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Increased Frequency of Learning Disability in Patients With Primary Progressive Aphasia and Their First-Degree Relatives

Emily Rogalski, PhD, **Nancy Johnson, PhD**, **Sandra Weintraub, PhD**, and **Marsel Mesulam, MD**
Cognitive Neurology and Alzheimer's Disease Center (Drs Rogalski, Johnson, Weintraub, and Mesulam) and Departments of Psychiatry (Drs Johnson and Weintraub) and Neurology (Dr Mesulam), Northwestern University, Chicago, Illinois.

Abstract

Background—Although risk factors for Alzheimer disease have been well studied, much less is known about risk factors for primary progressive aphasia (PPA).

Objective—To demonstrate that learning disabilities (LDs) are more common in patients with PPA and their first-degree family members.

Design, Setting, and Patients—Self-report endorsement of an individual and family history of an LD in a sample of 699 subjects from the Northwestern Alzheimer's Disease Center registry. We compared 3 dementia groups (PPA, typical amnestic Alzheimer disease, and the behavioral variant of frontotemporal dementia) and 1 elderly control group. A retrospective medical record review in the PPA probands was used to obtain additional information.

Main Outcome Measure—Prevalence of LDs among probands and their first-degree relatives.

Results—The patients with PPA and their first-degree family members had a significantly higher frequency of LD compared with the other dementia groups and the controls. Some of the families of patients with PPA displayed unusual concentrations of LD, especially dyslexia.

Conclusion—These results suggest that LD may constitute a risk factor for PPA, providing additional clues concerning the determinants for the selective vulnerability of the language network in this syndrome.

Primary progressive aphasia (PPA) is a neurodegenerative syndrome characterized by the progressive loss of language functioning over time with relative preservation of other cognitive domains within the first 2 years of symptom onset.1,2 Neuroanatomically, the pathological changes in PPA are frequently asymmetric and most severe in the hemisphere (usually left) dominant for language. 3–6 Neuropathologically, most of the patients show changes similar to those of frontotemporal lobar degeneration,7 but nearly 30% show changes similar to those of Alzheimer disease (AD).8

Correspondence: Emily Rogalski, PhD, Neurological Sciences, Rush University Medical Center, Cohn Research Building, Third Floor, 1735 W. Harrison St, Chicago, IL 60612 (erogalski@gmail.com).

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Although risk factors for AD have been well studied, much less is known about risk factors for PPA. Our group has previously shown that the apolipoprotein E4 allele, a known genetic risk factor for AD, is not associated with increased risk of PPA.[9] Demographic estimates of the disease suggest that symptom onset is generally in the presenium (before 65 years of age) and that a slightly greater incidence of the disease occurs in men than in women.[5,10] This represents a profile different from that of AD, in which most patients are older than 65 years and female.[11,12]

Initial observations on a small set of subjects suggested a higher frequency of learning disabilities (LDs) in patients with PPA and their first-degree relatives than in patients with clinical AD.[13] To test the validity of this observation in a larger set of subjects, the prevalence of self-reported LDs was compared among 4 different groups in the Northwestern Alzheimer's Disease Center registry: PPA, typical amnestic AD, behavioral variant of frontotemporal dementia (FTD), and healthy elderly control subjects.

METHODS

On enrollment into the Northwestern Alzheimer's Disease Center registry, subjects gave written informed consent and completed a detailed demographic and medical history interview. During this initial interview, subjects were asked 2 questions about a history of LD: "Do you have a history of a learning disability?" and "Have any of your first-degree family members (eg, mother, father, siblings, and children) had a history of a learning disability?" Based on the initial results, we also conducted a retrospective medical record review of the patients with PPA who gave affirmative answers to either of the 2 questions. Some of the reviewed medical records included additional illustrative information on unusual familial concentrations of LD in these families.

Information was available on 699 individuals who responded to the questions about LD. Of these, 353 individuals were classified as controls, 154 as having typical amnestic AD according to the criteria of McKhann et al,[14] 84 as having the behavioral variant of FTD according to the criteria of Neary et al,[15] and 108 as having PPA according to the criteria of Mesulam.[1] Clinical diagnoses were made by the consensus of a neurologist (including M.M.) and a neuropsychologist (including N.J. and S.W.) at the Northwestern Alzheimer's Disease Center. Although the tendency now is to classify PPA into agrammatic/dysfluent, semantic, and logopenic variants,[16] we did not make such distinctions for the purpose of this study. The demographic characteristics for the diagnostic groups are described in Table1. Separate χ^2 tests were conducted to determine whether the prevalence of LD differed between the patient history of each diagnostic group and/or the patient's family history.

