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; Marsel Mesulam, MD

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.

Arch Neurol. 2008;65(2):244-248

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 mem-

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Table 1. Demographic Information

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Subjects (n=353)</th>
<th>Typical Amnestic AD (n=154)</th>
<th>Behavioral Variant of FTD (n=84)</th>
<th>PPA (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>71.0 (2.8)</td>
<td>60.3 (9.2)</td>
<td>62.9 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>14.0 (3.0)</td>
<td>14.9 (2.8)</td>
<td>15.3 (2.6)</td>
<td></td>
</tr>
<tr>
<td>IQ, mean (SD)</td>
<td>109.1 (8.3)</td>
<td>111.9 (6.8)</td>
<td>112.9 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>274</td>
<td>102</td>
<td>38</td>
<td>56</td>
</tr>
<tr>
<td>Male</td>
<td>79</td>
<td>52</td>
<td>46</td>
<td>52</td>
</tr>
</tbody>
</table>

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

a The IQs were determined according to Barona et al.17

Table 2. Percentage of Individual and Family History of a Learning Disability

<table>
<thead>
<tr>
<th>Group, No. (%)</th>
<th>History of Learning Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Subjects (n=353)</td>
</tr>
<tr>
<td>Individual</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Family</td>
<td>24 (6.8)</td>
</tr>
</tbody>
</table>

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.

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 χ² for individual history, 33.15; P<.001; Pearson χ² 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.

Table 3. Percentage of Individual and Family History of a Learning Disability

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

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 LDs. 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.8,18 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, 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 hemispheric hypometabolism and a decreased size of the left frontal and temporal lobes. 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. 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 ex-
amples 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.12 Patients who have recovered from poliomyelitis can develop, decades later, a progressive motoneuron disease in the previously affected muscles.21 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 observations13 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.

Accepted for Publication: May 8, 2007.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by the National Institute on Aging, by Alzheimer’s Disease Core Center grant AG 13854, and by grant DC008552 from the National Institute on Deafness and Other Communication Disorders.

Additional Contributions: Katie Cohen helped organize the data for this project.


New Initiatives: Clinical Trials and Videos

We have embarked on 2 new initiatives: Clinical Trials and video presentations. We welcome manuscripts that describe double-blind, randomized, placebo-controlled clinical trials as our primary area of interest. Open-label studies will also receive our special attention. We plan on expediting the review process and time to publication and to include them online ahead of print as these studies are time sensitive and of direct benefit to our patients. We hope you will take advantage of this new initiative. Please refer to the Instructions for Authors when submitting a Clinical Trials paper, including the requirement to register the trial with an accepted clinical trials site.

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