Primary Progressive Aphasia
Longitudinal Course, Neuropsychological Profile, and Language Features

Sandra Weintraub, PhD; Nan P. Rubin, MS; M.-Marcel Mesulam, MD

- Four patients with the clinical syndrome of primary progressive aphasia and a nonfluent aphasia profile were followed up over a period of 3 to 5 years. Extensive neuropsychological data for three patients revealed a progressive, quantitative decline of language with relative stability of memory, visuospatial skills, and reasoning. Comportment and most activities of daily living were preserved even when speech was unintelligible. Although several aphasia types may be associated with primary progressive aphasia, a nonfluent aphasia profile and phonemic paraphasic errors are most useful in differentiating it from the much more common clinical syndrome, "probable Alzheimer's disease." The clinicopathological correlates of probable Alzheimer's disease differ from those associated with primary progressive aphasia. Therefore, the clinical distinction between the two syndromes may be important for predicting the underlying pathophysiologic changes during the life of the patient. (Ann. Neurol. 1990;47:1329-1335)

The clinical syndrome of primary progressive aphasia (PPA) was originally described in six patients who experienced the insidious onset (usually in the presenium) and gradual worsening of aphasic symptoms over a period of 5 to 11 years. In these patients, memory, reasoning, insight, judgment, and comportment remained relatively preserved, and these patients remained independent in activities of daily living for many years. It was proposed that PPA (originally termed slowly progressive aphasia) represents a relatively selective left perisylvian degeneration and that its clinical profile is distinguishable from the more generalized, and usually amnestic, dementia of probable Alzheimer's disease (PRAD). Additional examples of this syndrome have since been reported.

Positron emission tomographic studies have shown a selective reduction of glucose metabolism in the left cerebral hemisphere (but not in the right) of two patients with PPA. One case studied with single photon emission tomography also demonstrated physiologic alterations confined to the left cerebral hemisphere. None of the eight clinically clearcut cases for which neuropathologic data are available have shown the characteristic multifocal plaque-tangle concentrations of Alzheimer's disease (AD). A ninth patient, albeit with a relatively more rapid course to a generalized dementia, did display these features. Although a clinical diagnosis of progressive amnestic dementia (PAM; probable AD) has a high likelihood of being associated with multifocal plaque-tangle concentrations at autopsy, a clinical diagnosis of PPA appears to be associated with this pathologic condition in only a minority of cases.

Several aspects of clinical research on PPA need further exploration. First, it has been argued that the observed language deficits do not occur in isolation but are, instead, accompanied by more widespread cognitive impairment. Second, longitudinal study is necessary to document the progressive nature of the language impairment and the relative stability of nonverbal cognitive abilities and activities of daily living. A third issue is whether or not at least some cases of PPA can be associated with a distinctive pattern of language deficits that differentiate it from the aphasia accompanying other degenerative diseases, including the typical forms of Alzheimer's disease (AD).

We previously presented a brief retrospective account of formal neuropsychological test findings in two of our original patients, indicating that reasoning, memory, and visuospatial functions were in the normal, even superior, range despite these patients' severe aphasia. In this article, we present a longitudinal, prospective follow-up study of four additional cases of PPA distinguished by a nonfluent aphasia profile.

PATIENTS AND METHODS

Patients

Four consecutive patients with a clinical diagnosis of PPA and a nonfluent aphasia profile were examined. In addition to the standard criteria for the diagnosis of a degenerative dementia, the following features were required to make the initial diagnosis of PPA: (1) at least a 2-year history of progressive decline of language; (2) prominent language deficits on testing with normal or relatively preserved performance on tests of other mental functions; and (3) independence in activities of daily living.