RESULTS

Our results indicated that the patients with PPA and their first-degree family members had a significantly higher frequency of LDs compared with the other dementia and control groups (Pearson χ^2 for individual history, 33.15; $P<.001$; Pearson χ^2 for first-degree family members, 41.57; $P<.001$) (Table 2). Table 3 provides more specific personal and family history information from a subset of 23 patients with PPA to illustrate the unusually high concentration of LDs, especially dyslexia, within some of the families.

COMMENT

Responses to questions about the presence of an LD in 699 probands and their first-degree relatives showed the prevalence of LDs to be higher in PPA than in controls, typical amnestic AD, and the behavioral variant of FTD. A retrospective medical record review in a subset of

the patients with PPA showed families with unusually high concentrations of LD. For example, in 3 cases (patients 3, 4, and 8) 9 of the 10 children (and in patients 14 and 23, all 8 siblings) of the probands were reported to have a history of specific LD in the area of language (Table 3). These results suggest that LD may constitute a risk factor for PPA, providing additional clues concerning the selective vulnerability in this syndrome.

All neurodegenerative syndromes, including AD, FTD, and PPA, are clinically characterized by exquisite specificity, especially during the initial stages. In the case of PPA, neuroimaging and neuropsychological examination results show a selective impairment of word usage and a corresponding concentration of atrophy and hypometabolism within the left hemisphere language network. [1] How does a disease process become distributed asymmetrically, and how does it target the language network? An exploration of specific risk factors for PPA may help to address these questions.

Several differential risk factors set PPA apart from other degenerative syndromes. For example, the apolipoprotein E4 allele is a risk factor for AD but not PPA.9 Furthermore, the H1/H1 haplotype of the tau gene and the MV polymorphism in codon 129 of the prion protein gene have emerged as potential risk factors for PPA.[18,19] In rare cases, PPA may be associated with causative genetic mutations. For example, in 2 families in which all affected members (5 of 7 siblings in 2 kindreds) displayed the typical PPA phenotype, mutations in the progranulin gene (*PGRN*) segregated with the clinical disease.[20] However, such mutations are detected in only a few patients with PPA. Similar *PGRN* mutations can give rise to the behavioral variant of FTD in other families,[20] making it necessary to look for additional risk factors that determine the clinical selectivity of the PPA syndrome.

Some potential risk factors for PPA may be developmental or environmental rather than genetic. In 2 patients who experienced the onset of PPA in their seventh decade of life, brain imaging showed left hemicraniosynostosis and a decreased size of the left frontal and temporal lobes.[21] In another case, a man who experienced onset of typical PPA at age 70 years had a history of an abscess that had been surgically removed from the left temporal lobe at age 11 years.[13] In these 3 patients, an early injury to the left hemisphere that was neurologically compensated for through much of adulthood seemed to have provided a “locus of least resistance” for the concentration of neurodegeneration within the language-dominant left hemisphere. There are other examples of analogous phenomena. Women who recover from Sydenham chorea in childhood, a disease thought to be associated with antibodies to the basal ganglia, can experience chorea gravidarum during pregnancy in response to alterations of the hormonal milieu.[22] Patients who have recovered from poliomyelitis can develop, decades later, a progressive motoneuron disease in the previously affected muscles.[23] Finally, patients who have recovered from childhood hemiplegia can develop, later in life, a progressive hemiparkinsonism on the side of the recovered weakness.[24]

Questions may be raised about the specificity and reliability of these findings. For example, subjects with relatively uncommon diagnoses such as PPA might be more likely to report a history of LD because they may be more inclined to explore their family history for similar disorders. This phenomenon is well described in Parkinson disease.[25] Although this possibility of biased reporting needs to be considered, it may be no more relevant to PPA than to FTD and AD in this study. The question of specificity is more difficult to address definitively. Our survey of the literature did not produce evidence of a relationship between premorbid LD and Huntington disease or Parkinson disease. However, there are indications that a subset of schizophrenia characterized by receptive language dysfunction may be associated with a premorbid LD for language.[26] Specific LDs may therefore constitute premorbid phenotypical markers for other neuropsychiatric disorders as well.

