Title
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Journal
JAMA Neurology, 70(2)

ISSN
2168-6149

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Publication Date
2013-02-01

DOI
10.1001/2013.jamaneurol.139

Peer reviewed

ONLINE FIRST

Sporadic Jakob-Creutzfeldt Disease Presenting as Primary Progressive Aphasia

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Objective: To report the clinical, neuropsychological, linguistic, imaging, and neuropathological features of a unique case of sporadic Jakob-Creutzfeldt disease in which the patient presented with a logopenic variant of primary progressive aphasia.

Design: Case report.

Setting: Large referral center for atypical memory and aging disorders, particularly Jakob-Creutzfeldt disease.

Patient: Patient presenting with logopenic variant primary progressive aphasia initially thought to be due to Alzheimer disease.

Results: Despite the long, slow 3.5-year course, the patient was shown to have pathology-proven sporadic Jakob-Creutzfeldt disease.

Conclusions: These findings expand the differential of primary progressive aphasia to include prion disease.

Arch Neurol. Published online November 5, 2012. doi:10.1001/2013.jamaneurol.139

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A DIAGNOSIS OF PRIMARY PROgressive aphasia (PPA), as defined by Mesulam,[1] requires that the patient have a progressive language disorder for 2 years before the onset of other neurological symptoms. Primary progressive aphasia can be divided into 3 clinical syndromes: nonfluent/agrammatic variant PPA, semantic variant PPA, and logopenic variant PPA.[2] Patients with logopenic variant PPA have impairments of naming and repetition in the context of relatively spared syntactic, semantic, and motor speech abilities. Alzheimer disease is the most common underlying pathology, followed by frontotemporal lobar degeneration.[2] Herein, we report the first case, to our knowledge, of sporadic Jakob-Creutzfeldt disease (CJD) fulfilling Mesulam's criteria for PPA.[1]

REPORT OF A CASE

A 56-year-old man was seen for a second opinion (by M. D. Greicius, at Stanford University, Palo Alto, California) after 22 months of progressive, mild, nonfluent aphasia. His condition had been diagnosed as PPA, likely due to Alzheimer disease. His first symptoms were word-finding problems and paraphasic errors (semantic and phonemic), followed 16 to 18 months later by mild difficulty with speech comprehension, but he showed no other symptoms. He continued to drive a truck for work, ride a mountain bike, kayak, and practice daily yoga.

A neurological evaluation only revealed language deficits and mild depression. His Mini-Mental State Examination score was 28.5/30, with points lost for naming and repetition. He had anomia with low-frequency words. He had no significant medical history and took no medications. His mother developed dementia in her 80s (and died at 86 years of age), and his father was 90 years of age and healthy. Careful review of magnetic resonance imaging (MRI) scans of the brain taken at another hospital, however, revealed findings suggestive of CJD (**Figure**).[3,4] An electroencephalogram showed left temporal slowing. He was referred to UCSF for a second opinion and our sporadic CJD treatment trial.

Twenty-four months after onset, his Mini-Mental State Examination score was 24. The neurological examination revealed impairments of word finding, repetition, and comprehension of longer

