

Primary Progressive Aphasia— Differentiation from Alzheimer's Disease

In 1982, I described six patients who experienced a gradually worsening aphasia without the additional manifestations of dementia [10]. Language abilities deteriorated relentlessly whereas most other cognitive and behavioral functions appeared relatively spared. Upon quantitative neuropsychological examination, many of these patients obtained normal and sometimes superior scores in tests of reasoning, visuospatial skills, and memory [11]. Interpersonal conduct, social skills, judgment, and insight remained intact, and some of the patients acquired strategies for circumventing the language deficit. Appropriate comportment, concern for the predicament, and the preservation of memory for daily events constituted important deviations from the customary clinical picture of Alzheimer's disease. In terminal stages, but not before eight to twelve years after onset, other cognitive and behavioral impairments emerged in some of the patients. Cerebrovascular disease could not be implicated. The suggestion was advanced that this clinical picture represented a distinct syndrome based on a focal degenerative process involving the left perisylvian region. Additional patients with these characteristics have since been reported from our clinic and other centers in the United States, Switzerland, and the United Kingdom [1, 2, 5-8, 12].

The syndrome of primary progressive aphasia needs to be differentiated from the aphasic type of Alzheimer's disease. Aphasia is not uncommon in Alzheimer's disease and occasionally emerges as the presenting symptom [3, 8]. However, this is soon accompanied by major disturbances of memory and other cognitive functions. Independence in daily living activities, judgment, insight, and overall comportment deteriorate in Alzheimer's disease, whereas these aspects remain relatively intact until the terminal stages of the disease in patients with primary progressive aphasia. Despite eight years of gradually worsening aphasia, for example, one of our patients travels to Boston by commercial airline for his yearly examination. During his last visit, the language problem was so severe that he had to carry a card with written instructions for the taxi driver; he nevertheless successfully negotiated all the complex details of long-distance travel. Another one of our patients had to retire from his position as vice-president of a mortgage company but continued to offer sound financial advice and took up intensive gardening. A professor with this syndrome quit classroom teaching but maintains her active

membership on several prominent boards of trustees.

The language disorder in these patients rarely fits neatly into the existing typology of aphasia. The specific deficits may vary from patient to patient but anomie properties are the most common. Agrammatical and nonfluent features (of the type seen in Broca's aphasia) are becoming recognized with increasing frequency in patients with primary progressive aphasia, whereas this kind of language deficit is rarely, if ever, prominent in the aphasias associated with Alzheimer's disease. Patients with primary progressive aphasia manage to convey information effectively (if not by speech, then by written messages, gestures, and even sign language) in contrast to patients with Alzheimer's disease, who are relatively inept at making themselves understood when aphasic.

The impression of left perisylvian degeneration in primary progressive aphasia is supported by serial computed tomographic scans showing a gradual widening of the left Sylvian fissure and by positron emission tomographic evidence of focal cortical hypometabolism in left perisylvian regions [2, 10]. Accentuated left hemisphere hypometabolism has also been reported in patients with the aphasic type of Alzheimer's disease [4]. However, these patients show additional subnormal metabolism in the right hemisphere, whereas patients with primary progressive aphasia usually do not [2].

The report by Kirshner and colleagues in this issue of *Annals* [7] provides a much needed and careful clinicopathological correlation in two patients with the syndrome of primary progressive aphasia. The results show an absence of changes associated with Alzheimer's, Pick's or Jakob-Creutzfeldt's disease. Instead, these two patients had a focal spongiform degeneration of the left perisylvian region. In a paper given at the 1986 meeting of the American Neurological Association, Mehler and colleagues [9] described two patients with clinical features that appear similar to those of primary progressive aphasia (though perhaps with a more rapid course). The microscopic examination of the brain, reported for one of these patients, did not detect the dense plaque and tangle formations characteristic of Alzheimer's disease. Instead, non-specific degenerative alterations were noted. Another patient with some components of this syndrome was presented during the weekly clinicopathological conferences of the Massachusetts General Hospital [1a]. Examination of the cerebral cortex revealed a predom-

inantly bifrontal but relatively nonspecific atrophy (without Pick bodies or multifocal plaque-tangle formations) that was most pronounced in the left hemisphere. In one of the patients included in my 1982 report, a biopsy specimen obtained from the left superior temporal region also failed to show any of the diagnostic features seen in Alzheimer's or Pick's disease [10]. Two additional patients with a clinical picture reminiscent of primary progressive aphasia, one reported by Wechsler and colleagues [12] and another by Holland and colleagues [6], had neuropathological changes consistent with Pick's disease but not with Alzheimer's disease. In one of these two patients, neurofibrillary tangles were encountered but not neuritic plaques [6].

