What Is Semantic Dementia?

A Cohort Study of Diagnostic Features and Clinical Boundaries

Andrew Kertesz, MD; Sarah Jesso, BA; Michal Harciarek, PhD; Mervin Blair, MA; Paul McMonagle, MD

Objectives: To describe a large, clinically defined cohort of patients with semantic dementia (SD) that highlights important, sometimes overlooked features and to compare it with similar entities.

Design: Cohort study.

Setting: A cognitive neurology clinic.

Patients: A population of 48 patients clinically diagnosed with SD was contrasted with 52 patients with progressive nonfluent aphasia, 42 patients with a behavioral variety of frontotemporal dementia, and 105 patients with Alzheimer disease on speech output characteristics, comprehension, naming, and repetition subtests of the Western Aphasia Battery, the Frontal Behavioral Inventory, and other cognitive tests. Neuroimaging was visually analyzed, and 6 patients with SD had autopsy.

Results: Of 37 patients with probable SD, 48.6% had semantic jargon; 21.6%, excessive garrulous output; and 75.7%, some pragmatic disturbance. Semantic substitutions were frequent in SD (54.1%) but phonological errors were absent, in contrast to progressive nonfluent aphasia with the opposite pattern. All but 3 patients with probable SD questioned the meaning of words. Patients with SD had significantly lower naming and comprehension scores, and their fluency was between progressive nonfluent aphasia and Alzheimer disease or behavioral frontotemporal dementia. Behavior was abnormal in 94.6% of patients with probable SD.

Conclusions: Semantic dementia is distinguishable from other presentations of frontotemporal dementia and Alzheimer disease, not only by fluent speech and impaired comprehension without loss of episodic memory, syntax, and phonology but also by empty, garrulous speech with thematic perseverations, semantic paraphasias, and poor category fluency. Questioning the meaning of words (eg, “What is steak?”) is an important diagnostic clue not seen in other groups, and behavior change is prevalent.

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Semantic dementia (SD) designates a progressive cognitive and language deficit, primarily involving comprehension of words and related semantic processing. These patients lose the meaning of words, usually nouns, but retain fluency, phonology, and syntax. Pick described similar patients as having “pure word deafness” in association with left temporal atrophy. Transcortical sensory aphasia was used for similar cases. Semantic aphasia was a term used by Head in war-injured patients for a 2-way disturbance of comprehension and naming. The condition was called gogi (meaning) aphasia in Japan. Some patients were considered to have loss of semantic memory and others a language impairment. Semantic dementia has been further elaborated as the degradation of a single central network of conceptual knowledge. The definition of SD originates from Snowden et al and has been adopted by others, including the consensus criteria of Neary et al, as a variety of frontotemporal dementia (FTD). The incidence of SD is estimated by one clinic to be 25% in their patients with FTD.

Semantic dementia has been equated with fluent progressive aphasia. Fluent aphasia, however, is common in Alzheimer disease (AD) and, at the onset, all patients with progressive aphasia are fluent, even those who become nonfluent later. The fluency-nonfluency distinction is often arbitrary and rarely quantitated. Primary progressive aphasia is subdivided variably and sometimes includes SD. Here we used the term progressive nonfluent aphasia (PNFA) for a comparison group. Semantic deficits, considered basic to SD, also appear in AD. Because of these overlapping features from different clinical and biological entities, the diagnostic boundaries remain uncertain.
Some features of SD such as distinctive speech output characteristics, impaired pragmatics (the study of the give-and-take and efficiency of communication), “What is...” questioning of meaning, and behavioral abnormality are relatively unexplored. We aimed to study SD in a cognitive neurology clinic population of patients in an attempt to delineate the syndrome from the behavioral presentation of patients with FTD (bvFTD), PNFA, and AD. In addition to comparing neurocognitive features with related conditions, we characterized the pragmatics of speech and quantitated language, including fluency and the behavioral abnormality. In view of a recent suggestion associating a specific pathology with SD,19 the study of clinical boundaries of SD is even more relevant. We report autopsy confirmation in 6 of 48 patients.

