Very Early Semantic Dementia With Progressive Temporal Lobe Atrophy

An 8-Year Longitudinal Study

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Background: Semantic dementia is a syndrome within the spectrum of frontotemporal lobar degenerations characterized by fluent progressive aphasia (particularly anomia) and loss of word meaning.

Objective: To report a unique case of very early semantic dementia with a slowly progressive course, allowing insights into the early natural history of this disorder.

Design: Case report.

Setting: A tertiary care center.

Patient: A 62-year-old woman who presented with “memory loss” complaints.

Main Outcome Measures: Clinical course, neuropsychological data, and magnetic resonance imaging results.

Results: The patient was first evaluated when the results of standard neuropsychological measures were normal but subtle left anterior temporal lobe atrophy was present. During the follow-up period of 8 years, she developed profound anomia and loss of word meaning associated with progressive left anterior temporal lobe atrophy, consistent with semantic dementia. In more recent years, anterograde memory impairment and mild prosopagnosia evolved in association with left hippocampal atrophy and subtle atrophy in the homologous gyri of the right anterior temporal lobe. She remains functionally independent despite her current deficits.

Conclusions: Early identification of patients who will develop semantic dementia is difficult and might be missed with standard clinical, neuropsychological, and structural neuroimaging evaluations. Recognition of this relatively rare syndrome is important for early diagnosis and prognostication and particularly for therapeutic interventions in the future.

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IN 1982, MESULAM FIRST DESCRIBED A SERIES OF PATIENTS WHO HAD APHASIA WITHOUT DEMENTIA; HE LATER NAMED THIS SYNDROME PRIMARY PROGRESSIVE APHASIA. SUCH PATIENTS CAN BE DISTINGUISHED ON THE BASIS OF FLUENCY OF SPEECH, HAVING EITHER PROGRESSIVE NONFLUENT OR FLUENT APHASIA. THE TERM SEMANTIC DEMENTIA REFERS TO FLUENT APHASIA WITH ADDITIONAL LOSS OF WORD MEANING. CLINICALLY, PATIENTS HAVE IMPAIRMENT IN LANGUAGE FUNCTION AND OBJECT REPRESENTATION WITH PRESERVATION OF EPISODIC MEMORY AND ABSENCE OF DEFICITS IN OTHER COGNITIVE DOMAINS DURING THE FIRST 2 YEARS OF THE ILLNESS. IMAGING STUDIES REVEAL DISTINCT FOCAL ATROPHY INVOLVING THE INFEROLATERAL TEMPORAL LOBES, USUALLY IN AN ASYMMETRIC DISTRIBUTION. THERE HAVE BEEN ADVANCES IN DETERMINING THE UNDERLYING NEUROPATHOLOGIC FEATURES OF FRONTOTEMPORAL DEMENTIA, AND MOST PATIENTS WITH SEMANTIC DEMENTIA HAVE Ubiquitin-positive, tau-negative inclusions as the correlate of their disease. More recent analyses have shown that such inclusions immunostain with TAR-DNA binding protein 43 (TDP-43). There also have been reports of tauopathies and Alzheimer disease in patients with semantic dementia, although differentiating features might be found on neuropsychological testing and brain imaging. The early natural course of semantic dementia is largely unknown, and many patients only come to medical attention when either profound anomia is already established or additional behavioral symptoms have developed. We describe a unique patient who presented to our clinic early in her illness and developed slowly progressive semantic dementia with typical clinical and radiologic features, allowing insights into the early natural history of the disorder.
The patient was evaluated once yearly for 8 years by comprehensive neurologic examination, neuropsychological testing, and magnetic resonance imaging (MRI) of the brain as a participant in the Mayo Alzheimer Disease Research Center program, a Mayo Foundation institutional review board–approved research program.