Longitudinal Assessment

The patients with PPA were given selected subtests of the Boston Diagnostic Aphasia Examination (BDAE), the Boston Naming Test, and the Token Test, part V. Other tests included selected subtests from the Wechsler Adult Intelligence Scale-Revised and the Wechsler Memory Scale; Raven's Progressive Matrices; Visual-Verbal Test (the 53 items requiring a shift in object selection); Judgment of Line Orientation Test; Facial Recognition Test; Hooper Visual Organization Test; Rey Auditory Verbal Learning Test (trial V), Three Words-Three Shapes Test, and the Shipley-Hartford Institute of Living Scale. Not all patients received the same set of tests in each session, either because of the severity of the aphasia or time constraints. However, for several tests comparable information on all patients existed.

Table 1 presents selected longitudinal test scores at annual examinations for cases 1 through 3. Patient 4 was only seen once due to travel limitations. The language examination was administered annually in each of the other categories of behavior, at least one test was administered over all of the years of study, with the exception of patient 2. The percentage of change (initial test score minus last test score divided by initial test score) was calculated for each test for each patient and represented in graph form (Figs 1 through 3). Because of the numerical properties of the data and the sample size, statistical analyses were not attempted.

Naming Errors: PPA vs PRAD

Even in the earliest examinations, we observed the frequent occurrence of phonemic paraphasic errors in the speech of our patients. This type of error is rarely reported in patients with language deficits associated with an amnestic dementia. To highlight this difference, we compared the naming errors made by patients 1 through 3 with those made by three patients with a clinical diagnosis of PRA...
based on accepted criteria who were matched for age and total score on the Boston Naming Test. Errors were coded according to the following categories: (1) semantic substitution (a word similar to the target in meaning, e.g., "airplane" for "helicopter"); (2) phonemic paraphasia (substitution, omission, or transposition of one or more sounds in the target word, e.g., "optopus" for "octopus"); (3) perceptual error (erroneous recognition of the target picture, e.g., "roof" for "pyramid"); (4) circumlocution (explanation of the function of the target object or descriptive information, e.g., "You brush your teeth with it" for "toothbrush"); and (5) other ("Don't know" or no response).

**REPORT OF CASES**

CASE I.—At the age of 47 years, a strongly right-handed industrial relations executive was aware of trouble pronouncing and finding words while giving public addresses. Over the next 5 years, his symptoms worsened and problems with oral reading and writing emerged. At the age of 52 years, he was referred to our clinic, 5 years after the onset of symptoms.

Computed tomographic scans and an electroencephalogram were unremarkable. Positron emission tomographic studies performed 2 years after his initial examination revealed reduced glucose metabolic activity in the left parietotemporal region but not in the right cerebral hemisphere (case 2 of reference 3).

Test scores from initial and follow-up examinations are depicted in Table 1, and change in scores over time is represented in Fig 1. In the initial examination, the patient was meticulously groomed and fully oriented. Elementary neurologic examination was remarkable only for a very mild right facial weakness, not detected in subsequent examinations. Spontaneous speech was well articulated but marked by occasional hesitation, minor syntactical errors, and phonemic and semantic paraphasias. The oral description of the Cookie Theft picture from the BDAE appears in Fig 4. Repetition and oral reading were only mildly impaired. Confrontation naming contained phonemic paraphasic errors. Auditory and reading comprehension, and writing were relatively intact, but the patient complained that he had difficulty composing letters. Buccofacial and limb apraxias were absent. Performance on tests of memory, reasoning, calculations, and visuospatial skills was within the normal range. Insight, judgment, comportment, and effectiveness in most activities of daily living were unaffected.

Over the next 5 years, language functions declined. In the most recent examination (ie, 9 years after onset), spontaneous speech was marked by frequent hesitation, paraphasias, less-sophisticated syntax, and more grammatical errors. The dramatic change is apparent in the patient's oral description of the Cookie Theft picture (Fig 4). Narrative writing reflected a similar pat-

