American Journal of Alzheimer's Disease & Other Dementias®
26(1) 72-77

DOI: 10.1177/1533317510391239
http://aja.sagepub.com

Extrapyramidal Signs in the Primary Progressive Aphasias

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Abstract

Background: Extrapyramidal signs (EPS) may vary across 3 major subtypes of primary progressive aphasia (PPA): progressive nonfluent aphasia (PNFA), semantic dementia (SD), and progressive logopenic aphasia (PLA). **Methods:** We reviewed initial neurological examinations from a clinical PPA cohort (PNFA = 49, SD = 26, PLA = 28) to determine the prevalence of specific categories of EPS. **Results:** The presence of any EPS was more common in PNFA (38.8%) and PLA (35.7%) than in SD (3.8%). The PNFA group exhibited the highest prevalence of bradykinesia (PNFA: 22.4%, SD: 3.8%, PLA: 0.0%) and rigidity (PNFA: 30.6%, SD: 0.0%, PLA: 10.7%). Calculated positive likelihood ratios indicated bradykinesia (12.1) or rigidity (5.5) was more strongly associated with PNFA than other PPAs. **Conclusion:** These findings suggest that on initial presentation, specific EPS may help distinguish PPA subtypes when linguistic and/or neuroimaging profiles are indistinct. Moreover, EPS could represent a marker of underlying tauopathy, linking clinical presentation to neuropathology in PPA.

Keywords

primary progressive aphasia, parkinsonism, progressive nonfluent aphasia, semantic dementia, logopenic aphasia

Introduction

Primary progressive aphasia (PPA) encompasses 3 main syndromes: progressive nonfluent aphasia (PNFA), semantic dementia (SD), and progressive logopenic aphasia (PLA). All 3 subtypes are insidious in onset, gradual in progression, and initially characterized by a predominantly isolated linguistic impairment for at least 2 years.[1,2] Progressive nonfluent aphasia presents with effortful, agrammatic speech, anomia, and occasional motor programming difficulties, with relatively spared word comprehension and object knowledge.[3] Semantic dementia is associated with fluent, grammatic speech but loss of single-word comprehension and object knowledge.[3] The term logopenia was used in the past to describe prominent word-finding difficulty with preserved syntax.[4] More recently, PLA has been considered a distinct third subtype of PPA, characterized by frequent word-finding pauses and impaired phrase repetition but intact syntax and motor speech.[5] Structural magnetic resonance imaging (MRI) typically shows left frontal atrophy in PNFA, bilateral anterior temporal atrophy in SD, and left superior temporal and inferior parietal atrophy in PLA.[3] Hypometabolism on positron emission tomography (PET) is generally concordant with these patterns of regional atrophy.[2] Progressive nonfluent aphasia is commonly associated with tau-positive intraneuronal inclusions.[6-14] Semantic dementia is frequently associated with ubiquitin-positive, tau-negative intraneuronal inclusions.[8,15] Progressive logopenic aphasia is often associated with Alzheimer's Disease (AD) pathology.[16,17] However, despite attempts at accurate clinicopathological correlation, the link between linguistic phenotype and underlying pathology remains imperfect.

Progressive nonfluent aphasia and SD are clinical entities subsumed under the umbrella of frontotemporal lobar degeneration (FTLD).[18] Traditionally, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) were considered separate from FTLD, presenting with parkinsonism but no cognitive or language deficits. However longitudinal studies indicate that many patients presenting with PNFA may evolve into CBS or PSP[6,7,9,11,12] or develop behavioral changes similar to behavioral variant frontotemporal dementia.[7,10,19,20]All cases of PSP and most cases of CBS are characterized by an underlying primary tauopathy on neuropathological examination.[9,21-23]

Extrapyramidal symptoms (EPS) are commonly found in patients with PPA. Early reports of individual patients and case

