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Primary Progressive Apraxia of Speech Caused by TDP-43

A Case Report

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Abstract

Objectives

To introduce the first case in which primary progressive apraxia of speech (PPAOS) is associated with TAR DNA-binding protein 43 (TDP-43) instead of 4-repeat tau.

Methods

This patient was identified through a postmortem autopsy. Following an initial diagnostic evaluation, he participated in 3 annual research visits during which speech, language, cognitive, and neurologic assessments were administered. Neuroimaging was also acquired.

Results

Apraxia of speech was diagnosed at his initial visit with a comprehensive neurologic examination further revealing subtle motor findings in the right hand. At subsequent visits, agrammatic aphasia and motor symptoms consistent with corticobasal syndrome were evident. Cognition and behavior remained relatively intact until advanced stages. FDG-PET revealed hypometabolism in the right temporoparietal cortex and left premotor and motor cortices. There was also low-level signal in the right temporoparietal cortex on tau-PET. A sequence variation in the progranulin gene was identified (GRN c.1A>C, p.Met1). Pathologic diagnosis was TDP-43 Type A with an atypical distribution of inclusions in premotor and motor cortices.

Discussion

This case report demonstrates that TDP-43 Type A inclusions in an atypical distribution can present clinically as PPAOS. The sequence variation in the progranulin gene and asymmetric temporoparietal cortex involvement were the strongest indications of the unusual neuropathophysiology prior to autopsy.

Introduction

Primary progressive apraxia of speech (PPAOS) is a form of frontotemporal lobar degeneration syndrome characterized by the insidious onset of difficulties with motor speech programming. Patients describe knowing exactly what they want to say in their heads, but due to disrupted motor plans, their verbal output contains articulatory errors (e.g., distortions, distorted substitutions, restarts), is slower, and can be segmented at the syllable level. Although speech difficulties are the initial symptom and often remain the most prominent, these patients typically develop a broader clinical phenotype that can include aphasia, cognitive impairment, and other motor

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symptoms (e.g., spasticity, rigidity, ideomotor apraxia) that can resemble corticobasal syndrome or progressive supranuclear palsy.[1] [^{18}F]-fluorodeoxyglucose (FDG) PET is the most sensitive neuroimaging technique early in the disease course, typically revealing hypometabolism in the supplementary motor area and precentral gyrus.[1,2] Together, this clinical progression and the corroborating neuroimaging findings are highly predictive of abnormally hyperphosphorylated 4-repeat (4R) tau depositions in the brain at autopsy, including progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).[3-6] The patient reported here initially presented with PPAOS and subsequently developed atypical parkinsonism that resembled CBS, which is also commonly associated with 4R tau accumulation.[7] Unexpectedly, postmortem tau immunohistochemistry was almost completely negative; rather, TAR DNA-binding protein 43 (TDP-43) Type A was the primary pathology. Subsequent genetic testing revealed a sequence variation in the progranulin gene (GRN c.1A>C, p.Met1).

Case

This study was approved by the Mayo Clinic Institutional Review Board, and the patient provided written informed consent for enrollment.

