Slowly Progressive Aphasia Without Generalized Dementia

M.-Marsel Mesulam, MD

Six right-handed patients experienced a slowly progressing aphasic disorder without the additional intellectual and behavioral disturbances of dementia. The symptoms almost universally started in the presenium. The initial difficulty was an anomic aphasia in five of the patients and pure word deafness in the sixth. Continuous and gradual deterioration occurred in the five patients who presented with an anomic aphasia. They eventually experienced additional impairment of reading, writing, and comprehension. In four patients, other areas of comportment were not involved within the 5 to 11 years of follow-up. A more generalized state of dementia may have emerged in the other two patients, but only after 7 years of progressive and debilitating aphasia. Neurodiagnostic procedures were consistent with preferential involvement of the left perisylvian region. In one patient, cortical biopsy did not show any pathognomonic change; specifically, no neurofibrillary tangles, amyloid plaques, neuronal inclusions, or gliosis were seen. This condition may constitute a syndrome of relatively focal cerebral degeneration with a predilection for the left perisylvian region.

Case Reports

Patient 1

At the age of 69 years, a right-handed woman started to experience progressive difficulty in writing and in finding names for objects. Initial examination showed a severe anomic aphasia characterized by low speech output and dysgraphia without any difficulty in comprehension or repetition of speech. Calculations and buccofacial praxis were also moderately impaired. However, orientation, memory, and visuospatial tasks were virtually intact. She performed at the ninety-fifth percentile on Raven's Standard Progressive Matrices, a test which requires visuospatial skills and analogical reasoning. Insight, judgment, comportment, concern for hygiene, and effectiveness in performing customary daily activities were preserved. She continued to live independently, hold a part-time job, manage finances, and drive a car despite the severe aphasia, which interfered with effective communication. She was frustrated by her predicament and often wept in exasperation.

Yearly reexaminations for 5 years showed gradual worsening of the aphasia, with additional difficulties in repetition despite preserved comprehension (Table). She could not even write "cat" to dictation or find names of common objects. Reading became impaired, particularly for small grammatical words. With the exception of calculations, other areas of cognition and comportment continued to remain relatively intact.

The neurological findings were confined to mild right facial paresis and mild hyperreflexia on the right. The electroencephalogram (EEG) was normal in the first year but showed theta slowing in the left temporopolar region during subsequent years. Computerized tomographic (CT) scans were unremarkable in the first 3 years, but asymmetrical expansion of the left lateral ventricle and left sylvian fissure was noted during the fourth year of her condition.

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Patient 2
At the age of 57 years, a right-handed man reported that he had difficulty finding the correct words but no difficulty with comprehension of speech or with writing. Very gradual progression occurred over subsequent years. On examination 8 years after onset, he had an aphasia of moderate severity with long word-finding pauses, severe naming difficulty, and a mild comprehension difficulty for written and spoken language, especially for names of body parts and geometric shapes. Other cognitive functions were normal, if not superior. Verbal IQ was 112 and performance IQ 125. Judgment and insight were preserved, and he continued to perform all his professional, household, and civic activities.

Reexamination 9, 10, and 11 years after onset showed further deterioration in speech and comprehension (see the Table). He could no longer read or write at all. He therefore had to retire. However, other behavioral and intellectual functions remained intact, and he became well known in his neighborhood for his ability to fix electrical devices. He was deeply frustrated by his condition, but his judgment and insight remained intact. Elementary neurological function was normal. A CT scan showed asymmetrical enlargement of the sylvian fissure and temporal horn on the left.

Patient 3
When she was 48 years of age, a right-handed woman noted difficulties with speech, spelling, and reading. Slow but definite worsening occurred during the next 4 years. Examination 4 years after onset showed that running speech was labored, diminished in quantity, and dysarthric. The pattern was otherwise consistent with an anomic aphasia. She could name 25 of 84 objects by confrontation and could write only her name. Profound limb and buccofacial apraxia was also present. Other cognitive areas, judgment, and insight were preserved. She was depressed and wept frequently. However, she continued to drive a car, take care of her household, and maintain her customary wit.

Reexamination 5, 6, 7, and 8 years after onset showed gradual worsening. The aphasia first assumed characteristics of Broca's aphasia, but she was eventually reduced to mutism. As long as they were testable, other functions remained relatively preserved. In fact, even as the aphasia progressed, she acquired some ability to communicate by sign language messages which she could not utter or write. She eventually developed a condition of generalized akinnesia and became bedridden.

