Sporadic Fatal Insomnia Masquerading as a Paraneoplastic Cerebellar Syndrome

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Background: Sporadic fatal insomnia is a rare prion disease that has recently been recognized.

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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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, endomysial 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 × 40.0 × 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 degeneration...
Our patient did have elevated levels of thyroglobulin antibodies, she did not respond to infused corticosteroids or plasma exchange.

A negative finding of 14-3-3 protein or nonspecific enolase 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 insomnias. The key distinguishing features that differentiate sporadic from familial fatal insomnias 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.