A New PRNP Mutation (G131V) Associated With Gerstmann-Sträussler-Scheinker Disease

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Background: Gerstmann-Sträussler-Scheinker disease is a rare form of prion disease.

Objective: To determine the prion mutation in a 51-year-old man without a family history of neurologic disease who died from Gerstmann-Sträussler-Scheinker disease.

Patient and Methods: The patient was a 51-year-old man who died after a 9-year illness characterized by dementia and eventually ataxia. Neuropathologic studies were performed, the results of which revealed abundant prion protein–immunopositive amyloid plaques in the cerebellum without spongiform degeneration.

Results: Genetic analysis of the prion protein gene showed a novel mutation at codon 131 that caused a valine-for-glycine substitution (G131V) and homozygosity at codon 129 (129M). Proteinase K–resistant prion protein was detected by Western blot analysis.

Conclusions: This is the first mutation described in the short, antiparallel β-sheet domain of the prion protein. This report highlights the importance of genetic analysis of patients with atypical dementia even in the absence of a family history.

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GERSTMANN-STÄUSSLER-SCHEINKER disease (GSS) is an autosomal dominant neurodegenerative disease caused by mutations in the prion protein gene (PRNP). Clinically, it is characterized by progressive ataxia and dementia; pathologically, it is characterized by prion protein (PrP) amyloid plaques and neuronal loss.

Mutations in PRNP have been found to be associated with GSS, Creutzfeldt-Jakob disease (CJD), and fatal familial insomnium. The GSS phenotype has been associated with point and insertional mutations. Some of these PRNP mutations have been used to establish genetic linkage between the mutation and the disease phenotype. Herein, we report a novel PRNP mutation in a patient with an unusual phenotype.

RESULTS

NEUROPATHOLOGIC FINDINGS

On autopsy, the brain weighed 1243 g. There was mild cerebral and cerebellar atrophy. Microscopically, numerous congoophilic amyloid plaques were found in the cerebellum. For immunohistochemical detection of the PrP deposits, antibodies recognizing the N-terminus (PrP 23-40), midregion (PrP 95-108, 3F4), and C-terminus (PrP 220-231) of PrP were used (Figure 1). The PrP immunoreactivity was intense in the molecular layer of the cerebellum. In addition, PrP deposition was found in the following brain regions: Ammon horn; frontal, temporal, and parietal cortices; and corpus striatum and thalamus. In addition, PrP was not detected in the midbrain, pons, medulla, and mamillary bodies. There was no spongiform degeneration.

By modified Bielschowsky stain, occasional neurons with neurofibrillary tangles (NFTs) were seen in the Ammon horn and entorhinal cortex. However, NFTs were not found in any other area of the central nervous system.

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PATIENT AND METHODS

A white man, born in 1945, resigned in 1987 from his position as a teacher following complaints from colleagues regarding his inability to discipline his class. His driving was erratic and he was unable to find his way on the roads. There was impairment of his short-term memory, reduced learning capacity, perseverence, and emotional immaturity. His family reported aloofness, anxiety, and increasing anger. The family, including the patient’s 2 siblings, who are in their 50s, and his teenage son, has no history of neurologic disease.

In 1987, during a neurologic examination, the man appeared to have no insight into his condition. He was apraxic and had a tremor of the limbs and the body. Visuospatial skills and spatial orientation were impaired and he was dyscalculic. The deep tendon reflexes were pathologically brisk; the cranial nerve examination results and peripheral motor systems were otherwise normal. There was no ataxia.

A neuropsychological assessment revealed a Mini-Mental State Examination score of 22/30 and a verbal IQ of 88, a performance IQ of 67, and a full-scale IQ of 78. Results of block design and object assembly subtests from the Wechsler Intelligence Scale were abnormal. He was grossly impaired on tests of verbal short-term memory, reasoning, comprehension of visual information, and visuospatial organization. The computed tomography and magnetic resonance images showed cerebral and cerebellar atrophy.

Results of examination of the cerebrospinal fluid were normal, except for a slightly elevated protein level concentration of 0.046 g/dL (reference range, 0.015–0.045 g/dL). The electroencephalogram did not show periodic sharp waves.

His dementia progressed and ataxia developed. He eventually required institutionalization in a locked ward because of uncontrollable aggressive behavior. He died by choking at the age of 51 years, 9 years after the onset of symptoms.

The nucleotide number is shown in the upper left of each row and the normal sequence at the top of each row; slashes represent homology to the wild-type sequence. The nucleotide number is shown in the upper left of each row. The sequence of our patient X96/323 is shown under the wild-type sequence and the codon number is under each rectangular shaded box. The controls were run concurrently. D98-414 is a healthy patient; D92-307, familial Creutzfeldt-Jakob disease with codon 178 mutation; D94-483, familial fatal insomnia with codon 200 mutation; and D94-483, familial fatal insomnia with codon 178 mutation. Identical results were obtained on 3 separate runs with sequencing performed in a forward (F) and reverse direction.

