REVIEW ARTICLE

CURRENT CONCEPTS

Primary Progressive Aphasia — A Language-Based Dementia

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Dementia is a generic term used to designate chronically progressive brain disease that impairs intellect and behavior to the point where customary activities of daily living become compromised.[1,2] In some patients, specific abnormalities, such as a vitamin B_{12} deficiency, normal pressure hydrocephalus, multiple strokes, paraneoplastic encephalitis, or human immunodeficiency virus infection, are identified as the underlying cause. In others, characteristic sensory or motor abnormalities indicate that the dementia is a component of a more extensive neurologic disease such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, or multiple sclerosis. In the majority of patients with dementia, however, none of these diseases are diagnosed. These patients can be said to have a "primary" dementia that is characterized by four features: normal findings on elementary neurologic examination, signs and symptoms confined to abnormalities of behavior or cognition, brain scans that may reveal the anatomical distribution of disease but that do not show its specific nature, and identification of the exact cause of the dementia only on postmortem examination.

Alzheimer's disease is the single most common cause of primary dementia. Its cardinal feature is a progressive loss of memory of recent events and experiences. The high prevalence of Alzheimer's disease may lead to the belief that dementia is always due to Alzheimer's disease and that, as stated in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*,[3] memory loss is a feature of all dementias. A rapidly growing body of evidence, however, indicates that nearly a quarter of all primary dementias, especially those of presenile onset, may be caused by diseases other than Alzheimer's disease and that some of these so-called atypical dementias involve cognitive abnormalities in areas other than memory.[1,4-6] This review summarizes current knowledge about primary progressive aphasia, an atypical dementia characterized by a relentless dissolution of language with memory relatively preserved. Once thought to be a rare condition, primary progressive aphasia is now commonly included in the list of dementia syndromes, and hundreds of patients have been described.[7] Many of these reports, however, have appeared in highly specialized journals, so that the diagnosis of primary progressive aphasia is frequently overlooked in general clinical practice.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with Alzheimer's disease come to medical attention because of forgetfulness, usually accompanied by apathy. Misplacing personal objects, repeating questions, and forgetting recent events are among the presenting symptoms. Although the patient may forget people's names, word-finding during conversation is usually not a major problem. In contrast, patients with primary progressive aphasia come to medical attention because of the onset of word-finding difficulties, abnormal speech patterns, and prominent spelling errors. Primary progressive aphasia is diagnosed when other mental faculties, such

as memory of daily events, visual and spatial skills (assessed by tests of drawing and face recognition), and behavior (assessed by a history obtained from a third party), remain relatively intact; when language is the only area of prominent dysfunction for at least the first two years of the disease; and when structural brain imaging studies do not reveal a specific lesion, other than atrophy, that can account for the language deficit.[8]

Standardized neuropsychological tests are helpful in reaching an early diagnosis,[9-11] but because most of them depend on verbal instructions, verbal responses, or covert verbal reasoning, the strict reliance on these tests occasionally leads to the erroneous conclusion that areas other than language are also impaired. Scores on the Mini–Mental State Examination,[12] for example, may exaggerate the degree of disability. Although the language disorder in primary progressive aphasia may interfere with the patient's ability to memorize word lists or solve reasoning tasks, the patient typically has no difficulty in recalling daily events or behaving with sound judgment, indicating that explicit memory, reasoning, and social skills remain relatively intact (Table 1).

Table 1. Diagnostic Criteria for Primary Progressive Aphasia.*

There is an insidious onset and gradual but progressive impairment of word finding, object naming, syntax, or word comprehension manifested during conversation or assessed with the use of standard neuropsychological tests of language.
All major limitations in activities of daily living can be attributed to the language impairment for at least two years after onset.
Premorbid language function (except for developmental dyslexia) is known to be intact.
Prominent apathy, disinhibition, loss of memory of recent events, visuospatial impairment, visual-recognition deficits, and sensory-motor dysfunction are absent during the initial two years of illness, as indicated by the history, evaluation of activities of daily living, or neuropsychological testing, so that the patient would not fulfill diagnostic criteria for any other dementia syndrome.
Acalculia (inability to perform simple mathematical calculations) and ideomotor apraxia (inability to pantomime movement as instructed by an examiner) can be present even in the first two years of illness, and deficits in copying simple drawings and perseveration may also be noted, but neither visuospatial deficits nor behavioral disinhibition substantially limits activities of daily living.
Other cognitive functions may be affected after the first two years of illness, but language remains the most impaired function throughout the course of the illness and deteriorates faster than other affected functions.
Specific causes of aphasia, such as stroke or tumor, as ascertained by neuroimaging, are absent.