### METHODS

The target population was 48 patients with SD who were diagnosed clinically using the Neary et al criteria13 from a cohort of 361 patients with FTD or Pick complex. Patients with SD had progressive loss of naming and comprehension, with preserved syntax, phonology, fluency, and relatively preserved episodic memory. They were followed up at yearly intervals,20 but only the results of the first examination were used for the statistical analyses in this study. Thirty-seven patients were considered to have probable SD (Table 1). This group had prominent comprehension and word-finding difficulty, either from the beginning of the illness or by the first time they were seen. Patients with possible SD (n=11) were cases with atypical features and were not included in the statistical analysis. One patient had epilepsy and another panic attacks. Five possible cases had predominant behavioral disturbance and only incipient SD by the first clinical visit, and 1 had mixed nonfluent and SD features.

Behavioral FTD was diagnosed clinically when a patient presented with mainly behavioral or personality disturbance, fulfilling Neary and colleagues’ criteria,13 and no significant language impairment was evident on the first examination. Patients with PNFA had an initial deficit of language output and pres-
ervation of comprehension, memory, and visuospatial ability. Patients with additional memory and comprehension problems in their history were excluded as having possible PNFA. Alzheimer disease was diagnosed when the primary deficit was (episodic) memory impairment and the patients fulfilled the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) criteria.

The patients were grouped on the basis of a clinical interview and neurological examination, independently of the neuropsychological assessment to avoid circularity. The Mini-Mental State Examination, Dementia Rating Scale, Clock Drawing Test, and Category fluency (animals per minute) tests measured cognition. Language testing was performed with the Western Aphasia Battery (WAB). The aphasia quotient represents a total score and overall measure of the severity of language impairment; major subtests are fluency, speech content, comprehension of nouns and sentences, repetition, naming, reading, and writing. A subset of patients with SD was also examined for the supplementary reading and writing of irregular words. The clinical description of conversational speech characteristics was additional to formal language assessment with the WAB. Behavior and personality change was rated on the Frontal Behavioral Inventory, with higher score indicating greater behavioral change.22 The side and lobar locations of prominent atrophy or hypometabolism on magnetic resonance imaging or computed tomography and hexethylpropylene amine oxime–single-photon emission computed tomography was reviewed by A. K. and P. M. (Table 1) but the radiological features were not used in patient grouping.

Patients with SD and bvFTD were younger than those with AD and PNFA (Table 2). The sex distribution was 16 women to 21 men in the SD group, 13 to 29 in bvFTD group, 32 to 22 in the PNFA group, and 41 to 64 in the AD group. χ² analysis showed that the PNFA group had significantly more women than the bvFTD (χ²=7.7; P = .006) and AD groups (χ²=5.9; P = .02). The time from onset of illness to first examination was longer in patients with SD. The institutional review board of University of Western Ontario approved the study of human subjects.

RESULTS

COGNITION

Table 2 shows the results of comparison of all groups on cognitive and behavioral tests. Analyses of variance and Tukey post hoc tests showed significantly better performance by the bvFTD group when compared with the PNFA and AD groups on the Mini-Mental State Examination and the Dementia Rating Scale. Patients with SD were also better, but not significantly. The animal fluency task revealed that patients with SD performed significantly worse than those with AD and bvFTD. Not only was visuospatial function preserved in our SD cohort, but we also observed a heightened, at times obsessive, inclination to paint and complete jigsaw puzzles in 9 patients with SD (Table 1). Visual object agnosia (13 of 37