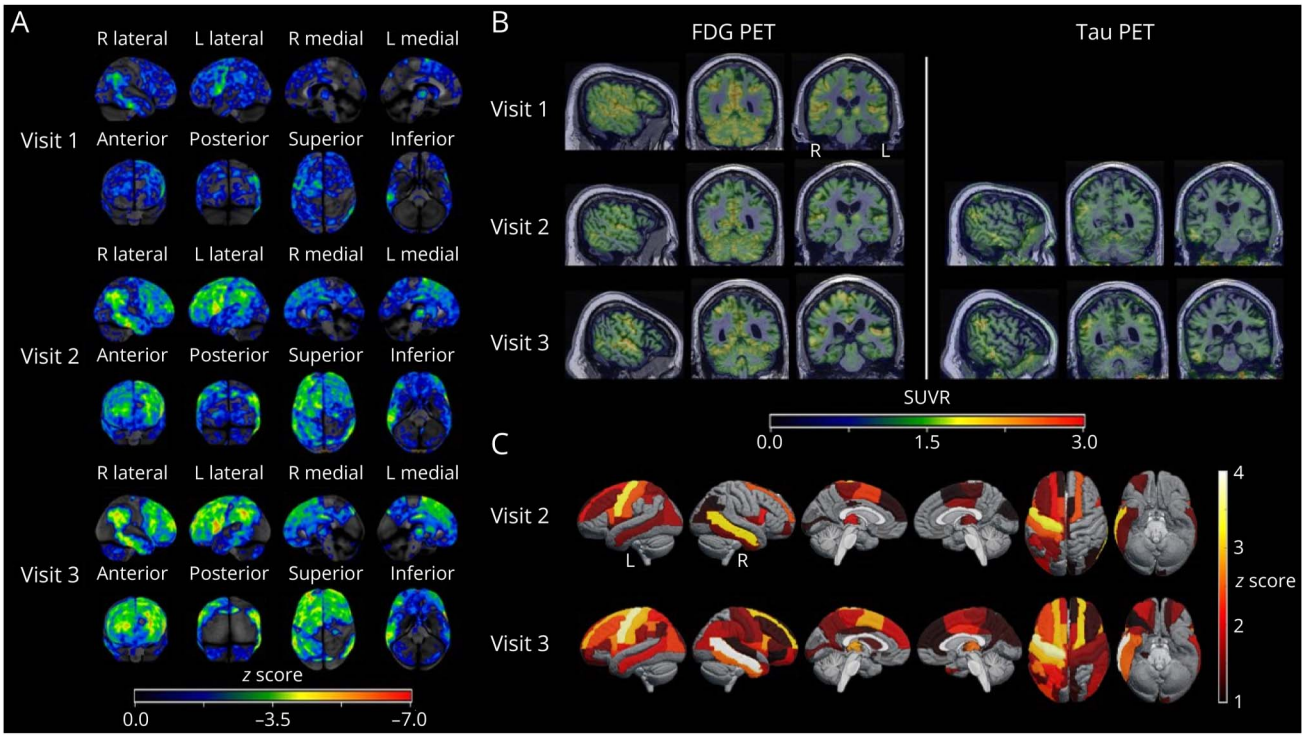
Clinical History

At baseline, the patient was a successful entrepreneur who was right-handed with 18 years of education. At the age 57 years, he presented to the Mayo Clinic with a 1.5-year history of progressive speech difficulties and an outside diagnosis of ataxia with no evidence of cerebellar atrophy on MRI. He reported having an articulation disorder in childhood that had fully resolved. His medical history was otherwise notable for hypercholesterolemia, hypertension, obstructive sleep apnea and insomnia, and gout. Family history was negative for dementia or related disorders.

The patient recalled that he first noticed difficulty saying the word "statistically" and described his speech as occasionally "jumbled." His speech pattern was consistent with apraxia of speech. There was no evidence of aphasia on examination despite subjective reports that spelling and handwriting had become more problematic. His neurologic examination was largely unrevealing, except for potential myoclonus when his fingers were outstretched, but it was unclear at the time whether this was related to recent shoulder surgery. He was diagnosed with mild-moderate PPAOS and referred for enrollment in our research protocol.

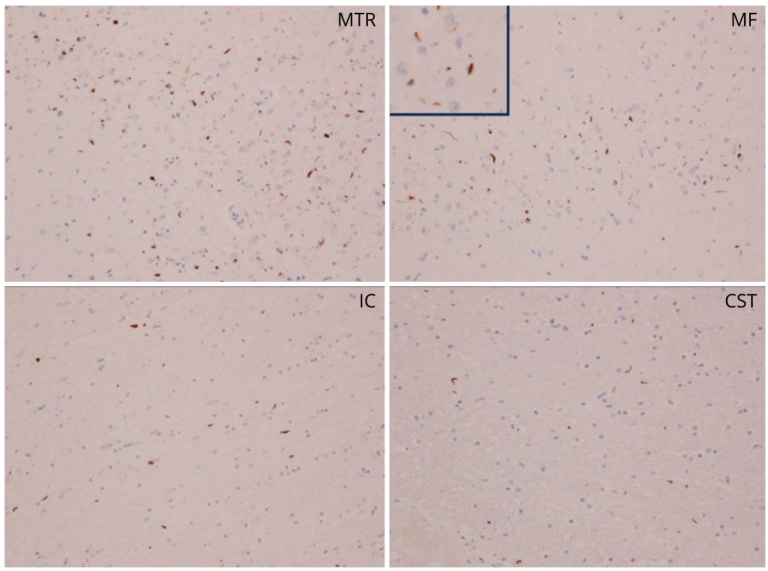
At the first research visit 2 months later, he continued to meet diagnostic criteria for PPAOS with primarily phonetic features, including distortions and distorted substitutions that increased

Figure 1 Neuroimaging Results



(A) Cortex ID z-score maps for the FDG-PET scans across the 3 research visits, referenced to the pons. (B) FDG-PET and tau-PET standardized uptake value rations (SUVR) images overlaid on the MRI. FDG-PET images are referenced to the pons, and tau-PET images are referenced to the cerebellar crus grey matter. (C) Three-dimensional surface renderings with degree of volume loss of each brain region depicted as a z-score compared with age-matched controls (greater z-score represents greater volume loss). Brain regions were defined using the Mayo Clinic Adult Lifespan Template. Atrophy maps are not available for Visit 1 because a 1.5 T scanner was used and regional volumes could not be accurately calculated.