The only consistent elementary finding was a mild right facial paresis. EEG during the fifth year showed intermittent left-sided frontotemporal sharp and slow waves. A CT scan during the third year showed asymmetrical enlargement of the left frontal horn and sylvian fissure as well as an area of probable low density in the left posterior temporal area (Fig 1). A biopsy from the left superior temporal gyrus showed normal meninges. Cortical myeloarchitecture and cytoarchitecture were preserved, without gliosis. Mild neuron loss could not be excluded. No neuronalophagia, vascular cufing, neurofibrillary tangles, plaques, granulovacular changes, Hirano bodies, or argentophilic inclusions were seen. Under fluorescence microscopy, many of the larger pyramidal neurons contained autofluorescent (425 nm) granules that appeared to be lipofuscin [2] (Fig 2). It was not clear if the quantity of this pigment was above that which would be considered normal for 52 years of age.

Patient 4
At the age of 17 a right-handed girl started to have difficulty comprehending speech from a distance even though recognition of other sounds and comprehension for written language remained intact. This state of pure word deafness progressed over the next 4 years and then apparently stabilized. She was examined 7 years after onset and was found to have preserved auditory acuity. She could comprehend sounds such as crumbling of paper and jingling of keys but was severely impaired in the comprehension of spoken speech if the speaker's lips were concealed. She did well with lip reading and reading comprehension. Other cognitive areas, as well as insight and judgment, were intact.

Reexamination 8, 9, and 10 years after onset did not reveal any change in the state of word deafness. Other functions remained intact and she became more proficient in reading lips, acquired a driver's license, and gave birth to a child whom she mothers well.

A pure-tone audiogram 7 years after onset was reported to be normal, but repeat audiograms during the ninth and tenth years raised the possibility of bilateral partial sensorineural hearing loss. Evoked auditory potentials showed normal brainstem components but depressed cortical components, especially on the left. Somatosensory evoked potentials were normal. EEG and CT scans were unremarkable.

Patient 5
At the age of 54, a right-handed man started to experience gradually progressive speech difficulties. Examination 5 years after onset showed an anomic aphasia with paraphasias and moderate impairment of speech repetition, especially for small grammatical words. Comprehension of spoken and written language was intact and he could write grammatically. With the exception of a mild constructional difficulty, other areas of cognition and behavior appeared intact and he continued to hold his job. Follow-up examination was not possible, but his local physician was contacted by telephone 9 years after onset. Apparently, the aphasia had continued to progress. In addition, the patient had become withdrawn, lost his customary interest in music, and had quit working. It is not clear whether these changes reflect the emergence of a more widespread dementia or a reactive depression. EEGs 3 and 5 years after onset showed left temporal slowing. CT scans obtained at the same time showed asymmetrical widening of the sylvian fissure on the left.

Patient 6
At 61 years of age, a right-handed man noticed progressive difficulties in finding the right words. With the exception of calculations, other areas of cognition and behavior were relatively intact. Four years after onset, at a time when he

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Clinical Details on Six Patients with Progressive Aphasia

<table>
<thead>
<tr>
<th>Patient No. and Sex</th>
<th>Age at Onset (yr)</th>
<th>Years of Follow-up</th>
<th>Initial Condition</th>
<th>Language at Advanced Stage of Aphasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Running Speech</td>
</tr>
<tr>
<td>1, F</td>
<td>69</td>
<td>5</td>
<td>Anomic aphasia</td>
<td>Logopenia, long word-finding pauses, circumlocution, rare paraphasias</td>
</tr>
<tr>
<td>2, M</td>
<td>57</td>
<td>11</td>
<td>Anomic aphasia</td>
<td>Logopenia, long word-finding pauses, circumlocutions, rare paraphasias</td>
</tr>
<tr>
<td>3, F</td>
<td>48</td>
<td>8</td>
<td>Anomic aphasia</td>
<td>Logopenia, long word-finding pauses, no paraphasias, dysarthria</td>
</tr>
<tr>
<td>4, F</td>
<td>17</td>
<td>10</td>
<td>Pure word deafness</td>
<td>Normal</td>
</tr>
<tr>
<td>5, M</td>
<td>54</td>
<td>9</td>
<td>Anomic aphasia</td>
<td>Normal quantity, circumlocutions, some paraphasias</td>
</tr>
<tr>
<td>6, M</td>
<td>61</td>
<td>8</td>
<td>Anomic aphasia</td>
<td>Logopenia, long word-finding pauses, circumlocutions, rare paraphasias</td>
</tr>
</tbody>
</table>

