Clinical Characterization of a Kindred With a Novel 12-Octapeptide Repeat Insertion in the Prion Protein Gene

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Objective: To report the clinical, electroencephalographic, and neuroradiologic findings in a kindred with a novel insertion in the prion protein gene, PRNP.

Design: Clinical description of a kindred.

Setting: Mayo Clinic Alzheimer Disease Research Center (Rochester, Minnesota).

Subjects: Two pathologically confirmed cases and their relatives.

Main Outcome Measures: Clinical features, electroencephalographic patterns, magnetic resonance imaging abnormalities, genetic analyses, and neuropathologic features.

Results: The proband was a woman with clinical and neuroimaging features of atypical frontotemporal dementia and ataxia. Generalized tonic-clonic seizures developed later in the disease course, and electroencephalography revealed spike and wave discharges but no periodic sharp-wave complexes. Her affected sister and father also exhibited frontotemporal dementia–like features, and both experienced generalized tonic-clonic seizures and gait ataxia late in the disease course. Genetic analyses in the proband identified a novel defect in PRNP, with 1 mutated allele carrying a 288–base pair insertion consisting of 12 octapeptide repeats. Neuropathologic examination of the proband and her sister revealed prion protein–positive plaques and widespread tau-positive tangles.

Conclusions: This kindred has a unique combination of clinical and neuropathologic features associated with the largest base pair insertion identified to date in PRNP and underscores the need to consider familial prion disease in the differential diagnosis of a familial frontotemporal dementia–like syndrome.

Arch Neurol. 2011;68(9):1165-1170

Numerous point mutations and insertions in the prion protein gene, PRNP, have been identified in the familial human prion disorders Creutzfeldt-Jakob disease (CJD), fatal familial insomnia, and Gerstmann-Straussler-Scheinker syndrome.¹ The phenotypes associated with each genetic alteration have varied across and within families, but the duration of symptoms has tended to be several years compared with a year or less, which is more typical of sporadic CJD. Although many patients with familial human prion disorders develop dementia and some are initially diagnosed as having probable Alzheimer disease, few develop clinical features of frontotemporal dementia (FTD) or progressive nonfluent aphasia. Several octapeptide base pair insertions (BPIs) in PRNP have been identified, ranging from 24 to 216 base pairs.²⁻²³ Compared with patients with other PRNP mutations, those with BPIs tend to have an earlier age at onset and longer duration of illness and are less likely to have cerebellar signs, myoclonus, or extrapyramidal signs.¹ Seizures have been reported in patients with CJD who have BPIs⁷⁻¹⁰,¹¹,¹³,¹⁴ and other familial CJD subtypes, but the specific electroencephalographic (EEG) findings are rarely described (other than the absence of periodic sharp-wave complexes). Specific findings on magnetic resonance imaging (MRI) in BPI cases have not been described in detail, and many reports do not include data on 14-3-3 protein and neuron-specific enolase levels in the cerebrospinal fluid (CSF). The prion protein immunostaining patterns in BPI cases include fine granular and occasional perivacuolar preponderance, fleecy or blurred staining pattern in the cortex, and kuru and multicentric plaques.³
In this article, we report the antemortem findings in a kindred associated with a novel BPI and compare and contrast the findings in this kindred with those in other kindreds with familial prion disease and BPIs.

METHODS

ANTEMORTEM DATA

The proband was referred to us for evaluation of atypical dementia and was monitored in the Mayo Alzheimer Disease Research Center (Rochester, Minnesota) as part of an institutional review board–approved protocol. She underwent comprehensive neurobehavioral examinations, and the clinical, EEG, and radiologic data were reviewed and analyzed. Magnetic resonance imaging was performed using a 1.5-T scanner (GE Healthcare, Waukesha, Wisconsin), and images of the brain were obtained in the sagittal, axial, and coronal planes. All available clinical data regarding the only other affected relatives—her sister and father—were also reviewed.

PATHOLOGIC AND GENETIC DATA

The neuropathologic material of the proband's sister was examined with consent from next of kin. The proband died several years later, and her tissue was examined similarly with consent from next of kin. Genetic analyses were performed on the proband.