* These criteria are adapted from Mesulam,[7] with the permission of the publisher.

In some patients, the principal signs and symptoms are confined to the area of language for as many as 10 to 14 years. In others, impairments in other cognitive functions emerge after only a few years, but the deficit in language remains the salient feature throughout the illness and progresses more rapidly than deficits in other areas.[9] Primary progressive aphasia is considered a form of dementia because it causes a gradual cognitive decline to the point where activities of daily living become compromised, but it is an unusual dementia because core memory functions remain largely preserved. In contrast to many patients with Alzheimer's disease, who tend to lose interest in recreational and social activities, some patients with primary progressive aphasia maintain and even intensify their involvement in complex hobbies such as gardening, carpentry, sculpting, and painting. One patient continued to fly his airplane until aphasia prevented him from communicating with ground control.

Primary progressive aphasia should be differentiated from states of pure progressive dysarthria or phonologic disintegration (disruption of the formation of words rather than of their use).[13] It should also be differentiated from Alzheimer's disease and the frontal variant of frontotemporal degeneration (frontal-lobe dementia), which may be marked by disturbances in word finding (anomia) or diminished speech output, but which in Alzheimer's disease are accompanied by more obvious impairments of memory and in frontal dementia of behavior. In the literature, the designation "semantic dementia" is used for patients with a combination of impaired word comprehension and impaired recognition (agnosia) of faces and objects.[14,15] The presence of prominent visual agnosia during the initial two years is incompatible with a diagnosis of primary progressive aphasia. In common practice, however, patients with fluent aphasia and impaired word comprehension often receive a diagnosis of semantic dementia even in the absence of visual agnosia. According to the diagnostic criteria listed in Table 1, such patients (in whom the temporal variant of frontotemporal degeneration is occasionally diagnosed) may be described as having a type of primary progressive aphasia.

LANGUAGE IN PRIMARY PROGRESSIVE APHASIA

Language allows the communication and elaboration of thoughts and experiences by means of cul-

turally defined, arbitrary symbols known as words. The neurologic basis of language is controlled by a network of neocortical areas centered in the perisylvian regions of the left hemisphere of the brain. The term "aphasia" denotes a disorder in language processing due to damage to this network. Aphasia takes different forms depending on the distribution of lesions in the areas of the brain where the language network resides.[16] For this reason, in primary progressive aphasia the clinical picture may vary from patient to patient, depending on the distribution of the disease process. Some patients cannot find the right words to express their thoughts. Others cannot understand the meaning of words either heard or seen. Still others cannot name objects in their environment. The language impairment can be categorized as fluent (normal articulation, word flow, and number of words per utterance) or as nonfluent.[9,17-21] In patients with Alzheimer's disease, if aphasia develops, it is almost always fluent, whereas in patients with primary progressive aphasia, it can be nonfluent.[9,22] In some patients with primary progressive aphasia, the ability to write language may be less impaired than the ability to speak it.

The single most common sign of primary progressive aphasia is anomia, the inability to retrieve the right word in conversation or to name objects as requested by an examiner. The early stages of anomia can be revealed by asking the patient to name geometric shapes, parts of the body, or components of common objects (the cap of a pen or the wristband of a watch). Many patients remain in an anomic stage through most of the course of the disease, with a gradual intensification of word-finding deficits almost to the point of mutism. In some patients, however, distinct forms of agrammatism or deficits in word comprehension develop.

Agrammatism denotes inappropriate word order and the misuse of word endings, prepositions, pronouns, conjunctions, and verb tenses. One patient, for example, sent the following e-mail message to her daughter: "I will come my house in your car and drive my car into chicago. . . . You will back get your car and my car park in my driveway. Love, Mom." Comprehension deficits start with an occasional inability to understand single words and gradually progress to incomprehension of conversational speech. Depression and frustration are common in patients with such deficits, but suicide has not been reported. In the advanced stages of primary progressive aphasia, when all aspects of language are severely compromised, prominent memory impairments, behavioral changes marked by loss of inhibitions, and motor deficits may also emerge.

