Primary Progressive Aphasia

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Primary progressive aphasia (PPA) is a focal dementia characterized by an isolated and gradual dissolution of language function. The disease starts with word-finding disturbances (anomia) and frequently proceeds to impair the grammatical structure (syntax) and comprehension (semantics) of language. The speech output in PPA can be fluent or nonfluent. Memory, visual processing, and personality remain relatively well-preserved until the advanced stages and help to distiguish PPA from frontal lobe dementia and the typical forms of Alzheimer's disease. The term "semantic dementia" was originally introduced to designate a different group of patients with a combination of verbal and visual processing deficits. In practice, however, this diagnosis is also being used in a variant sense to denote a subtype of PPA with fluent speech and impaired comprehension, even in the absence of visual processing deficits. Insofar as the diagnosis of semantic dementia can have these two different meanings, it is important to specify whether it is being used in the original sense or to denote a subtype of PPA. Structural and physiological neuroimaging confirms the selective predilection of PPA for the left hemisphere, especially for its language-related cortices. A few patients with PPA display the neuropathological markers of Alzheimer's disease, but in an unusual distribution. The majority of the autopsies in PPA have shown either Pick's disease or lobar atrophy without distinctive histopathology. The suggestion has been made that PPA and frontal lobe dementia constitute phenotypical variations of a unitary disease process within the "Pick-lobar atrophy" spectrum. Recent advances in chromosome 17-linked dementias justify a rigorous search for tau polymorphisms and tauopathy in sporadic PPA. An informed approach to this syndrome will increase the effectiveness with which clinicians can address the unique challenges associated with the diagnosis and care of PPA.

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The primary progressive aphasia (PPA) syndrome has been attracting considerable interest in the context of new developments related to non-Alzheimer dementias. The defining feature of PPA is a gradual and isolated impairment of word usage and comprehension (Table). The diagnosis is made when other mental faculties such as memory, visuospatial skills, reasoning, and comportment remain relatively intact and when language is the only area of dysfunction, for at least the first 2 years of the disease.[1] Standardized neuropsychological tests of language function are helpful for reaching an early diagnosis.[2–4] However, a strict reliance on neuropsychological tests, most of which depend on verbal instructions, verbal responses, or covert verbal reasoning, may occasionally lead to the erroneous conclusion that nonlanguage domains are also impaired. Although the language disorder in PPA may interfere with the ability to memorize word lists or solve reasoning tasks, the patient typically has no difficulty recalling daily events or behaving with sound judgment, indicating that explicit memory, executive functions, and social skills remain intact. Numerous anecdotes confirm the behavioral focality of the deficit. One of our patients built a log cabin at a time when he could not express the simplest thought; another became an expert organic gardener at a time when she could not name the vegetables she was growing; still another continued to pilot his plane until he could no longer hail ground control.

In some patients, the principal signs and symptoms are confined to the area of language for as many as 10–14 years. Impairments in other domains can eventually emerge after the initial few years, but the language dysfunction remains the most salient feature and progresses most rapidly, throughout the course of the illness (Fig 1). Primary progressive aphasia is a form of dementia in that it causes a gradual cognitive decline to the point where daily-living functions become compromised. It is also an unusual dementia insofar as memory function remains largely preserved. Primary progressive aphasia should be differentiated from states of pure progressive dysarthria or phonological disintegration, in which the formation rather than the usage of words becomes disrupted.[5] It should also be differentiated from typical Alzheimer's disease (AD) and frontal lobe dementia, in which word-finding disturbances (anomia) or a paucity of speech output may arise but

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Table. Diagnostic Criteria for Primary Progressive Aphasia

1. Insidious onset and gradual progression of word finding, object-naming, or word-comprehension impairments as manifested during spontaneous conversation or as assessed through formal neuropsychological tests of language
2. All limitation of daily living activities attributable to the language impairment, for at least 2 years after onset
3. Intact premorbid language function (except for developmental dyslexia)
4. Absence of significant apathy, disinhibition, forgetfulness for recent events, visuospatial impairment, visual recognition deficits or sensory-motor dysfunction within the initial 2 years of the illness. (This criterion can be fulfilled by history, survey of daily living activities, or formal neuropsychological testing.)
5. Acalculia and ideomotor apraxia may be present even in the first 2 years (Mild constructional deficits and perseveration (as assessed in the go no–go task) are also acceptable as long as neither visuospatial deficits nor disinhibition influences daily living activities.)
6. Other domains possibly affected after the first 2 years but with language remaining the most impaired function throughout the course of the illness and deteriorating faster than other affected domains
7. Absence of "specific" causes such as stroke or tumor as ascertained by neuroimaging

on a background of more salient impairments of memory and behavior, respectively. In contrast to the case with AD, age of onset in PPA is characteristically in the presenium (age 55–65 years), there is a preponderance of male patients, and the e4 allele of apolipoprotein E is not a risk factor.[1,6]