NEUROPSYCHOLOGICAL TESTING

The patient underwent serial neuropsychological testing, including assessment of global functioning (Folstein Mini-Mental State Examination),<sup>10</sup> Kokmen Short Test of Mental Status,<sup>11</sup> learning and memory (Logical Memory and Visual Reproductions subtests of the Wechsler Memory Scale–Revised, Percent Retention on the Auditory Verbal Learning Test), executive functioning (Trail Making Test parts A and B), Digit Symbol subtest of the Wechsler Adult Intelligence Scale–Revised, language functioning (Boston Naming Test, Controlled Oral Word Association Test, category fluency), and visuospatial functioning (Block Design subtest of the Wechsler Adult Intelligence Scale–Revised, Rey-Osterrieth Complex Figure Test, and Judgment of Line Orientation). Mayo Older American Normative Studies norms were used to determine scaled scores for these tests, in which 10 represents the mean and 3 the SD.<sup>12–15</sup>

BRAIN IMAGING

The MRIs were performed using a Signa MRI scanner (General Electric Medical Systems, Waukesha, Wisconsin) at 1.5 Tesla, and images of the brain were obtained in sagittal (T1-weighted), axial (proton-density, T2-weighted, fluid-attenuated inversion recovery), and coronal (T1-weighted) planes.

REPORT OF A CASE

A 62-year-old woman was referred to our behavioral neurology clinic with a 6-month history of “memory loss,” specified as problems recalling names of people and objects. She had mild difficulties in organizational skills and complex decision making, such as cooking a meal following a detailed recipe, but was highly functional in her activities of daily living and engaged in various social activities. Her medical history was significant for treated pernicious anemia and hypothyroidism. The patient had recently retired from teaching and led a health-conscious lifestyle. She reported that several second-degree family members had been diagnosed as having late-onset Alzheimer disease. The results of general neurologic examination and standard laboratory workup were unremarkable. Her mental status examination revealed a score of 33/38 on the Kokmen Short Test of Mental Status, recalling 3 of 4 items correctly on delay. On detailed neuropsychological testing, performance on learning and memory, language, and other cognitive domains was within the low average to average range (Figure 1). The results of the initial MRI of the brain were considered normal for the patient’s age, although in retrospect, subtle widening of the collateral sulcus and thinning of the superior temporal gyrus in the left anterior temporal lobe were present (Figure 2). The patient was seen on return visits for the following 8 years. Two years after onset of her complaints, her husband reported that she was substituting words, speaking in a circumlocutory manner, and making semantic and frequent spelling errors. Formal speech evaluation by an experienced speech pathologist (J.R.D.) demonstrated normal motor speech, verbal comprehension and retention, verbal expression, and reading and writing skills but a marked deficit in word retrieval (less than the fifth percentile on the Boston Naming Test). Furthermore, she often did not recognize missed target words when they were provided to her. During the following years, the patient had progression of anomia as documented by decline in scores on the Boston Naming Test and category fluency. In contrast, scores remained average to above average for attention/executive functioning and visuospatial tasks. She performed near or above generally accepted cutoff scores on screening measures (eg, ≥24 on the Folstein Mini-Mental State Examination and ≥29 on the Kokmen Short Test of Mental Status). Anterograde memory performance was variable across follow-up with generally impaired visual reproductions of the Wechsler Memory Scale–Revised and percent retention on the Rey Auditory Verbal Learning Test performance for the last 3 to 5 years. In the most recent evaluation, all measures of anterograde memory were impaired (Figure 1). On serial language examinations, she developed surface dyslexia, loss of word meaning, and difficulties in recognizing famous faces; she clearly met criteria for semantic dementia.<sup>7</sup> Serial MRIs documented progressive left anterior inferolateral temporal lobe atrophy with relative sparing of the hippocampus until age 68 (Figure 2). On the most recent MRIs, there is evidence of right temporal lobe atrophy in a strikingly similar pattern of topography compared with the left side. From a behavioral standpoint, the patient has become slightly more rigid mentally but remains independent in her simple and complex activities of daily living.