PATHOPHYSIOLOGY

The language network is almost always located in the left hemisphere of the brain and includes the perisylvian portions of the inferior frontal and temporoparietal regions, known as Broca's and Wernicke's areas, respectively, as well as surrounding regions of the frontal, parietal, and temporal cortex. In many patients with primary progressive aphasia, these regions display atrophy (indicative of neuronal loss), electroencephalographic slowing, decreased blood flow (measured by single-photon-emission computed tomography), and decreased glucose use (measured by positron-emission tomography).[8,23-26] The clinical signs and symptoms of primary progressive aphasia thus match the anatomical selectivity of the underlying pathologic process (Fig. 1, 2, and 3). In patients with nonfluent aphasia and intact language comprehension, there tend to be metabolic dysfunction and atrophy in perisylvian regions, including the left inferior frontal cortex, whereas in patients with fluent aphasia and comprehension deficits, metabolic dysfunction and atrophy tend to affect the middle, inferior, and polar regions of the temporal lobe.[14,27] Despite marked metabolic dysfunction in the left hemisphere, the metabolic state of the right hemisphere may remain in the normal range, especially early in the course of the disease.[23,24]

Functional imaging studies allow the identification of areas of the brain that become engaged in the performance of specific cognitive tasks. In a study of language processing, components of the language network were activated to the same extent in patients with primary progressive aphasia as in age-matched controls. The only marked abnormality in these patients was greater neuronal activation during the performance of language tasks but outside the areas traditionally considered part of the language network.[28] The magnitude of this compensatory or deviant activation was correlated with the degree of impairment assessed with the use of a standardized naming test.

NEUROPATHOLOGY

Observations of nearly 50 patients with the clinical syndrome of primary progressive aphasia have yielded neuropathological information.[8,29-31] Although

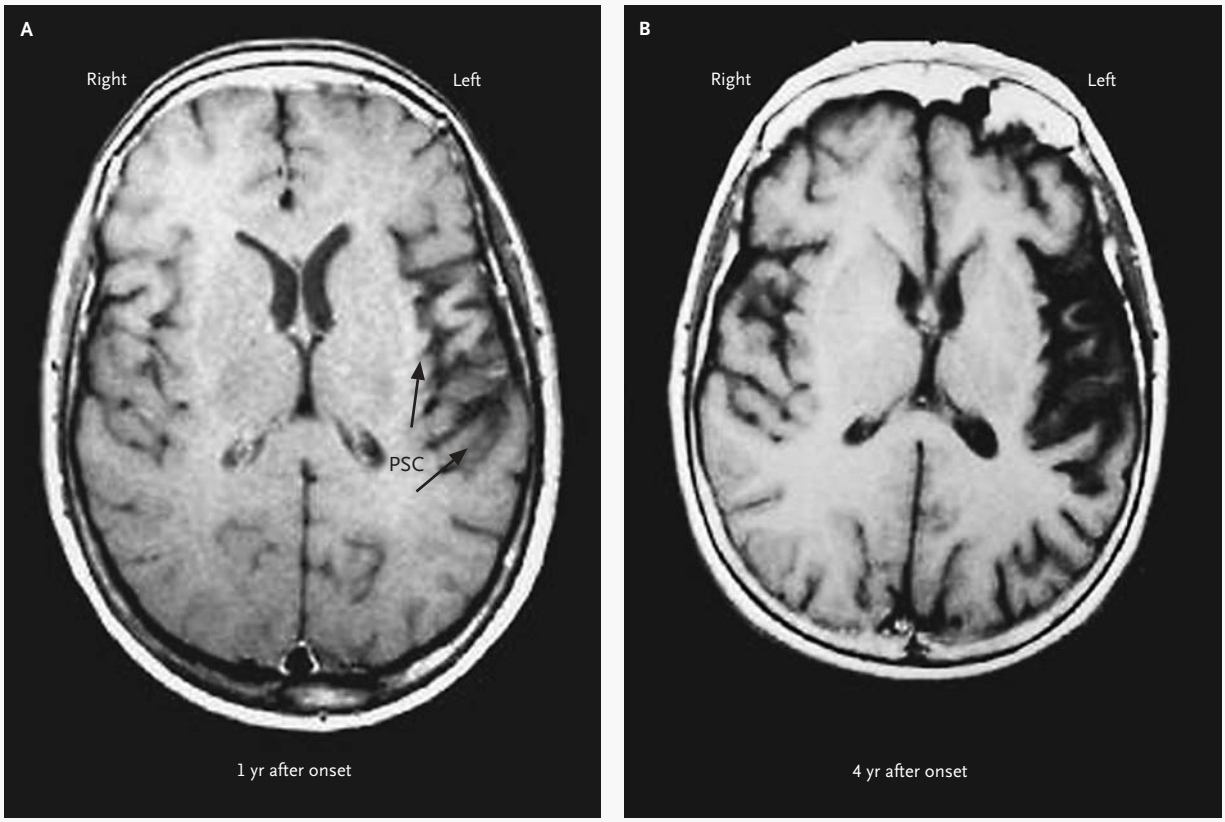

Figure 1. Magnetic Resonance Imaging Scans from a Patient with Primary Progressive Aphasia in Whom Symptoms First Developed at the Age of 61 Years.