<table>
<thead>
<tr>
<th>Variable</th>
<th>SD (n=37) Mean (SD)</th>
<th>bvFTD (n=31) Mean (SD)</th>
<th>AD (n=105) Mean (SD)</th>
<th>PNFA (n=52) Mean (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.92 (8.38)</td>
<td>58.48 (8.43)</td>
<td>67.67 (8.62)</td>
<td>64.37 (7.30)</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years ill</td>
<td>4.0 (2.13)</td>
<td>2.96 (2.92)</td>
<td>2.59 (1.67)</td>
<td>2.65 (1.43)</td>
<td>.09</td>
</tr>
<tr>
<td>MMSE (max: 30)</td>
<td>25.03 (4.43)</td>
<td></td>
<td>19.71 (7.26)</td>
<td>19.44 (7.71)</td>
<td>.004</td>
</tr>
<tr>
<td>FBI (max: 72, cutoff: 30)</td>
<td>36.84 (11.52)</td>
<td></td>
<td>14.61 (10.40)</td>
<td>16.86 (11.21)</td>
<td>.001</td>
</tr>
<tr>
<td>DRS (max: 144)</td>
<td>120.19 (25.75)</td>
<td></td>
<td>105.33 (21.26)</td>
<td>99.09 (30.16)</td>
<td>.003</td>
</tr>
<tr>
<td>Clock drawing test (max: 10)</td>
<td>8.21 (1.87)</td>
<td></td>
<td>6.37 (3.03)</td>
<td>6.12 (3.38)</td>
<td>.015</td>
</tr>
<tr>
<td>Animal Fluency (normal above 12)</td>
<td>11.67 (5.87)</td>
<td></td>
<td>9.22 (4.44)</td>
<td>7.83 (5.10)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; bvFTD, behavioral frontotemporal dementia; DRS, Dementia Rating Scale; FBI, Frontal Behavioral Inventory; max, maximum; MMSE, Mini-Mental State Examination; PNFA, progressive nonfluent aphasia; SD, semantic dementia.

a-eScores are significantly different in pairwise comparison (Tukey, post hoc) in each row (eg, in the MMSE row, only 2 comparisons are significant, bvFTD with PNFA and bvFTD with AD).

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patients) and prosopagnosia (15 of 37 patients) was obvious enough to be observed by the caregivers or the examiner (Table 1).

**SPEECH OUTPUT**

Speech output in patients with SD was fluent (WAB fluency rating of 6 or higher) in all cases. Eighteen of the 37 patients had semantic jargon, defined as speech that is meaningless and irrelevant but grammatically and phonologically correct, consisting of real words. Empty speech is similar, but has some coherence and conversational relevance (n=4). Nine patients had significant thematic or semantic perseveration (stereotypy), and 8 patients were garrulous, with excessive output that incorporated some of the above features. Altogether, pragmatic difficulties including failure of topic maintenance, perseveration, and failure to switch speaker roles, were present in 35 of 37 patients (Table 1).

Semantic substitutions in spontaneous speech were frequent in SD (54.1%) when compared with PNFA (7.5%; \( \chi^2 = 24.9; P = .001 \)) but phonological paraphasias were absent in SD and frequent in PNFA (41.5%; \( \chi^2 = 20.3; P = .001 \)), a significant double dissociation. Fifteen of the patients with PNFA were nonfluent, scoring 5 or less on the standardized fluency rating of the WAB. Another 10 had aphemia, stuttering, or apraxia of speech; some were only anomic and logopenic at the time of first examination but none had clinically significant comprehension or semantic difficulty. Questioning the meaning of words heard in conversation was typical and occurred in 34 of 37 of the patients with SD. This feature was recorded in 4 of 6 of the autopsied SD cases and was not seen in any other groups (Table 1).

**LANGUAGE**

The Figure shows the results of the quantitative aspects of language performance on the WAB, comparing the SD group (n=31) with the bvFTD (n=17), PNFA (n=32), and AD groups (n=105). Analysis of variance showed a significant difference between the groups as measured by the aphasia quotient; the AD and bvFTD groups had significantly less language deficit than the SD group. The AD group was significantly more fluent than the SD group, and patients with PNFA were significantly less fluent than the bvFTD and AD groups but not significantly different from the SD group. Auditory (single noun) word recognition and sequential commands (sentence comprehension) were significantly lower in SD than AD patients. In naming objects, the SD group was significantly worse than all others.

Using the WAB classification criteria, our patients with SD were classified as follows at baseline: 24, anomic; 4, transcortical sensory; and 3, Wernicke’s aphasia. The last visit classification changed to mostly Wernicke’s and transcortical sensory aphasia. Surface dyslexia and dysgraphia (patients retain phonological processing and regularize words when they cannot read or write them by meaning), elicited by reading and writing irregular words, was observed in 18 of 19 patients with SD (Table 1).