The existence of progressive aphasias has been known for more than 100 years. Pick, Sérieux, Franceschi, and Rosenfeld were among the first to report such patients.[7–11] Many of these patients would fail to meet the current diagnostic criteria for PPA because of early and pronounced impairments of comportment and personality. Pick's 1892 patient, for example, threatened his wife with a knife soon after disease onset. The patients reported by Sérieux and Rosenfeld fulfill current diagnostic criteria. At the age of 47 years, Sérieux's patient experienced the insidious onset of word deafness, followed by a relentless and progressive impairment of language comprehension over the subsequent 8 years. The postmortem examination, conducted by Dejerine and Sérieux,[12] revealed massive bitemporal atrophy, with loss of pyramidal neurons and intracortical fibers, a description that this author was unable to improve upon during a microscopic reexamination of the sections more than 100 years later.

The resurgence of interest in progressive aphasias can be traced to a 1982 report of 6 patients and to the subsequent delineation of the PPA syndrome.[1,13,14] Since that time, dozens of publications have appeared on this subject, and it is reasonable to assume that there are thousands of patients suffering from this disorder.[1,15,16] Patients who would otherwise fulfill the criteria for PPA have also received diagnoses such as semantic dementia, progressive aphasia, dysphasic dementia, left temporal variant of frontotemporal dementia, and frontotemporal lobar atrophy with aphasia. An international PPA and Related Disorders Database (accessible through www.brain.northwestern.edu) has been launched in order to promote research and patient care in this field.

Symptom Complex of PPA

The left hemisphere is dominant for language function. Wernicke's area (located at the left temporoparietal junction) and Broca's area (located within the inferior and middle gyri of the left frontal lobe) constitute the two interconnected epicenters of a distributed language network.[17] Wernicke's area can be said to provide a critical gateway for linking the sensory patterns of words to the distributed associations that encode their meaning. Its dysfunction interferes with the comprehension of words and with the translation of thoughts into words. Broca's area helps to generate articulatory sequences so that thoughts can be transformed into statements containing the proper phonology and syntax. Its dysfunction interferes with articulation, word order, grammar, and lexical retrieval.

A diagnosis of aphasia is made when there is an impairment in the usage or comprehension of words, not just in their articulation. The study of patients with cerebrovascular lesions has led to the delineation of distinctive aphasia (or dysphasia) subtypes, each linked to a preferred lesion site within the language network.[18] Patients with PPA, however, rarely fit these "classical" clinicopathological patterns, probably because the causative lesions are multifocal, partial, and progressive. The aphasia in PPA can be fluent (that is, with normal articulation, rate of utterance, and phrase length) or nonfluent, and may or may not impair phonology, syntax, or verbal semantics (comprehension of word meaning).[2,13,19–22] There is thus no single type of language dysfunction that is pathognomonic for PPA. In comparison to AD, in which aphasia, when present, is almost always of the fluent type, many (but not all) patients with PPA display a nonfluent aphasia.[2,23] On occasion, patients with early PPA may also show mild ideomotor (usually buccofacial) apraxia, dyscalculia, disinhibition in go no–go tasks, and constructional deficits. These additional signs reflect a spread of dysfunction to prefrontal and parietal cortices immediately adjacent to the language network. The frequency of these additional but relatively mild neuropsychological deficits in PPA is currently unknown.

