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

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A man in his late 40s presented with cognitive decline characterized by gradually increasing difficulty expressing his thoughts and ideas. His family noted word-finding difficulty, especially with the names of people, 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.

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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. Two of his relatives developed dementia in their 70s.

His initial mental status examination findings were notable for problems with calculation, abstraction, and recall, while his language examination revealed difficulty following complex commands and anomia on confrontational naming with intact repetition. His neurologic examination findings were otherwise normal.

Findings of an extensive workup, including laboratory studies and neuroimaging, were unremarkable. He returned a few months later, at which point neuropsychometric testing revealed markedly impaired category and letter fluency, impaired registration on logical and audio-verbal memory, poor comprehension of complex instructions, and severe anomia.

At follow-up 2 years after his initial presentation, he had developed more comprehension difficulties and had resorted to pointing at objects because of his profound word-finding difficulty. At 4-year follow-up, his memory for recent events as well as his reasoning abilities had declined, although he still was independent in most of his activities of daily living including managing medications, driving, and dressing. He could read some words in the newspaper but could not understand what they meant. The following year, he was noted to have more difficulty with concepts and planning and was unable to name or demonstrate the use of a knife or a saw. His vocabulary became more restricted, and he often used the word "job" instead of specific nouns. At his last follow-up 10 years after symptom onset, he had very few vocalizations and minimal comprehension. He also had developed apathy, a preference for sweets, and disinhibition. He had no eye movement abnormalities, no pyramidal or extrapyramidal signs, and no hallucinations. He became mute, moved into a skilled nursing facility shortly afterward, and was dependent in all activities of daily living until he died more than a decade later, 22 years after symptom onset.

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.