The scan in Panel A was obtained one year after the onset of symptoms and the scan in Panel B was obtained four years after the onset. The progression of atrophy in the left perisylvian cortex (PSC) indicates that the disease remained focal as it progressed. Reproduced from Mesulam[7] with the permission of the publisher.

postmortem examinations are usually performed in patients who have reached the final stage of the disease, when the behavioral specificity may no longer be conspicuous, the reported neuropathological changes have tended to be more pronounced in the frontal lobe, perisylvian regions, and temporal cortex of the left hemisphere than in the hippocampal or entorhinal areas, which are the areas most damaged in Alzheimer's disease.[30-32] At autopsy, approximately 60 percent of patients have a focal degeneration characterized by neuronal loss, gliosis, and mild spongiform changes in the superficial cortical layers. This pattern is known as nonspecific focal (or lobar) atrophy or "dementia lacking distinctive histology." The cerebral cortex may contain occasional ballooned neurons filled with phosphorylated neurofilament protein, as well as neuronal and glial inclusions containing ubiquitin or the cytoskeletal protein tau.[33-38] Pick's disease, characterized by tau-positive spherical neuronal inclusions, occurs in an additional 20 percent of patients with primary progressive aphasia.[8,36] Cholinergic innervation of the cerebral cortex, which is severely depleted in patients with Alzheimer's disease, is generally spared in this group of patients.[39]

Postmortem examination of approximately 20 percent of patients with primary progressive aphasia has shown the pathological features of Alzheimer's disease, sometimes with unusual distributions of the two major markers of the disease, senile plaques and neurofibrillary tangles.[32] Even this small proportion may be an overestimate of the role of Alzheimer-type pathological changes in primary progressive aphasia, since the postmortem examination usually occurs 10 to 20 years after the onset of the disease, by which time the plaques and tangles that