The principal function of the language network is to label, categorize, and communicate thoughts through the mediation of arbitrary symbols (words). Damage to any part of the language network can interfere with

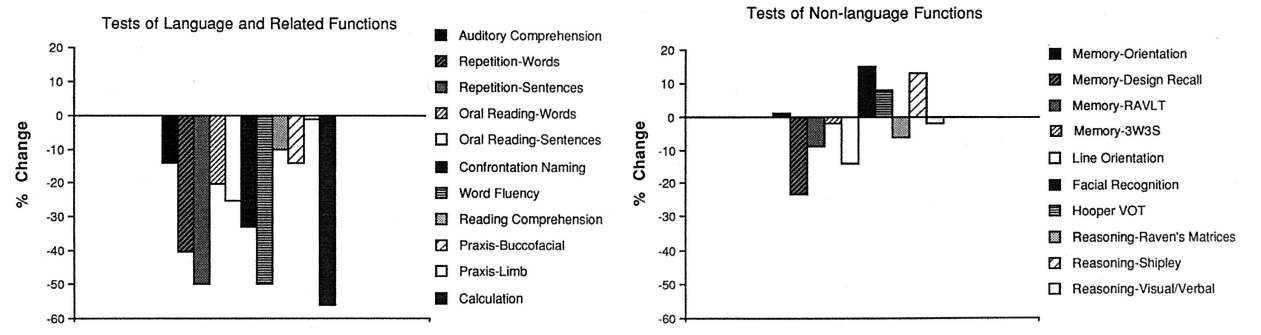


Fig 1. Performance in neuropsychological tests of language (left) and nonlanguage (right) functions expressed as a change score from 6 to 9 years after onset in a patient who developed primary progressive aphasia (PPA) at the age of 40 years. Language and related functions deteriorate within this 3 year interval, whereas nonlanguage functions remain stable. Reprinted from Weintraub et al.[2]

word usage and word finding. Such anomic deficits provide sensitive markers for dysfunction within the language network. Consequently, anomia emerges as a nearly universal finding in the early stages of PPA. Many patients remain in an anomic phase through most of the disease and experience a gradual intensification of word-finding deficits to the point of near-mutism. Others, however, proceed to develop distinct forms of agrammatism and/or word-comprehension deficits. At the terminal stages, the production and comprehension of language are both severely compromised. Depression and frustration are common, but suicide has not been reported.

The Anomic Stage

The naming of objects may become impaired, and speech may display a halting quality because of frequent word-finding pauses. These two aspects of anomia (impaired object naming and word finding) may be dissociated from each other. A patient with long word-finding pauses, for example, may have little difficulty naming common objects. Conversely, a patient with impaired object naming may produce fluent speech, although careful listening may show that the patient is automatically circumventing word-finding difficulties through the substitution of slightly less apt alternatives. Word-finding deficits lead to *simplification* (the use of a generic and loosely fitting word instead of a less common but more appropriate one), *circumlocution* (the circuitous articulation of a thought when the concise word cannot be retrieved), *substitution by fillers* (saying "the thing" or "whatchamacallit" instead of the missing word), and the production of *paraphasias* (substitution of incorrect words). Paraphasias can be phonemic (substitution of an incorrectly sounding word) or semantic (substitution of sounds within a word). Phonemic paraphasias are common in PPA but rare in AD.[2] Word-finding deficits may lead to "empty" speech, which appears to have preserved melody and fluency but conveys little information.

At the anomic stage of PPA, patients who cannot name objects that they are shown can point to the appropriate object when the name is provided by the examiner. The naming deficit is, therefore, "one-way," indicating an impairment at the level of lexical retrieval rather than word comprehension. The naming of geometric shapes and/or body parts tends to be particularly challenging. The anomia may be category-specific, some patients showing a greater impairment in naming inanimate objects, whereas others may have greater deficits naming living things. The patient will volunteer that he or she "knows" what to say but that the word cannot be found. Rarely, the patient does much better when asked to respond in writing. Grammar and syntax are largely preserved. Repetition of sentences may or may not be impaired. When repetition is impaired, the clinical picture fits the definition of conduction aphasia. Comprehension of language is excellent. Reading is preserved, but dysgraphia is frequent. In some patients, fluency becomes undermined by word-finding pauses, labored speech, and, rarely, dysarthria. In others, fluency and the melody of speech are preserved. Anomia in PPA can thus emerge against a background of either fluent or nonfluent speech.