**BEHAVIOR**

Only 6 cases presented with relatively pure SD without behavioral change. All but 2 of these cases developed the behavioral features eventually. One died of motor neuron disease a year after being seen; the other was lost to follow-up. In 16 of 37 patients, the behavioral symptoms were noticed first (Table 1). On the Frontal Behavioral Inventory, the bvFTD and SD groups scored significantly higher (more behavioral abnormality) than the PNFA and AD groups. Item analysis of the Frontal Behavioral Inventory that compared the SD and bvFTD groups is summarized in Table 3. Only apathy, aspontaneity (closely related), and personal neglect differed sig-

**Figure.** Language function on the subtests of the Western Aphasia Battery comparing semantic dementia (SD) with behavioral frontotemporal dementia (bvFTD), primary progressive aphasia (PPA) (progressive nonfluent aphasia), and Alzheimer disease (AD). Raw scores are converted to percentages of the maximum score, usually achieved by controls. *P < .05; significant difference from semantic dementia.
nificantly between the two groups. These are all negative items (deficiency behaviors). When all of the negative (Table 3) items are combined in a subscale, the SD group scored significantly lower (better) than bvFTD group ($t_{63} = -3.945; P < .001$; effect size $d = 0.97$), a large effect. Whereas, on the positive subscale (disinhibition or excess behaviors, the other 12 items), the difference between the groups was moderate ($t_{63} = -2.050; P = .04; d = 0.51$).

### Comment

The diagnosis of SD is far from unequivocally defined or universally practiced. Numerous studies have approached theoretical issues exploring semantic memory using a few patients with SD at a time. We focused on the clinical features and quantitation of language and behavior in a larger cohort. Although the language results could be considered circular, because SD was defined by fluent speech and poor comprehension, patient selection was based on caregiver history and neurocognitive examination; language and behavioral quantitation, neuropsychological tests, and imaging were performed independently.

Semantic dementia should be suspected when a patient with progressive aphasia has significant or early difficulty with single-word comprehension.$^{1,12,23}$ The semantic loss becomes clinically evident when the patient questions the meaning of words, usually nouns in conversation. The “What is...?” questioning was frequently observed in the population with SD, and it appeared to be a highly diagnostic feature because it was absent in all other patient groups. This is even more striking considering patients demonstrated preserved repetition and phonological competence, eg. “Gorilla? ... gorilla. ... what is gorilla?” Naming was the worst in our SD group, confirming that it is a major, albeit less specific, feature.$^{1,12,23}$ Patients with AD also forget words early, perform poorly on naming tests, and substitute words from the same semantic or superordinate category.

A most remarkable feature in our SD cohort was the severe pragmatic disturbance with garrulous, excessive, disinhibited output, stereotypic thematic perseveration, and semantic jargon. Perseverating with their own agenda and not stopping to listen are features that distinguish early SD from PNFA and AD. Others have explored singular aspects of pragmatics such as coherence in SD.$^{24}$ The conversational peculiarity appears early but the casual observer may not notice it. Later it may be compounded, even overshadowed by the altered personality and unacceptable behavior, although it contributes significantly to the social handicap.

A comprehensive yet practical-length language test such as the WAB is helpful to quantify fluency, comprehension, repetition, naming, reading, and writing and to follow the course of the illness.$^{17}$ Formal testing of comprehension with the WAB or verbal intelligence tests may alert the examiner to SD. Word comprehension was unimpaired in PNFA initially. Sentence comprehension was impaired in both patients with SD and PNFA but each may have different mechanisms, as suggested in the literature; one has increasing loss of word meaning while the other has significant loss of syntax.$^{12,25}$ We also documented the high frequency of surface dyslexia, confirming the loss of reading of irregular words by the semantic route.$^{12,26}$

The fluency-nonfluency distinction is controversial and rarely based on a standardized, scorabable scale such as in our study. A recent editorial warned against such an oversimplified dichotomy of progressive aphasia.$^{22}$ There are different definitions of fluency$^{28,29}$ or logopenia.$^{29}$ Furthermore, fluency is stage related,$^{16,20}$ and 4 of 6 of our autopsied patients with SD were recorded to be nonfluent or mute eventually. Particularly problematic is the inclusion of all fluent aphasics as having SD, potentially resulting in including patients with early PNFA or AD in SD groups. Recent usage includes SD under the primary progressive aphasia umbrella, in addition to PNFA and logopenic progressive aphasia, which turns out to be aphasic AD in many cases.$^{20-31}$ Some ambiguous cases have been called mixed progressive aphasia.$^{31}$ This category is similar to our designation of possible SD in this study or possible primary progressive aphasia previously.$^{20}$ Semantic paraphasias were characteristic of SD and phonological ones of PNFA, confirming other studies$^{12,28}$ and demonstrating a double dissociation. Phonological paraphasias, however, are also a feature of logopenic progressive aphasia$^{32}$ and develop in later stages of AD.$^{15}$