COMMENT

We report a case of very early semantic dementia with longitudinal neuropsychological and radiologic follow-up, allowing insights into the early natural course of this syndrome. Our patient exemplifies the way that subjective “memory loss” complaints precede objective evidence of cognitive impairment by standard testing methods. Her course during 8 years was remarkably slow in its progression, compared with previously published data, which gave an estimated mean survival time of 8 years after diagnosis.<sup>10</sup> On initial evaluation, both her neuropsychological assessment and imaging findings were believed to be normal, although in hindsight subtle atrophy of the left collateral sulcus and superior temporal gyrus was present on MRI. The striking asymmetry of temporal lobe atrophy with predilection for the dominant hemisphere has been well described,<sup>4,17,18</sup> and relative sparing of the mesial temporal lobe structures seems to account for preservation of episodic memory, at least during the initial years. Later in the course, the opposite homologous temporal lobe regions tend to become atrophic in the exact same topography, as seen in our patient. The underlying mechanisms of focal atrophy and eventual homologous opposite hemisphere involvement in seman-
tic dementia are unknown, but one could hypothesize that apoptosis and/or transcallosal degeneration is at play. Making an early diagnosis and differentiating among the various dementia syndromes remain challenging even for behavioral neurologists, stressing the need for diagnostic biomarkers. Furthermore, correlating the clinical dementia syndrome with underlying pathophysiologic changes has proven to be difficult in frontotemporal lobar degenerations. In a postmortem study, semantic dementia has been shown to be associated with...

Figure 1. Longitudinal performance in screening mental status examinations and key cognitive domains for specific neuropsychological tests. Tests covered the following areas: A, Folstein Mini-Mental State Examination; B, language; C, attention/executive; D, Kokmen Short Test of Mental Status; E, memory; and F, visuospatial. All raw scores were converted to scaled scores based on Mayo Older American Normative Studies (MOANS) norms (mean, 10; SD, 3). Shaded areas represent scores in the abnormal range. Note that impaired performance on the Boston Naming Test preceded impairment on semantic fluency, and impairment in verbal and visual memory coincided with impaired naming. By history, a decline in the patient’s episodic memory was only noted at evaluation 7. AVLT-PR indicates percentage of retention on the Auditory Verbal Learning Test; BNT, Boston Naming Test; COWAT, Controlled Oral Word Association Test; JLO, Judgment of Line Orientation; ROCF, Rey-Osterrieth Complex Figure Test; TMT, Trail Making Test; WAIS-BD, Block Design subtest of the Wechsler Adult Intelligence Scale–Revised; WMS-LM, Logical Memory of the Wechsler Memory Scale–Revised; and WMS-VR, Visual Reproductions of the Wechsler Memory Scale–Revised.
Figure 2. Magnetic resonance images (MRIs) showing progressive left anterior temporal lobe atrophy. Left column, Serial coronal T1-weighted images. Right column, Axial fluid-attenuated inversion recovery (FLAIR) images. Note subtle widening of the left collateral sulcus and thinning of the superior temporal gyrus on early MRIs with clear progression to atrophy, a hazy increased signal in the left mesial temporal lobe on FLAIR images, and development of atrophy in homologous regions in the right anterior temporal lobe over more recent MRIs. Numbers on the left represent the patient’s age (in years) corresponding to that row of images.
tau-negative, ubiquitin-positive inclusions in 13 of 18 cases. The ubiquitinated protein recently has been identified as TDP-43, raising hope for future treatment strategies targeting TDP-43 pathophysiological mechanisms. Treatment is most likely to be beneficial the earlier it is instituted but, as exemplified by this case, early diagnosis will be challenging using standard neuropsychological measures and MRI.

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REFERENCES


Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of Archives of Dermatology (2005;141:76-77). Also see the Instructions to Authors on our Web site: www.archneurol.com.