A Young Man With Progressive Language Difficulty and Early-Onset Dementia

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Report of a Case

A right-handed man in his late 40s with 12 years of education presented with a 1.5-year history of cognitive decline, characterized by gradually increasing difficulty expressing his thoughts and ideas. His family noted word-finding difficulty but no problems with his memory for recent events. Initial workup findings were unremarkable, but during the course of the next decade left anterior temporal atrophy was noted on magnetic resonance imaging and the patient developed increasing reasoning difficulty, apathy, and disinhibition. Several degenerative causes were considered. The patient died 22 years after symptom onset, and the final diagnosis was confirmed at autopsy.

Laboratory and Neuroradiologic Data

Imaging

While magnetic resonance imaging findings of his brain during initial workup were unremarkable, at 6 years into the illness there was marked left anterior and inferior temporal lobe atrophy (Figure 1). Left insular atrophy with widening of the perisylvian fissure also was evident. Four years later, repeated imaging showed interval worsening of the left anterior and inferior temporal atrophy, with a knife-edge appearance of the gyri at the temporal pole.

Laboratory Studies

As part of his initial evaluation, he had complete blood cell count, basic metabolic profile, vitamin B₁₂, folate, thyroid function cascade, and syphilis testing performed, all of which had results that were negative or within normal limits. A lumbar puncture revealed 2 nucleated cells, 52% lymphocytes (to convert to proportion of 1.0, multiply by 0.01), a glucose level of 55 mg/dL (to convert to millimoles per liter, multiply by 0.0555), a protein level of 52 mg/dL (reference range <35 mg/dL), and negative results with Gram staining, bacterial and fungal cultures, and cytologic analysis.

Clinical Discussion (Dr Botha)

The presentation is that of an early-onset, progressively dementing illness. Early-onset dementia usually is defined as acquired cognitive impairment interfering with activities of daily living, with onset before age 65 years. The distinction is important because nondegenerative and potentially treatable causes are far more common in this age group. Autoimmune, inflammatory, and infectious
causes are especially important to identify, but in the current case a degenerative etiology is almost certain given the long duration and steady decline as well as the slowly worsening atrophy on imaging.

This patient presented with language dysfunction, and aphasia seems to have dominated the early phase of his disease. Furthermore, there is nothing to suggest significant impairments in his activities of daily living, beyond difficulties related to his aphasia, early in the disease course. As the illness progressed, the patient developed more general cognitive impairment as well as a prominent behavioral syndrome. The patient would meet core criteria for a diagnosis of primary progressive aphasia (PPA).1 His bedside cognitive examination and formal neuropsychometric testing did show impaired performance on nonlanguage tasks, but it is clear that these tests may also be negatively affected by an underlying aphasia and should not preclude a diagnosis of PPA.2

More specifically, within the PPA framework, the patient’s presentation is most consistent with semantic dementia (SD), or the semantic variant of PPA.1,3 As one of the language variants of frontotemporal dementia, it is well known to result in a secondary behavioral syndrome in a subset of patients. The prominent and early comprehension difficulties as well as calculation difficulty are somewhat atypical, but in light of the prominent anterior temporal atrophy as well as the apparent loss of object knowledge and word meaning, SD remains the most appropriate classification. Patients with SD may present with memory concerns and tend to perform poorly on verbal tests of episodic memory, often leading to an incorrect diagnosis of Alzheimer disease (AD).4

Approximately three-quarters of SD cases have underlying TAR DNA-binding protein 43 (TDP-43) pathology, usually type C, with tau and AD neuropathologic change (AD pathology) accounting for the rest (for a recent review, see the article by Harris and Jones5). Pick disease, characterized by 3-repeat tau deposition, accounts for the overwhelming majority of cases with tau pathologic features. Although the proportion of cases due to AD pathology varies significantly from center to center, recent amyloid positron emission tomographic imaging suggests that it might account for more cases than suggested by pathologically confirmed series, which would make it the second most common cause of SD.3

The main diagnostic challenge in this case involves predicting which of these 3 pathologies underlies the patient’s presentation. No definitive pathologic signatures exist, but there are clues we can use to adjust our base probability, which would place TDP-43 as the most likely.

A secondary behavioral syndrome is common in both TDP-43- and Pick disease–related SD but is virtually unreported in cases with AD pathology.6 Early executive dysfunction and dyscalculia were found to be more common in Pick disease cases than among TDP-43 cases, although the small number of Pick disease cases in the study...
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Pathological Discussion (Dr Parisi)

The profoundly atrophic formalin-fixed left hemibrain weighed 340 g (left hemisphere weight, 270 g; left cerebellum and brainstem weight, 70 g). There was severe and sharply circumscribed lobar atrophy with a knife-edge/walnut appearance of gyri in the frontal and temporal lobes, with relative sparing of the precentral and postcentral gyri and the posterior two-thirds of the superior temporal gyrus, less severe involvement of the parietal lobe, and relative preservation of the occipital lobe (Figure 2A).

Coronal sections through the cerebral hemispheres demonstrated marked frontal and temporal atrophy, prominent flattening of the head of the caudate nucleus (Figure 2B, left image), with relative sparing of the remainder of the basal ganglia and the thalamus, thinning of the corpus callosum, enlargement of the lateral ventricles, and reduction of the centrum semiovale. The amygdala and entorhinal cortex were severely atrophic (Figure 2B, middle image), while the hippocampus was relatively spared (Figure 2B, right image). Transverse sections through the brainstem revealed slight pallor of the pars compacta of the substantia nigra.