In our study, one-third of our patients with SD (Table 1) had clinically evident visual object use agnosia and prosopagnosia in addition to the language deficit. Caregivers often described loss of object recognition beyond word finding or naming impairment, usually

<p>| Table 3. Scores of Patients With SD and bvFTD on Items of the Frontal Behavioral Inventory |
|---------------------------------------------|---------------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>FBI Item</th>
<th>Mean (SD) SD</th>
<th>Mean (SD) bvFTD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy$^a$</td>
<td>1.16 (1.24)</td>
<td>2.09 (1.06)</td>
<td>.002</td>
</tr>
<tr>
<td>Apomotivit$^a$</td>
<td>1.20 (1.30)</td>
<td>2.24 (0.92)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Indifference</td>
<td>1.13 (1.23)</td>
<td>1.85 (1.08)</td>
<td>.01</td>
</tr>
<tr>
<td>Inflexibility</td>
<td>1.61 (1.31)</td>
<td>1.85 (1.02)</td>
<td>.41</td>
</tr>
<tr>
<td>Personal neglect$^b$</td>
<td>0.87 (1.06)</td>
<td>1.91 (1.08)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Disorganization</td>
<td>1.94 (1.03)</td>
<td>2.50 (0.79)</td>
<td>.02</td>
</tr>
<tr>
<td>Inattention</td>
<td>2.06 (1.06)</td>
<td>2.21 (1.01)</td>
<td>.58</td>
</tr>
<tr>
<td>Loss of insight</td>
<td>1.35 (1.36)</td>
<td>2.09 (1.11)</td>
<td>.02</td>
</tr>
<tr>
<td>Perseverations/obessions</td>
<td>1.87 (1.20)</td>
<td>2.09 (1.03)</td>
<td>.44</td>
</tr>
<tr>
<td>Irritability</td>
<td>1.13 (1.15)</td>
<td>1.68 (1.25)</td>
<td>.07</td>
</tr>
<tr>
<td>Jocularity</td>
<td>0.84 (1.13)</td>
<td>0.97 (1.17)</td>
<td>.65</td>
</tr>
<tr>
<td>Poor judgment/impulsivity</td>
<td>1.42 (1.20)</td>
<td>1.57 (0.98)</td>
<td>.57</td>
</tr>
<tr>
<td>Inappropriateness</td>
<td>1.71 (1.32)</td>
<td>2.03 (1.03)</td>
<td>.28</td>
</tr>
<tr>
<td>Restlessness/roaming</td>
<td>1.10 (1.16)</td>
<td>1.44 (1.28)</td>
<td>.26</td>
</tr>
<tr>
<td>Aggression</td>
<td>0.84 (1.16)</td>
<td>1.00 (1.23)</td>
<td>.59</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>0.84 (1.10)</td>
<td>1.71 (1.24)</td>
<td>.004</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>0.45 (0.96)</td>
<td>0.59 (1.08)</td>
<td>.59</td>
</tr>
<tr>
<td>Utilization</td>
<td>0.52 (0.89)</td>
<td>0.59 (1.02)</td>
<td>.76</td>
</tr>
<tr>
<td>Incontinence</td>
<td>0.23 (0.68)</td>
<td>0.62 (1.04)</td>
<td>.09</td>
</tr>
<tr>
<td>Hoarding</td>
<td>0.89 (0.89)</td>
<td>1.08 (1.08)</td>
<td>.24</td>
</tr>
</tbody>
</table>

Abbreviations: bvFTD, behavioral frontotemporal dementia; FBI, Frontal Behavioral Inventory; SD, semantic dementia.

$^a$Indicates significant difference after Bonferroni corrections; $P < .002$. 