The results of our study add further credence to earlier observations[13] that patients with PPA and their first-degree relatives display a higher frequency of LD, especially of the dyslexic type. The higher frequency of LD in the PPA group may provide a marker for preexisting developmental or acquired susceptibilities targeting the language network. Primary progressive aphasia may thus represent the tardive manifestation of an antecedent vulnerability that remains neurologically compensated for during much of adulthood but that eventually becomes a nidus for the anatomical distribution of a degenerative disease that would have had a different distribution in individuals with different susceptibilities. The higher frequency of LD not only in probands but also in first-degree relatives raises the possibility that this risk factor has a genetic component that is developmentally expressed as dyslexia in some individuals and as a neurodegenerative disease, also affecting language, in others. This relationship may exist in only a small subgroup of persons with dyslexia without necessarily implying that the entire population with dyslexia or their family members are at higher risk of PPA.

In our clinical practice, we encounter many patients with PPA who report that spelling was never their "strong suit" or that they could not learn new languages, but who would not have identified themselves as having an LD. Furthermore, family history in these patients is likely to be incomplete, especially in a complex area such as LD. It is therefore reasonable to assume that the frequency of LD shown in Table 1 may be an underestimation. This possibility could be addressed in a larger epidemiological study that also determines the nature of the LD in each proband and family member.

The clinical classification of PPA is moving toward the identification of 3 variants—agrammatic/dysfluent, semantic, and logopenic—each associated with a slightly different set of underlying molecular neuropathologic features. [8,16] We did not subdivide our patients into these variants because most were entered into the study before the acceptance of this classification. Although the details of the aphasia and the underlying neuropathologic features in our patients with PPA may be heterogeneous, the group has the common denominator of having the language network of the brain as the principal locus of degeneration. The common feature, for which LD may be an antecedent risk factor, is the anatomical locus of involvement at the level of a specific interconnected neural network rather than the nature of the underlying disease. Future studies, however, may show that the incidence of LD is higher in some variants of PPA than in others.

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Table 1

Demographic Information

Characteristic	Group			
	Control Subjects (n=353)	Typical Amnestic AD (n=154)	Behavioral Variant of FTD (n=84)	PPA (n=108)
Age at onset, mean (SD), y	69.4 (8.2)[a]	71.2 (9.5)	60.3 (9.2)	62.9 (8.3)
Education, mean (SD), y	15.8 (2.6)	14.0 (3.0)	14.9 (2.8)	15.3 (2.8)
IQ, mean (SD)[b]	112.1 (6.6)	109.1 (8.3)	111.9 (6.8)	112.9 (6.5)
Sex, No.				
Female	274	102	38	56
Male	79	52	46	52

Abbreviations: AD, Alzheimer disease; FTD, frontotemporal dementia; PPA, primary progressive aphasia.

[a] Because there was no age at disease onset for the controls, the age at their first visit is provided.

[b] The IQs were determined according to Barona et al.[17]

Table 2

Percentage of Individual and Family History of a Learning Disability

History of Learning Disability	Group, No. (%)			
	Control Subjects (n=353)	Typical Amnestic AD (n=154)	Behavioral Variant of FTD (n=84)	PPA (n=108)
Individual	5 (1.4)	7 (4.5)	6 (7.1)	16 (14.8)[a]
Family	24 (6.8)	16 (10.4)	12 (14.3)	32 (29.6)[a]

Abbreviations: AD, Alzheimer disease; FTD, frontotemporal dementia; PPA, primary progressive aphasia.

[a]The individual and family history of learning disability is significantly elevated in the PPA group compared with the other groups, $P<.001$.

