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Case 1-2017: A 70-Year-Old Woman with Gradually Progressive Loss of Language

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PRESENTATION OF CASE

Dr. Bradford C. Dickerson: A 70-year-old woman was seen in the memory disorders clinic of this hospital because of progressive cognitive difficulties involving word finding. She was interviewed with the assistance of her daughter.

The patient had reportedly been well until approximately 8 years before this evaluation, when gradually progressive difficulties with word finding developed, along with associated confusion about the meaning of some words. For example, during a conversation about a recent family event, she did not understand what the phrase “punch bowl” meant. She also had increased egocentric behavior, during which she spoke most frequently about herself. She had a good memory for recent events of her life and could recount multiple stories (at times to an excessive extent during history taking, such that she required refocusing). She had an excellent sense of direction. She had an uncharacteristically matter-of-fact reaction to the death of a sibling and of her dog (being less upset than her family expected). She occasionally had mildly inappropriate behavior, such as saying “I love you” to people to whom she was not particularly close.

The patient was right-handed. Approximately 10 years earlier, she had a tick bite and was treated with antibiotic agents after a test for Lyme disease was positive. When she was 7 years of age, she fell out of a tree and hit her head, but she did not lose consciousness and was not hospitalized. There was no history of recent head injury, stroke, seizure, transient ischemic attack, meningitis, encephalitis, exposure to human immunodeficiency virus, thyroid disorder, heart disease, hypertension, hyperlipidemia, diabetes mellitus, liver disease,

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A video showing a portion of the patient evaluation is available at NEJM.org

kidney disease, cancer, pulmonary disorders, exposure to heavy metals, or learning disability. Her only surgical history included three cesarean sections. Her medications were a multivitamin, vitamin C, ginkgo biloba, calcium, magnesium, and zinc, and she had no known allergies. Since the death of her husband 10 years earlier, she had lived alone (in a different state than her daughter) and was able to perform all activities of daily living independently, including managing her money, paying bills, and volunteering in the community (i.e., visiting senior centers to play piano and attending regular community choir practices). She drank alcohol once or twice per month and did not smoke or use illicit drugs. She had been a teacher and had later worked in business with her husband until his death. A brother in his 60s had Parkinson's disease, and a sister in her 80s had Parkinson's disease and dementia. Her six children and her grandchildren were healthy.

On examination, the patient was alert, attentive, well-groomed, cooperative, and pleasant. The blood pressure was 120/70 mm Hg, the pulse 78 beats per minute and regular, and the weight 68.6 kg. She had a score on the Mini-Mental State Examination of 28 (with scores ranging from 0 to 30 and higher scores indicating better cognitive function), because she was unable to recall the name of the hospital or the county. She had a score on the Clinical Dementia Rating scale of 0 (with scores ranging from 0 to 3 and lower scores indicating better cognitive function). The neurologic examination was normal, including evaluation of the 2nd through 12th cranial nerves, power, bulk, tone, coordination, stance, and gait; the deep tendon reflexes were 1+ throughout. The platelet count was 362,000 per cubic millimeter (reference range, 150,000 to 350,000), and the folate level was 20 ng per milliliter (45 nmol per liter; reference range, 3 to 17 ng per milliliter [7 to 39 nmol per liter]). The hematocrit, hemoglobin level, white-cell count, and blood levels of vitamin B₁₂, electrolytes, glucose, calcium, total protein, albumin, globulin, and thyrotropin were normal, as were the results of renal- and liver-function tests. A rapid plasma reagin test was nonreactive, and testing for antibodies to *Borrelia burgdorferi* was negative. As part of the standard evaluation for a suspected cognitive impairment, the patient was referred for neuropsychological testing, speech pathological evaluation, and imaging studies of the head.

Dr. Janet C. Sherman: On neuropsychological testing, the patient's performance on a screen of non-verbal abilities indicated that she had average pre-morbid intellectual abilities. Language impairment was evident both through clinical observations and when she performed verbal tasks, including tasks of confrontation naming, verbal fluency (for which she had substantially more difficulty with semantic fluency than with phonemic fluency), verbal abstraction, and comprehension of individual words. Her spontaneous speech was fluent, but she had notable difficulty with word finding and made occasional paraphasic errors. She often had difficulty comprehending words, such as "cork," "misplaced," "bored," and "pessimism." Her performance on tests of attention and executive functioning varied; her greatest impairments were evident when the tasks required language mediation, and these impairments contrasted with her generally normal performance on tasks that were not verbally mediated. Similarly, her performance was normal on a test of nonverbal memory but was substantially impaired on a test of verbal memory. Her storage of verbal information was difficult to assess because of her impaired acquisition and anomia. Her storage of nonverbal information was normal, as was her performance on visuospatial tasks. She did not report symptoms of depression or anxiety on self-reported assessments.