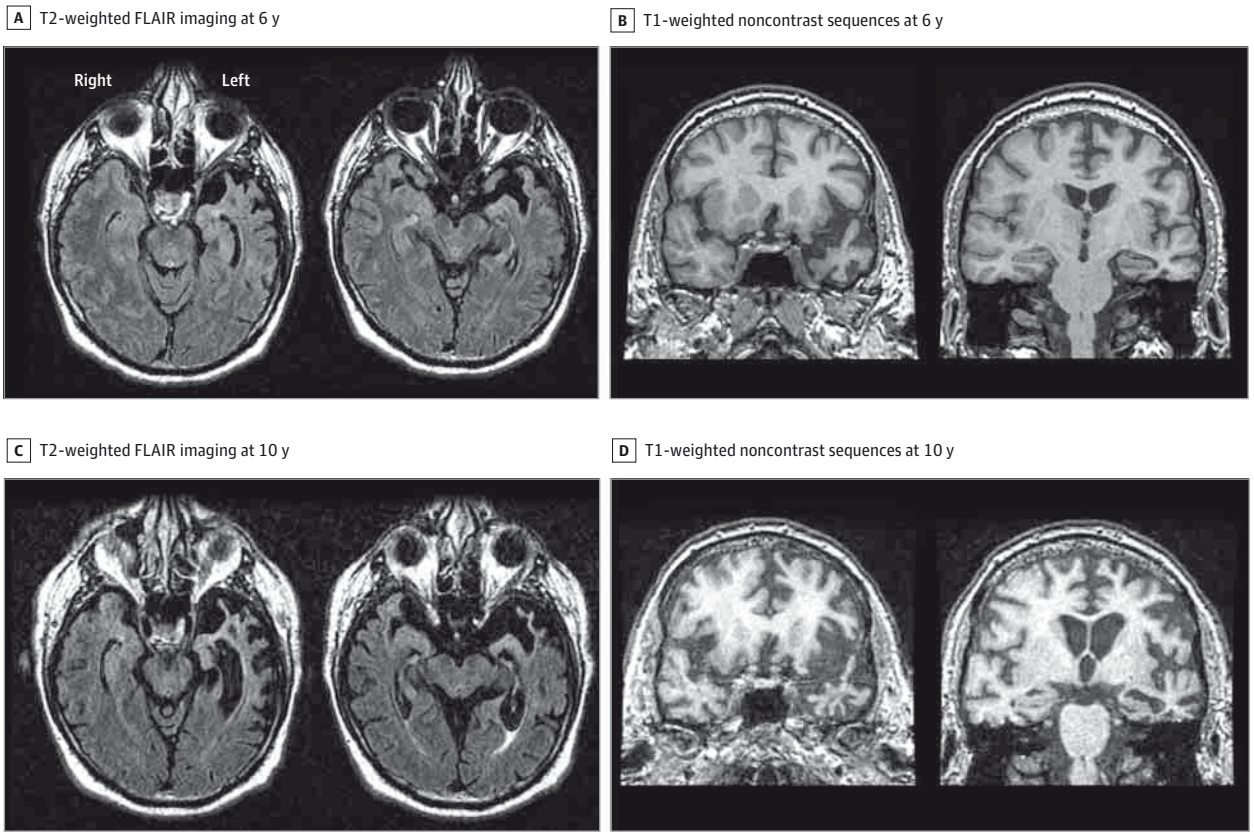
Laboratory Studies

As part of his initial evaluation, he had complete blood cell count, basic metabolic profile, vitamin B_{12}, 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

Figure 1. Magnetic Resonance Images



A and B, T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging (A) and T1-weighted noncontrast sequences (B) 6 years after symptom onset show marked left anterior temporal atrophy. C and D, T2-weighted FLAIR imaging (C) and T1-weighted noncontrast sequences (D) 10 years after symptom onset show further left temporal atrophy, with knife-edge gyral atrophy.

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 Jones[5]). 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

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

Feature	Pathology[a] TDP-43	Tau	AD
Approximate prevalence,[5] %	74	14	12
Clinical feature			
Secondary behavioral syndrome[2,12]	++	++	–
Secondary corticobasal or marked amnestic syndrome[12]	–	+/–	+
Early dyscalculia[6]	–	+	–
Early phonologic errors[12]	+/–	+	+/–
Mutism at any time in disease course[6]	–	–	+
Signs of motor neuron disease at any time in disease course[13]	++	–	–
Imaging finding			
Knife-edge atrophy[6,10]	+	++	+/–
Very asymmetrical atrophy[6]	+	++	+/–
Anterior > posterior temporal atrophy[13]	+	+	–

Abbreviations: AD, Alzheimer disease; TDP-43, TAR DNA-binding protein 43; ++, highly supportive; +, supportive; +/–, indeterminate; –, not supportive.

[a] 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.

is an obvious limitation.[6] Mutism, regardless of initial presentation, is often seen later in Pick disease cases.[6] Age at onset within SD does not seem to differ depending on underlying pathology.[4] Both TDP-43 type C and Pick disease pathology can result in remarkably long disease durations in SD.[6]

A family history of dementia in SD is rare[4] but is estimated to be around 2% to 7%. However, truly *familial* SD is extremely rare. Progranulin gene (*GRN*) mutations can present with strikingly asymmetric atrophy of the left temporal lobe, often presenting with a hybrid between PPA subtypes or atypical logopenic progressive aphasia, but pure SD cases due to *GRN* mutations are exceedingly rare.[7]

A central problem with imaging predictors of pathology is the fact that regional atrophy is associated with clinical features to a greater extent than with pathologic findings.[8] This is certainly true of TDP-43– and Pick disease–related SD, where the regional atrophy pattern is indistinguishable.[6,8] The degree of asymmetry may be helpful: it tends to be greater in Pick disease cases than in TDP-43 cases, and greater in either of these than in cases with AD pathology.[6,8] Marked, focal atrophy such that only a sliver of brain remains, so-called knife-edge atrophy, as well as relative sparing of the posterior two-thirds of the superior temporal gyrus are widely reported as suggestive of underlying Pick disease.[9] However, these findings were originally described at gross pathology and have not been well studied in the antemortem stage. Knife-edge atrophy has been reported on magnetic resonance imaging in cases due to TDP-43 proteinopathy, corticobasal degeneration, and progranulin mutations, to name a few non–Pick disease etiologies.[10] Even at autopsy, superior temporal gyrus sparing does not appear to be specific for Pick disease in the case of SD.[11] Some imaging differences do, however, exist between SD due to AD pathology and tau or TDP-43 pathology. Extrahippocampal atrophy is less marked in AD pathology cases but when present tends to involve the superior temporal gyrus, and knife-edge atrophy has not been reported.[8] Furthermore, severe atrophy involving the fusiform gyrus suggests non-AD pathology.[8] The main distinguishing features are summarized in the **Table**. Although there are several features in this case that hint at Pick disease as the underlying pathology, it is difficult to choose it over TDP-43 given the high prior probability of the latter.