### Table 1.—Longitudinal Neuropsychological Test Scores

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from onset, y</td>
<td>5</td>
<td>6</td>
<td>7</td>
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<tr>
<td>Language Test Scores*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory Comprehension (Token Test, part V) (23)</td>
<td>21</td>
<td>19</td>
<td>17</td>
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<tr>
<td>Repetition (BDAE) Words (10)</td>
<td>8</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Sentences (10)</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Oral Reading (BDAE) Words (10)</td>
<td>10</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Sentences (16)</td>
<td>8</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Boston Naming Test (80)</td>
<td>48</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>Word Fluency Animal Naming in 60 s—I (BDAE)</td>
<td>16</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Reading Comprehension (BDAE) Sentences (10)</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Praxis Buccofacial (7)</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Limb (6)</td>
<td>8</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Nonlanguage Test Scores†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Design Recall (9/8/13)</td>
<td>13</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test (Trial V) (13/15/15)</td>
<td>13</td>
<td>14</td>
<td>12</td>
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<tr>
<td>Three Words—Three Shapes Test (5/6)</td>
<td>6</td>
<td>6</td>
<td>NA</td>
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<tr>
<td>Visuospatial Tests Line Orientation (20-26/30)</td>
<td>28</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>Facial Recognition (41-54)</td>
<td>40</td>
<td>46</td>
<td>43</td>
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<td>Hooper Visual Organization Test (20-30)</td>
<td>26</td>
<td>29</td>
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<tr>
<td>Reasoning Tests Raven’s Progressive Matrices (25-34/60)</td>
<td>47</td>
<td>45</td>
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<tr>
<td>Shipley-Hartford Institute of Living Scale Conceptual Quotient (90-110)</td>
<td>86</td>
<td>97</td>
<td>98</td>
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<tr>
<td>Visual-Verbal Test (28-31/33)</td>
<td>NA</td>
<td>31</td>
<td>30</td>
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* Numbers in parentheses beside each test indicate maximum score. For language and nonlanguage test scores, NA indicates not administered. BDAE indicates Boston Diagnostic Aphasia Examination.
†Numbers in parentheses beside each test indicate range of normal performance for individuals 45 to 65 years of age. Number following slash is the maximum score. Normative data are not available for the shortened version of the Visual-Verbal Test reported here but the expected range is approximated from available norms.
tern of deterioration. Confrontation naming and repetition were more impaired as well, but auditory comprehension was im-
paired only for complex grammatical struc-
tures.

With few exceptions and no consistent pattern, scores on tests of reasoning, non-
verbal memory, and visuospatial skills did not assume the course of deterioration over-
time seen in language (Table 1 and Fig 1).

To circumvent his increasing speech limita-
tions in daily activities, he carried a set of
laminated index cards with written instruc-
tions for a number of commonly encoun-
tered situations, such as directing a cab
driver. He continued to make his own long-
distance travel arrangements for annual vis-
ts to the clinic. Social graces were pre-
served. He remained concerned and ap-
propriately saddened by his condition. Because of increased difficulty with communication, he was forced to retire, 9 years after the
onset of symptoms.

**Case 2.** At the age of 56 years, a right-
handed banking executive began to experi-
ence word-finding difficulty that gradually progressed over the next 2 years and inter-
fered with his work responsibilities. His
wife reported that he was occasionally tear-
ful over his condition but otherwise had no personality changes. Neurologic consulta-
tion was sought 2 years after onset.

The computed tomographic scan was nor-
mal, as was the electroencephalogram.

Test performance in initial and follow-up
examinations is represented in Table 1 and
Fig 2. The initial elementary neurologic ex-
amination showed normal findings. He was
well-dressed, alert, fully oriented, and in-
sightful about his situation. Auditory com-
prehension was intact. Spontaneous speech
was distinctly abnormal with nonfluent output, mild dysarthria, and frequent, pre-
dominantly phonemic, paraphasias. Gram-
matical form was impoverished and limited
to simple declaratives and stertotypic ut-
terances. The oral description of the Cookie
Theft picture appears in Fig 4. Repetition
and oral reading were impaired. Confronta-
tion naming contained frequent phonemic paraphasias. Reading comprehension was
only mildly compromised. Spontaneous
writing paralleled speech, but sentences to
diction were written relatively well.

