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DIFFUSE LEUKOENCEPHALOPATHY WITH SPHEROIDS PRESENTING AS PRIMARY PROGRESSIVE APHASIA

A 52-year-old right-handed man reported 2 years of progressive word-finding difficulties. He noticed hesitations when retrieving words and difficulty writing and calculating while working in his carpentry business. He was taking pravastatin for hyperlipidemia. Memantine was started prior to our clinical evaluation, and had no measurable effect. He had a great aunt with late-life amnesic dementia, his father died at age 59 years from lung cancer, and his mother died at age 75 of unknown causes. He had 18 years of education and no history of learning disabilities.

Clinical evaluation 2 years after onset demonstrated frequent word-finding pauses and circumlocution in speech, with intact grammar, repetition, and language comprehension. Word list generation (lists of animals or words starting with the letter “a”) was decreased. He had mild difficulty with the Tower of London task, and made errors of commission on a Go-No Go task with the right hand, but not the left. Overall, he had relatively preserved orientation, attention, comportment, episodic memory, and visuospatial skills. Customary activities were limited only by the aphasia. His sensorimotor function, tone, reflexes, motor speech, cerebellar function, and gait were all unremarkable. He was given a diagnosis of primary progressive aphasia (PPA), logopenic subtype, and enrolled in a longitudinal research program approved by the Institutional Review Board of Northwestern University.

The initial brain MRI (figure) showed pronounced left posterior parietal atrophy and punctate scattered subcortical white matter hyperintensities (WMH) on T2-weighted images. Laboratory studies including complete blood count, electrolytes, liver function, kidney function, coagulation panel, erythrocyte sedimentation rate, antinuclear antibodies, B₁₂, thyroid-stimulating hormone, and rapid plasma reagin were unremarkable, and mitochondrial genetics for encephalopathy were negative. CSF contained 0 leukocytes/ μ L, 231 erythrocytes/ μ L, glucose 69 mg/dL, and protein 55 mg/dL. β -Amyloid (125 pg/mL) and phospho-tau (61.7 pg/mL) levels were borderline for underlying Alzheimer pathology. The patient was homozygous for *APOE* allele ϵ 3.

Five years after onset, the aphasia had progressed to involve agrammatism, and the patient quit working. Other areas of behavior and cognition remained relatively intact, but he developed a right spastic hemiparesis. A repeat MRI revealed progression of the WMH (figure). In the year prior to his death, 7 years after onset, he had 2 seizures with head turning to the left followed by generalized tonic-clonic movements. He was treated with levetiracetam and lamotrigine. Repeat MRIs showed pronounced extension of the WMH and small areas of restricted diffusion within the centrum semiovale bilaterally, with the same regions appearing hypointense on apparent diffusion coefficient sequences.

The patient died 8 years after purported onset. Autopsy confirmed asymmetric cortical atrophy and severe white matter degeneration, predominantly in the left frontal and parietal regions. Microscopic evaluation of the white matter showed severe rarefaction, with sparse to moderate neurofilament-positive axonal spheroids, as well as pigmented glia and reactive astrocytes (figure). Ballooned neurons were noted in the left frontal cortex and left anterior cingulate gyrus. In addition, the cortex had severe cerebral amyloid angiopathy, but was devoid of microhemorrhages or infarcts. There were sparse neuritic amyloid plaques in entorhinal cortex and inferior parietal cortex, sparse neurofibrillary tangles (NFTs) in entorhinal cortex, and focally severe NFTs in left and focally moderate NFTs in right inferior parietal cortex. The principal and clinically most concordant autopsy findings in this patient are consistent with a diagnosis of diffuse leukoencephalopathy with spheroids (DLS).¹

Concomitant cerebral amyloid angiopathy in DLS has been previously reported.² Genetic testing for the *CSF1R* gene, known to be associated with the hereditary form of DLS, was negative for known mutations in exons 11–22.³

Discussion. DLS has been associated with seizure-like events, motor impairments, and neuropsychiatric symptoms sometimes mimicking frontotemporal dementia and corticobasal syndrome, but not progressive aphasia.^{4,5} We cannot exclude the possibility that Alzheimer disease (AD) pathology in the left inferior parietal region played a role in the clinical phenotype of this patient; however, the

Figure MRI and gross pathology of leukoencephalopathy presenting as primary progressive aphasia

Axial fluid-attenuated inversion recovery sequences of MRI as the disease progressed (A) from 3 years from onset and (B) 6 years from onset. (C) Gross coronal section of autopsied brain shows mild on the right, and severe on the left, parietal white matter degeneration and (D) axonal spheroids, neurofilament immunohistochemistry (Dako, Carpinteria, CA).

DLS was the predominant pathologic finding. This is a novel report of PPA secondary to DLS. Previous clinicopathologic correlates of PPA have reported 9 underlying pathologies, including Alzheimer pathology; frontotemporal lobar degeneration (FTLD)-tau of the corticobasal degeneration type, progressive supranuclear palsy type, and Pick type; FTLD-TDP types A, B, and C; mixed AD and dementia with Lewy body pathology⁶; and sporadic Creutzfeldt-Jakob disease.⁷ The hemispheric asymmetry is the common denominator for neuropathologic entities underlying PPA. The leukoencephalopathy in our patient showed a preference for the left hemisphere even after 8 years

of illness. This case adds a new pathologic correlate of PPA, and further prompts the question of why certain diseases remain asymmetric throughout the span of disease course.

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