Published in final edited form as:

Parkinsonism Relat Disord. 2012 August ; 18(7): 890–892. doi:10.1016/j.parkreldis.2012.04.011.

Parkinsonian motor features distinguish the agrammatic from logopenic variant of primary progressive aphasia

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Abstract

Background—Few studies have assessed parkinsonian motor features across variants of primary progressive aphasia (PPA). Our objective was to compare degree of parkinsonian motor features between two PPA variants.

Methods—Parkinsonian motor features were assessed with the Unified Parkinson's Disease Rating scale in prospectively recruited PPA subjects, classified based on recently published criteria. Comparisons across groups were performed with Fisher's exact test for binary data and Mann-Whitney U test for continuous data.

Results—Twenty-three PPA subjects were diagnosed with logopenic (n=11) or nonfluent/agrammatic (n=12) aphasia. There were no significant differences in illness duration (agrammatic=3.4 years; logopenic=3.3 years) or age at onset (nonfluent/agrammatic =67.3; logopenic=62.0), but those with logopenic aphasia were more impaired on Mini-Mental State Examination (21.7/30 points vs. 26.1/30; p=0.04). In contrast, those with logopenic aphasia had fewer parkinsonian motor features than those with agrammatic aphasia (5.7/132 vs. 16.8/132; p=0.003) which was driven by bradykinesia (p=0.02) and speech facial/expression (p=0.04); less so rigidity (p=0.06). Dysarthria was more frequent in the nonfluent/agrammatic subgroup.

Conclusions—Nonfluent/agrammatic subjects have more parkinsonian motor features than logopenic subjects, likely reflecting underlying tau pathology in the agrammatic variant.

Keywords

Parkinsonism; primary progressive aphasia; logopenic aphasia; agrammatic aphasia; extrapyramidal

INTRODUCTION

The term primary progressive aphasia (PPA) implies a neurodegenerative disorder characterized by progressive aphasia, in the absence of early cognitive deficits. [1] Three variants are well recognized, nonfluent/agrammatic (PPA-agrammatic), semantic and logopenic (PPA-logopenic), with each variant distinguished by differing patterns of language impairment.[2] The nonfluent/agrammatic variant is characterized by

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agrammatism, apraxia of speech and impaired comprehension of complex sentence structure with spared object knowledge; the semantic variant by loss of word meaning and impaired comprehension of single words; and the logopenic variant by impaired repetition and word retrieval with phonological errors and spared motor speech. Distinguishing the nonfluent/agrammatic variant from the logopenic variant can be difficult however, since apraxic speech errors may be misconstrued as phonological errors and vice-versa. Furthermore, the division into these two variants is important because agrammatic patients are typically characterized by tau pathology [3] while logopenic patients generally have Alzheimer disease pathology. [4] Given the different underlying pathologies, non-language clinical features may be useful in distinguishing these two variants. Therefore, our objective was to systematically compare the degree of parkinsonian motor features in these two variants of primary progressive aphasia. We hypothesized that the nonfluent/agrammatic variant would have more parkinsonian motor features than the logopenic variant since other tauopathies are associated with significant parkinsonism.

DESIGN/METHODS

Subjects

All patients with a clinical diagnosis of primary progressive aphasia(1) referred to the department of neurology at our institution were prospectively enrolled between July 1, 2010 and July 31st 2011 and underwent standardized and validated assessments. Subjects were excluded if they met criteria for another neurodegenerative disorder such as corticobasal syndrome, behavioral variant frontotemporal dementia, or progressive supranuclear palsy. For this study, clinical features were abstracted including age, sex, illness duration, age at onset, and Mini-Mental status examination (MMSE) score for assessment of cognitive severity. Parkinsonian motor features were assessed by one movement disorder specialist (KAJ) with the Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating scale part 3 in these prospectively recruited PPA subjects. For analysis, the UPDRS was also subdivided into five sections: speech facial/expression, rigidity, bradykinesia (finger tapping, hand movement, pronation, toe tapping, leg agility, body bradykinesia), gait/posture (arising from chair, gait, freezing of gait, postural stability) and tremor (kinetic tremor, rest tremor, constancy of rest tremor). All subjects were diagnosed via consensus between two speech-language pathologists (JRD and EAS). The diagnosis of PPA- nonfluent/agrammatic and PPA-logopenic were based on recent published criteria and are summarized in table 1.[2] In order for a consensus diagnosis, each individual patient underwent a video and audio recording of their speech and language evaluation which was then reviewed at a consensus meeting. All subjects underwent brain fluorodeoxyglucose positron emission tomography (PET) scans as part of their evaluation.

Statistical Analysis

Statistical analyses were performed utilizing the JMP computer software (JMP Software, version 9.0.0; SAS Institute Inc, Cary, NC) with α set at 0.05. Chi-square tests were used to compare categorical data across groups of interest (Fishers exact test for cells with small N). Nonparametric, Mann Whitney U tests were used to compare continuous data across both groups. Correlations were performed using Spearman Rank correlation. Logistic regression was used to adjust for age at onset as a potential confounder of UPDRS to predict variant.

The study was approved by the Mayo Clinic IRB and was carried out with written informed consent of the subjects involved.