Ms. Daisy Hochberg: Speech pathological evaluation revealed that the patient had fluent, articulate speech with pauses for word finding, vague word substitutions, and circumlocutions. She was somewhat tangential in her speech and was fixated on telling stories from her life, such that she required frequent refocusing on the topic at hand. She had substantial impairment on a test of naming, with superordinate responses, and she had impairment on word–picture matching. Rare phonemic paraphasias were present. Auditory comprehension was impaired for words she no longer recognized and for sentences with complex syntax. Sentence repetition was intact. A written language assessment revealed that she could read normally and had mild agrammatism in written language samples. A semantic picture–picture matching test revealed no evidence of visual agnosia. (A portion of the speech pathological evaluation is shown in Video 1, available with the full text of this article at NEJM.org.)

Dr. Dickerson: A clinical diagnosis was made, and additional diagnostic tests were performed.

CLINICAL DIFFERENTIAL DIAGNOSIS

Dr. M.-Marsel Mesulam: As a behavioral neurologist, my first task is to make a syndromic diagnosis on the basis of the distribution of impaired and preserved functional domains. This 70-year-old, right-handed woman presented with language dysfunction characterized by impairment of word finding, object naming, and word comprehension. She had a few peculiarities of comportment, such as blunted empathy and excessive conviviality, but other aspects of behavior and cognition had remained mostly intact. Therefore, her principal diagnostic feature is aphasia.

APHASIA

The differential diagnosis of aphasia includes a long list of left-hemisphere diseases, including stroke involving the middle cerebral artery, hemiplegic migraine, cancer, herpes simplex encephalitis, multiple sclerosis, and many others. However, this patient's symptoms progressively worsened over an 8-year period, and none of these processes take that long to develop. On the basis of the long time course of her syndrome, we can infer that this patient had a neurodegenerative disease. The only alternative diagnosis to consider is Creutzfeldt–Jakob disease, which can cause a focal progressive aphasia that may evolve over a period of 3 or 4 years but almost never over a period of 8 years.^{1,2}

PRIMARY PROGRESSIVE APHASIA

On the basis of the long time course, we can confidently conclude that she had the syndrome of primary progressive aphasia, an acquired language disorder caused by a neurodegenerative process, with relative preservation of other domains.^{3,4} In contrast to typical dementias that occur in late life, primary progressive aphasia most commonly starts before 65 years of age and is not associated with memory loss. There are three variants of primary progressive aphasia: agrammatic, logopenic, and semantic.⁵

The agrammatic variant is characterized by the construction of grammatically incorrect sentences and a loss of fluency in the setting of preserved word comprehension. The

logopenic variant is characterized by impairment of word finding, poor language repetition, and fluctuating fluency in the setting of preserved grammar and word comprehension. The semantic variant is characterized by impairment of object naming and word comprehension in the setting of preserved fluency, repetition, and grammar. Pauses for word finding and impaired object naming can occur in each of the variants. The most distinctive feature of this patient's presentation is the loss of word comprehension, a finding that most closely fits the semantic variant of primary progressive aphasia (Fig. 1).

One alternative clinical diagnosis to consider is the closely related syndrome of semantic dementia, in which the deficit of word comprehension is accompanied by additional associative agnosias (impairments in recognition) of objects and faces.⁶ These features were not present in this patient.

Asymmetric degeneration of the cerebral cortex in the language-dominant (usually left) hemisphere is a common feature present in all patients with primary progressive aphasia. Cortical areas remaining outside the left-hemisphere language network and nearly all cortical areas of the right hemisphere may remain unaffected for years, which explains why patients with primary progressive aphasia are typically able to perform most activities of daily living, as shown by this patient's score of 0 on the Clinical Dementia Rating scale (indicating no functional impairment).

Each variant of primary progressive aphasia is associated with a different anatomical site of peak atrophy in the left-hemisphere language network: the inferior frontal gyrus (Broca's area) in the agrammatic variant, the temporoparietal junction (Wernicke's area) in the logopenic variant, and the anterior temporal lobe in the semantic variant.^{7–10} In semantic dementia, preferential atrophy of the anterior temporal lobe also occurs but usually in a more symmetric pattern that involves both hemispheres.¹¹

Given that this patient's presentation is most consistent with a diagnosis of the semantic variant of primary progressive aphasia, I expect that structural magnetic resonance imaging (MRI) will show severe atrophy in the anterior temporal lobe that is much more pronounced on the left side of the brain than on the right side. Furthermore, as part of the standard evaluation for a patient such as this one, I would perform ¹⁸F-fluorodeoxyglucose-positron-emission tomography (FDG-PET) to see if there is hypometabolism, particularly on the left side, which can also extend to additional ipsilateral and contralateral cortical areas that are interconnected with the left anterior temporal lobe.