RESULTS

The pedigree of this family is shown in Figure 1.

CLINICAL, LABORATORY, AND NEUROIMAGING DATA

Case I-1

The proband's father died when he was 53 years old as the result of a pulmonary embolism. He had a history of cognitive decline for 10 years before his death, personality and behavioral changes were obvious during the final 5 years of his life, and he experienced several generalized tonic-clonic seizures late in the course of the disease. He was known to become lost in his house, and he had a craving for sweets. Gait impairment and frequent falls evolved in the final 2 years of his illness. An autopsy was performed elsewhere, but this did not include examination of the brain.

Case II-1

The proband's sister died at 51 years of age after a 7-year history of cognitive and behavioral decline. Her family described her as having slowness of thought since childhood, requiring repeated instructions in school and everyday activities, but she was able to graduate from high school. Her illness was characterized by a change in personality, inappropriate comments, restless behavior, and a tendency to seek out food. Four years before her death, a clinical diagnosis of Alzheimer dementia was made. During the course of her illness, the woman experienced 3 generalized tonic-clonic seizures. Gait ataxia was a late manifestation.

Case II-2

The proband's other older sister is 57 years old. She has no neurologic symptoms.

Case II-3

The proband was a right-handed woman who was brought by her healthy sister to our institution for evaluation of a 6-year history of cognitive decline and gait impairment, which began at age 45 years. Her initial symptoms were difficulties in signing her name, followed by the inability to find the right words to express herself. These changes included a decrease in the overall amount of speech, a decrease in the initiation of speech, and use of brief and unelaborated sentences during conversations. She would inconsistently count and sing with others, sometimes verbally responding to yes/no questions, occasionally saying a phrase spontaneously, and she infrequently would use just single words or short phrases during telephone conversations. When she did speak, her speech was clear, although delays in answering questions were apparent. She would not initiate common activities of daily living (eg, dressing and eating), but she would eat when cued (eg, a fork placed in her right hand).

The woman had also exhibited changes in her behavior and personality during the preceding 3 years. Her behavior was more childish, with inappropriate grinning and laughing at home and in restaurants. She exhibited repetitive and ritualistic behavior. She became more withdrawn, apathetic, and intermittently impulsive but lacked insight into these and other changes. Her attention to personal care declined. She also had experienced difficulties with balance and gait during the preceding 3 years. Generalized body jerks and occasional limb posturing had developed during the preceding year. She had been significantly dependent on her healthy sister for most activities of daily living for 2 years. Her medical history included rheumatoid arthritis, which was diagnosed 3 years before presentation. Her arthritic symptoms had improved with methotrexate sodium and prednisone therapy. She also had a history of hypertension and hyperlipidemia. Her medications included hydrochlorothiazide, verapamil hydrochloride, atorvastatin calcium, methotrexate, folic acid, prednisone, naproxen sodium, lisinopril, and coenzyme Q.
On her initial examination at our institution, standard language evaluation was not possible because of her significant cognitive impairment. Her spontaneous activities consisted primarily of smiling, laughing, and an infantile-appearing touching or hiding of her face while smiling or laughing. She did not follow any simple 1-step commands (eg, “close your eyes”), even on imitation, and she was unable to confirm, with yes/no answers, the identity of simple line drawings of objects. She failed to correctly orient a card of large-print words presented to her. She did not initiate any verbal or nonverbal communicative interaction with the clinician or her family members throughout the evaluation. Her spontaneous utterances were brief and unelaborated (eg, “yeah”) and were perseverative or echolalic but accurate phonemically. She had difficulty performing automatic speech tasks (eg, reciting the alphabet), although she did sing a few lines of “Happy Birthday” and “Jingle Bells,” with adequate melody and lyrics, along with her sister. Oral mechanism examination failed to identify asymmetry or weakness, but there was some spontaneous dystonic posturing of the lips and, perhaps, tongue. Her articulation was mildly imprecise, dystonic perioral and lingual movements were evident during speech, and loudness was reduced. Voice quality and resonance were normal. Her overall speech pattern was suggestive of a mixed hypokinetic-hyperkinetic (dystonic) dysarthria. There was no evidence of apraxia of speech. Her overall pattern of responding was not clearly indicative of any focal aphasia; although she obviously had prominent difficulties with communication, they seemed more attributable to widespread impairment in cognitive and affective functioning.