Pathological Discussion (Dr Parisi)

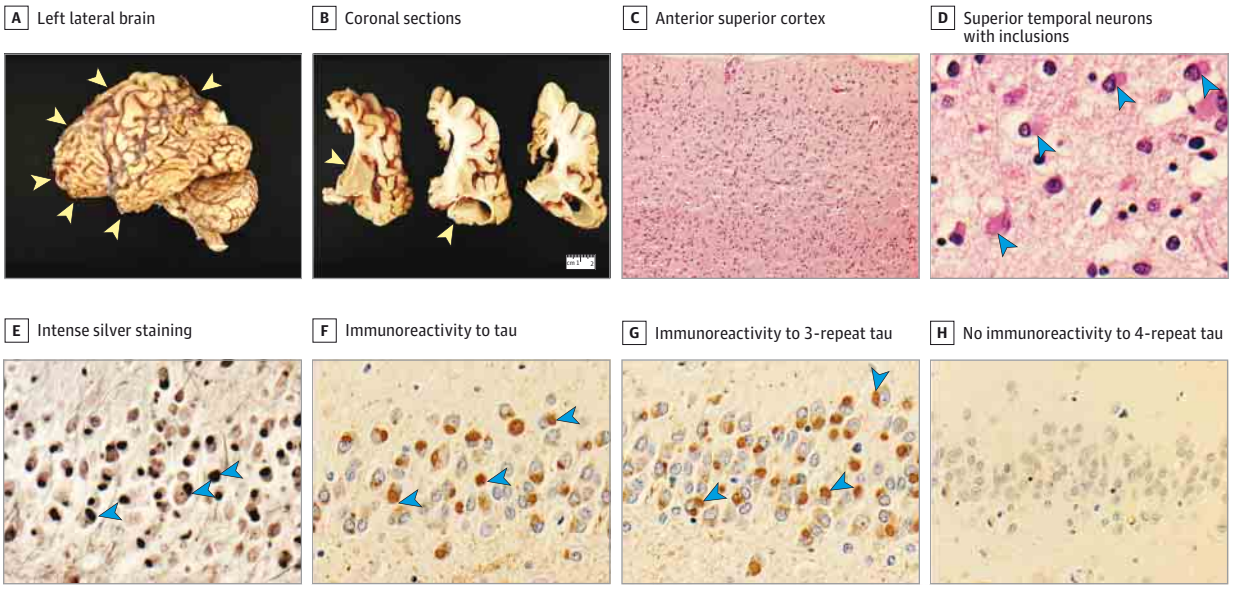
The profoundly atrophic formalin-fixed left hemibrain weighed 340 g (left hemisphere weight, 270 g; left cerebellum and brainstem weight, 70 g). There was severe and sharply circumscribed lobar atrophy with a knife-edge/walnut appearance of gyri in the frontal and temporal lobes, with relative sparing 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 2**A).

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 (Figure 2H). The findings in this patient were characteristic of Pick disease. No significant coexisting AD neuropathologic changes, α-synuclein–immunoreactive lesions, or TDP-43–immunoreactive lesions were noted.

Figure 2. Pathological Findings



A, Left lateral view of the brain showing marked circumscribed atrophy of the frontal and anterior temporal lobes with less severe involvement of the parietal lobe (arrowheads). B, Coronal sections demonstrate marked thinning of the frontal and anterior temporal neocortex with flattening of the caudate head (left image, arrowhead). The amygdala and entorhinal cortex are severely atrophic (middle image, arrowhead), while the hippocampus is relatively preserved (right image). C, The anterior superior temporal cortex shows severe pancortical neuronal loss and gliosis or status spongiosis (hematoxylin-eosin, original magnification ×100). D, Surviving superior temporal neurons contain distinctive, well-demarcated, slightly basophilic, rounded inclusions (arrowheads) characteristic of Pick bodies (hematoxylin-eosin, original magnification ×600). E-H, Pick bodies are consistently present in the dentate fascia of the hippocampus, showing intense staining with silver (arrowheads) (Bielschowsky silver stain) (E), striking immunoreactivity to tau (arrowheads) (AT8 antibody) (F), and selective tau staining with immunoreactivity to 3-repeat tau (arrowheads) (G) but not to 4-repeat tau (H) (original magnification ×600).

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.[14] 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.[6,14] 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.[9] 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.[6,14] 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.

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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.

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