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series included a range of EPS, including decreased arm swing,[12] unilateral and bilateral rigidity,[7,11,24] intermittent freezing,[7] and bradykinesia.[11] More recent work incorporating current PPA diagnostic criteria[1] indicates that EPS (rigidity, akinesia, or apraxia) were seen in 12.5% of patients with PNFA.[14] In a case series, all 4 patients presenting with PNFA developed various EPS, such as hypomimia, diffuse bradykinesia, bradyphrenia, increased rigidity, reduced arm swing, and slow rapid alternating movements.[25] A separate case report of PNFA documented a normal neurological examination at presentation, with subsequent emergence of bradykinesia, decreased arm swing, cogwheeling, falls, and rigidity over the next 3 years.[6] Longitudinal follow-up of a cohort of 20 patients with PPA over 6 years revealed that all of the participants developed asymmetric rigidity and dystonia, and 80% met criteria for PNFA.[26] Similarly, studies incorporating newly proposed international PPA criteria[27] have reported the development of EPS (rigidity, bradykinesia, rest tremor, or postural instability) in 56% to 83% of patients with PNFA and 10% to 50% of patients with PLA.[3,28] The majority of patients with SD shows very little or no parkinsonism.[3,14,19] However, the concordance between PPA subtype and prevalence of EPS is not absolute.[14,26,28,29]

In the absence of reliable biomarkers for these phenotypes, detailed linguistic and neuroimaging assessments remain the primary methods for distinguishing the PPAs and deducing their underlying pathologies.[3,20] Although diagnostic criteria have been proposed to standardize and improve the classification of patients with PPA,[2,27] discerning between subtypes can be challenging due to overlapping linguistic characteristics (e.g., hesitant slow speech, speech pauses, and anomia in PNFA and PLA). In such cases, additional clinical features may improve diagnostic certainty. While clinicians and investigators have noted the presence of EPS in the PPAs, the prevalence of specific EPS features, such as rigidity and bradykinesia, among the different PPA subtypes has not been directly assessed. Progressive logopenic aphasia has only recently been recognized as a separate PPA subtype and there have been relatively few descriptions of its clinical phenotype.[3,5,30] Extrapyramidal symptoms may represent a diagnostic feature that complements established linguistic and imaging profiles of the PPA subtypes. The aim of this study was to explore the relationship between EPS and clinical diagnoses in a large PPA cohort.

Table 1. Proposed Clinical Criteria for Diagnosis of Primary Progressive Aphasia[27]

All subtypes
- Most prominent clinical feature is difficulty with language
- Approximately 2 years duration (could be less, but language was first and most prominent)
- All but 1 feature must be present to qualify as a particular variant

Nonfluent variant
- Grammatical difficulty in language production (reduced mean length of utterance, grammatical morpheme omissions such as prepositions)
- Impaired motor speech (effortful, melodic disturbance and groping)
- Impaired comprehension of syntactically complex sentences
- Errors in spontaneous speech production, repetition, and naming (eg, phonemic distortions, articulatory struggle, and groping as in apraxia of speech)
- Spared word comprehension and object knowledge

Semantic variant
- Poor word comprehension, particularly for unfamiliar items
- Poor object knowledge, particularly for unfamiliar items
- Poor confrontation naming, particularly for unfamiliar items
- Intact motor speech, spontaneous speech is melodic and grammatical
- Spared single-word repetition

Logopenic/phonologic variant
- Impaired word retrieval in spontaneous speech and confrontation naming
- Impaired repetition of sentences, particularly for low predictable sentences
- Phonologic substitution errors in spontaneous speech and naming
- Spared word comprehension and object knowledge
- Motor speech is spared (ie, no groping, no distortions, no dysarthria, or dysphonia)

Exclusion criteria
- Progressive dysarthria, pure motor speech disorder
- Discourse abnormality without other language abnormalities
- Predominant visuoperceptual or memory disorder
- Nonprogressive etiologies (eg, stroke, hydrocephalus, head trauma, space-occupying lesions (eg, tumor, AVM), medical (eg, thyroid), primary psychiatric disorder).

Abbreviation: AVM: arteriovenous malformation.