IMAGING STUDIES

Dr. R. Gilberto Gonzalez: MRI of the head (Fig. 2), performed without the administration of gadolinium, revealed asymmetric volume loss of the left temporal lobe — especially its anterior and mesial aspects, including the subcortical white matter, amygdala, and hippocampus — along with corresponding dilatation of the left temporal horn. A fluid-attenuated inversion recovery (FLAIR) image (not shown) revealed slightly increased hyperintensity of the anterior temporal lobe, as compared with the right side, but there was no other signal abnormality.

Dr. Keith A. Johnson: Four months after the patient's initial evaluation, FDG-PET revealed hypo-metabolism of the bilateral frontal lobes asymmetrically and of the bilateral temporal lobes that was greater on the left side than on the right side (Fig. 3).

DIFFERENTIAL DIAGNOSIS

NEURODEGENERATIVE DISEASES OF THE ANTERIOR TEMPORAL LOBE

Dr. Mesulam: The anterior temporal lobe is an area of the brain that is critically involved in object naming and word comprehension. Multiple lines of evidence suggest that the left anterior temporal lobe is specialized for word comprehension (recognition), whereas the right anterior temporal lobe may serve a similar function for objects and faces. Disease of the anterior temporal lobe therefore leads to the semantic variant of primary progressive aphasia when it occurs predominantly on the left side, to semantic dementia with extensive impairment of word, face, and object recognition when it occurs bilaterally, and to progressive associative agnosias when it occurs predominantly on the right side.^{11–15} In this patient, the finding of asymmetric atrophy of the left anterior temporal lobe is consistent with the clinical diagnosis of the semantic variant of primary progressive aphasia rather than semantic dementia.

In patients with primary progressive aphasia, the underlying pathologic process is usually caused by frontotemporal lobar degeneration or Alzheimer's disease. Approximately 60% of cases of primary progressive aphasia are associated with frontotemporal lobar degeneration, and 40% are associated with Alzheimer's disease. PET with amyloid-binding compounds (amyloid PET) would be useful in this patient to determine whether her primary progressive aphasia is likely to be caused by Alzheimer's disease. A positive result on amyloid PET increases the likelihood of Alzheimer's disease, whereas a negative result definitively rules out Alzheimer's disease and makes frontotemporal lobar degeneration the most likely cause. Therefore, the next step in this patient's evaluation should be to perform amyloid PET.

Dr. Johnson: Amyloid PET was performed with the administration of ¹¹C-labeled Pittsburgh compound B, in accordance with a research protocol. The imaging study showed elevated uptake in the medial and lateral prefrontal and temporoparietal cortices (Fig. 4).

Dr. Mesulam: The positive result on amyloid PET in this case is thought-provoking but needs to be interpreted with consideration of the patient's age at the time of imaging. A positive result on amyloid PET can be seen in elderly persons with no known cognitive abnormalities.¹⁶ Furthermore, prominent impairment of single-word comprehension of the type described in this patient and severe focal degeneration of the anterior temporal lobe are two features of primary progressive aphasia that are almost never encountered when the condition is caused by Alzheimer's disease.¹⁷ There is a strong correlation between the semantic variant of primary progressive aphasia and a type of frontotemporal lobar degeneration that is linked to the presence of abnormal deposits of TAR DNA-binding protein 43 (TDP-43), an RNA-binding protein with a wide range of targets. TDP-associated frontotemporal lobar degeneration has several subtypes, defined according to the pattern of inclusions, and the semantic variant of primary progressive aphasia is associated with type C in 80% of cases. Therefore, despite the positive result on amyloid PET, I think that this

patient's primary progressive aphasia is caused by TDP-associated frontotemporal lobar degeneration, type C, rather than Alzheimer's disease.

Dr. Eric S. Rosenberg (Pathology): Dr. Dickerson, would you tell us your clinical impression when you evaluated this patient and also what happened with her?