PPA with Agrammatism

These patients have many of the word-finding deficits described above. Fluency is frequently impaired because of labored articulation and, less frequently, dysarthria. Speech is characterized by abnormally short (telegraphic) phrases, which tend to lack function words. Some patients display striking abnormalities of syntax (word order) and tend to misuse closed-class elements, tenses, plurals, possessives, and pronouns.[19] Despite these difficulties, the patients can successfully communicate their thoughts in a pithy style, occasionally embellished by gesture and pantomime.[24] Some patients may temporarily improve their communicative skills by signing. Ideomotor apraxia, dysgraphia, and impaired repetition of speech, especially for closed-class function words, are

common and lead to a clinical picture reminiscent of Broca's aphasia.[2,25] Comprehension is excellent, except in the case of grammatically complex sentences with possessive and embedded clause constructions. For example, a patient who understands the events described by the statement "a tiger ate a lion" may be unable to understand the flow of events when told that "a lion was eaten by a tiger." In some patients, reading is selectively impaired for grammatical words. Thus a patient who has no difficulty reading "alligator" or "table" may not be able to read "to" or "she." This stage of PPA eventually leads to extreme impairments of fluency, to the point where utterances become limited to one or two repetitive syllables or grunts. Singing (melodic intonation) may occasionally improve articulation but not the propositional content of the utterance.

PPA with Comprehension (Verbal Semantic) Deficits

Fluency is usually preserved, but frequent word-finding pauses can also emerge. Deficits of word comprehension arise at several levels of severity. At the initial stages, the patient may follow most conversation except for occasional "lexical–semantic lacunae." In the course of an otherwise uneventful conversation, for example, the patient may suddenly assume a perplexed expression and ask "School? What does 'school' mean?" Many of the naming deficits at this stage are "two-way" so that the patient can neither name an object nor point to it when the examiner provides the name. This represents a state in which the semantic "knowledge" related to the object cannot be accessed trough the verbal route. In contrast, the knowledge related to the same object can be accessed through the visuoperceptual route, because the patient can describe (through circumlocutions, paraphasias, and pantomime) the nature of the object shown by the examiner. In some patients, the two-way naming deficits can display striking category specificity for animate vs inanimate things.[26,27] In time, even the most common words fail to be decoded and the comprehension of conversation becomes impossible, although visual recognition of objects and faces remains relatively preserved. In addition to comprehension deficits, the patients are also unable to find the correct words to express their thoughts. Speech becomes increasingly more "empty," paraphasic, and circumlocutious, eventually leading to the appearance of neologisms. These are the most challenging patients to evaluate clinically, in that the incoherent speech and the inability to comprehend the examiner's questions may give the mistaken impression of global dementia. Reading and writing are frequently impaired but may initially remain relatively better preserved than spoken language. Repetition of language may be preserved (in which case the clinical picture resembles that of a transcortical sensory aphasia) or impaired (in which case the clinical picture is that of Wernicke's aphasia).

End-Stage PPA

Vocalization may be reduced to the point where only incoherent grunts are emitted. The patients cannot comprehend speech or gestures and may not even respond to their names. At this stage, it is impossible to assess the state of other mental functions. An occasional smile upon encountering a familiar face may be the only remaining indication of meaningful interactions with the environment. Abnormal, bizarre behaviors and purposeless restlessness may also emerge at this stage.

The PPA-Plus Syndromes and Relationship to Semantic Dementia

The language network abuts the prefrontal, motor, and visual recognition networks of the brain. PPA-causing diseases can spread into these adjacent networks, giving rise to various "PPA-plus" syndromes. Conversely, primary diseases targeting adjacent networks can spread into the language areas of the brain and lead to additional, but usually mild, impairments of word usage.

PPA, Semantic Dementia, and Visual Recognition Deficits

Nonverbal visual processing deficits are not part of the clinical presentation in PPA. Patients with PPA may not be able to name a visually presented object or recognize its name but can surmise its use and nature, at least until the terminal stages of the disease. The term "semantic dementia" was introduced to designate a unique syndrome in which a prominent fluent aphasia with impaired comprehension emerges in the presence of prominent deficits of visual recognition (or perception).[28–31] These patients display combined and profound deficits of verbal and visual semantics so that neither the name nor the sight of an object can evoke the relevant associations related to the nature of the object. In clinical practice, however, the term "semantic dementia" has also been used in a different sense, to denote patients with a fluent aphasia and verbal comprehension deficit, even in the absence of visual processing deficits. If the diagnosis of semantic dementia is to be used, terminological confusion could be avoided by specifying whether the term is being used in the strict sense (aphasia plus visual processing deficit) or in the variant sense (subtype of PPA).