No cranial nerve deficits were noted. She had mild generalized paratonia but no cogwheel rigidity or tremor. She had marked truncal ataxia and was unable to walk without assistance. To the extent that she could follow instructions during examination of limb motor and cerebellar functions, there was no significant weakness or dysmetria. Her reflexes were symmetrically brisk with flexor plantar responses. A bilateral grasp reflex was present. Skeletal changes involving small joints of the hand associated with rheumatoid arthritis were also noted.

The results of all blood, serum, and urine studies for infectious, inflammatory, metabolic, and paraneoplastic disorders, as well as inborn errors of metabolism, were negative or normal, except that the erythrocyte sedimentation rate was elevated to 44 mm/h (reference range, 0-29 mm/h), rheumatoid factor was elevated at 1360 IU/mL (reference, <15 IU/mL), and the antigliadin antibody (IgA) was 66 U/mL (reference, <50 U/mL). A skin biopsy showed no evidence of storage disease, and ultra-thin sections studied by electron microscopy were normal. Cerebrospinal fluid cell count, glucose, proteins, lactate, and IgG index and synthesis rate were within normal limits, and bacterial culture, cryptococcal antigen, polymerase chain reaction for JC polyomavirus, and Treponema whippelii were negative. The CSF 14-3-3 protein was normal, and the neuron-specific enolase level was mildly elevated at 39.5 ng/mL (reference, <20 ng/mL). The CSF β-amyloid 42 (Aβ42; 255 pg/mL) and total tau (1921 pg/mL) protein levels were consistent with a diagnosis of Alzheimer dementia. A brain MRI (Figure 2A and B) showed generalized hemispheric atrophy that was more prominent in the frontal lobes compared with the parietal and occipital lobes. In addition, significant atrophy was present in the corpus callosum and midline cerebellum. An EEG showed diffuse, generalized theta and delta frequency slowing. Superimposed on the slow background were generalized spike
and sharp-wave discharges (Figure 3A), with marked activation of the generalized spike and wave discharges with photic stimulation (Figure 3B). Treatment with nightly clonazepam was initiated to minimize the chance of nocturnal seizures. Weeks later, she experienced multiple partial seizures and generalized tonic-clonic seizures, which were refractory to clonazepam and gabapentin but were better managed with levetiracetam. She remained bedbound, rigid, and variably responsive for the terminal 6 months of her life and died at age 52 years.

GENERATIONS III AND IV

Family members and treating clinicians have chosen to remain unaware of the genetic status of the members of generations III and IV. The children of the affected individuals in generation II have been evaluated annually for 5 or more years, except for III-1 (first seen in 2008) and III-4, whom we have not met. Their ages range from 25 to 39 years. Four of the 7 members of generation III are described as “slow” by the family, but only one (III-6) has below-normal scores in tests indicative of baseline intellectual function. One of the 4 (III-1) had a recent decline in scores on tests of executive function, and another has variable, below-normal scores on tests of visuospatial function (III-2); both report recent behavioral and cognitive changes. All 4 individuals that are described as “slow” have subtle bifrontal and cerebellar atrophy on serial MRI scans.25

NEUROPATHOLOGIC DATA

The pathologic findings in case II-1 and case II-3 were very similar: bilateral frontal atrophy was present, but the mesial temporal structures showed no significant atrophy. Both patients had striking dense multicentric plaques that were negative for Aβ40 and Aβ42 but positive for prion protein. The plaques were particularly frequent in the cerebellar cortex. There were also numerous tau-positive neurofibrillary tangles and neuropil threads in the neocortex. There were no Lewy bodies or Pick bodies. Case II-3 also had findings suggestive of subacute leptomeningeal acanthamoeba infection. Neuropathologic characterization of these 2 patients will be reported in detail elsewhere.