PrP ANALYSIS

Protein was extracted from the cerebellum and processed as previously described. The presence of protease-resistant PrP was determined by digestion with proteinase K (PK) and fractionation in sodium dodecyl sulfate–polyacrylamide gel electrophoresis. The gels were probed with the monoclonal antibody 3F4 (1:50000), which recognizes positions 109 to 112 of human PrP. The immunoblots were visualized using electrochemiluminescence. Non–PK-treated samples contained PrP species of...
approximately 18, 26 to 27, and 31 to 36 kd. In addition, PK digestion demonstrated evidence of proteinase-resistant PrP with bands at approximately 8, 18, 26, and 31 kd (Figure 3).

COMMENT

The transmissible spongiform encephalopathies represent a unique group of neurologic conditions in which genetic disorders can lead to transmissible neurologic disease. Herein, we describe a de novo mutation in PRNP associated with a GSS phenotype. In the proband’s family, there was no history of neurologic disorders, and his 2 siblings, in their 50s, were examined by one of the authors (P.K.P.) and were found to be free of neurologic signs. They declined predictive gene testing despite counseling. The absence of a family history might suggest that this is a new mutation; however, this is rare for PRNP mutations.

More than 20 mutations in PRNP have been described that cause CJD, GSS, fatal familial insomnia, and PrP cerebral amyloid angiopathy with different clinical and neuropathologic phenotypes. Clinically, GSS is characterized by ataxia, parkinsonism, signs, and dementia. In the proband, ataxia and dementia were the main signs. The most common mutation associated with GSS is P102L, but other point mutations at codons 105, 117, 198, 202, 212, and 217 and insert mutations (6 to 9) between codons 51 and 91 have been described. The disorders caused by these mutations have their onset in the third to sixth decades of life and usually present with cerebellar ataxia that evolves to dementia. Our patient had cognitive impairment before the onset of ataxia, with survival of about 9 years. Cognitive impairment before the onset of ataxia has also been documented in a family with a mutation at codon 198. Phenotypic heterogeneity has been previously emphasized in GSS, and it has been recently demonstrated again in 2 studies of an English and French family with the A117V mutation and an octapeptide insertion mutation, respectively. The presence of neurologic and psychiatric symptoms in members of these 2 families further illustrates the phenotypic variability of these conditions.

Our patient was homozygous for methionine at codon 129. Homozygosity for either methionine or valine affects susceptibility to CJD and the phenotypic expression of mutations. For example, in the case of the D178N mutation, the haplotype D178N is associated with fatal familial insomnia and the haplotype D178N is associated with CJD.

Prion diseases share a similar pathogenetic mechanism that involves the conversion of a normal PrP (PrPc) into a pathologic form that is insoluble in detergents and PK resistant (PrPres). Previous studies have shown that patients with GSS accumulate N- and C-truncated PrPres fragments of approximately 8 to 15 kd and variable amounts of higher-molecular-weight isoforms. In addition, in the GSS variant P102L, PrPres species of approximately 21 to 30 kd, identical to those described in CJD, are also present when this variant is associated with severe spongiform degeneration. The pattern of PrPres bands in the proband does not present CJD-like isoforms (ie, 21- to 30-kd bands). This case is characterized by PrPres species that are similar to those described in GSS F198S and Q217R, 2 GSS variants without spongiform degeneration. The mutation reported herein is the first one to cause an amino acid substitution (G → V) in a short, antiparallel β-sheet domain comprising residues 128 to 131. The impact of such mutation on PrP folding and processing remains undetermined.

In the proband, NFTs were observed in the hippocampus and entorhinal cortex. The NFTs have been previously described in GSS with mutations F198S and Q217R. In these 2 GSS variants, tau-immunopositive NFTs were widespread in the neocortex and subcortical nuclei and were associated with neuritic plaques. The occurrence of different degrees of tau pathologic findings in GSS, including the G131V variant, requires further investigation to determine whether hyperphosphorylation of the microtubule-associated protein tau and the formation of paired helical filaments are secondary events to the presence of specific conformations of PrP or reflect a nonspecific phenomenon.

The G131V mutation is another example of the wide spectrum of phenotypes associated with GSS and PRNP gene mutations and highlights the importance of the molecular classification of prion disorders, even in the absence of an identifiable family history. The diagnostic workup of patients with early-onset dementia and the suspicion of prion disease necessitates analysis of the PRNP gene, since neuropathologic features, typical of prion diseases, might not always be found.

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