In another set of patients, the visual recognition networks of the occipital, parietal, and temporal lobes can become the primary targets of neural degeneration, leading to progressive visual agnosias, including prosopagnosia.[32–35] The dysfunction in these patients may eventually spread into components of the language network and may lead to word-comprehension deficits. The clinical picture in these patients is dominated by

the visual recognition rather than aphasic deficits and has not received the designation of either PPA or semantic dementia.

Aphasia with Motor Disturbances and Dysarthria
A nonfamilial condition known as the "motor neuron disease (MND)–dementia complex" can present with prominent signs of frontal lobe dysfunction and dysarthria but is rarely associated with aphasia.[36] Occasionally, patients with otherwise typical amyotrophic lateral sclerosis may display anomia and other features of aphasia, sometimes as the presenting feature.[37–39] Corticobasal degeneration (CBD) frequently presents with lateralized cognitive and extrapyramidal dysfunction. When CBD predominantly affects the left hemisphere, the right-side motor deficits can be accompanied by prominent and progressive aphasic disturbances.[40] An isolated progressive dysarthria (or phonological disintegration) can emerge without any obvious sign of upper or lower motor neuron dysfunction. Some of these patients are misdiagnosed as having PPA despite the preservation of word usage, word comprehension, and writing. In others, the dysarthria eventually evolves into nonfluent PPA.

Aphasia and Frontal Dementia
The vast majority of patients with frontal lobe dementia (FLD) have no aphasia, and the vast majority of patients with PPA have no prominent disinhibition, apathy, or executive dysfunction, at least until late in the course of the disease.[3] The decreased language output (economy of expression) in FLD may occasionally lead to the erroneous diagnosis of PPA.[41] Some patients with typical FLD may also develop dysarthria, phonological disintegration, and relatively mild aphasic impairments, usually of the anomic type.[42] These patients do not qualify for the diagnosis of PPA, because aphasia is not the dominant feature of the clinical picture. Patients at moderately advanced stages of PPA can display distinct impairments of conduct and, occasionally, swallowing, indicating a spread of the dysfunction into adjacent prefrontal and motor areas of the brain.

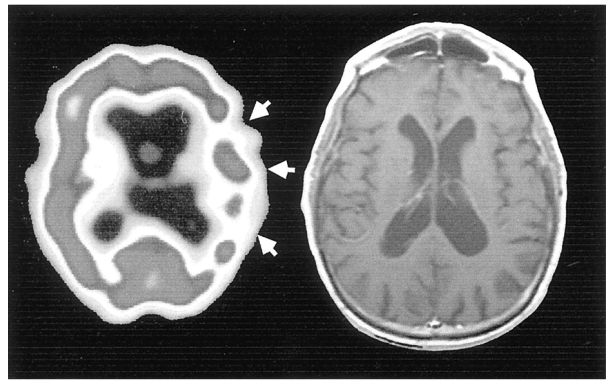
Autosomal Dominant Progressive Aphasias
Progressive aphasia can be seen in patients with autosomally dominant dementias linked to chromosome 17.[43–46] In some kindreds, this has been called "familial dysphasic dementia" or "hereditary dysphasic disinhibition dementia." However, the early emergence of prominent memory, behavior, and motor impairments differentiates this condition from typical PPA.

Aphasia and Creutzfeldt-Jacob Disease
Some patients with Creutzfeldt-Jacob disease (CJD) present with what appears to be typical PPA, but with an accelerated course, leading to additional cognitive and motor deficits within 12 months.[47] Survival can be as long as 4 years, and the characteristic electroencephalographic (EEG) complexes, myoclonus, and startle may be lacking despite definite molecular and neuropathological evidence of CJD.

The System-Level Dysfunction in PPA

Functional Neuroanatomy
The vast majority of patients with PPA display gyral atrophy, EEG slowing, hypoperfusion (measured by SPECT), and hypometabolism (measured by positron emission tomography) in the frontal, temporal, and parietal components of the left hemisphere language network.[1,48–50] The clinical focality of PPA is thus matched by the anatomical selectivity of the underlying pathological process for components of the language network in the left hemisphere. Abnormalities of blood flow and metabolism may emerge prior to the atrophy, and the neurodiagnostic abnormalities progress in tandem with the clinical deterioration (Figs 2, 3). Even those components of the language network that are not atrophic may display aberrant functional activation, probably on the basis of perturbed interregional connectivity.[51] Nonfluent patients with intact comprehension tend to have metabolic dysfunction within the anterior parts of the perisylvian language areas, whereas fluent patients with comprehension deficits tend to have dysfunction in the temporal parts of the language network.[52] On occasion, the atrophy may be most severe in the inferior and even medial parts of the left temporal lobe, especially in patients with language-comprehension deficits. Despite marked left hemisphere dysfunction, the metabolic state of the contralateral right hemisphere tends to remain within the