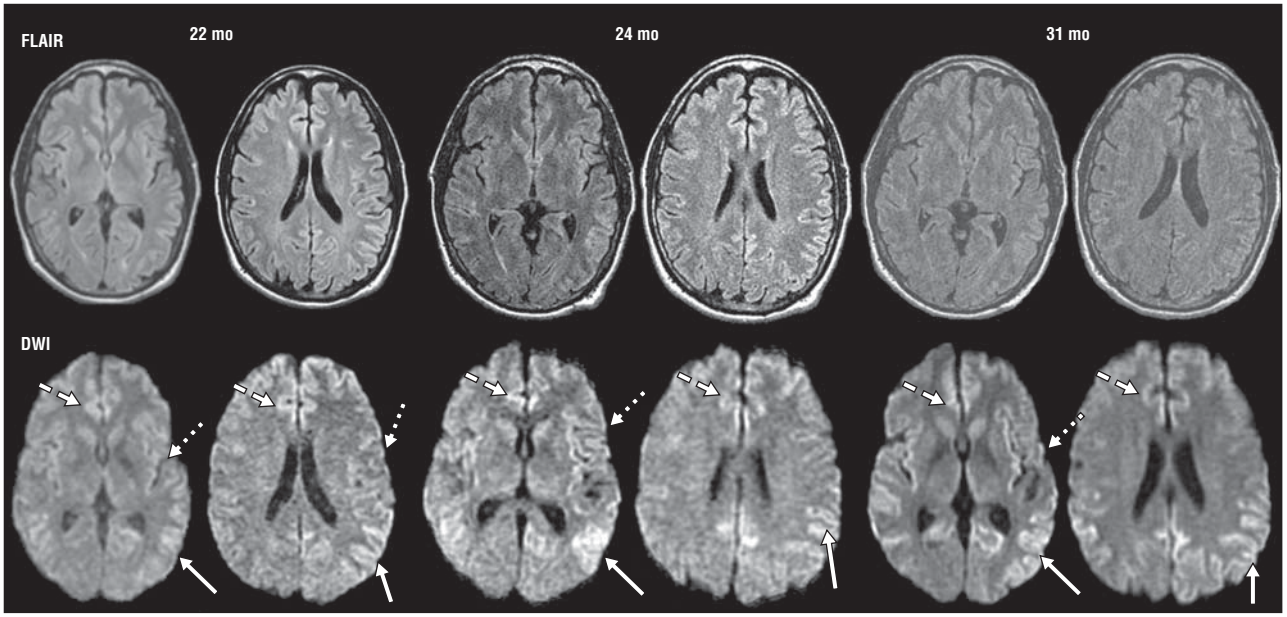

Figure. Axial fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI)/magnetic resonance imaging scans at 22, 24, and 31 months after onset showing extensive left greater than right cortical ribboning (hyperintensity) in the insula and peri-insular cortex (dotted arrow) and the cingulate gyrus (dashed arrow) and left greater than right cortical ribboning in the parietal-temporal cortex (angular gyrus; solid arrow). There is also a slight bilateral caudate hyperintensity. The apparent diffusion coefficient map confirmed restricted diffusion (not shown). Images are per radiological convention; thus, right is left and left is right.

utterances, with occasionally paragrammatic language, likely due to word-finding deficits. Confrontation naming for objects and famous people was impaired, although person knowledge was spared. Phonological paraphasias were evident on repetition of multisyllabic words. Impairment of comprehension and of repetition of sentences was consistent with verbal working memory deficits. Reading of regular and exception words (eg, knight), as well as pseudowords, was largely spared. There was no dysarthria or speech apraxia.

Neuropsychological testing revealed impairments of episodic memory, with superior performance on visual relative to verbal memory tasks. A motor examination revealed only subtle parkinsonism, with slightly decreased right arm swing and mild elbow cogwheeling with activation. He was able to partake in all activities of daily living, and he had a total Clinical Dementia Rating of 0.5.[5] The results of another MRI were the same as those from the MRI performed at another hospital, and a second electroencephalogram was now normal.

The results of a thorough rapid dementia workup were unrevealing.[6] The results of standard cerebrospinal fluid testing were normal. The Aβ42 level in a sample of cerebrospinal fluid was low to normal at 373.9 pg/mL; there was a mildly elevated level of phosphorylated tau at 77 pg/mL and an elevated level of total-tau protein at greater than 1200 pg/mL, which was interpreted (by Athena Diagnostics, Worcester, Massachusetts) as being consistent with Alzheimer disease, although a total-tau protein level greater than 1200 pg/mL was also considered consistent with CJD. The 14-3-3 protein level was inconclusive (from the National Prion Disease Pathology Surveillance Center, Cleveland, Ohio), and the level of neuron-specific enolase was mildly elevated at 35 ng/mL (a level from ≥15 ng/mL to ≤35 ng/mL is considered "intermediate"; a level of >35 ng/mL is considered consistent with levels associated with CJD, by the Mayo Medical Laboratories, Rochester, Minnesota). He was enrolled in our sporadic CJD treatment trial and was randomly assigned to receive either quinacrine hydrochloride or placebo.[7,8]

Twenty-six months after onset, he reported worsening language. His mild depression had improved when he was treated with escitalopram oxalate. His work routine, fitness routine, activities of daily living, Barthel index, and Clinical Dementia Rating were all unchanged. He exhibited more paraphasic errors and increased difficulty with reading, word finding, and verbal working memory. Spontaneous speech was fluent but increasingly vague, with more false starts and incorrect grammar associated with word-finding difficulty. Comprehension had worsened. Another motor examination revealed very mild dysarthria, mild right leg dysmetria, and slightly increased reflexes in the right arm and left leg and a worsening right arm swing. The results of another MRI showed no significant changes. Another electroencephalogram revealed mild persistent irregular focal slowing in the left mid- to posterior temporal area, consistent with a focal abnormality of cortical and subcortical elements. Cerebrospinal fluid samples showed an elevated protein level (55 mg/dL; normal range, 15-45 mg/dL), a higher Aβ42 level (549.25 pg/mL), a lower total-tau protein level (1107 pg/mL), and an unchanged phosphorylated tau level (77 pg/mL). The 14-3-3 protein level was again inconclusive. There was no evidence of toxicity from the quinacrine or serological testing. Following protocol, the patient chose to receive open-label quinacrine.

By 31 months, his family reported that his facility for language worsened and that he experienced mental ri-

gidity and episodes of confusion. He had retired 3 months prior. An examination revealed increased phonemic paraphasias and decreased fluency and precision in spontaneous speech. Comprehension had declined. Another motor examination revealed mildly increased tone on the right upper extremity but no cogwheeling. He was able to partake in all activities of daily living (Barthel index, 100) and had an essentially unchanged Clinical Dementia Rating. Results of MRI of the brain revealed increased intensity of cortical ribboning, but the ribboning was confined to fewer gyri (Figure). Another electroencephalogram showed mild focal left temporal slowing during drowsiness.