Methods

Participants

We reviewed the charts of 164 patients seen in the UCLA Frontotemporal Dementia Clinic from 1995 to 2009 and diagnosed with PPA.[2] Of these, 108 had routine initial neurological examinations performed by a single clinician (M.F.M.) and were included in our analyses. Diagnoses were reclassified (by M.F.M.) according to newly proposed PPA criteria[27] (see Table 1), yielding 49 patients with PNFA, 26 with SD, and 28 with PLA. In all, 5 patients did not meet criteria for any of these specific diagnoses and were excluded from further analyses. Postmortem examinations were performed for 4 participants (3 PNFA and 1 SD). This project was approved by the University of California, Los Angeles Institutional Review Board.

Assessment of EPS

Motor examinations, as documented in the clinical chart, were independently graded by 2 raters blinded to clinical diagnoses for the presence of 5 categories of EPS, regardless of severity derived from the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS)[31]: (1) bradykinesia: decreased amplitude and/or speed of spontaneous movement, hypomimia; (2) tremor: resting and/or postural; (3) rigidity; (4) impaired motor programming: decreased amplitude and/or speed of finger

Table 2. Demographic Characteristics[a]

Demographics	PNFA	SD	PLA	χ^2/F	*P*
N	49	26	28		
Gender (male/female)	20/29	12/14	17/11	2.86	.240
Handedness (R/L)[b]	46/2	24/2	26/1	0.57	.753
Years of education[b]	14.7 (2.4)	14.2 (3.0)	15.7 (2.8)	2.26	.111
Age at onset[b]	65.1 (9.8)[c]	59.3 (7.2)[d]	66.5 (9.2)[c]	4.95	.009
Age at presentation	68.7 (9.4)[c]	63.4 (7.3)[d]	70.1 (8.8)[c]	4.54	.013
Symptom duration in years[b]	3.3 (1.9)	4.1 (2.4)	3.5 (1.8)	1.28	.300

Abbreviations: PNFA, progressive nonfluent aphasia; SD, semantic dementia; PLA, progressive logopenic aphasia;
[a] Values in parentheses denote standard deviations. Groups denoted by the superscript letters c and d differ by $P < .05$.
[b] Number of patients with missing data: handedness: 2; education: 11; age at onset and symptom duration: 6.