Fig 2. (Left) Technetium SPECT scan of a 73-year-old man 3 years after primary progressive aphasia (PPA) onset. Arrows *point to perfusion defects in the frontal and parietal lobes. (Right) T1-weighted magnetic resonance imaging of the same patient obtained at the same time as the SPECT. Almost no atrophy is seen in the areas of hypoperfusion, indicating that functional impairment emerges before tissue loss.*



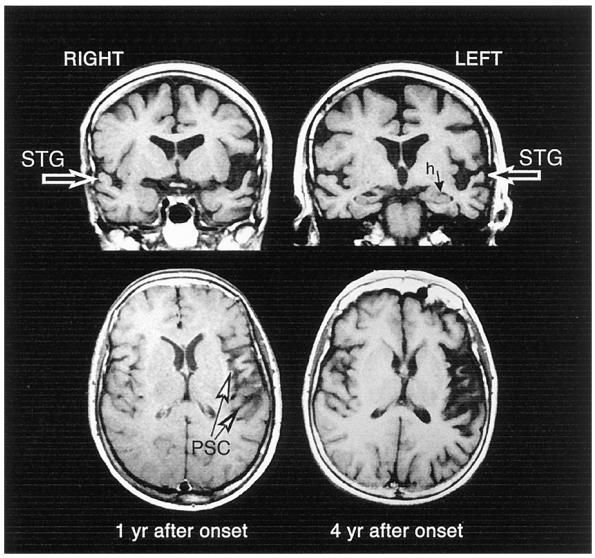


Fig 3. (Top) Coronal sections of T1-weighted magnetic resonance imaging (MRI) obtained 6 years after disease onset in a patient who developed primary progressive aphasia (PPA) at the age of 60 years. There is a high level of specificity in the distribution of atrophy. The left superior temporal gyrus (STG) is very atrophic and the left Sylvian cistern is enlarged, whereas the hippocampus (h) shows no atrophy. (Bottom) Horizontal sections of T1-weighted MRI obtained 1 and 4 years after onset in a patient who developed PPA at the age of 61 years. There is a clear progression of atrophy, predominantly within the left perisylvian cortex (PSC).

normal range.[48,49] When asked to identify homonyms or synonyms in the course of functional magnetic resonance imaging (MRI) experiments, PPA patients and age-matched controls activate the same components of the language network.[53] However, in contrast to neurologically intact subjects, the PPA patients display additional (compensatory or deviant) activations within regions of the brain that normally remain outside of the classic language network.[51,53] Although postmortem examinations tend to occur at the end stage of the disease, at a time when the behavioral focality may no longer be conspicuous, the reported neuropathological changes have tended to be more pronounced in frontal cortex, perisylvian area, and temporal cortex than in the hippocampus or entorhinal cortex and usually more severe in the left hemisphere.[54–56]

Neuropathology

Nearly 50 patients with the clinical syndrome of PPA have yielded neuropathological information.[1,54,55,57] Fewer than 20% have shown the pathology of AD, some with distinctly unusual distributions of neurofibrillary tangles, others with no evidence of the senile plaques characteristic of AD pathology.[56] Even this low number may overestimate the role of AD in PPA the neuropathological examination is done 10–20 years after disease onset, at an age when the plaques and tangles of AD are endemic. In fact, the neuropathological diagnosis of AD in a patient with the clinical picture of PPA and a distribution of neurofibrillary tangles and amyloid plaques typical of AD should be met with skepticism; such a diagnosis would have failed to establish a credible clinicopathological correlation. The distinction of PPA from AD is further supported by the observations that patients with PPA have different patterns of apolipoprotein E genotypes and that none of the genetically caused forms of AD leads to early or prominent language deficits.[6]