GENETIC DATA

No mutations were present in presenilin 1 (PSEN1) or microtubule-associated protein tau (MAPT), but sequence analysis of the proband’s PRNP gene (Figure 4) showed a mutated allele carrying a 288-BPI consisting of 12 octapeptide repeats (Figure 4C). No such insertions were present on testing 100 control samples.
The clinical and pathologic features in this kindred contrast with other reported CJD cases with BPIs. All 3 affected members of this kindred had cognitive and behavioral changes more consistent with FTD than with Alzheimer disease or CJD. Dementia is usually present in CJD with BPIs, but most reports have not included the specific cognitive and behavioral features that permit comparisons with the “modern” syndromic terminology of, for example, FTD, progressive nonfluent aphasias, and corticobasal syndrome. The speech and language features in the proband were not consistent with the progressive nonfluent aphasias but were nonetheless abnormal. Gait ataxia is not typical of FTD, and this clinical feature in all 3 patients represented a clue to a disorder not usually considered within the FTD spectrum.

Elevations in 14-3-3 and neuron-specific enolase levels are common in sporadic CJD, but there are minimal data on values in familial prion disorders, and increases in CSF 14-3-3 or neuron-specific enolase levels are not specific to prion disorders. Despite the long duration of symptoms in the proband (6 years from the onset of symptoms to the time that her CSF was examined), the mildly elevated neuron-specific enolase level suggested a prion disorder. The low CSF Aβ42 and high total tau levels observed in the proband are typical of Alzheimer’s Disease—a false-positive result that reinforces the observation that such values need not be present even in familial CJD with BPIs. All 3 affected members of this kindred had cognitive and behavioral changes on fluid attenuation inversion recovery or diffusion-weighted images. Clinical or electrophysiologic evidence of epileptiform activity was present in all affected members of this kindred. Seizures have been reported in the P301S MAPT mutation but rarely, if ever, in the other MAPT mutations. Furthermore, seizures, particularly the spike and wave pattern apparent on EEG, are uncommon in the familial prion disorders. Although we cannot exclude the possibility of another source for the seizures and EEG findings, we suspect that the EEG pattern and seizures are related to the underlying prion disorder. This constellation of antemortem findings is therefore unique to this kindred.

The pathologic findings in both cases are more in keeping with the few other familial prion disorders with BPI of 8 octapeptide repeats or more, in which the pathologic phenotype shares many similarities with Gerstmann-Straussler-Scheinker syndrome. We suspect that the topographic involvement of pathologic findings in the bifrontal regions explains the FTD-like clinical and radiologic features, and involvement in the cerebellum explains the gait ataxia. If one can surmise the topographic evolution of pathologic findings in cases such as these on the basis of their evolution of symptoms and findings, it appears that significant frontotemporal pathologic changes occur before the development of significant cerebellar pathologic findings. This sequence of evolution can also occur in Gerstmann-Straussler-Scheinker syndrome as a result of point mutations in PRNP, potentially leading to diagnostic confusion with the disorders more typically associated with FTD.

The cases in this kindred therefore exemplify that a familial prion disorder should be considered in the setting of an autosomal dominant FTD-like syndrome, particularly if gait ataxia or generalized tonic-clonic seizures are present and if no mutations are present on PSEN1 and MAPT testing.

Accepted for Publication: February 15, 2011.

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Financial Disclosure: Dr Boeve has served as an investigator for clinical trials sponsored by Cephalon, Inc and Allon Pharmaceuticals; receives royalties from the publication of a book entitled Behavioral Neurology of Dementia (Cambridge Medicine, 2009); has received honoraria from the American Academy of Neurology; and receives research support from the National Institute on Aging (P50 AG16574 [as a coinvestigator], U01 AG06786 [coinvestigator], and RO1 AG32306 [coinvestigator]) and the Center for Inherited Disease Research (U24 AG026395 [coinvestigator]).

Funding/Support: These research activities were supported by grants P50 AG16574 and PO1 AG07216 from the National Institute on Aging and RO1 NS065782 from the National Institute of Neurological Disorders and Stroke.

Additional Contributions: We are particularly thankful to the patients and their relatives for participating in this research.

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