EDITORIAL

Primary progressive aphasia

New insights paving the way toward clinical research tools

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When a patient presents with acute aphasia, today's neurologist takes swift action to characterize the clinical syndrome and use neuroimaging and other tools to identify its pathophysiologic basis. One goal of these urgent efforts is to determine whether the patient has an ischemic process that merits thrombolytic intervention. We can only hope that tomorrow's neurologist is as well-equipped with clinical and pathobiologic assessment tools when faced with a patient with progressive aphasia. Three articles in the current issue move us in this direction.

Patients with primary progressive aphasia (PPA) may exhibit impairments spanning the spectrum of speech and language function,[1] with 3 major subtypes currently recognized and ongoing efforts to reach consensus regarding diagnostic criteria.[2] Although the classification of patients with aphasia as fluent or nonfluent may be difficult because of the multifaceted nature of fluent speech,[3] it has been obvious for many years that some patients with PPA mostly exhibit difficulties understanding the meaning of words but are generally able to speak fluently—this is semantic dementia (SD),[4] or the PPA-semantic variant. Other patients may be able to understand word meaning well but have difficulty with the rate, rhythm, grammatic structure, or articulation of speech. Originally termed nonfluent or progressive nonfluent aphasia (PNFA), many clinicians are now classifying these patients as agrammatic or logopenic[5] based on their language characteristics. Patients with logopenic PPA may be variably fluent depending on the type of conversational exchange or test being undertaken.[1] Partly because of this variability, research groups have differed in their approach to classifying this type of PPA.

Two of the present studies employ quantitative psycholinguistic analysis of speech samples to investigate further the underlying mechanisms of impaired speech fluency in patients with progressive aphasia. In their 16 patients with PNFA, Gunawardena et al.[6] found that the nearly 70% reduction in words per minute compared to controls was related to the level of grammatic impairment and not to the level of speech-sound errors or executive dysfunction. This finding supports the concept that, at least in this patient sample using these measures, nonfluent speech is related to agrammatism. It was somewhat surprising that speech-sound errors did not make some contribution given that 9 of the patients had a motor speech disorder.

The study by Rohrer et al.[7] provides complementary data by including all 3 major PPA subtypes as well as a larger variety of psycholinguistic measures. Their patients, whose MRI data were recently published elsewhere, were classified into 1 of 4 groups based on whether or not there was agrammatism or apraxia of speech (AOS) in speech samples (semantic patients were classified separately). Using these categories, they then examined psycholinguistic features, which generally fit well with the characteristics proposed as being central to the diagnostic subtypes. Another group of 3 patients—all with mutations in the progranulin gene—had different characteristics that will be important to investigate in other patient cohorts.

As for the quantitative speech analysis, rate of speech in the 2 groups that fit with PNFA was reduced to a similar level as that in the study by Gunawardena et al. (~70% lower than controls), while that in the logopenic group was reduced by 50%. The quantitative analysis of speech samples is a cumbersome activity that requires significant skill, and it will be of great interest to see these datasets further explored for additional measures, such as mean and variance in length of utterance, the latter potentially capturing a core feature of logopenic PPA (LPA).

These data are convergent with other recent studies aiming to quantify psycholinguistic deficits in PPA subtypes, and highlight the importance of assessments of grammar,[8] motor speech,[9] and other language features in differentiating forms of PPA. The initial success of these studies provides further support for the efforts of the working group to refine the clinical diagnostic crite-

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ria for PPA subtypes, and for the ongoing work initiated by a working group convened by the National Institute on Aging and National Institute of Neurological Disorders and Stroke to develop a uniform set of neuropsychologic and psycholinguistic instruments that could be used by multiple centers for assessment.

In addition to investigations of the clinical and psycholinguistic features of impaired fluency in PPA, one of this issue's trio of articles aims to determine whether it is possible to predict pathobiological characteristics in patients with these forms of PPA. Because of previous studies suggesting that logopenic PPA is associated with a relatively high rate of pathobiologic abnormalities (autopsy, CSF, amyloid–PET imaging) consistent with Alzheimer disease (AD), Hu et al.[10] analyzed their cohort of individuals with logopenic or PNFA who had CSF or autopsy data available and found that 63% of patients with LPA had markers consistent with AD, which accords well with other recent pathobiologic studies,[11-13] indicating that a substantial majority of—but by no means all—patients with LPA harbor AD pathology. In contrast, 32% of patients with PNFA exhibited markers consistent with AD, which is generally higher than many recent studies published after the adoption of the 3-variant model.

