Mother With Amyotrophic Lateral Sclerosis and Daughter With Creutzfeldt-Jakob Disease

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Objective: To describe a mother who had autopsy-proved amyotrophic lateral sclerosis and her daughter who had clinically diagnosed Creutzfeldt-Jakob disease.

Design: Case reports with molecular genetic analyses.

Setting: A tertiary care center.

Patients: The mother had progressive upper and lower motor neuron symptoms and signs starting at the age of 54 years. Electrophysiological testing supported the diagnosis of amyotrophic lateral sclerosis. Autopsy results confirmed the diagnosis. Her daughter had received injections of human growth hormone prepared from pooled human pituitary glands as a child. At the age of 31 years, she experienced the onset of gait ataxia and dysarthria. Cerebrospinal fluid showed the 14-3-3 protein. Cognitive difficulties ensued. She progressed to a nearly akinetic and mute state. She had overt visible fasciculations and muscle atrophy in the legs.

Main Outcome Measures and Results: Neither patient carried a mutation in the prion protein gene. Both were homozygous for methionine at the polymorphic codon 129. Neither patient carried a deletion of the 5 exons of the superoxide dismutase 1 gene.

Conclusions: It is uncertain whether the 2 cases occurred in the same family by chance or whether the patients shared genetic risk factors for the 2 diseases. The possibility that homozygosity at codon 129 is a risk factor for amyotrophic lateral sclerosis is being tested in a case-control study.

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The cause of sporadic amyotrophic lateral sclerosis (ALS) is unknown. Of the cases, 5% to 10% are familial, and the superoxide dismutase 1 (SOD1) gene mutation accounts for only about 20% of these cases. It is, therefore, appropriate to remain open minded about possible causes or modes of pathogenesis. We encountered a mother with ALS and her daughter with growth hormone-induced Creutzfeldt-Jakob disease (CJD), a combination not previously reported, to our knowledge. The likelihood of this co-occurrence must be small, as statistically unlikely as conjugal cases of either ALS or CJD. Although the minicluster is probably a statistical coincidence, the 2 conditions may be related.

RESULTS

MOLECULAR GENETICS

Methods

Screening for a PRP gene mutation was carried out by denaturing gradient gel electrophoresis of DNA extracted from white blood cells, with amplification by the polymerase chain reaction of the open reading frame of the PRP gene. Confirmation of sequences was performed with an automated DNA sequencer. The entire region of the open reading frame was sequenced bidirectionally using dye-primer chemistry. Screening for the SOD1 gene mutation was performed similarly using genomic DNA prepared from the patients’ blood samples using a standard technique. All 5 exons were amplified by polymerase chain reaction from genomic DNA using specific pairs of primers designed according to published sequences. Screening for point mutations was performed by single strand conformation polymorphism against positive and negative controls.

Results

In both subjects, the sequence of the PRP gene was normal. In both, the polymorphic codon 129 of the PRP gene was homozygous for methionine. In addition, we found no deletion or abnormal patterns of the 5 exons of the SOD1 gene in either subject.
PATIENTS AND METHODS

PATIENT 1 (THE MOTHER)

Patient Characteristics

At the age of 34 years, in February 1995, this woman noted weakness of the right hand. In November 1995, there was weakness and wasting of muscles of the right hand and arm; fasciculation was seen in both arms. Tendon reflexes were overactive throughout, with bilateral Hoffmann signs and clonus at the right ankle but no Babinski sign. In August 1997, she was quadriplegic, barely able to make sounds or swallow, and constantly dyspneic. Fasciculations were seen in the tongue. Her neck movements were weak, and the limbs were immobile. Fasciculation was still evident in the biceps, and tendon reflexes were still overactive except for absent ankle jerks. There were no Hoffmann or Babinski signs.

The results of laboratory studies showed no conduction block, monoclonal paraprotein, or antibodies to GMI or myelin-associated glycoprotein. Examination of the cerebrospinal fluid showed no abnormality, and electromyography gave evidence of chronic denervation in 3 limbs. The patient died in August 1997, 30 months after the onset of symptoms.

Autopsy Results

The autopsy was performed by one of us (S.S.C). The number of Betz cells in the precentral gyrus was much decreased, particularly in the leg area. In the cerebral peduncle of a midbrain section, the pyramidal tract showed vacuolar change and foamy macrophages. The medulla showed neuronal loss in the hypoglossal nucleus and reactive astrogliosis. In the spinal cord, there was marked loss of large motor neurons at all levels, with only rare chromatolytic changes. Occasional Bunina bodies, spheroids, and astrogliosis were seen. The anterior and lateral corticospinal tracts showed loss of myelinated fibers with marked pallor, vacuolar changes, and foamy macrophages. The throracic nucleus was unremarkable. The anterior nerve roots were atrophic; the posterior nerve roots were normal. No senile plaques, neurofibrillary tangles, or Lewy bodies were seen. There was some spongy change in layer II of the precentral gyrus but no frank spongiosis. The findings were typical of ALS, with no histological evidence of prion protein (PrP) disease. There was no evidence of protease-resistant PrP by Western blot analysis of a section of brain cortex and upper spinal cord using the monoclonal anti-PrP 3F4 antibody.