Table 3

Concentration of LDs in a Subset of Patients With PPA and Their Family Members

Patient No.	LD		Total No. of 1st-Degree Family Members With LD	Total No. of Family Members With LD	LD Description
	In Patient	In 1st-Degree Family			
1	No	Yes	1	1 of 4 Children, 0 of 1 sibling	Son was diagnosed as having dyslexia
2	No	Yes	1	1 of 4 Children, 0 of 4 siblings	Son had problems with speech, reading, spelling, writing, and arithmetic
3	Yes	Yes	5	3 of 3 Children, no siblings, 2 of 2 granddaughters	Patient did not learn to read until age 9 or 10 y and his spelling was always poor; despite trying, patient was unable to learn a foreign language; all of the patient's children and 2 grandchildren were described as dyslexic; only 1 of the patient's sons was able to graduate from high school
4	Yes	Yes	3	3 of 3 Children	3 Sons had problems with speech, reading, spelling, writing, arithmetic, and learning language
5	Yes	Yes	1	1 of 3 Children, 0 of 1 sibling	Patient reports always having difficulty spelling; 1 son had difficulty with spelling and reading
6	No	Yes	1	1 of 2 Children, 0 of 1 sibling	Daughter had a positive LD history consistent with mild dyslexia; patient reports she was never "good at languages" and her mother had difficulty pronouncing long words
7	Yes	Yes	2	1 of 4 Children, 1 of 3 siblings	Patient reported having persistent difficulty with arithmetic; history of dyslexia reported in patient's younger sister, daughter, paternal uncle, and nephew
8	Yes	Yes	3	3 of 4 Children, 0 of 1 sibling (died at age 10 y)	Patient reportedly did well in mathematics and science but struggled with English and literature; patient received therapy for early speech problem and was a below-average speller; 3 children (2 sons, 1 daughter) had difficulty with spelling and 1 of the sons also had difficulty with reading
9	No	Yes	2	1 of 1 Sibling, 1 of 2 parents	Patient's father stuttered as a child; brother had a history of LD and was held back in school for poor spelling; 1 nephew diagnosed as having dyslexia
10	Yes	No	0	0 of 1 Children, 0 of 1 sibling	Patient always had difficulty spelling
11	Yes	No	0	0 of 2 Children, 0 of 1 sibling	Patient reports persistent spelling difficulties since childhood; she attended a spelling course as a child
12	Yes	Yes	1	1 of 5 Children, 0 of 3 siblings, 0 of 2 parents	Patient had difficulty with mathematics and writing as a child; patient's daughter had a similar history of LD
13	Yes	Yes	2	2 of 3 Children, 0 of 1 sibling	Patient was a slow reader and had difficulty with mathematics and spelling as a child; 2 of patient's sons were diagnosed as having ADD
14	No	Yes	5	5 of 5 Siblings	All of patient's siblings had persistent difficulty with reading and spelling

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Patient No.	LD		Total No. of 1st-Degree Family Members With LD	Total No. of Family Members With LD	LD Description
	In Patient	In 1st-Degree Family			
15	Yes	Yes	1	1 of 2 Children, 0 of 1 sibling	Patient had difficulty reading, consistent with dyslexia, and was never good at spelling; his son also has a history of dyslexia
16	No	Yes	1	0 of 1 Children, 1 of 1 sibling	Brother had difficulty with speech as a child and needed speech therapy; brother's 2 children also have difficulty with speech
17	Yes	No	0	0 of 4 Children, 3 of 9 grandchildren	Patient was never a good speller; 3 of patient's grandsons have a positive history of LD, 1 of which has severe dyslexia
18	Yes	Yes	1	1 of 3 Children	Son has LD for language
19	No	Yes	1	0 of 4 Children, 1 of 1 sibling	Brother is reported to have LD consistent with mild dyslexia
20	Yes	Yes	1	1 of 2 Children, 0 of 4 siblings, 0 of 2 parents	Patient had trouble with speech as a child and took special speech classes; patient's son also received speech therapy
21	Yes	No	0	0 of 3 Children, 0 of 2 siblings, 0 of 2 parents	Patient was enrolled in special education class for kindergarten and has LDs consistent with dyslexia
22	Yes	Yes	1	0 of 6 Children, 1 of 13 siblings, 0 of 2 parents	1 Brother has reported dyslexia
23	Yes	Yes	5	2 of 2 Children, 3 of 3 siblings	3 Brothers and 2 sons have reported a history of language LD

Abbreviations: ADD, attention deficit disorder; LD, learning disability; PPA, primary progressive aphasia.