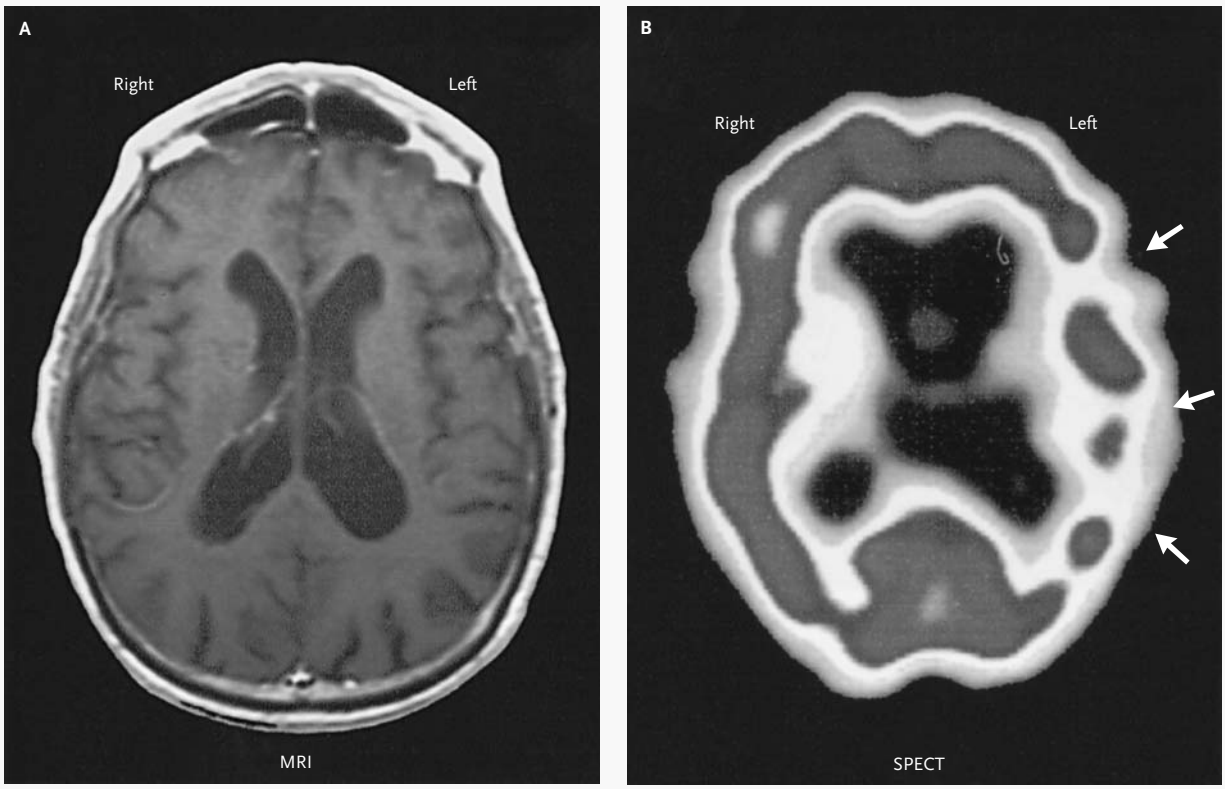

Figure 2. A Magnetic Resonance Imaging Scan (Panel A) and a Technetium Single-Photon-Emission Computed Tomographic Scan (Panel B) in a 73-Year-Old Man in the Early Stage of Primary Progressive Aphasia.

The MRI scan shows no atrophy, but the SPECT scan, obtained at the same time, shows decreased blood flow in the left perisylvian regions (arrows). Reproduced from Mesulam[7] with the permission of the publisher.

mark Alzheimer's disease are endemic.[1,40] For this reason, the true neuropathological basis of the progressive aphasia in these patients may remain undetected even post mortem, because it may lack distinctive features other than atrophy and spongiosis. Differentiation of primary progressive aphasia from Alzheimer's disease is further supported by the fact that the ϵ4 allele of apolipoprotein E, which is a risk factor for Alzheimer's disease, is not associated with primary progressive aphasia.[41]

NOSOLOGY

Primary progressive aphasia may represent a clinical syndrome that is linked to multiple diseases that share neuroanatomical features. Alternatively, primary progressive aphasia may reflect a unitary disease process that leads to a highly targeted focal degeneration of the brain. This alternative is supported by investigations of frontotemporal lobar atrophies linked to chromosome 17, which carries the gene for the tau protein. The resultant dementias, some of which are associated with point mutations in the *tau* gene, can lead to lobar atrophy (that is, dementia without distinctive histopathological characteristics) in the temporal or frontal lobes, or both, and may be associated with tau-positive inclusions, some of which have characteristics of Pick bodies.[42-46] Affected persons have dementias characterized by a mixture of language, behavioral, and motor abnormalities. In some cases, however, these diseases lead to relatively isolated frontal dementias or aphasic syndromes.[44,47] Primary progressive aphasia and frontal-lobe dementia may thus represent anatomically distinct manifestations of a unitary spectrum of degenerative brain diseases, also