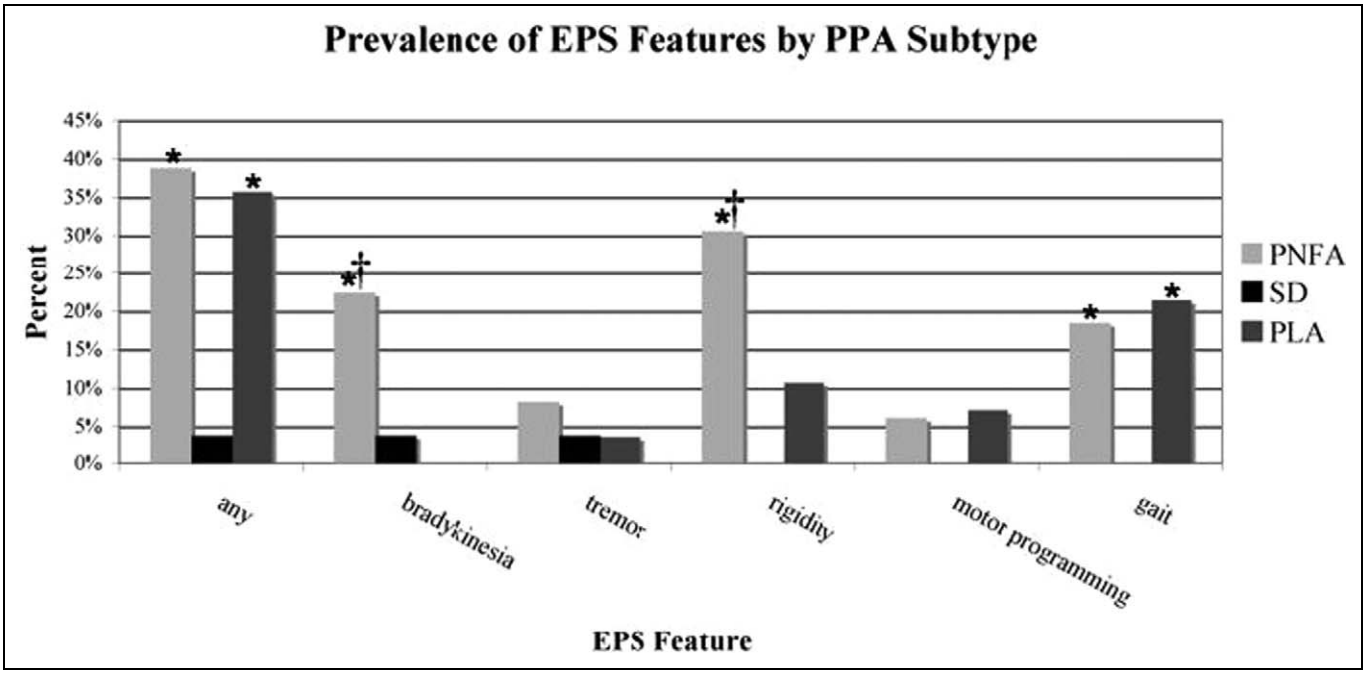

Figure 1. Prevalence of EPS features by PPA subtype. EPS indicates extrapyramidal symptoms; PPA, primary progressive aphasia; PNFA, progressive nonfluent aphasia; SD, semantic dementia; PLA, progressive logopenic aphasia. *$P < .05$ vs SD; †$P < .05$ vs PLA.

tapping, opening/closing of hands, rapid alternating movements, or leg agility; and (5) disturbance in gait/station: stooped posture, postural instability, decreased arm swing, short steps, en bloc turns, and/or festination. Inter-rater reliabilities for the presence of any EPS ($\kappa = .95$, $P < .001$) and specific EPS categories (κs ranging from .79 to 1.0, Ps < .001) were excellent. Discordant ratings were adjudicated by a third blinded rater.

Data Analysis

Statistical analyses were performed using SPSS 16.0 for Mac (SPSS Inc, Chicago, Illinois). Dichotomous data were compared using Kruskal-Wallis tests and continuous data compared with one-way analysis of variance. Post hoc analyses were conducted with Mann-Whitney *U* (dichotomous data) or Fisher Least significant difference (continuous data) tests. Associations between age, EPS, and clinical subtypes were assessed with logistic regression.

Results

Demographic data for the different PPA subgroups is shown in Table 2. Handedness, gender, education, and symptom duration were similar between PPA subgroups (Ps > .1). The SD group was significantly younger than the PNFA and PLA groups at both symptom onset and initial examination (Ps < .05).

The prevalence of any EPS and specific categories of EPS in each PPA subgroup is shown in Figure 1. Of the patients with PPA, 29% demonstrated at least 1 EPS. The prevalence of any EPS was significantly greater in the PNFA and PLA groups than in the SD group (Ps < .05). This effect of PPA subtype remained robust when analyzed with logistic regression adjusted for age at presentation (PPA subtype: $\beta = .713$,

Table 3. Extrapyramidal Symptoms in PNFA Versus Other PPA Groups

	Sensitivity	Specificity	LR+	LR−
Any	0.39 (0.26-0.54)	0.79 (0.66-0.89)	1.9 (1.0-3.5)	0.77 (0.61-0.97)
Bradykinesia	0.22 (0.12-0.37)	0.98 (0.88-0.99)	12.1 (1.62-90.5)	0.79 (0.68-0.92)
Rigidity	0.31 (0.19-0.46)	0.94 (0.83-0.99)	5.5 (1.69-17.9)	0.73 (0.61-0.89)
Gait disturbance	0.18 (0.92-0.33)	0.89 (0.77-0.95)	1.7 (0.63-4.31)	0.92 (0.8-1.05)

Abbreviations: LR, likelihood ratio; CI, confidence interval.
[a] Values in parentheses denote 95% CI.

$e^{\beta} = 2.040$, $P = .034$; age at presentation: $\beta = .031$, $e^{\beta} = 1.032$, $P = .225$).

