Sporadic Fatal Insomnia Masquerading as a Paraneoplastic Cerebellar Syndrome

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Background: Sporadic fatal insomnia is a relatively recently described prion disease with only a limited number of cases reported in the published literature to date.1-3 We describe a unique autopsy-proven case in a woman who clinically had progressive cerebellar deterioration of approximately 18 months’ duration.

Objective: To report a unique case of sporadic fatal insomnia in a woman with progressive cerebellar deterioration who was originally thought to have a paraneoplastic cerebellar syndrome.

Design: Case report describing a patient with autopsy-proven sporadic fatal insomnia.

Patient: A 56-year-old woman with progressive cerebellar ataxia who was found to have a retroperitoneal non-Hodgkin lymphoma.

Results: Autopsy demonstrated marked degenerative changes in the thalamus, cerebellum, and inferior olivary nucleus. A mild spongiform change was present in the thalamus and cortical gray matter. Western blot analysis confirmed the presence of abnormal, protease-resistant prion protein (PrPSc), characteristic of sporadic fatal insomnia.

Conclusions: Clinicians should be aware of this rare prion disease and should strongly consider the importance of autopsy toward the investigation of unusual neurological diseases.

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Sporadic fatal insomnia is a relatively recently described prion disease with only a limited number of cases reported in the published literature to date.1-3 We describe a unique autopsy-proven case in a woman who clinically had progressive cerebellar deterioration of approximately 18 months’ duration.

A 56-year-old, right-handed woman presented with 1 year of progressive gait disturbance. One year before her gait disturbance, she experienced 2 episodes of binocular and horizontal diplopia. These episodes were transient and the diplopia never returned. When she noticed difficulties with her gait, she was unsteady and began to veer to her right. During the next 3 months, she required a walker for assistance. The progressive gait deterioration was so severe that she required the use of a wheelchair 6 months after onset.

Our patient also had difficulty with manual coordination, affecting her ability to type on a keyboard and to use utensils. Her speech soon became slurred to the point that it was difficult for family and friends to understand her. She had difficulty with short-term memory and had insomnia for the past 2 years.

Her medical history was significant for Lyme disease 12 years prior to presentation and a remote closed head injury. Her surgical history included a single oophorectomy and hysterectomy 30 years ago. She did not consume any alcohol, tobacco, or illicit substances. She denied any history of exposure to industrial chemicals or heavy metals. Her family history was significant for breast cancer in her mother and hypertension in her father.

The neurological examination revealed some memory impairment, recalling only 1 of 3 objects after 5 minutes. She had horizontal nystagmus on left lateral gaze, hypermetric saccades, and severe dysarthria. She had poor palatal closure and had marked difficulty with labial and lingual sounds. Her strength was intact and she had slightly increased tone in her upper extremities. Severe dysmetria was present with finger-to-nose and heel-to-shin testing. There was reduction in appreciation of temperature below the knees. Reflexes were symmetric bilaterally except in her upper extremities in which the
brachioradialis and triceps reflexes were brisk. A mild jaw jerk was present. There were crossed adductor and hip adductor reflexes. Her plantar responses were equivocal bilaterally. She was unable to walk and even had difficulty rising from a chair due to her severe ataxia. Retropulsion and tandem gait could not be tested.

Magnetic resonance imaging of the brain revealed prominent vermian cerebellar atrophy with some cortical atrophy (Figure 1). Cerebrospinal fluid test results were unremarkable for the following: Borrelia burgdorferi antibody, herpes simplex virus, and Mycoplasma pneumoniae by polymerase chain reaction, fluorescent Treponema antibody, paraneoplastic antibodies (including anti-Ma, Ri, Hu, Yo, Ta, CV2, Zic-4), angiotensin-converting enzyme, oligoclonal bands, 14-3-3 protein, and nonspecific enolase. Cytological examination and flow cytometry did not identify abnormal cells. Fungi, bacteria, and viral cultures did not reveal any growth. Serum studies included evaluations for anticardiolipin antibodies, gliadin antibodies, endomyosial antibodies, thyroid peroxidase antibodies, vitamin E, vitamin B₁, vitamin B₁₂, homocysteine, free thyroxine, and thyroid-stimulating hormone, and these were either absent or unremarkable. Arsenic, lead, and mercury levels were unremarkable. Testing did reveal an elevated thyroglobulin antibody level of 30.7 IU/mL (reference range, 0.0-14.4 IU/mL), an elevated thyroid-stimulating hormone receptor antibody level of 17% (negative range, <10%), and a slightly elevated cerebrospinal fluid protein level of 61 mg/dL (reference range, 15-45 mg/dL). Samples of cerebrospinal fluid and serum failed to show any immunoreactivity against rat brain tissue. Results of ultrasonography of the thyroid were also unremarkable. Electroencephalography results were normal. Nerve conduction studies and electromyography did not reveal any abnormalities.