By 41 months, he became increasingly paranoid, verbally agitated, and noncompliant with medications. He was admitted to a local hospital and died from aspiration pneumonia 42 months after onset.

An autopsy confirmed prion disease with coarse pathologic prion protein (PrP^{Sc}) deposition and mild to severe vacuolation. The most significant pathology was in the frontal, parietal, calcarine, and inferior and superior temporal cingulate cortices, the medial thalamus, and the putamen. Relative sparing was found in the pons and medulla; the midbrain had only sparse PrP^{Sc} deposition, and the cerebellum had no significant pathology but frequent PrP^{Sc} deposition. The pathology fit an MM2-cortical pattern,[9] but genetic and Western blot analysis (National Prion Disease Pathology Surveillance Center) revealed an MV2 subtype (and no *PRNP* mutation).[9]

COMMENT

To our knowledge, this is the first published case of prion disease meeting Mesulam's criteria for PPA.[10] Although common in prion disease, aphasia is an atypical presenting feature, and only a few cases in the English literature have presented with isolated aphasia. One patient with sporadic CJD had pure aphasia for 12 months,[11] and 2 other patients had aphasia for a few months prior to onset of other symptoms.[12,13] In a prior study,[14] we found that 6% of patients with sporadic CJD had a language problem as their first symptom. A few cases of aphasia in genetic prion disease are reported in the Japanese literature,[15] but none met Mesulam's criteria.[10]

Our patient's condition also met new international PPA criteria for logopenic variant PPA.[16] His aphasia then evolved into a more complicated condition. The underlying pathology for PPA usually includes frontotemporal lobar degeneration and corticobasal degeneration, and the underlying pathology for logopenic variant PPA usually includes frontotemporal lobar degeneration, corticobasal degeneration, and, in particular, Alzheimer disease.[16] Our case expands the underlying pathology for PPA to include CJD.

This case underscores the necessity for improved diagnostic criteria for sporadic CJD. The variability of sporadic CJD, in duration and in symptom progression, emphasizes the importance of ancillary tests, particularly diffusion-weighted/apparent diffusion coefficient MRI.[17] Whereas the progression of sporadic CJD is typically rapid, with 90% of patients surviving less than 1 year and with a median duration of survival of 6 months,[18,19] some patients live 15 months or longer.[9] Our patient survived for more than 3.5 years, exemplifying the range of survival possible with sporadic CJD.

Although, technically, our patient did not have dementia at presentation to our centers, he met the UCSF criteria for probable sporadic CJD based on his symptoms and ancillary test results,[20] but he did not meet the current World Health Organization criteria, even for most of his disease course. This is because the UCSF criteria for probable sporadic CJD include other "focal cortical signs" (eg, aphasia, apraxia, acalculia, and neglect) and allow for the use of brain MRI as an ancillary test.[8,21] This case also illustrates that the clinical syndrome criteria must be improved to allow for an earlier CJD diagnosis so that treatments may be introduced earlier as they become available.

Accepted for Publication: August 2, 2012.
Published Online: November 5, 2012. doi:10.1001/2013.jamaneurol.139
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Author Contributions: *Study concept and design:* Johnson, Dunkelberger, Haman, DeArmond, Miller, Gorno-Tempini, and Geschwind. *Acquisition of data:* Johnson, Haman, Greicius, Wong, DeArmond, Gorno-Tempini, and Geschwind. *Analysis and interpretation of data:* Johnson, Dunkelberger, Henry, DeArmond, Gorno-Tempini, and Geschwind. *Drafting of the manuscript:* Johnson, Dunkelberger, Henry, Haman, DeArmond, Gorno-Tempini, and Geschwind. *Critical revision of the manuscript for important intellectual content:* Johnson, Greicius, Wong, Miller, Gorno-Tempini, and Geschwind. *Statistical analysis:* Johnson, DeArmond, and Gorno-Tempini. *Obtained funding:* Gorno-Tempini and Geschwind. *Administrative, technical, and material support:* Johnson, Dunkelberger, Henry, Haman, Greicius, Wong, Gorno-Tempini, and Geschwind. *Study supervision:* Haman, Wong, Miller, and Geschwind.
Conflict of Interest Disclosures: Dr Miller reports that he was a consultant for Tau Rx, Allon Therapeutics, Bristol-Myers Squibb, and Siemens, that he received grants from the National Institutes of Health/National Institute on Aging and Novartis, and that he received royalties of Cambridge University Press. Dr Geschwind reports that he has done consulting for Neurophage, Gerson Lehrman Group, and MEDACorp and has received grants from the National Institutes of Health/National Institute on Aging.
Funding/Support: This work supported by grants R01 AG031189, K23 AG021989, and AG10129 from the National Institutes of Health/National Institute on Aging and by UCSF–Clinical Translational Science Institute grant UL1 RR024131 from the National Institutes of Health/National Center for Research Resources.
Additional Contributions: We thank the National Prion Disease Pathology Surveillance Center for molecular classification and the family of our patient.

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