Figure 2 Neuropathology Results



Postmortem histology results showing TDP-43 in the medial temporal lobe (MTR), medial frontal lobe (MF), internal capsule (IC), and corticospinal tract (CST). Magnification is 200×; inset magnification is 400×.

with utterance complexity[8] Phonetic predominant PPAOS was originally referred to as type 1.[9] There was no evidence of dysarthria or aphasia. Neurologic testing again raised concern for myoclonus and tremulousness, particularly on the right side, but was otherwise unremarkable. Neuropsychological assessment revealed that his mental flexibility and immediate visual episodic memory were below average and slightly below expectations. Assessment results from all research visits are available in the eTable.

By his follow-up visit 1 year later, almost 3 years following the onset of his symptoms, his apraxia of speech had progressed to moderate-severe and continued to be his most prominent symptom. Phonetic (i.e., articulatory) features continued to dominate. He had developed mild hypokinetic dysarthria and mild aphasia, primarily characterized by agrammatism in his speech and writing. Word retrieval was a relative strength. He had slow movements and ideomotor apraxia, more so on the right, meeting criteria for possible CBS.[10] He also demonstrated impaired performance on formal measures of auditory/spatial attention, visuomotor sequencing, visuoconstruction, and abstract reasoning, but continued to work.

His third and final research visit 1 year later revealed marked decline. He had significant difficulty communicating, including with an augmentative communication device, and was unable to complete most formal testing. He required assistance with activities of daily, both because of his severe ideomotor apraxia and his inability to sequence. He had also developed dysphagia. He had begun falling, but up and down gaze remained normal. Unfortunately, he died several months later, approximately 4.5 years following his initial symptoms.

Neuroimaging

FDG-PET and MRI scans were collected at all 3 research visits, an (11)C-labeled Pittsburgh Compound-B (PiB) PET scan was collected at Visit 2, and a tau-PET scan was collected at Visits 2 and 3. The first FDG-PET scan showed hypometabolism in the right temporoparietal cortex, with additional involvement of the frontal lobes, especially the premotor and motor regions (see Figure 1). The frontal hypometabolism was most pronounced in the left hemisphere, which remained the case throughout subsequent scans. The MRI scans similarly showed atrophy in the temporoparietal cortex, with greater involvement of the right hemisphere, as well as left frontal atrophy, particularly involving the supplementary motor and motor cortices (see Figure 1C). Atrophy worsened over time in these regions and spread to involve both frontal lobes. The PiB-PET scan was negative for β-amyloid deposition. Flortaucipir-PET scans at years 2 and 3 suggested that Alzheimer disease type tau was unlikely the primary pathology, with only very low levels of uptake in the white matter of the right temporoparietal cortex.

Genetics and Pathology

Postmortem genetic testing revealed a sequence variation in the progranulin gene (GRN c.1A>C, p.Met1). Tau immunohistochemistry on the left hemisphere was almost completely negative. There were neuritic processes and neuronal cytoplasmic inclusions with TDP-43 immunohistochemistry (see Figure 2). Morphology of the TDP-43 pathology was consistent with Type A, but with an atypical distribution, including severe involvement of the left premotor and motor cortices.[11] There were also TDP-43–positive oligodendroglial inclusions of the corticospinal

tract from the cortex to the cervicomedullary junction. The hypoglossal nucleus was well populated and free of Bunina bodies and TDP-43 inclusions. Alzheimer type pathology (Thal phase 2, Braak stage III) was also present, but judged to be consistent with pathologic aging rather than Alzheimer disease.

Data Availability

Anonymized data will be made available by request from any qualified investigator.

Discussion

PSP and CBD are the 2 most common pathologies known to cause PPAOS, in which apraxia of speech is the presenting and primary symptom.[4] Before now, TDP-43 Type A had only been associated with apraxia of speech in the context of related syndromes, including progressive agrammatic aphasia, behavioral variant frontotemporal dementia, and classic CBS. Overall, the clinical features and course for this patient were in keeping with expectations for PPAOS patients, albeit with a rapid progression relative to expected survival rates for this disorder (i.e., 9 years on average).[1] The sequence variation in the progranulin gene could have been a strong indication of TDP-43 pathology before autopsy.[12] Asymmetric involvement of the temporoparietal regions on neuroimaging has also previously been associated with TDP-43 type A pathology and progranulin sequence variations.[13,14] In this case, the TDP-43 had an unusual distribution including prominent involvement of the left motor and premotor cortices, which likely contributed to the apraxia of speech. There were also TDP-43–positive inclusions in the corticospinal tract, raising suspicion for motor neuron disease. In conclusion, although considerably less common than PSP or CBD, TDP-43 Type A should be considered on the list of possible causes of PPAOS and testing for sequence variations in the progranulin gene may be helpful in identifying potential patients. Future studies should examine the rate of decline in PPAOS and evaluate if that, too, might be a biomarker for non-tau pathology.

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Jennifer L. Whitwell, PhD	Department of Radiology, Mayo Clinic	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
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Joseph R. Duffy, PhD	Department of Neurology, Mayo Clinic	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Heather M. Clark, PhD	Department of Neurology, Mayo Clinic	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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