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manifesting as difficulty finding an object in their sight or not knowing how to use it. Visual, face, and sound agnosia as well as the behavioral abnormality have been associated with right temporal involvement and language-predominant symptoms with left temporal atrophy. Visual agnosia can also be a feature of posterior cortical atrophy, which most often has AD pathology but the apperceptive deficit and the presence of Balint syndrome distinguished that condition from SD.33

The association of SD with the behavioral manifestations of FTD occurred with few exceptions. This has been previously recognized to a variable extent but, in our opinion, it has not received enough emphasis. In some studies, SD often appears as a separate syndrome and little, if any, mention is made of the behavioral abnormalities. We have previously shown that the presence of more than one Pick complex syndrome (eg, disinhibition plus aphasia) is associated with FTD rather than other pathology at autopsy.30 In another study of SD, the presence of behavioral change also seemed to correspond to the presence of FTD pathology.37 Others consider the behavioral abnormalities in SD to be distinct from those of bvFTD.34 For example, patients with SD have food fads and are social seekers, while patients with bvFTD have gluttony and social avoidance.34 We also found on item analysis that negative symptoms such as apathy and personal neglect were more severe in bvFTD, but the disinhibition items were involved more similarly. This suggests a different involvement of the medial frontal cingulate and the anterior temporal orbitofrontal circuits earlier in the disease. Semantic dementia without behavioral impairment may appear early in the illness. On the other hand, SD often appears secondarily to bvFTD and remains undiagnosed. From our longitudinal cohort study of FTD, only patients with bvFTD developed SD later (approximately 20%). Conversely, more patients with SD (76%) developed bvFTD as a secondary syndrome compared with other presentations, suggesting an association of bvFTD with SD.29 In the present study, the Frontal Behavioral Inventory, as expected, showed the greatest behavior impairment in the bvFTD group. Nonetheless, the SD group also obtained higher scores (more behavioral abnormalities) compared with AD and PNFA.

In this study, patients with SD and PNFA performed worse than the other groups on the Mini-Mental State Examination and the Dementia Rating Scale because these tests have significant language components. Clinically, these patients are more aphasic than demented. Although episodic and nonverbal visuospatial memory is preserved in SD,32 family reports of forgetfulness of names were common (28 of 37 in Table 1). Poor performance on verbal memory tests related to verbal semantic loss and reversal of the temporal gradient for episodic memory in SD has been observed by others.38,39 The present study also indicates that the category fluency is significantly worse in the SD group, likely owing to lexicosemantic rather than executive dysfunction. The incidence of SD was estimated in one clinic as 25% in the FTD population vs 10% in ours. This may reflect differences in selection or referral but incidence data from a well-designed epidemiological study are lacking.

Greater left than right temporal atrophy has been previously described as characteristic of SD;12,37; our data confirm this. Marked temporal atrophy should alert the clinician to the diagnosis. There are exceptions, however, suggesting that neuroimaging should be used as an adjunct rather than primary diagnostic criterion. Neuroimaging is also stage related and, eventually, both temporal lobes and frontal areas become involved.40

The underlying pathology is most often ubiquitin positive.19,37,41 In our series, 5 of 6 autopsies had ubiquitin-positive, tau-negative inclusions and 1 had dementia that lacked distinctive histopathology. Recent studies suggested an association with more neuritic ubiquitin deposits with few cytoplasmic inclusions.19 So far we do not have sufficient data to confirm or contradict this correlation.

In conclusion, the cardinal diagnostic features of SD based on our findings are (1) the questioning of the meaning of words, which is a striking manifestation of the comprehension deficit of single nouns (SD may be called the “What is...?” disease after this singularly characteristic clue); (2) garrulous, empty, fluent speech output with thematic perseveration and semantic jargon; and (3) the strong association between SD and bvFTD—the two presentations often converge. The equation with all fluent aphasia is an overinclusive dilution of a clinically and possibly biologically distinct presentation. The overlap with aphasic AD, logopenic progressive aphasia, and early PNFA creates diagnostic uncertainties until the characteristic features of SD emerge. Nevertheless, the identification of SD is valuable, particularly in view of the recent advances in pathology and molecular biology of FTD that suggest a potential for specific treatment of different varieties of the presentation.

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REFERENCES