Reexamination 6 years after onset documented progression of the aphasia and emergence of difficulties in repetition and comprehension (see the Table). In addition to speech, calculations were also impaired. Other areas of cognition as well as judgment, insight, and social graces were preserved if not superior. According to his wife, the patient started to experience difficulties with activities of daily living about 7 years after the onset of the aphasia and died during the eighth year of his condition. No autopsy was performed.

An EEG 4 years after onset was essentially normal. Repeat EEG 6 years after onset showed marked asymmetry with irregular theta slowing on the left, especially in the parietal and midtemporal areas. Four CT scans between the fourth and sixth years documented a gradually enlarging area of low absorption in the posterior temporal area on the left side.

Discussion

These six right-handed patients experienced the insidious onset and gradual progression of an aphasic disorder (see the Table). With the exception of Patient 1, symptoms started in the presenium. In Patients 2, 3, and 6, the initial difficulties were mild and for several years eluded detection by observers so that the complaints were first attributed to stress and could not even name a cup or a pipe, his performance IQ was reported as 112 in contrast to a verbal IQ of 90. Speech output was severely depressed from the onset, but the condition otherwise had the characteristics of an anomic aphasia.

Fig 1. CT section from Patient 3 shows a larger frontal horn and sylvian fissure on the left. There is also an area of low attenuation in the posterior temporal region on that side. (Left side of brain is on left side of photograph.)
language at advanced stage of aphasia

<table>
<thead>
<tr>
<th>Confrontation Naming</th>
<th>Speech Grammar</th>
<th>Reading Comprehension</th>
<th>Writing</th>
<th>Affect</th>
<th>Findings on Neurodiagnostic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severely impaired</td>
<td>Normal</td>
<td>Impaired, especially for grammatical words</td>
<td>Severely impaired</td>
<td>Depressed</td>
<td>EEG—theta in left temporopolar region; CT—enlarged left lateral ventricle and sylvian fissure</td>
</tr>
<tr>
<td>Severely impaired</td>
<td>Normal</td>
<td>Severely impaired</td>
<td>Severely impaired</td>
<td>Depressed</td>
<td>CT—sylvian fissure and temporal horn enlarged on the left</td>
</tr>
<tr>
<td>Severely impaired</td>
<td>Probably impaired</td>
<td>Severely impaired, especially for grammatical words</td>
<td>Severely impaired</td>
<td>Depressed</td>
<td>EEG—left frontotemporal sharp and slow waves; CT—enlarged frontal horn and sylvian fissure on the left</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Auditory evoked potentials—compromised function in left auditory area</td>
</tr>
<tr>
<td>Moderately impaired</td>
<td>Normal</td>
<td>Normal</td>
<td>Mildly impaired</td>
<td>Normal</td>
<td>EEG—left temporal slowing; CT—enlarged perisylvian fissure on the left</td>
</tr>
<tr>
<td>Severely impaired</td>
<td>Normal</td>
<td>Moderately impaired</td>
<td>Severely impaired</td>
<td>Depressed</td>
<td>EEG—theta in left parietal and midtemporal area; CT—enlarged perisylvian fissure on the left</td>
</tr>
</tbody>
</table>

anxiety. In Patient 4, the youngest in the series, the condition apparently progressed for only 4 years and then stabilized, even though her pure-tone audiograms suggested further deterioration of auditory function. In the other five, the progression was relentless for 5 to 11 years and resulted in severe and incapacitating aphasic conditions. In Patients 1, 2, and 4, who have been followed for up to 11 years, a severe aphasia remains as the only abnormality with virtually no additional disturbances of intellect or comportment. Patient 3 also had a virtually isolated aphasic-apraxic disorder for 6 years but then developed an akinetic state. Patients 5 and 6 experienced an isolated progressive aphasia for at least 7 years but then developed additional difficulties which may well represent progression to a generalized state of dementia. Patients 1 and 6 also had deficits in manipulating numbers, and this was the most common additional cognitive loss. The few neurological signs that could be elicited were confined to mild paresis (especially facial) and slightly enhanced deep tendon reflexes on the right side in Patients 1 and 3.