Apraxia was not present. Performance on
tests of reasoning, memory, and visuospa-
tial skills (except Judgment of Line Ori-
entation) was within the normal range with
no evidence of the degree of abnormality
observed in language. He was on medical
leave of absence from work because of his
communication difficulties, but activities of
daily living were otherwise unaffected.

Examination a year later showed rela-
tively little objective change. Because of his
communication difficulties, however, the
patient had been forced to retire but con-
tinued to manage the finances of his family
and those of a close friend. Moreover, he
expanded his interest in gardening, suc-
cessfully cultivating species not indigenous
to his region.

In the last examination, speech was se-
verely nonfluent, agrammatic, dysarthric,
and paraphasic. At times it was unintelli-
gible, but the patient was often able to
communicate his needs with rudimentary
writing. His oral description of the Cookie
Theft picture appears in Fig 4. Writing both
spontaneous and to dictation declined in
parallel to spontaneous speech. Deteriora-
tion was also noted in repetition, praxis,
and confrontation naming. Comprehension
was impaired only for complex grammatici-
al constructions. Reading comprehension
was mildly impaired.

With the exception of Raven’s Progres-
sive Matrices, memory, reasoning, and
visuospatial test scores did not change over
time and, by the final examination, some
was intact. Spontaneous speech

![Fig 1. — Percent of change from the first to the last administration of language and nonlanguage tests for patient 1. Refer to Table 1 for raw scores. RAVLT indicates Rey Auditory Verbal Learning Test; 3W3S, Three Words—Three Shapes Test; Hooper VOT, Hooper Visual Organization Test; Raven’s Matrices, Raven’s Progressive Matrices; Shipley, Shipley-Harford Institute of Living Scale; and Visual/Verbal, Visual-Verbal Test.](https://example.com/fig1.png)
was dysprosodic with occasional paraphasic errors, phonemic more than semantic. Grammatical form was simplified with numerous morphosyntactic errors. Dysarthria was not present. The oral description of the Cookie Theft picture appears in Fig 4. Repetition and oral reading were moderately impaired at the sentence level. confrontation naming was relatively intact. Reading comprehension was good at the paragraph level. Praxis was normal with the exception of her inability to execute the command "cough," for which the patient repeatedly uttered "Cough, cough." Narrative writing paralleled spontaneous speech, but sentences written to dictation contained only minor errors. Reasoning, memory, and visuospatial test scores were in the superior range.

One year later, evidence was present for a significant decline of speech and language functions, and the patient was forced to resign her teaching post. However, she remained very active as a member of several institutional boards and as a volunteer worker. The patient was motivated to learn functional sign language and, although it was not entirely normal, it allowed her to effectively communicate with deaf friends. Performance in other areas of testing remained unchanged, as were the results from the neurolinguistic examination.

Two years later, marked deterioration in the patient's ability to communicate was noted. With the exception of reading comprehension, the other language test scores decreased by at least 70%. Spontaneous speech was palilalic and, except for the rare occurrence of a clearly articulated word, unintelligible. Her oral description of the Cookie Theft picture appears in Fig 4. She augmented speech with writing and was often able to communicate her ideas by writing words and short phrases. Narrative writing, however, was even more telegraphic than in the past. Deterioration was also noted in repetition, oral reading, bucocofacial praxis, and confrontation naming. Neuropsychological test scores for memory, reasoning, and visuospatial functions, with the exception of the Facial Recognition Test, remained above average to superior.

Insight, judgment, and comportment remained intact and the results from the elementary neurolinguistic examination remained unchanged. She continued to be actively involved with her church and with the hearing-impaired community. Her signing was functional but further simplified. She purchased a teletype system so that she could maintain telephone contact with her siblings.

Case 4.—At the age of 74 years, a right-handed retired judge began experiencing word-finding difficulty that gradually worsened over the next 5 years. Nonetheless, he continued to pursue his hobby of photography and remained an active member of the Rotary Club. No changes in personality or intellect were reported. His medical history was remarkable for surgery for varicosties, an atrioventricular block, and sinus bradycardia. He was referred for examination 5 years after the onset of symptoms.