Dr. Dickerson: On the basis of our clinical evaluation and imaging studies, our initial diagnosis was primary progressive aphasia. Once this diagnosis was made, we had to deliver the news that, at present, there are no disease-modifying therapies and few symptomatic therapies for primary progressive aphasia. Nevertheless, the cognitive and behavioral symptoms are treatable, and treatment is best determined by a multidisciplinary team of specialists.¹⁸ Treatment includes pharmacologic and nonpharmacologic management of symptoms, management of coexisting conditions, psychosocial support, and education of the patient and family.¹⁹

As is the case for many patients with primary progressive aphasia, new symptoms beyond those affecting language began to arise in this patient with time.²⁰ As she progressively lost semantic memory, she was no longer able to carry out instrumental activities of daily living, and she moved to an assisted-living facility when she was 72 years of age. Behavioral symptoms,²¹ including compulsivity, disinhibition, and agitation when efforts were made to curb her behavior, became prominent. Citalopram was used with some benefit to treat these symptoms. However, over time, her symptoms progressed and led to her placement in an acute geriatric psychiatry unit, where she was treated with olanzapine and lorazepam. Her symptoms continued to progress, and she was placed in a skilled nursing facility when she was 74 years of age. She had increasing difficulty with recognizing even close family members, as well as urinary and bowel incontinence and diminished ability to carry out basic activities of daily living, such as showering, dressing, and brushing her teeth. Ultimately, she "forgot" how to walk. When the patient was 77 years of age, she had decreased interest in food and increased difficulty with swallowing, and hospice services were engaged. She was enrolled in a Namaste Care program (i.e., a program for persons with advanced-stage dementia),²² which provided her with calming, supportive end-of-life care, and she passed away peacefully 1 day before her 78th birthday. A limited autopsy was performed.

CLINICAL DIAGNOSIS

Primary progressive aphasia, semantic variant.

DR. M.-MARSEL MESULAM'S DIAGNOSIS

Primary progressive aphasia, semantic variant, due to TAR DNA-binding protein 43 (TDP-43)-associated frontotemporal lobar degeneration, type C.

PATHOLOGICAL DISCUSSION

Dr. Matthew P. Frosch: The autopsy was limited to an examination of the central nervous system. The brain weighed 1020 g in the fresh state, and there was evidence of atrophy of

the temporal lobes that was more severe in the left hemisphere than in the right hemisphere (Fig. 5A). Within the temporal lobes, the atrophy was more severe in the inferomedial portion than in the superior portion. There was mild atrophy involving the frontal lobe, without notable asymmetry. After cutting into the coronal plane, there was evidence of moderate cortical atrophy involving the frontal and superior temporal lobes and extreme atrophy involving the inferior and medial temporal lobes (Fig. 5B and 5C). There was enlargement of the lateral ventricle and of the temporal horn of the ventricle, and there was volume loss in the hippocampus (Fig. 5C). The most severe cortical atrophy resulted in friable tissue without well-defined gray–white distinction.

Microscopic examination of the most severely affected cortical regions revealed near-complete neuronal loss with corresponding extensive reactive gliosis. In areas of the cortical region that had less-severe atrophy on gross examination, there was mild neuronal loss with corresponding mild gliosis. A range of immunohistochemical studies was performed as a routine assessment for neurodegenerative diseases. The most prominent finding was the presence of long TDP-43–positive neuropil threads and dystrophic neurites in temporal and frontal cortexes (Fig. 5D and 5E). There were very few neuronal cytoplasmic inclusions and no evident neuronal intranuclear inclusions. In keeping with the presence of TDP-43–positive inclusions, there was severe neuronal loss from area CA1 of the hippocampal formation without accumulation of a substantial burden of neurofibrillary tangles (Fig. 5E); this pattern meets the neuropathological definition of hippocampal sclerosis. The severity of the focal cortical atrophy (lobar atrophy) and the presence of TDP-43–positive inclusions accompanied by hippocampal sclerosis support the neuropathological diagnosis of TDP-43–associated fronto-temporal lobar degeneration, type C.^{23,24}

Immunohistochemical assessment revealed the presence of β -amyloid deposits in the neocortex, hippocampal formation, striatum, and brain stem but not in the cerebellum; this distribution corresponds to Thal stage 4 of 5 for amyloid deposition.²⁵ Immunohistochemical assessment for tau revealed the presence of neurofibrillary tangles in the entorhinal cortex, subiculum, and portions of the cornu ammonis; this distribution corresponds to Braak and Braak stage II of VI.²⁶ Assessment for neuritic plaques, performed according to the Consortium to Establish a Registry for Alzheimer's Disease criteria, revealed that plaques were only sparsely present in the cerebral cortex.²⁷ This combination of results merits a score of A3B1C1 according to the 2012 National Institute on Aging–Alzheimer's Association guidelines for the neuropathological assessment of Alzheimer's disease; the score reflects the severity of three variables — deposition of β -amyloid, accumulation of neurofibrillary tangles, and burden of neuritic plaques — on a scale ranging from 0 to 3, with higher scores indicating greater severity. This patient's score is associated with disease that has a low likelihood of resulting in cognitive impairment.²⁸