PATIENT 2

The daughter of patient 1 was born in 1964. Between the ages of 8 and 12 years, she was treated for short stature with injections of human growth hormone prepared from cadaver-derived pituitary glands. Some lots of the hormone she received were tested for prion protein and were found to transmit CJD to primates. She was neurologically asymptomatic until August 1993. Ataxia of gait and dysarthria progressed rapidly. In November 1995, James R. Miller, MD, found good cognition, severe dysmetria in all limbs, rigidity and spasticity, hyperactive tendon jerks, and bilateral Babinski signs. She noted no myoclonus. The results of brain magnetic resonance imaging and cerebrospinal fluid examinations were normal. The cerebrospinal fluid was tested in the laboratory of Paul Brown, MD, and showed the 14-3-3 protein. Dementia followed, and she remains in a long-term care facility. In August 1997, she was found by one of us (B.B.W.) to be mute and unresponsive to voice, bright light, noise, and visual threat. She had no startle responses or myoclonic jerks. Spontaneous and oculocephalic eye movements were of full range. The fundi and corneal reflexes were normal. Snout reflexes were active, but no pharyngeal reflex was elicited. No fasciculation was seen in the tongue. Her limbs were immobile and spastic, with flexion contractures at the knee and ankle. There was atrophy of distal leg muscles, and fasciculations were seen in the feet, gastrocnemius muscles, and quadriceps but not in the torso or arms. Tendon reflexes were overactive throughout, with bilateral Babinski signs and left ankle clonus.

FAMILY HISTORY

There was no consanguinity. The mother had an asymptomatic son and daughter in addition to the affected daughter. There was no other neurologic or psychiatric disease in the family.

PRION GENETICS AND SUSCEPTIBILITY TO PRION DISEASES

In this family, the daughter had the characteristic clinical findings of iatrogenic growth hormone–related CJD, as well as a positive 14-3-3 protein test result. She had both upper and lower motor neuron signs, including amyotrophy. However, the diagnosis has not been proved by pathological features, documentation of PrP deposition, or transmission. Autopsy examination of the mother confirmed the clinical diagnosis and showed typical ALS pathological features with no spongiform change. Gene sequencing failed to reveal a mutation in the PRP gene in either, and the mother met none of the criteria for prion disease. Both were homozygous for methionine at codon 129 of the PRP gene.

The polymorphism at codon 129 of the PRP gene modifies the risk of sporadic and iatrogenic CJD and alters the phenotype and course of certain familial prion diseases. Among normal individuals in several countries, about half of the people are homozygous for either methionine or valine. In contrast, in people with iatrogenic CJD induced by cerebral transmission (electrodes and dural grafts), 93% are homozygous at codon 129, as are 91% of those who received growth hormone prepared from human pituitary glands. The frequency of homozygosity at codon 129 is also much higher in persons with sporadic CJD than in the general population.
Sporadic prion syndromes may also differ clinically and pathologically as a result of the polymorphisms at codon 129.\textsuperscript{17} Familial CJD and fatal familial insomnia result from a mutation at codon 178.\textsuperscript{18} In these families, codon 129 of the PRP gene encodes valine in those with CJD and methionine in those with fatal familial insomnia. The codon 129 polymorphism on the nonmutant PRP gene also influences the rate of disease progression.\textsuperscript{19} This polymorphism may influence the age at onset and duration of other familial prion diseases\textsuperscript{20} and may impair cognitive performance in people without prion disease.\textsuperscript{21}

Since the mother and daughter described herein were homozygous for methionine at codon 129, they were presumably at higher risk for prion disease than are heterozygous people. However, there was no clinical, DNA, or histopathological evidence that the mother had a prion disease. There was no mutation of the PRP gene sequenced from the DNA of blood leukocytes of the mother and daughter. The cerebrospinal fluid test\textsuperscript{6} was not applied to the mother, and a brain biopsy has not been proposed for the daughter.

These cases remind us that these 2 neurodegenerative conditions occasionally share clinical features. In 1 series,\textsuperscript{22} 10% of patients with CJD showed amyotrophy. In the present study, the daughter had fasciculations and wasting; to our knowledge, she is the first person described with iatrogenic CJD and amyotrophy. The concurrence of the 2 diseases in mother and daughter could be merely a horrible coincidence, the daughter having inherited the “prion susceptibility” polymorphic genotype from her parents and then being challenged with an inoculum of prions from growth hormone. This would have no implications whatsoever about the pathogenesis of ALS in her mother or anyone else.

The issues raised by this family suggest a need for further study. The possibility that homozygosity at codon 129 is a risk factor for ALS is being tested in a case-control study. We address the significance of amyotrophy in prion disease in a separate review.

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