Importantly, in addition to reporting these new clinicobiological observations, Hu et al.[10] investigated models for predicting AD vs non-AD biology comparing clinical, neuropsychological, and imaging variables and using multivariate models. The use of the clinical syndromic diagnoses alone resulted in sensitivity/specificity = 72%/65%, while the combination of multiple types of measures improved performance (neuropsychologic and clinical = 100%/80%; neuropsychologic and MRI = 78%/90%).

The findings of these studies and similar results from other groups emphasize at least 3 major points in PPA research. First, we need to continue to refine clinical, psycholinguistic, and neuropsychologic assessment methods. Our ability as clinicians to recognize these syndromes early and to determine whether interventions make meaningful differences in patients' lives will depend on increasingly sophisticated, but also efficient, clinical assessment instruments, such as those employed by the authors of the present reports. Second, advanced technology needs to be applied to measurement of the biology of these conditions, including imaging and biofluid, genetic and pathologic analyses. Predictive algorithmic and statistical models should be built to determine how these measures interrelate and can be combined to offer maximal utility. The work in these articles provides excellent examples, but it would be valuable to see how well the psycholinguistic and biologic classification models work on independent samples to determine whether they are generalizable. Finally, and related to this last point, additional efforts to develop collaborative and data-sharing infrastructure will be critical to the PPA field (e.g., for the sharing of speech samples, imaging data, or biologic samples). An exciting recent development in this regard was the recent launching of the IMPPACT Web site and registry for PPA (http://www.ppaconnection.org/).

Ultimately, research of the sort in this trio of articles will shed new light on the forms of language dysfunction that may occur in PPA and their biologic basis. Advances in this fundamental knowledge will undoubtedly translate into clinically useful tools, which are desperately needed for the planning of multicenter clinical research and trials and, ultimately, for more accurate diagnoses, prognoses, and treatments for our patients.

DISCLOSURE

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REFERENCES

1. Mesulam M, Weintraub S. Primary progressive aphasia and kindred disorders. Handb Clin Neurol 2008;89:573–587.
2. Grossman M. Primary progressive aphasia: clinicopathological correlations. Nat Rev Neurol 2010;6:88–97.
3. Hillis AE. Aphasia: progress in the last quarter of a century. Neurology 2007;69:200–213.
4. Hodges JR, Patterson K. Semantic dementia: a unique clinicopathological syndrome. Lancet Neurol 2007;6:1004–1014.
5. Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. Cognition and anatomy in three variants of primary progressive aphasia. Ann Neurol 2004;55:335–346.
6. Gunawardena D, Ash S, McMillan C, Avants B, Gee J, Grossman M. Why are patients with progressive nonfluent aphasia nonfluent? Neurology 2010;75:588–594.
7. Rohrer JD, Rossor MN, Warren JD. Syndromes of nonfluent primary progressive aphasia: a clinical and neurolinguistic analysis. Neurology 2010;75:603–610.
8. Mesulam M, Wieneke C, Rogalski E, Cobia D, Thompson C, Weintraub S. Quantitative template for subtyping primary progressive aphasia. Arch Neurol 2009;66:1545–1551.
9. Josephs KA, Duffy JR, Strand EA, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain 2006;129:1385–1398.
10. Mesulam M. Primary progressive aphasia pathology. Ann Neurol 2008;63:124–125.
11. Rohrer JD, Ridgway GR, Crutch SJ, et al. Progressive logopenic/phonological aphasia: erosion of the language network. Neuroimage 2010;49:984–993.
12. Rabinovici GD, Jagust WJ, Furst AJ, et al. A-beta amyloid and glucose metabolism in three variants of primary progressive aphasia. Ann Neurol 2008;64:388–401.
13. Hu WT, McMillan C, Libon D, et al. Multimodal predictors for Alzheimer disease in nonfluent primary progressive aphasia. Neurology 2010;75:595–602.