTLD-TDP

Table 1

Parkinsonian phenotypes and relationship with FTLD

	Major motor features	Association with FTD/pathology
FTD-P	Parkinsonian features are more common in FTDP-17T/MAPT than in FTDP-17U/PGRN	Strong–early/tauopathy
PSP (classical)	Postural instability and falls within the first year of disease, slowing of vertical saccades or supranuclear gaze palsy, pseudobulbar palsy, parkinsonism minimally or unresponsive to levodopa. Median survival is 6 years.	Strong–early/tauopathy Familial (FTDP-17) Sporadic H1 haplotype
PSP-PAGF/PPFG	Freezing of gait or speech, with no rigidity or tremor, with no sustained response to levodopa, and no dementia or ophthalmoplegia within the first 5 years. Median survival is 10 years.	Weak–late/tauopathy
PSP-PNFA and CBS-PNFA	Severe language deficits, primarily PNFA or apraxia of speech, accompany a hypokinetic-rigid syndrome suggestive of PSP (PSP-PNFA) or CBS (CBS-PNFA).	Strong–early/tauopathy
CBS	Markedly asymmetric parkinsonism with ideomotor apraxia, myoclonus, dystonic posture, alien limb syndrome, and sensory or visual neglect.	Moderate–late/tauopathy Familial (FTDP-17) sporadic H1 haplotype
FTD-MND	Rapidly progressive frontal dementia, aphasia, parkinsonism unresponsive to levodopa, and weakness of limbs and orofacial muscles.	Strong–early/TDP-43 proteinopathy (without PGRN mutation).
Perry syndrome	Levodopa-responsive parkinsonism, vertical gaze palsy, hypoventilation, weight loss, and depression or psychiatric symptoms.	Unclear/TDP-43 proteinopathy

PAGF pure akinesia with gait freezing, *PPFG* primary progressive freezing gait, *PNFA* progressive nonfluent aphasia, *MND* motor neuron disease

Table 2

Overlapping clinical features between PSP and CBS and the frequency of the reported pathologies

	PSP	CBS
Cognitive impairment	Frontal dysexecutive, early	Frontal dysexecutive, late
Speech	Dysarthria, early	Dysarthria, late; apraxia of speech
Language	Fluent perserverative	Nonfluent (PNFA)
Saccades	Normal latency but slow velocity and decreased amplitude (hypometric)	Delayed latency but normal velocity and amplitude (non-hypometric)
Motor phenotype	Typically symmetric akinesia with axial-predominant rigidity, but lateralized features[a] may predominate	Typically lateralized features, but symmetric akinesia with axial-predominant rigidity may predominate
Common pathologies (approx. frequency)	PSP, 80%	CBD, 35%
	CBD, 10%	AD, 20%
	FTLD-Tau, 10%	PSP, 15%
		FTLD-TDP, 15%
		FTLD-Tau, 15%

[a]Lateralized motor features mostly apply to unilateral dystonia or myoclonus; lateralized cognitive features mainly apply to unilateral ideomotor apraxia, cortical sensory signs, or visual neglect.

Table 3

FTDP-17T/*MAPT* vs. FTDP-17U/*PGRN*

	FTDP-17T/MAPT	FTDP-17U/PGRN
Age	Younger, 40s	Older, >50 years
Predominant clinical phenotype	Parkinsonism and personality change are more common	Language abnormalities, parkinsonism less common (except for CBS)[a]
Most common presenting deficits	Behavioral/personality changes, semantic impairment	Anomia, apathy (or disinhibition), apraxia
Penetrance	Nearly 100% (false sporadic cases are rare)	Age dependent: 90% reached by 70 years
Disease duration	Mean, 5 years	Mean, 7 years
	Range, 3–10 years	Range, 1–15 years
Common clinical presentations	bvFTD, CBS, PSP, AD	PNFA, CBS, AD, PDD/DLB
Response to levodopa	Commonly present but rarely sustained	Rarely present
Distribution of atrophy	Anteromedial temporal lobe and orbitofrontal region; caudate	Inferior frontal, temporal, and inferior parietal lobe
Symmetry of atrophy	Symmetric	Asymmetric. Asymmetry becomes greater over time

[a] Although pathology of FTDP-17U/*PGRN* is always FTLD-TDP, MND is exceptionally rare among *PGRN* carriers

bvFTD behavioral variant of frontotemporal dementia, *PNFA* progressive nonfluent aphasia, *PDD* Parkinson's disease dementia, *DLB* dementia with Lewy bodies