Owing to our concerns of a possible paraneoplastic process causing the cerebellar degeneration, computed tomography of the chest, abdomen, and pelvis was performed. It revealed a retroperitoneal mass measuring 9.3 × 4.0 × 2.9 cm. Subsequent biopsy revealed this mass to be a follicular B-cell, non-Hodgkin lymphoma. At this time, the working diagnosis was a seronegative paraneoplastic cerebellar degeneration because no paraneoplastic antibodies could be identified. Despite receiving chemotherapy for her lymphoma, the patient’s neurological status continued to decline. Despite treatment with monthly intravenous corticosteroids and even plasma exchange, our patient did not exhibit any improvement. She died 18 months after the discovery of her lymphoma due to complications of cachexia.

A complete autopsy was performed and revealed no evidence of residual lymphoma or the presence of any neoplasm. Gross examination of the brain confirmed marked atrophy of the cerebellum. On microscopical examination, there was remarkable degeneration of the thalamus (Figure 2) with particular involvement of the dorsomedial nucleus, cerebellar gray matter including the dentate nucleus, and inferior olivary nucleus with loss of neuronal cells and marked astrogliosis. A mild spongiform change was present in the thalamus and cortical gray matter. These findings were consistent with prion disease, and the histological pattern was suggestive of fatal insomnia. Frozen and fixed brain tissue samples were analyzed by the National Prion Disease Pathology Surveillance Center by Western blot, immunohistochemical, and molecular genetic testing. The Western blot analysis demonstrated the presence of abnormal, protease-resistant prion protein (PrPSc) that had a mobility and glycosylation pattern consistent with that of sporadic fatal insomnia (Figure 3). Sequence analysis of the prion protein gene revealed no mutation in the open reading frame and methionine homozygosity at codon 129.

This case illustrates the difficulty in establishing a definitive diagnosis of sporadic fatal insomnia in a patient who clinically exhibited progressive cerebellar degener-
disorder. Although our patient did have elevated levels of tau and amyloid protein in the cerebrospinal fluid, this does not exclude prion diseases. Microscopical and immunohistochemical studies of brain tissues are required to confirm the diagnosis. A negative finding of 14-3-3 protein or nonspecific enolase does not exclude prion disease. The utility of biological markers of prion disease is limited.

Figure 3. Western blot analysis of prion protein (PrP). A, Brain tissues from the examined case, lanes 5, 6, and 8 were from the cerebral cortex and lanes 14, 15, and 17 were from the cerebellum. For the sporadic Creutzfeldt-Jakob disease PrPSc type 2 control, the molecular weights of protein standards are labeled on the left side of each blot. B, Lane 29 from the present case, only a faint band migrating at approximately 20 to 21 kDa was barely detectable in the lane loaded with 15 µL of BH from the cerebral cortex. A faint band migrating at approximately 24 to 28 kDa, and approximately 19 to 21 kDa in the 2 lanes loaded with 4 µL (lane 6) and 15 µL (lane 8) of BH. The unglycosylated PrP band in lane 6 migrated at approximately 19 kDa, which is similar to sporadic Creutzfeldt-Jakob disease PrPSc (protease-resistant PrP) type 2 control. The slow migration of PrP bands in lane 8 was due to overloading of the sample. The molecular weights of protein standards are labeled on the left side of each blot.

Sporadic fatal insomnia is a relatively recently described and rare form of prion disease. Its clinical phenotype is very similar to that of the better-known familial fatal insomnia. Early features include disturbances of sleep, which are often overlooked or regarded as minor, and fluctuating diplopia. Signs and symptoms of cerebellar dysfunction, dysautonomia, and deterioration of cognition often follow. Electroencephalography is usually not of value owing to the absence of spike discharges that may be seen in Creutzfeldt-Jakob disease. Imaging has often been nonspecific, with key findings consisting of cerebellar and cortical atrophy. Positron emission tomography, which we did not use, can demonstrate thalamic hypometabolism in early stages of fatal insomnias. The distributions of the pathogenic isoform of the prion protein (PrPSc) are also similar in familial and sporadic fatal insomnia. The key distinguishing features that differentiate sporadic from familial fatal insomnia are the absence of a family history and the characteristic Asp178Asn PRNP mutation.

This case is another example of sporadic fatal insomnia presenting as a progressive cerebellar syndrome. The diagnosis was complicated by the clinical and laboratory findings that pointed toward a paraneoplastic process. Further awareness of this disorder is warranted, and this case underscores the importance of autopsy in the investigation of unusual neurological diseases.

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