Primary progressive aphasia is characterized by a clinical profile that sets it apart from Alzheimer's disease. All seven patients with this clinical picture and for whom pathological information is available show findings that rule out the diagnosis of Alzheimer's disease. It is impossible to be certain that no patient with this condition will ever turn out to have microscopic features consistent with Alzheimer's disease (perhaps with a focal left perisylvian emphasis of pathology). However, the information that is currently available indicates that the syndrome of primary progressive aphasia has a high likelihood of being associated with a degenerative process *not* of the Alzheimer type. It remains to be seen whether the pattern described by Kirshner and colleagues [7] will constitute its most common pathological substrate.

In view of the present tendency for overdiagnosing Alzheimer's disease when faced with gradually progressive deficits of higher cortical function, the identification of patients with primary progressive aphasia should improve the accuracy of clinicopathological correlation. Although no specific therapy is available, the patient as well as the family can be reassured that the clinical course of primary progressive aphasia is somewhat more benign and that the widespread mental deterioration associated with Al-

zheimer's disease is a more remote prospect. The neurobiological mechanisms underlying the anatomical selectivity of this disease process remain to be elucidated.

M-Marsel Mesulam, MD
Behavioral Neurology
Beth Israel Hospital
330 Brookline Avenue
Boston, MA 02215

References

1. Assal G, Favre C, Regli F: Aphasia as a first sign of dementia. In *Senile Dementia: Outlook for the Future*. New York: Alan R Liss, 1984, pp 279-282
- 1a. Case Records of the Massachusetts General Hospital (Case 16-1986). *N Engl J Med* 314:1101-1111, 1986
2. Chawluck JB, Mesulam MM, Hurtig H, et al: Slowly progressive aphasia without generalized dementia: studies with positron emission tomography. *Ann Neurol* 19:68-74, 1986
3. Cummings JL, Benson DF, Hill MA, Read S: Aphasia in dementia of the Alzheimer type. *Neurology* 35:394-397, 1985
4. Foster NL, Chase TN, Fedio P, et al: Alzheimer's disease: focal cortical changes shown by positron emission tomography. *Neurology* 33:961-965, 1983
5. Heath PD, Kennedy P, Kapur N: Slowly progressive aphasia without generalized dementia. *Ann Neurol* 13:687-688, 1983
6. Holland AL, McBurney DH, Moossy J, Reinmuth OM: The dissolution of language in Pick's disease with neurofibrillary tangles: a case study. *Brain Lang* 24:36-58, 1985
7. Kirshner HS, Tanridag O, Thurman L, Whetsell WO: Progressive aphasia without dementia: two cases with focal spongiform degeneration. *Ann Neurol* 22:527-532, 1987
8. Kirshner HS, Webb WG, Kelly MP, Wells CE: Language disturbance—an initial symptom of cortical degenerations and dementia. *Arch Neurol* 41:491-496, 1984
9. Mehler MF, Dickson D, Davies P, Horoupian DS: Primary dysphasic dementia: clinical, pathological and biochemical studies. *Ann Neurol* 20:126, 1986
10. Mesulam M-M: Slowly progressive aphasia without generalized dementia. *Ann Neurol* 11:592-598, 1982
11. Mesulam M-M, Weintraub S: Diffuse involvement in progressive aphasia (reply). *Ann Neurol* 13:225, 1983
12. Wechsler AF, Verity MA, Rosenschein S, et al: Pick's disease: a clinical, computed tomographic and histologic study with Golgi impregnation observations. *Arch Neurol* 39:287-290, 1982