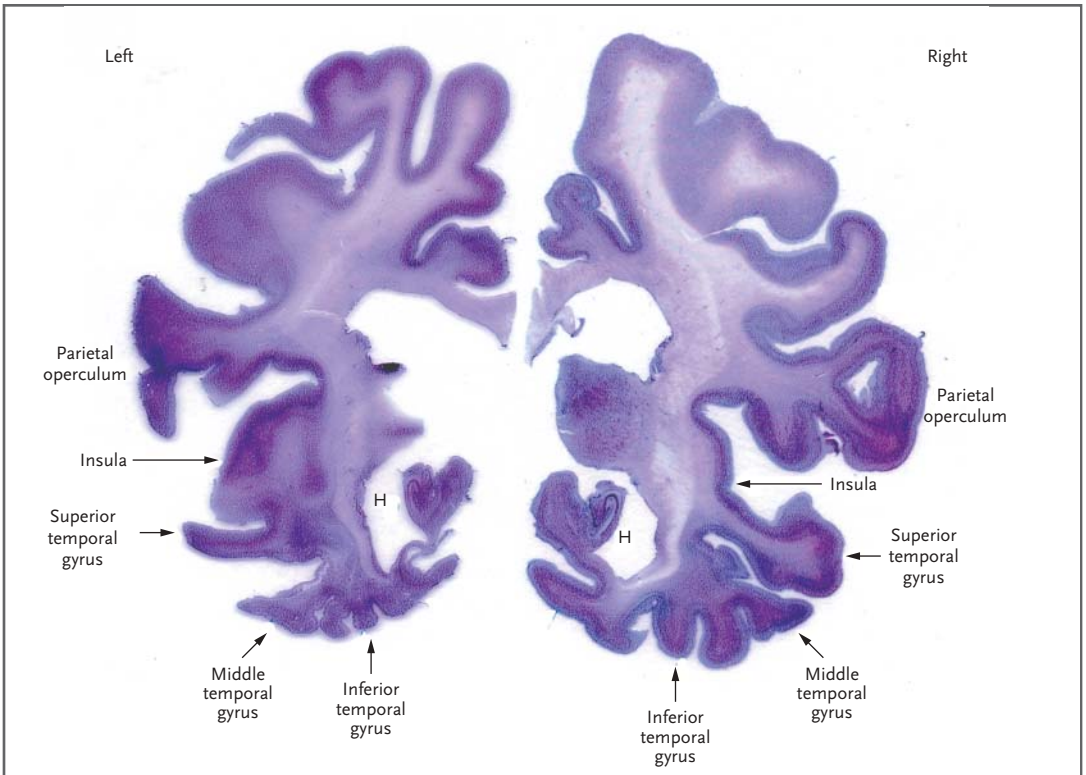

Figure 3. Postmortem Specimen from a Woman with Primary Progressive Aphasia in Whom the Disease Developed at the Age of 44 Years.

The patient died 16 years after onset in a state of mutism and severe dementia. Postmortem neuropathological examination showed findings typical of Pick's disease. Even in the terminal stage of the disease, there is greater atrophy (thinning of the cortical band) in the parietal operculum, the insula, and the superior, middle, and inferior temporal gyri of the left hemisphere, and the disease has spread to the hippocampus (H).

known as frontotemporal degeneration, marked by variable combinations of lobar atrophy, neuronal loss, spongiosis, gliosis, ubiquitin-positive inclusions, and tauopathy, this last occasionally taking the form of Pick bodies.[2,36,42] This contention has gained support from the finding that a specific haplotype (H1) of the *tau* gene appears to be overrepresented in patients with the sporadic form of primary progressive aphasia.[48]

In a recent report, 3 of 4 siblings had a typical form of primary progressive aphasia, although none of the 12 members of the parental generation were affected.[49] Neuropathological examination of one of the three affected siblings detected the pattern of dementia lacking distinctive histology but with ubiquitin-positive cortical neurons. The sequencing of the *tau* gene in one of the affected siblings did not show any of the mutations known to be associated with autosomal dominant forms of frontotemporal degeneration. The large number of siblings affected in this family strengthens the contention that primary progressive aphasia represents a coherent disease entity, but it also raises the possibility that the disease may be based on a recessive form of inheritance unrelated to known *tau* mutations or caused by exposure to common environmental factors that remain to be identified.

Why does a lobar degeneration affect the prefrontal cortex in one patient and the language network in another? One hypothesis is that a personal or family history of dyslexia or of a developmental anomaly such as left hemicranial hypoplasia may be a risk factor for the development of primary progressive aphasia, at least in some patients.[50] This hypothesis suggests that primary progressive aphasia may develop in a person with a genetic or developmental vulnerability in areas of the brain related to language.[8] Such tardive manifestations of remote

vulnerabilities are not unknown in neurology. For example, one study showed that patients who had recovered from childhood hemiplegia reported the progressive emergence of hemiparkinsonism later in life on the side of the original weakness.[51] In another study, presymptomatic persons who were carrying a highly penetrant mutation for frontal-lobe dementia had neuropsychological evidence of frontal-lobe dysfunction decades before the predicted onset of dementia.[52]

CONCLUSIONS

Primary progressive aphasia should be considered in the differential diagnosis of dementia. The manifestations of this disease are distinctly different from those of typical Alzheimer's disease. Different aspects of the activities of daily living are impaired and different sorts of intervention are required. Some patients can learn sign language, and some find it useful to carry laminated cards that provide information to assist themselves and others in specific situations. Others benefit from voice synthesizers or personal computers that digitally store words and phrases. Evaluation by a speech therapist is useful for exploring alternative communication strategies. Unlike patients with Alzheimer's disease, who cannot retain new information in memory, patients with primary progressive aphasia can recall and evaluate recent events even though they may not be able to express their knowledge verbally. Explaining this phenomenon to the family of the patient and offering an objective assessment of how the aphasia interferes with verbal expression and language comprehension can help the family cope with the patient's impairments.

The epidemiology of primary progressive aphasia and risk factors for the disorder are largely unknown. There is currently no effective pharmacologic treatment for this condition. From the vantage point of research, primary progressive aphasia provides a rare opportunity for investigating the molecular mechanisms of focal neurodegeneration and the neuropsychological organization of language function.

