Association Between the Prevalence of Learning Disabilities and Primary Progressive Aphasia

Primary progressive aphasia (PPA) is a syndrome that arises when the language-dominant (usually left) hemisphere is selectively targeted by a neurodegenerative disease. The underlying neuropathology can be either frontotemporal lobar degeneration (FTLD) or an atypical form of Alzheimer disease (AD). The factors that make the language network selectively susceptible to these neurodegenerative diseases remain unknown. One potential clue emerged from our previous report, which showed a history of learning disability (LD), including developmental dyslexia, to be significantly higher in patients with PPA (n = 108) and their first-degree relatives than in cognitively healthy control individuals (n = 353), as well as dementia of the Alzheimer type (n = 154) or the behavioral variant of frontotemporal dementia (n = 84).

The prevalence of LD in logopenic PPA (PPA-L) was reported to be approximately twice the rate expected in the general population. Logopenic PPA is the subtype most commonly caused by AD, raising the possibility that LD becomes a particularly prominent susceptibility factor for the atypical aphasial manifestation of AD. In our initial report, clinical subtype was not considered and autopsies were not available. The current follow-up study examined 66 consecutive autopsies of patients with PPA to determine whether the presence of LD in either patients or their first-degree family members was associated with a specific aphasia subtype or pathology. In this group, 58 patients with PPA had sufficient information on the status of LD and were included in analyses. Twenty of these were part of our previous report.

Methods | Consensus criteria were used for the diagnosis and subtyping of PPA and for the pathological diagnoses of AD and FTLD. Participants were recruited from Northwestern University’s Alzheimer Disease Center and/or the PPA Research Program. Written informed consent was obtained from each participant. The Northwestern University institutional review board approved this study. The LD status was specifically queried during the clinical interview of patients and families and recorded in the medical record.

Results | Fifty percent of the cases (29 of 58 patients) had either a personal or family history of LD. This is even higher than the 37% prevalence in our original report but the difference was not statistically significant (P = .10, Fisher exact test). Demographics did not differ between the groups with and without a history of LD (Table).

The LD prevalence in PPA with AD (52%) was nearly identical to that in PPA with FTLD (48%). There were too few cases for separate analyses of FTLD subtypes. The incidence in PPA-L (41%) was no greater than that of the nonlogopenic patients (56%). Although the numbers were low, LD prevalence inagrammatic PPA (53%) did not seem to be higher than in nonagrammatic patients (49%).

Discussion | This set of 58 autopsies yielded an LD prevalence that was at least as high as that in our original study. The prevalence was higher than reported by Miller et al, probably because we also included incidence in first-degree relatives and were more inclusive in defining LD. Our findings are consistent with the report by Miller et al of a high LD prevalence in PPA-L. However, we did not find that LD was preferentially associated with AD vs FTLD pathology or with PPA-L vs other PPA variants. If LD does turn out to be a susceptibility marker for PPA, at least in some patients, it would seem to be exerting its influence regardless of the underlying pathology or aphasia type. Larger cohorts and greater specification of the LD history will help to refine and amplify these associations.

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Table. Demographic, Clinical, and Pathologic Features of Patients With PPA With and Without a Family or Personal History of LD

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patients With PPA With Personal or Family History of LD (n = 29)</th>
<th>Patients With PPA Without Personal or Family History of LD (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>60.4 (8.3)</td>
<td>62.0 (8.2)</td>
</tr>
<tr>
<td>Age at death, mean (SD), y</td>
<td>71.2 (7.2)</td>
<td>71.4 (7.1)</td>
</tr>
<tr>
<td>Duration of education, y</td>
<td>15.4</td>
<td>16.0</td>
</tr>
<tr>
<td>Male, %</td>
<td>69</td>
<td>52</td>
</tr>
<tr>
<td>Subtype, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPA-L</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>PPA-G</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>PPA-other*</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Primary pathologic diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPA-AD</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>FTLD*</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; FTLD, frontotemporal lobar degeneration; LD, learning disability; PPA, primary progressive aphasia; PPA-G, agrammatic PPA; PPA-L, logopenic PPA.

* Includes patients who were unclassifiable by the 2011 guidelines (n = 16) and 3 patients with semantic PPA because the numbers were too low for separate analyses.

* Combined group of FTLD-tau (n = 16) and FTLD-TDP (n = 11). No separate analyses of FTLD subgroups were done because of low numbers and heterogeneity of the tauopathies and FTLD-TDP subtypes.
COMMENT & RESPONSE

Therapeutic Hypothermia and Targeted Temperature Management After Cardiac Arrest

To the Editor: We read with great interest the Viewpoint by Little and Feldman titled “Therapeutic Hypothermia After Cardiac Arrest Without Return of Consciousness: Skating on Thin Ice.”1 The authors argued that literature has shed doubt on hypothermia for comatose cardiac arrest survivors, namely, research by Nielsen et al and the Targeted Temperature Management Trial investigators.2 The authors commented at the end of their article: “How can we ensure in the future that we commit resources to rigorous establishment of the value of a novel therapy before committing resources to its premature adoption with such a thin evidence base?”1 We find this last comment interesting given 2 randomized clinical trials in 2002 by Bernard et al3 and the Hypothermia after Cardiac Arrest Study Group,4 as well as the International Liaison Committee on Resuscitation/American Heart Association guidelines,5 which recommend the use of hypothermia. There is physiologic evidence that decreasing brain temperature reduces cerebral blood flow and cerebral oxygen consumption. While there are inherent complexities to cardiac arrest research, there are few randomized clinical trials that address the evidence base, and the literature has evolved over time. The Nielsen et al3 trial was methodologically different than the 2002 randomized clinical trials in which only ventricular tachycardia/ventricular fibrillation patients with coma were included. Also, in the Nielsen et al4 trial, they included pulseless electrical activity and asystolic patients who generally have poorer outcomes compared with ventricular tachycardia/ventricular fibrillation patients. The Nielsen et al4 trial also seemed to be structured as a noninferiority trial because it had 2 active treatment arms. The authors reported no superiority between temperatures 33°C and 36°C. However, 36°C is not technically normothermia because 37°C (98.6°F) is considered normothermia in most textbooks. Therefore, the 36°C arm might be considered a super mild hypothermia or forced normothermia therapeutic arm. The 36°C arm of the Nielsen et al4 study may in fact support Safar’s first 1964 description of the ABCs of cardiac arrest, with the H in the alphabet being for hypothermia if there is “no neuro recovery.”6 It is perhaps part of Safar’s wisdom that bundling intensive care unit interventions helps hospitals and teams to focus on details of critically ill cardiac arrest patients that lead to better outcomes rather than single intervention alone. Such bundles have been shown to improve care with ventilator-associated pneumonia and central catheter placement, for example.

Finally, we think national efforts to improve postcardiac arrest care by including hypothermia training or targeted temperature management (current term) to prevent and control fever should continue. The Nielsen et al4 study perhaps did not show a difference between the 2 groups because of overwhelming evidence that fever is detrimental to virtually all human brain-injury models including cardiac arrest.7 Perhaps it is not the depth of the hypothermia or targeted temperature management literature that should be questioned per se, but the optimal temperature range (33°C or 36°C) for cardiac arrest patients that is treading on “thin ice”?8

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References