The computed tomographic scan and electroencephalographic findings were consistent with his age.

The results from an elementary neurolinguistic examination were negative with the exception of a bilateral action tremor. He was fully oriented, well-groomed, and appropriately concerned about his situation. Spontaneous speech was characterized by frequent and prolonged hesitation, palilalia, and mild dysarthria. Grammatical form was preserved. Repetition and oral reading were mildly impaired, and simple confrontation naming was intact. Auditory and reading comprehension were mildly affected for complex material. Writing contained spelling errors. Praxis was normal.

On selected subtests of the Wechsler Adult Intelligence Scale—Revised25 (Information, Similarities, Block Designs, and Vocabulary), age-corrected scaled scores ranged from 10 to 14 (average to high average). The Memory Quotient on the Wechsler Memory Scale25 was 99 when calculated with reference to the oldest age group for that standardization sample (60 to 64 years).

Four years later, the patient and his wife were contacted by telephone. At that time, speech was severely limited, and he was able only to state his name, age, and the date. Comprehension was not tested in detail but was adequate for simple conversations. His wife's responses to a questionnaire about his activities of daily living were obtained. He remained entirely independent in all self-care activities (grooming, eating, and taking medications), continued to make repairs around the house, attended Rotary Club meetings, pursued his hobby of photography, and traveled to China with his wife.

In a telephone interview conducted 1 year later (10 years after onset and at the age of 84 years), his wife reported unrelenting deterioration in his husband's condition. He had been reduced to mutism. Despite this, he continued to be independent in activities of daily living, including helping with housework and attending Rotary Club meetings. However, his eating habits had become sloppy, and he was less concerned about tidiness around the home, but no other changes in personality were observed.

RESULTS OF NAMING ERROR ANALYSIS

The severity of the naming deficit was equivalent in the two groups as
judged by the ratio of erroneous attempts to the total number of targets missed and by the fact that no single item on the Boston Naming Test was associated with a higher error frequency than the others.

Table 2 compares the frequency of error types on the Boston Naming Test made by the two groups of patients ($\chi^2[4] = 51.07, P < .0001$). While both groups of patients had a similar proportion of semantic substitutions, they differed from one another with respect to the proportion of phonemic, perceptual, and circumlocutory errors. The patients with PRAD had more circumlocutory and perceptual errors, while those with PPA made more phonemic paraphasic errors, few circumlocutions, and no perceptual errors.

**COMMENT**

Quantitative, longitudinal examination of patients with a nonfluent subtype of PPA and a comparison of their naming performance with that of patients fulfilling established criteria for the diagnosis of PRAD have led to the following conclusions: (1) the language deficit in PPA is progressive, with a time course that can range from 5 to 10 years, leading to the almost total dissolution of language function; (2) memory, other cognitive functions, comportment, and activities of daily living (except for those that primarily depend on language functions) remain relatively preserved until late in the course of the disease; and (3) with respect to naming, the prominence of phonemic errors distinguishes patients with nonfluent forms of PPA from those with naming deficits in the context of the fluent aphasia associated with PRAD.

The involvement of morphosyntactic and phonologic features in these four patients with PPA stands in sharp contrast with the selective impairment of lexical and semantic aspects of language frequently observed in patients with a clinical diagnosis of PPA.

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Fig 3.—Percent of change from the first to the last administration of language and nonlanguage tests for patient 3. Refer to Table 1 for raw scores. RAVLT indicates Rey Auditory Verbal Learning Test; 3W3S, Three Words-Three Shapes Test; Hooper VOT, Hooper Visual Organization Test; Raven’s Matrices, Raven’s Progressive Matrices; Shipley, Shipley-Hartford Institute of Living Scale; and Visual/Verbal, Visual-Verbal Test.
PRAD.43,44 It is our impression that patients with PPA can have any type of aphasia, whereas patients with PRAD almost always have a fluent aphasia of the anomic, transcortical sensory, or Wernicke's type.45-46 Therefore, the one aphasic subtype that most clearly differentiates the two clinical syndromes is a nonfluent (Broca's or transcortical motor) type, since this is almost never reported in PRAD but is quite frequent in PPA.