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REFERENCES

1. Mesulam M-M. Aging, Alzheimer's disease, and dementia: clinical and neurobiological perspectives. In: Mesulam M-M, ed. Principles of behavioral and cognitive neurology. 2nd ed. New York: Oxford University Press, 2000:439-522.
2. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546-54.
3. Diagnostic and statistical manual of mental disorders, 4th ed.: DSM-IV. Washington, D.C.: American Psychiatric Association, 1994.
4. Grossman M. A multidisciplinary approach to Pick's disease and frontotemporal dementia. Neurology 2001;56:Suppl 4:S1-S2.
5. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113-24.
6. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. Neurology 2002;58:1615-21.
7. Mesulam M-M. Primary progressive aphasia. Ann Neurol 2001;49:425-32.
8. Mesulam M-M, Weintraub S. Spectrum of primary progressive aphasia. In: Rossor MN, ed. Ballière's clinical neurology: unusual dementias. London: Ballière Tindall, 1992: 583-609.
9. Weintraub S, Rubin NP, Mesulam MM. Primary progressive aphasia: longitudinal course, neuropsychological profile, and language features. Arch Neurol 1990;47: 1329-35.
10. Weintraub S, Mesulam M-M. Four neuropsychological profiles in dementia. In: Spinnler H, Boller F, eds. Handbook of neuropsychology. Vol. 8. Amsterdam: Elsevier, 1993:253-82.
11. Weintraub S, Mesulam M-M. From neuronal networks to dementia: four clinical profiles. In: Fôret F, Christen Y, Boller F, eds. La demence: pourquoi? Paris: Foundation Nationale de Gerontologie, 1996:75-97.
12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
13. Broussolle E, Bakchine S, Tommasi M, et al. Slowly progressive anarthria with late anterior opercular syndrome: a variant form of frontal cortical atrophy syndromes. J Neurol Sci 1996;144:44-58.
14. Mummery CJ, Patterson K, Wise RJS, Vandenbergh R, Price CJ, Hodges JR. Disrupted temporal lobe connections in semantic dementia. Brain 1999;122:61-73.
15. Snowden JS. Semantic dysfunction in frontotemporal lobar degeneration. Dement Geriatr Cogn Disord 1999;10:Suppl 1:33-6.
16. Damasio AR. Aphasia. N Engl J Med 1992;326:531-9.
17. Mesulam MM. Primary progressive aphasia — differentiation from Alzheimer's disease. Ann Neurol 1987;22:533-4.
18. Thompson CK, Ballard KJ, Tait ME, Weintraub S, Mesulam M. Patterns of language decline in nonfluent primary progressive aphasia. Aphasiology 1997;11:297-322.
19. Snowden JS, Neary D, Mann DMA, Goulding PJ, Testa HJ. Progressive language disorder due to lobar atrophy. Ann Neurol 1992;31:174-83.
20. Mehler MF. Mixed transcortical aphasia in nonfamilial dysphasic dementia. Cortex 1988;24:545-54.
21. Otsuki M, Soma Y, Sato M, Homma A, Tsuji S. Slowly progressive pure word deafness. Eur Neurol 1998;39:135-40.
22. Price BH, Gurvit H, Weintraub S, Geula C, Leimkuhler E, Mesulam M. Neuropsychological patterns and language deficits in 20 consecutive cases of autopsy-confirmed Alzheimer's disease. Arch Neurol 1993;50: 931-7.
23. Chawluk JB, Mesulam MM, Hurtig H, et al. Slowly progressive aphasia without generalized dementia: studies with positron emission tomography. Ann Neurol 1986; 19:68-74.
24. Tyrrell PJ, Warrington EK, Frackowiak RS, Rossor MN. Heterogeneity in progressive aphasia due to focal cortical atrophy: a clinical and PET study. Brain 1990;113: 1321-36.