RESULTS

Demographics and UPDRS scores are shown in table 2. There were no significant differences in illness duration or age at onset between both variants while those with agrammatic aphasia were more likely to have dysarthria ($p=0.006$). The PPA-logopenic subjects were more severely cognitively impaired on MMSE; ($p=0.04$) at the time of evaluation. In contrast, those with PPA-logopenic had fewer parkinsonian motor features than PPA-agrammatic ($p = 0.003$). For subscore analyses, there was a significant difference in bradykinesia ($p=0.02$), speech facial/expression ($p=0.04$) and a trend for a difference in rigidity ($p=0.06$) subscores. There was no significant difference in the gait/posture or tremor subscores. Age at onset did correlate with UPDRS score ($r=0.6$; $p=0.001$) but disease duration did not ($r=0.2$; $p=0.44$). After adjusting for age at onset, UPDRS score remained a predictor of PPA variant ($p=0.04$). For the PPA-logopenic group FDG-PET showed left temporoparietal hypometabolism for all subjects while the nonfluent/agrammatic group showed mainly left lateral frontal hypometabolism. Figure 1 demonstrates a representative FDG-PET image for each variant.

Discussion

We have demonstrated that the nonfluent/agrammatic variant has significantly more parkinsonian motor features than the logopenic PPA-variant. Given the worse scores on the MMSE in the logopenic subjects, our results are unlikely to be driven by disease severity. Instead, the findings possibly reflect underlying tau pathology associated with nonfluent/agrammatic variant. The relationship between underlying tau pathology and parkinsonian motor features is consistent with other well known tauopathies associated with parkinsonism including corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP).[5,6] In fact, we have previously shown that PSP and CBD pathology underlie progressive agrammatic aphasia.[3] Since both PSP and CBD affect the substantia nigra and basal ganglia [7] we hypothesize that parkinsonian motor features in agrammatic-PPA are due to substantia nigra and basal ganglia pathology.

The subscale analysis reveals that not all components of the UPDRS contributed to the differences in parkinsonian motor features across the two variants. Three subscales appeared to be contributing to the difference: speech facial/expression, bradykinesia and rigidity. The poorer performance in the speech/face subscale in the nonfluent/agrammatic aphasia subjects is in keeping with more dysarthria in this group. Bradykinesia and rigidity are very prominent and early features of PSP and CBD and therefore it is not surprising to find that these two features contributed to the difference in UPDRS score. The lack of any differences in the gait/posture and tremor subscales suggests that these two measures did not contribute much to the overall difference in the UPDRS part 3 scores. This is interesting since gait/posture is an early prominent feature of PSP. Hence, there are likely neuroanatomical differences between PSP pathology presenting as agrammatic aphasia, and PSP pathology presenting with classic features of PSP. One such regional difference linked to gait dysfunction, as well as eye movement abnormalities in classic PSP is the peduncular pontine nuclei.[8]

Longitudinal studies will be needed to assess the possibility that parkinsonian motor features in either PPA variant may increase with disease duration and determine whether our data reflect a different rate of progression between the two subgroups. It is possible the gait/posture and tremor subscales did not show a difference between these groups because of the insensitivity of the measuring these features with the UPDRS III ..

Our findings have clinical and research significance and may improve the specificity of the diagnostic criteria since parkinsonian motor features could be a useful feature to differentiate nonfluent/agrammatic variant from PPA-logopenic in difficult cases that have overlapping speech and language features that cannot be easily distinguished on the groups speech and language features alone. Furthermore, as treatments for neurodegenerative disorders arise, the ability to distinguish these two entities will become even more important as treatment will likely target the underlying proteinopathy which appear to differ across these two variants. Future research may identify additional motor manifestations that can further aid in distinguishing these two progressive aphasic variants.

Acknowledgments

This study was funded by NIH grant R01 DC010367

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Figure 1.
Representative FDG-PET images for nonfluent/agrammatic and logopenic primary progressive aphasia.

Table 1

Criteria used for PPA diagnoses

PPA-agrammatic	PPA-logopenic
<p>Agrammatism in spoken or written labguage and at least two of the following three features:</p> <ol style="list-style-type: none"> 1 impaired comprehension of syntactically complex sentences; 2 spared single word comprehension 3 spared object knowledge 	<p>Impaired naming and repetition of sentences due to word retrieval problems and at least three of the following four features:</p> <ol style="list-style-type: none"> 1 phonological errors, 2 absence of apraxia of speech 3 spared single word and object knowledge 4 absence of agrammatism.

* Based on recently published criteria[2]

Table 2

Demographic, clinical and cognitive and motor severity scores across the two PPA variants

	PPA-Agrammatic (n=11)	PPA-Logopenic (n=12)
Disease Duration, years	3.4 (1.3)	3.3 (1.3)
Age at onset, years	67.3 (5.4)	62 (9.4)
Presence of dysarthria	6 (54%)	0 (0%)
Mini-Mental State Examination /30	26.1 (2.7)	21.7 (5.7)
UPDRS Part III /132	16.8 (9.8)	5.7 (6.6)
Speech/facial expression /8	4.5 (1.2)	1.1 (1.4)
Rigidity /20	1.5 (0.9)	0.8 (1.0)
Bradykinesia/44	7.5 (6.7)	2.5 (4.3)
Gait/posture /20	1.9 (2.6)	0.9 (1.6)
Tremor /40	1.1 (1.4)	0.5 (1.2)

Data shown as mean unless otherwise specified with standard deviation in parenthesis UPDRS = Unified Parkinson's Disease Rating scale part 3