Frontal and temporal neocortex showed severe pancortical neuronal loss and gliosis (status spongiosis) (Figure 2C), while less involved regions showed neuronal loss and gliosis mainly in the third and fifth cortical layers. The subcortical white matter showed atrophy and gliosis corresponding to the degree of cortical atrophy.

Well-demarcated, amorphous, and slightly basophilic spherical neuronal cytoplasmic inclusions (Pick bodies) were present throughout affected cerebral cortex (mostly in layers II and III) and subcortical gray matter, and they were particularly abundant in the hippocampus (dentate fascia and cornu ammonis 1) and in affected regions of neocortex (Figure 2D). Pick bodies stain intensely with silver stains (Figure 2E) and show striking immunoreactivity to tau (Figure 2F) and 3-repeat tau (Figure 2G) but not to 4-repeat tau or subtypes of TDP-43. However, it is accepted that most TDP-43 cases were type C and most tau cases had changes consistent with modern definitions of Pick disease.

Table. Selected Features Shown to Predict Underlying Pathology in Cases of Semantic Dementia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pathology*</th>
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<tbody>
<tr>
<td></td>
<td>TDP-43</td>
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<tr>
<td>Approximate prevalence, %</td>
<td>74</td>
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<tr>
<td>Clinical feature</td>
<td></td>
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<tr>
<td>Secondary behavioral syndrome</td>
<td>++</td>
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<tr>
<td>Secondary corticobasal or marked amnestic syndrome</td>
<td>−</td>
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<tr>
<td>Early dyscalculia</td>
<td>−</td>
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<tr>
<td>Early phonologic errors</td>
<td>+/−</td>
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<tr>
<td>Mutism at any time in disease course</td>
<td>−</td>
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<tr>
<td>Signs of motor neuron disease at any time in disease course</td>
<td>++</td>
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<tr>
<td>Imaging finding</td>
<td></td>
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<tr>
<td>Knife-edge atrophy</td>
<td>+</td>
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<tr>
<td>Very asymmetrical atrophy</td>
<td>+</td>
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<tr>
<td>Anterior &gt; posterior temporal atrophy</td>
<td>+</td>
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Abbreviations: AD, Alzheimer disease; TDP-43, TAR DNA-binding protein 43; ++, highly supportive; +, supportive; +/−, indeterminate; −, not supportive.  
* Many of the pathologically confirmed series did not differentiate between 3-repeat and 4-repeat tau or subtypes of TDP-43. However, it is accepted that most TDP-43 cases were type C and most tau cases had changes consistent with modern definitions of Pick disease.
Conclusions

First described clinically by Arnold Pick in 1892, Pick disease is a rare cause of dementia. Disease onset mostly occurs before age 65 years, and there does not appear to be a sex predilection. Its clinical course can be variable, with some studies suggesting a rapid decline, but when the presentation is that of SD, disease duration ranges from 8 to 18 years and may be far longer as this case illustrates. Whereas Pick disease initially referred to a clinical syndrome distinct from AD, as well as a spectrum of pathologic changes, it is now reserved for the specific pattern of 3-repeat tau-related changes described earlier. It typically results in focal cortical atrophy, with the clinical syndrome depending on the area involved. The most common presentation is behavioral variant frontotemporal dementia, and the second most common is progressive agrammatic or nonfluent aphasia with or without apraxia of speech. Semantic dementia is estimated to make up fewer than 15% of Pick disease cases. By virtue of it being a rare cause of dementia, most of the literature is composed of case reports or small series; hence, antemortem clinical signatures of Pick disease have not been well studied, especially when SD is the presenting syndrome. Coupled with the aforementioned problems with imaging predictors of pathology, the result is that, to our knowledge, no evidence-based predictors of Pick disease exist. The hope is that the rise of tau positron emission tomography will address this, where a clinical presentation of SD with a tau-positive and amyloid-negative scan would be suggestive of Pick disease.

ARTICLE INFORMATION

Accepted for Publication: January 25, 2016.
Published Online: March 28, 2016. doi:10.1001/jamaneurol.2016.0246.

Author Contributions: Dr Boeve had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Botha, Parisi, Klaas.
Drafting of the manuscript: Botha, Parisi.
Critical revision of the manuscript for important intellectual content: Boeve, Jones, Parisi, Klaas.
Administrative, technical, or material support: Jones, Klaas.
Study supervision: Jones, Klaas.
Conflict of Interest Disclosures: Dr Boeve reported serving as an investigator for clinical trials sponsored by GE Healthcare and FORUM Pharmaceuticals; receiving royalties from the publication of Behavioral Neurology of Dementia (Cambridge Medicine, 2009); serving on the scientific advisory board of the Tau Consortium; serving as a consultant for Isis Pharmaceuticals; and receiving research support from the National Institutes of Health (grants U01 AG045390, US4 NS020389, P50 AG0165374, U01 AG006786, RO1 AG018566, RO1 AG023236, and RO1 AG041797) and the Mangurian Foundation. Dr Parisi reported serving on scientific advisory boards for the US Government Defense Health Board and the Subcommittee for Laboratory Services and Pathology; serving as a section editor for Neurology; receiving royalties from the publication of Principles and Practice of Neuropathology, second edition (Oxford University Press, 2003); and receiving research support from the National Institutes of Health as a coinvestigator (grant NS32352-13). No other disclosures were reported.
Funding/Support: This work was supported by grant P50 AG016574 from the Mayo Clinic Alzheimer’s Disease Research Center and by the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer’s Disease Research Program of the Mayo Foundation for Medical Education and Research.
Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review,
or approval of the manuscript; and decision to submit the manuscript for publication.

**Additional Contributions:** We thank the patient and his family for participating in aging and neurodegenerative disease research.

**REFERENCES**