When specific categories of EPS were considered, significant group differences were seen for bradykinesia and rigidity (Ps < .05). Gait disturbance was of borderline significance ($P = .05$). Relative to the other 2 groups, participants with PNFA exhibited higher rates of bradykinesia (PNFA vs SD: $z = -2.077$, $P = .038$; PNFA vs PLA: $z = -2.690$, $P = .007$) and rigidity (PNFA vs SD: $z = -3.133$, $P = .002$; PNFA vs PLA: $z = -1.972$, $P = .049$). Both the PNFA and PLA groups had a higher prevalence of gait disturbance than the SD group (PNFA vs SD: $z = -2.314$, $P = .021$; PLA vs SD: $z = -2.480$, $P = .013$). The presence of bradykinesia (positive likelihood ratio [PLR] = 12.1] or rigidity (PLR = 5.5) most effectively distinguished PNFA from the other PPA subtypes (see Table 3).

The frequency of specific EPS features within each of the 5 EPS categories are shown in Table 4. The most common manifestations of bradykinesia, rigidity, and gait disturbance were hypomimia, appendicular rigidity, and gait instability, respectively.

Autopsy results are available for only 4 participants (3 PNFA and 1 SD). One patient with PNFA who exhibited rigidity also had tau-positive pathology. In contrast, neither of the other 2 patients with PNFA displayed EPS or primary tau pathology: 1 had AD pathology with neurofibrillary tangles and amyloid plaques and the other had tau-negative pathology. The patient with SD had tau-negative pathology and no EPS.

Table 4. Specific Features of EPS

EPS Category	Manifestation	# of Patients (%)
Bradykinesia (n = 12)	Hypomimia	11 (92%)
	Decreased eye blink	2 (17%)
	Decreased spontaneity	1 (8.3%)
Tremor (n = 6)	Postural	4 (66%)
	Action	1 (17%)
	Intention	1 (17%)
Rigidity (n = 18)	Appendicular	12 (67%)
	Bilateral	6 (33%)
	Right-hand side	4 (22%)
	Left-hand side	2 (11%)
	Axial	5 (27%)
	Global	1 (5.5%)
Impaired Motor programming (n = 5)	Slow fine finger movements with decreased amplitude	5 (100%)
Gait Disturbance (n = 15)	Loss of balance or unsteadiness	8 (53%)
	Decreased arm swing	6 (40%)
	En bloc turns	3 (20%)
	Slowed gait	1 (6.6%)

Abbreviations: EPS, extrapyramidal signs.
[a] Number of patients in each EPS category is given within parentheses. Prevalence is shown as number of patients (% in each subgroup).

Discussion

This is the first study to examine EPS in PPA as defined by the recently proposed diagnostic criteria,[27] which recognize the logopenic variant as a separate PPA subtype. Different patterns of EPS were seen among the 3 PPA subtypes. Extrapyramidal symptoms were more common in PNFA and PLA and rare in SD. The PNFA group exhibited high rates of bradykinesia, rigidity, and gait disturbance. Although not all patients with PNFA exhibited EPS, the presence of bradykinesia or rigidity greatly increased the likelihood of this diagnosis. Hypomimia was the most common manifestation of bradykinesia, and it was present in all patients with PNFA. Appendicular rigidity was detected more often than axial rigidity and was frequently present bilaterally.

While the proportions of patients exhibiting any EPS were similar in the PNFA and PLA groups, a distinct pattern of specific EPS was seen in the PLA group, characterized only by an increased prevalence of gait disturbance. Although gait disturbance was seen more frequently in both the PNFA and PLA groups relative to the SD group, it does not appear to be a useful clinical feature for discriminating between PPA subtypes.

Our results are consistent with prior work, suggesting that mild parkinsonism may be seen more often in PNFA and PLA than in SD.[3,28] Extrapyramidal symptoms in PNFA are likely due to neurodegeneration in brain regions that subserve fronto-cortical–basal ganglia networks. Volumetric MRI studies of patients with PNFA have shown atrophy in the left middle frontal gyrus, bilateral caudate, and left putamen.[3,6] Likewise, decreased middle frontal gyrus volume correlates strongly with bradykinesia in cognitively normal elderly participants.[32] Furthermore, PET imaging in PNFA demonstrates decreased glucose hypometabolism in the left medial and dorsolateral frontal lobes and the left basal ganglia.[33]

