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The prevalence of learning disabilities in primary progressive aphasia is not segregated by pathology or subtype

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To the Editor

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's disease (AD)[1]. 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 PPA patients (n=108) and their first-degree relatives than in cognitively healthy controls (n=353), dementia of the Alzheimer type, (n=154) or the behavioral variant of frontotemporal dementia (n=84)[2].

Recently, prevalence of LD in logopenic PPA (PPA-L) was reported to be approximately twice the rate expected in the general population [3]. PPA-L is the subtype most commonly caused by AD, raising the possibility that LD becomes a particularly prominent susceptibility factor for the atypical aphasic 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 PPA patients 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 PPA patients had sufficient information on the status of LD and were included in analyses. Twenty of these were part of our previous report.

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Methods

Consensus criteria were used for the diagnosis and subtyping of PPA [4] and for the pathological diagnoses of AD and FTLD [5, 6]. Participants were recruited from Northwestern University's Alzheimer's 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 chart.

Results

Fifty percent of the cases (29/58 subjects) 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=0.10, Fisher's exact test)*. Demographics did not differ between the groups with and without a history of LD (Table 1).

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 non-logopenic patients (56%). Although the numbers were low, LD prevalence in agrammatic PPA (PPA-G) (53%) did not seem to be higher than in non-agrammatic 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 is higher than reported by Miller et al. [3], 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 versus FTLD pathology or with PPA-L versus 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 1

Demographic, clinical and pathologic features of PPA patients with and without a family or personal history of learning disabilities.

	PPA patients with personal or family history of LD (n=29)	PPA patients without personal or family history of LD (n=29)
Age at Onset	60.4 +/−8.3	62.0 +/−8.2
Age at Death	71.2 +/−7.2	71.4 +/−7.1
Education in years	15.4	16.0
Gender: % Male	69%	52%
Subtype	PPA-L: 9	PPA-L: 13
	PPA-G: 9	PPA-G: 8
	PPA-Other: 11	PPA-Other: 8
Primary Pathologic Diagnosis	PPA-AD: 16	PPA-AD: 15
	FTLD: 13	FTLD: 14

PPA-G: agrammatic; PPA-L: logopenic; PPA-Other: Includes patients who were unclassifiable by the 2011 guidelines (n=16) and also three PPA-S patients since the numbers were too low for separate analyses. FTLD: combined group of FTLD-tau (n=16) and FTLD-TDP (n=11). No separate analyses of FTLD subgroups was done because of low numbers and heterogeneity of the tauopathies and FTLD-TDP subtypes.