In Patient 4 the language difficulty emerged in the form of pure word deafness. In the other five cases, the presentation was characterized by an anomic aphasia consisting of word-finding difficulties during running speech without additional disturbances in the repetition or comprehension of spoken language. Disturbances of reading and writing followed, first as a slowing down of these activities and then as severe agraphias and dyslexias. Two of these five patients (Nos. 2 and 6) developed additional but lesser difficulties with the comprehension of spoken language. In Patients 1, 2, 3, and 6, speech was logopenic, slow, labored, and full of long word-finding pauses; paraphasias were rare. These four patients were very much distressed by their predicament; they showed signs of appropriate sadness and often wept.

The EEG, CT scan, and auditory evoked potentials implicated the left perisylvian region in each of the six patients. The EEG findings consisted of left temporal slowing. This must be interpreted with caution since such slowing may appear in the senium in otherwise normal individuals [1]. Since our patients were generally younger, the slowing in their EEGs probably reflects underlying changes that go beyond those which can be attributed to aging alone. The CT scans showed widening of the left frontal horn and perisylvian fissure. The extent of such changes in Patients 2 and 3 and the gradual expansion of low absorption areas in Patient 6 are almost certainly beyond the range of normal variations. In Patient 4, the EEG and CT scans were inconclusive but auditory evoked potentials were consistent with abnormal function predominantly of the left auditory cortex, whereas brainstem auditory potentials and somatosensory evoked potentials were reported to be normal. The biopsy from the temporal lobe of Patient 3 did not show the changes associated with
Pick's disease, Alzheimer's disease, arteritides, or other inflammatory conditions. However, pyramidal neurons contained lipofuscin or ceroid in quantities that might well be abnormal for her age.

The insidious onset, gradual progression, and prolonged course of aphasia point to a degenerative condition, predominantly of the left perisylvian region. The additional calculation deficits are consistent with impairment of function in this part of the brain. Progressive aphasia is not uncommon as part of degenerative conditions such as Pick's or Alzheimer's disease [5, 7-9, 11, 13, 15, 16, 19, 21, 22]. The language disturbance most commonly takes the form of an anomic aphasia [7, 8]. This was initially stressed by Pick [16], who indicated that the aphasia was of the anomic type because the middle and inferior temporal gyri were involved while Wernicke's area in the superior temporal gyrus remained intact. However, there are marked clinical differences between the patients described in this report and those who develop a progressive aphasia in conjunction with Alzheimer's or Pick's disease. For example, the aphasia in these two dementing conditions virtually never appears in isolation as the presenting sign and almost always parallels in intensity other underlying deficits of intellect, comportment, and personality [5, 8, 11, 15, 16, 19, 22]. This relationship occurs even when the atrophy is mostly in the left temporal lobe [7, 12, 13]. In our patients, however, the aphasia emerged in virtual isolation and progressed for up to 11 years without additional behavioral components of dementia. Furthermore, a discrepancy in favor of verbal over performance subtests in the Wechsler Adult Intelligence Scale (WAIS) is one of the most characteristic patterns seen in dementing conditions [8]. In the patients for whom we obtained the WAIS, the discrepancy was reversed. Also, the anomic aphasias that develop in conjunction with underlying dementias are usually fluent and logorrheic and contain multiple paraphasias [8]. In contrast, paraphasias were rare in our cases, and Patients 1, 2, 3, and 6 showed a logopenic anomia with long and frequent word-finding pauses. In Patients 1 and 3 the pattern of the language difficulty was reminiscent of anterior,
nonfluent aphasias of the Broca type. This kind of aphasia is virtually never described with progressive dementias. Another feature of the aphasias in Pick's or Alzheimer's disease is the apathy or even jocularity with which the patient reacts to the disability. Our patients, however, were deeply distressed and frequently showed signs of reactive depression.