The pattern of cerebral cortical atrophy is consistent with the clinical diagnosis of fronto-temporal dementia,²⁴ a clinical syndrome that is categorized as either the behavioral variant of frontotemporal lobar degeneration or primary progressive aphasia. Neuropathological classification of frontotemporal lobar degeneration, the condition that is typically present in patients with frontotemporal dementia, begins with separation into either the group characterized by the presence of tau-containing inclusions in the form of tangles and

neuropil threads (in the absence of β -amyloid plaques) or the group characterized by the presence of inclusions composed of TDP-43.²⁹ TDP-associated frontotemporal lobar degeneration is further classified into subgroups defined according to the pattern of inclusions: type A is associated with the presence of many neuronal cytoplasmic inclusions and short dystrophic neurites, type B with the presence of some neuronal cytoplasmic inclusions and rare dystrophic neurites, and type C with the presence of rare neuronal cytoplasmic inclusions and long dystrophic neurites (as was seen in this patient).²³ Although the clinicopathological correlations are not exact, type C lesions often occur with the semantic variant of primary progressive aphasia, semantic dementia, or the behavioral variant of frontotemporal lobar degeneration.

A Physician: Is there a difference in how a patient with primary progressive aphasia would be treated if the underlying cause is Alzheimer's disease versus frontotemporal lobar degeneration?

Dr. Mesulam: If the patient has a type of primary progressive aphasia that is frequently associated with Alzheimer's disease and biomarker studies are positive for Alzheimer's disease, medications such as cholinesterase inhibitors (e.g., galantamine, rivastigmine, and donepezil) and memantine would be indicated. However, there is no convincing evidence that these medications help the aphasia. A rigorous trial that includes only patients with primary progressive aphasia who have clinical and biomarker evidence supportive of Alzheimer's disease remains to be done.

ANATOMICAL DIAGNOSIS

Primary progressive aphasia, semantic variant, due to TAR DNA-binding protein 43 (TDP-43)–associated frontotemporal lobar degeneration, type C.

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Figure 1. Variants of Primary Progressive Aphasia
Data are adapted from Mesulam et al.⁴

Figure 2. MRI of the Head

A high-resolution coronal T₁-weighted image obtained at the level of the temporal lobes shows generalized loss of parenchymal tissue (arrow) and superimposed severe, asymmetric atrophy (arrowhead) of left temporal lobes, including cortical thinning of the temporal gyri and severe shrinkage of the left hippocampal formation, with resultant expansion of the left temporal horn and sulci.

Figure 3. ^{18}F -Fluorodeoxyglucose-Positron-Emission Tomographic (FDG-PET) Scans
 Four months after the initial evaluation, FDG-PET scans show hypometabolism of the bilateral frontal lobes asymmetrically and of the bilateral temporal lobes that is greater on the left side than on the right side. Panel A shows cortical surface projections of the FDG distribution. Panel B shows cortical surface projections of a statistical analysis derived from comparison of the patient's scans with a sample of normal scans; the distribution of the patient's abnormal metabolism in the frontal and temporal lobes is shown in dark blue, and normal variation in visual activation is shown in red and white. The color scale represents standard deviations from the normal scans. The letters surrounding each projection indicate the orientation of the image: A denotes anterior, I inferior, L left, P posterior, R right, and S superior.

Figure 4. PET Scans for Amyloid

Amyloid PET scans, obtained with the administration of ^{11}C -labeled Pittsburgh compound B, in accordance with a research protocol, show uptake in the medial and lateral prefrontal and temporoparietal cortices. The color scale represents the distribution volume ratio of ^{11}C -labeled Pittsburgh compound B. All images are displayed in radiographic orientation (i.e., the right side of the image is the patient's left side).

Figure 5. Autopsy Specimens

A photograph of the ventral surface of the brain shows atrophy of the temporal lobes that is greater on the left side than on the right side (Panel A). Photographs of coronal slabs obtained at the levels of the anterior and body of the hippocampus (Panels B and C, respectively) show severe atrophy of the inferior and medial temporal lobe and lesser degrees of atrophy of the insula, cingulate, and anterior frontal lobes. Immunohistochemical staining for TAR DNA-binding protein 43 (TDP-43) shows multiple long, dystrophic neurites (Panel D, arrow); a single long, dystrophic TDP-43–positive neurite (Panel E); and neuronal loss from area CA1 of the hippocampal formation (hippocampal sclerosis) (Panel F).