In patients with fluent aphasias from focal lesions in the left hemisphere, nonverbal test performance can often be compromised, although these patients cannot be considered to have a dementia or bihemispheric disease.47-50 Consequently, in patients with PPA and fluent aphasia types that are attended by comprehension deficits the disease process may spuriously appear more widespread than it is. In fact, Poeck and Luzzatti,11 who questioned the selective involvement of language in PPA, described three patients, all of whom had fluent aphasias with impairment of comprehen-

sion and the lexical/semantic features of language. We specifically identified only patients with PPA with nonfluent aphasia and relative preservation of lexical/semantic processing, since this subgroup most clearly illustrates the selectivity of the disease process and its differentiation from the customary clinical presentation of PRAD.

Throughout the course of the disease, even very aphasic patients with PPA seem to have an ability to make themselves understood, by signing if they cannot talk, or by writing and by using appropriate circumlocutions. They can make use of compensatory devices such as communication cards and notebooks. Furthermore, they maintain motivation and acquire new skills and hobbies even as language functions keep deteriorating. This is similar to the observations of patients with aphasia from focal lesions51 but differs from patients with PRAD who, when aphasic, do not seem to be adept at communication and who almost always show a gradual decline of motivation.

The clinical diagnosis of PPA can be made with greater confidence if the initial course is indolent and if the interval between onset and severe language difficulty is in the order of 3 years or more. A more rapid course makes it more difficult to differentiate the clinical picture of PPA from that of PRAD presenting with aphasia. Some patients who are later diagnosed as having AD may present with aphasia, but this is accompanied by other cognitive difficulties within a year or two. If patients with PPA are followed up for very long periods of time into the terminal stages of their illness, it is quite likely that other cognitive and comportmental difficulties will be identified.5 This is not peculiar to PPA but is characteristic of all end-stage disease. The end stages of supranuclear ophthalmoplegia and Parkinson's disease may both show pronounced rigid immobility, even though the two diseases are completely different entities based on the initial course.

The imaging studies performed relatively early in the course of the illness did not provide definitive evidence for asymmetrical abnormalities in the left cerebral hemisphere in the cases reported in this article. However, in two of Mesulam's5 initial six cases, progressive changes in the left temporal and parietal areas were observed on repeated computed tomographic scans. Thus, imaging studies may not always demonstrate asymmetries that are diagnostically useful, especially in the early stages of the illness.

Primary progressive aphasia and the cluster designated as PRAD are clinical syndromes, not diseases. Figure 5 schematically represents the relationship between the clinical and pathologic planes. The clinical syndrome of PRAD includes amnesia at its core and a pervasive impairment of activities of daily living. It is frequently (up to 70% of the time) associated with the pathologic disease entity known as AD and is defined by multifocal concentrations of plaques and tangles.5 However, PRAD can also be
associated with other neuropathologic entities, including Pick’s disease, cortical Lewy bodies, and nonspecific changes.17,18,19

The clinical syndrome of PPA, in contrast with PRAD, is characterized by a relative preservation of memory and activities of daily living in the face of an indolent but relentlessly progressive aphasia. At the neuropathologic plane, PPA has been described in the context of Pick’s disease,4,6,9 a focal left perisylvian-frontal atrophy,10,11 and, less frequently, AD.11 Thus, PRAD and PPA are both clinical syndromes of progressive cognitive alterations. The characteristic clinical profile of each corresponds to a distinctly different set of probabilities for associated neuropathology.22 The diagnosis of PRAD indicates that the likelihood of an underlying pathophysiologic process based on plaques and tangles is very high, whereas the diagnosis of PPA indicates that this likelihood is very low. Especially at a time when independent biomarkers for the underlying disease process are not available, the identification of clinical syndromes is of considerable heuristic value for predicting the possible nature of the underlying pathophysiology, for designing treatment, for counseling patients and caregivers, and for prognosis.

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