Despite these obvious clinical differences, the language difficulty and associated deficits in the manipulation of numbers may lead to an erroneous diagnosis of dementia in patients with progressive aphasia. It is important to avoid such errors since these patients may require different management. For example, the preservation of insight and judgment makes custodial care unnecessary, at least until the final stages. Furthermore, since other faculties are relatively intact, these patients can continue to engage in a wide variety of activities and may continue to hold gainful employment so long as this does not require intact language functions. In some cases, new skills can be acquired even as the aphasia keeps progressing. This may be useful in teaching these patients not only alternative means of communication but also behavioral strategies to help them circumvent the language disability.

Two reports in the literature may be relevant to our cases. Dejerine and Sériex reported the case of a 47-year-old woman in whom a state of pure word deafness progressively developed in the absence of other signs of dementia [4, 17]. Five years after onset, her condition advanced to a state of Wernicke's aphasia with underlying disorientation; she died 8 years after the emergence of the first symptoms. At autopsy, massive bitemporal atrophy was noted with relative preservation of the angular and supramarginal gyri; the rest of the brain appeared intact by macroscopic inspection. In the affected regions, intracortical fibers were decreased, neuroglia were increased, and pyramidal cells were diminished in number, especially small ones [4].

In another report, by Cole et al [3], a family was described in which ten members in three generations were affected with progressive aphasia. Age of onset ranged from 56 to 72 years and the duration of the condition from 5 to 13 years. In three patients, aphasia was the initial and most prominent finding. In two cases dementia was absent or slight. Histological examination in four patients showed astrocytosis and loss of neurons in layers II and III. Neither Alzheimer changes nor Pick inclusions were reported, but the condition was attributed to a familial type of Pick's disease [3].

Our patients had no familial incidence of similar conditions. The biopsy specimen from Patient 3 showed nonspecific lipofuscinosis and did not contain the changes reported by Dejerine and Sériex [4] or by Cole et al [3]. However, biopsy specimens may be notoriously difficult to interpret, especially in the case of progressive cortical degenerations other than Alzheimer's disease [20].

The classification of progressive cortical degenerations other than Alzheimer's disease continues to pose a difficult problem [14]. There is a common tendency to ascribe all lobar atrophies to Pick's disease, even in the absence of specific microscopic changes [21]. Since the patients described here did appear to have a lobar atrophy in the left temporal area, a common site of predilection for Pick's disease, this may well be one diagnostic possibility even though the absence of generalized dementia would be inconsistent with the other cases reported in the literature. The presence of lipofuscin, perhaps in excessive quantities, also raises the possibility of Kufs' or Kraepelin's disease [6, 18], but the absence of a family history is somewhat inconsistent with these diagnoses. Furthermore, the clinical manifestation of these tardive lipofuscinoses is also characterized by dementia. It appears, therefore, that these patients with relatively pure progressive aphasias do not easily fit into the established diagnostic entities. The case of Dejerine and Sériex, the family of Cole et al, and the six cases described here may thus belong to a special type of progressive degeneration of unknown cause(s) in which the common denominator is a predilection for the perisylvian region, especially on the left side.* It is conceivable that in another group of patients a similar specificity might exist for analogous parts of the right hemisphere. Such patients could manifest a progressive alteration of comportment, judgment, insight, and visuospatial skills, while other faculties, including language, could remain almost intact [10].

Selectivity in the distribution of degenerative conditions is the rule rather than the exception. In cases such as olivopontocerebellar degenerations or amyotrophic lateral sclerosis, the pattern of predilection is specific for groups of neurons involved in motor control. In Parkinson's and perhaps in Huntington's disease the pattern of predilection is based on the distribution of neurotransmitters. In Pick's and Alzheimer's disease the atrophy occurs mostly in association cortex, perhaps in areas that are phylogenetically and ontogenetically most recent [9]. Asymmetrical distribution can also occur. Pick's disease, for example, affects the left temporal lobe much more frequently than the right [9, 11, 21]. Our cases of progressive aphasia may reflect yet another

*At the cellular level there may be no unitary pathological abnormality. In certain cases some of the microscopic changes may even be indistinguishable from those of Alzheimer's. Pick's, or Kufs' disease.
pattern of predilection in which the distribution of degenerative changes is not only asymmetrical but also selective for language-related areas of the left hemisphere. The absence of additional components of dementia, at least until the final stages, provides further clinical evidence for a level of anatomical specificity higher than that usually encountered in Alzheimer’s disease, in Pick’s disease, or in the group of tardive lipofuscinoses.

References