The single most common pathological process associated with PPA is a focal degeneration characterized by neuronal loss, gliosis, and mild spongioform change within superficial cortical layers. This pattern is also known as "nonspecific focal atrophy" or "dementia lacking distinctive histological features." It is encountered in approximately 60% of patients with PPA. The cerebral cortex in these cases may contain occasional ballooned neurons filled with phosphorylated neurofilament protein as well as tau-negative ubiquitinilated inclusions and neurites but no Pick bodies, Lewy bodies, or plaques and tangles with an AD-like density.[29,58,59] In rare patients, massive tau-positive neuronal and glial inclusions have been observed in the absence of typical Pick bodies, especially within regions of the brain that contain components of the language network.[60,61] Pick's disease, with typical tau-positive and argyrophilic Pick bodies, occurs in an additional 20% of patients with PPA.[1,62]

Search for the Nosology of PPA

Nonspecific lobar atrophies and Pick's disease share many common features. Each can cause a focal degeneration of the frontal and/or temporal lobes, and each can give rise to PPA or frontal lobe dementia (FLD). This has led to the renewed suggestion that PPA and FLD represent different manifestations of a unitary "Pick–lobar atrophy" complex, also designated "frontotemporal dementia" (FTD) or "frontotemporal lobar degeneration" (FTLD).[28,62,63] Further support for such a unification has come from recent findings that frontal lobe dementia, progressive aphasia, lobar atrophy without distinctive histopathology, and Pick-like inclusions can each result from mutations within chromosome 17, some of which have been traced to the tau gene.[43,44,63–65] In many of these conditions, immunolabeling with antibodies to individual tau epitopes has revealed neuronal and glial tauopathy. Even within a single kindred, some patients develop a prominent aphasia, whereas others display a frontal dementia, indicating that chromosome 17 mutations are prone to marked phenotypical divergence.[46] These discoveries have raised the exciting possibility that sporadic FTD

(with or without Pick bodies and presenting as PPA or FLD) may also turn out to have a unitary pathogenesis, perhaps related to a tauopathy or to the impairment of some other function encoded by chromosome 17.

However, the relevance of chromosome 17-linked tauopathies to sporadic PPA remains to be established. First, patients with chromosome 17-linked hereditary progressive aphasias display early impairments of memory, personality, and movement, and the clinical focality that makes PPA so unique is, therefore, absent in the genetic disease. Second, the majority of autopsied PPA brains have shown no tauopathy that can be identified by currently available antibodies. Third, the Pick-like inclusions in the hereditary tauopathies do not have all the immunological signatures and argyrophilic properties of classic Pick bodies.[46,66] Fourth, autosomal dominant focal dementias can be linked not only to chromosome 17 but also to chromosome 3.[67] Despite these caveats, however, the discoveries related to chromosome 17-linked dementias offer compelling reasons for continuing to chase disease-specific polymorphisms in the tau gene and for using novel antibodies to detect histopathological tauopathy in sporadic PPA.

The use of the term "frontotemporal dementia" as a common designation for FLD and PPA may lead to potential inconsistencies. The term may be too restrictive with respect to neuroanatomy, insofar as many patients with PPA have early dysfunction in the parietal component of the language network (see Fig 2). Furthermore, the presence of a common pathogenesis does not necessarily justify the use of the same term for clinically distinct syndromes. For example, using a common diagnostic term for AD and hemorrhagic amyloid angiopathy (Dutch type), or for familial CJD and fatal insomnia, is of dubious value; the syndromes in each pair have completely different clinical pictures despite being caused by mutations of the same gene. Separate diagnoses, such as FLD and PPA, may thus be preferable in that they offer greater concordance with the observed signs and symptoms of the patient.

PPA may well be the fifth most common form of degenerative dementia, following in prevalence AD, FLD, Parkinson-related dementia, and dementia with Lewy bodies. The epidemiology and risk factors of PPA are largely unknown. The possibility of pharmacotherapy has not been explored in any systematic fashion. The preservation of other cognitive domains and the possible occurrence of potentially compensatory right hemisphere activations during language tasks raise the suggestion that speech therapy may be useful, at least during the initial phases of the disease. The slow dissolution of language in PPA and the anatomical selectivity of the initial neural dysfunction offer unique opportunities for exploring the cognitive architecture of the language network and the biological determinants of its selective vulnerability to disease processes. Although recent advances in the hereditary non-AD dementias have not yet resolved the question of nosology in PPA, they have triggered renewed interest in exploring the clinical and biological aspects of this unique syndrome.

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