25. Kempler D, Metter EJ, Riege WH, Jackson CA, Benson DF, Hanson WR. Slowly progressive aphasia: three cases with language, memory, CT and PET data. J Neurol Neurosurg Psychiatry 1990;53:987-93.
26. Catani M, Piccirilli M, Cherubini A, et al. Axonal injury within language network in primary progressive aphasia. Ann Neurol 2003;53:242-7.
27. Abe K, Ukita H, Yanagihara T. Imaging in primary progressive aphasia. Neuroradiology 1997;39:556-9.
28. Sonty SP, Mesulam M-M, Thompson CK, et al. Primary progressive aphasia: PPA and the language network. Ann Neurol 2003;53:35-49.
29. Chin SS-M, Goldman JE, Devanand DR, Weintraub S, Mesulam M. Thalamic degeneration presenting as primary progressive aphasia. Brain Pathol 1994;4:515. abstract.
30. Harasty JA, Halliday GM, Code C, Brooks WS. Quantification of cortical atrophy in a case of progressive fluent aphasia. Brain 1996;119:181-90.
31. Turner RS, Kenyon LC, Trojanowski JQ, Gonatas N, Grossman M. Clinical, neuroimaging, and pathologic features of progressive nonfluent aphasia. Ann Neurol 1996;39:166-73.
32. Galton CJ, Patterson K, Xuereb JH, Hodges JR. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. Brain 2000;123:484-98.
33. Rossor MN, Revesz T, Lantos PL, Warrington EK. Semantic dementia with ubiquitin-positive tau-negative inclusion bodies. Brain 2000;123:267-76.
34. Kinoshita A, Tomimoto H, Tachibana N, et al. A case of primary progressive aphasia with abnormally ubiquinated neurites in the cerebral cortex. Acta Neuropathol (Berl) 1996;92:520-4.
35. Lippa CF, Cohen R, Smith TW, Drachman DA. Primary progressive aphasia with focal neuronal achromasia. Neurology 1991;41:882-6.
36. Kertesz A, Hudson L, Mackenzie IRA, Munoz DG. The pathology and nosology of primary progressive aphasia. Neurology 1994;44:2065-72.
37. Ikeda K, Akiyama H, Iritani S, et al. Corticobasal degeneration with primary progressive aphasia and accentuated cortical lesion in superior temporal gyrus: case report and review. Acta Neuropathol (Berl) 1996;92:534-9.
38. Molina JA, Probst A, Villanueva C, et al. Primary progressive aphasia with glial cytoplasmic inclusions. Eur Neurol 1998;40:71-7.
39. Mehler MF, Horoupian DS, Davies P, Dickson DW. Reduced somatostatin-like immunoreactivity in cerebral cortex in nonfamilial dysphasic dementia. Neurology 1987;37:1448-53.
40. Braak H, Braak E. Evolution of the neuropathology of Alzheimer's disease. Acta Neurol Scand Suppl 1996;165:3-12.
41. Mesulam M-M, Johnson N, Grujic Z, Weintraub S. Apolipoprotein E genotypes in primary progressive aphasia. Neurology 1997;49:51-5.
42. Miller BL, Boone K, Geschwind D, Wilhelmsen BL. Pick's disease and frontotemporal dementias: emerging clinical and molecular concepts. Neurologist 1999;5:205-12.
43. Bird TD. Genotypes, phenotypes, and frontotemporal dementia: take your pick. Neurology 1998;50:1526-7.
44. Lendon CL, Lynch T, Norton J, et al. Hereditary dysphasic disinhibition dementia: a frontotemporal dementia linked to 17q21-22. Neurology 1998;50:1546-55.
45. Basun H, Almkvist O, Axelman K, et al. Clinical characteristics of a chromosome 17-linked rapidly progressive familial frontotemporal dementia. Arch Neurol 1997;54:539-44.
46. Wilhelmsen KC. Frontotemporal dementia is on the MAPtau. Ann Neurol 1997;41:139-40.
47. Zhukareva V, Vogelsberg-Ragaglia V, Van Deerlin VMD, et al. Loss of brain tau defines novel sporadic and familial tauopathies with frontotemporal dementia. Ann Neurol 2001;49:165-75.
48. Sobrido M-J, Abu-Khalil A, Weintraub S, et al. Possible association of the tau H1/H1 genotype with primary progressive aphasia. Neurology 2003;60:862-4.
49. Krefft TA, Graff–Radford NR, Dickson DW, Baker M, Castellani RJ. Familial primary progressive aphasia. Alzheimer Dis Assoc Disord 2003;17:106-12.
50. Alberca R, Montes E, Russell E, et al. Left hemicranial hypoplasia in two patients with primary progressive aphasia. Arch Neurol (in press).
51. Klawans HL. Hemiparkinsonism as a late complication of hemiatrophy: a new syndrome. Neurology 1981;31:625-8.
52. Geschwind DH, Robidoux J, Alarcón M, et al. Dementia and neurodevelopmental predisposition: cognitive dysfunction in presymptomatic subjects precedes dementia by decades in frontotemporal dementia. Ann Neurol 2001;50:741-6.