The anatomic underpinnings of gait disturbance in PLA are less clear. The most salient characteristic in our cohort was loss of balance or unsteadiness, a nonspecific neurologic sign that can be seen in conditions that do not involve extrapyramidal

dysfunction. In contrast, decreased arm swing and en bloc turning, which are more closely associated with Parkinsonian syndromes, were seen less frequently. Imaging studies of PLA typically reveal atrophy and decreased metabolism confined to nonmotor areas, such as the left angular gyrus, the posterior third of the middle temporal gyrus, the superior temporal gyrus, and inferior parietal lobule.[3,5,28] However, a prior study of patients with PLA reported Parkinsonism in 2 of 4 participants, neither of whom exhibited fluorodeoxyglucose (FDG) or Pittsburg Compound B (PIB) PET abnormalities in the left frontal cortex or the basal ganglia.[28]

Clinicopathological studies examining the evolution of PNFA into Parkinson-plus syndromes have established a strong but not absolute association between PNFA symptoms and tau pathology.[6,8,9,17,25,34-37] Previous case series have found primary tau pathology in 43% to 87% of patients with PNFA, with the remainder exhibiting either AD or ubiquitin pathology.[8,9,13,14,17,30,38] In contrast, neuropathology in SD is most frequently a non-tau ubiquitinopathy.[8,15] The absence of EPS in SD parallels the absence of tau pathology in SD[8] and bolsters the hypothesis that tau deposition is associated with extrapyramidal symptoms in PPA.[9,13]

The neuropathology of PLA has been less extensively characterized. Most cases, though not all, exhibit AD pathology.[17,28] The intermediate prevalence of EPS among our PLA participants is not unexpected, since mild Parkinsonism can be seen in AD.[39] The different patterns of EPS in the PLA and PNFA groups may reflect differences in tau neuropathology between AD and CBS or PSP. Alternatively, our PLA cohort may be pathologically heterogeneous, and those exhibiting EPS may have tau-positive intraneuronal inclusions similar to that seen with PNFA.[8,13]

Our patients with SD were significantly younger than our other patients with PPA, a demographic finding that replicates previous reports.[3,13,14] Since the frequency of mild Parkinsonism increases with normal aging,[39] the higher rates of EPS in the PNFA and PLA groups might merely reflect their older age. However, our findings survived adjustment for age, suggesting that EPS in PPA may indeed be a clinical marker of specific underlying neurodegenerative processes.

There are a number of factors that may limit the interpretation of our results. Patients were reclassified according to the current PPA criteria,[27] which have yet to be validated. Extrapyramidal symptoms were ascertained from documented clinical motor examinations that were not specifically intended for such use. Additionally, the design of the study did not include assessments of the severity or specific characteristics of EPS, such as more detailed analyses of gait disturbance. However, the same expert clinician examined all patients, and blinded inter-rater reliability of EPS ratings was high. In addition, we only considered motor examinations at a single time point (initial presentation), making it difficult to assess the time course of symptom emergence (linguistic versus motor) relative to disease evolution. Finally, our series had only a small number of cases that underwent postmortem examination. Given this limitation, the hypothesis that EPS in PNFA are due to underlying tauopathies remains speculative.

Our cross-sectional results suggest that the presence of EPS, particularly bradykinesia and rigidity, are extralinguistic features of PPA that are most commonly found in PNFA, as compared to SD and PLA. Careful consideration of these particular EPS features may provide supportive data for a clinical diagnosis when distinction of the linguistic profile of the PPA phenotype is difficult, especially early in the disease course. Moreover, our data provide limited additional support for the hypothesis that the presence of EPS may be an indicator of underlying tau-positive pathology in PPA. Some investigators have cautioned against predicting molecular pathology from the pattern of clinical presentation,[17] while others suggest that PPA variants can be classified based on both immunohistochemistry and anatomical location of neuropathological abnormalities.[40] Future studies with larger PPA cohorts, longitudinal evaluations using formal EPS measures, and more complete neuropathological data are necessary to validate these findings.

Acknowledgments

We would like to thank Deidre O'Neill for her assistance with data management and Jill Shapira, RN, PhD for her invaluable service in the UCLA Frontotemporal Dementia Clinic.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article: supported by a VA Special Fellowship for Geriatric Neurology (to S.A.K.)]).

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