

Pearls & Oy-sters: Rapid progression of prion disease associated with transverse myelitis

A rare presentation

Omar Hussein, MD,* Zachary Jordan, MD,* Ahmed Abd Elazim, MD, and Amro Stino, MD

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Correspondence

Dr. Hussein
oyhussein@yahoo.com

Pearls

- Longitudinally extensive transverse myelitis (TM) or TM with inconclusive CSF findings should raise concern for prion disease (also known as Creutzfeldt-Jacob disease [CJD]) especially in the setting of associated cognitive impairment.
- CJD associated with focal findings should raise suspicion for spinal cord involvement and warrants spinal imaging.
- Spinal cord involvement in CJD could suggest more rapid disease progression, although further investigations are warranted.

Oy-sters

- The MRI findings in the brain typically associated with CJD may not appear until later in disease progression.
- Evaluation of a patient presenting with subacute to acute myelopathy should include CSF testing for prion disease when there is associated rapid decline in mental status.

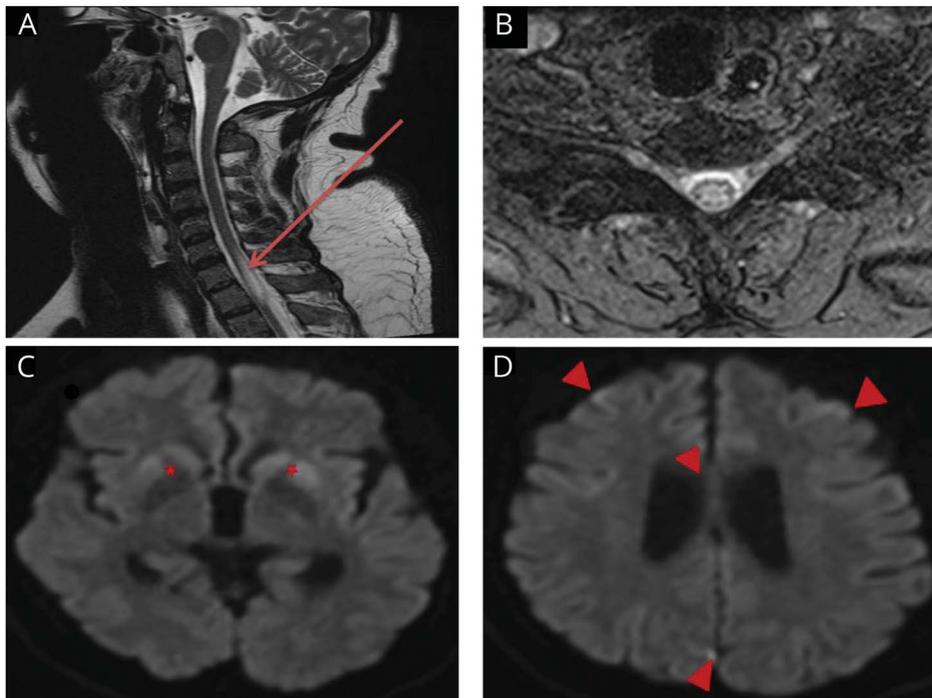
A 57-year-old man with a history of monoclonal B-cell lymphocytosis was admitted because of 2 months of progressive clumsiness, gait instability, and bowel/bladder incontinence. There was no family history of dementia or similar symptoms. Neurologic examination showed poor attention, tangential thinking, dysarthria, right leg weakness, right arm ataxia, tremors, and an upgoing right toe. There was no sensory level and jaw jerk was not tested. In addition to cerebral injury, these symptoms, together with incontinence, were clinically more suggestive of a primary myelopathy. However, uncertainty about spinal vs cortical pathology remained and thus MRI spine and brain were obtained. MRI spine (figure, A and B) demonstrated a longitudinally extensive transverse myelitic (LETM) lesion in the cervicothoracic (C6–T1) region while MRI brain was unremarkable.

CSF analysis demonstrated the following: glucose 93 mg/dL, protein 55 mg/dL, white blood cells <3, and red blood cells <3. Cytology showed no abnormal cells to suggest CNS lymphomatous involvement. Previous evaluation for monoclonal B-cell lymphocytosis revealed a kappa light chain restricted CD20+ population comprising 12% of the patient's lymphocytes. This was monitored biannually without treatment and was noted to have improved on its own by the time of hospital presentation. Further workup for LETM, including aquaporin-4 antibody, immunoglobulin G index, oligoclonal band index, antinuclear antibody, extractable nuclear antigen antibodies, vitamin B₁₂, copper, vitamin E, autoimmune, and paraneoplastic antibody testing, were all unrevealing. Infectious evaluation was negative in the CSF (including HIV, herpes simplex virus 1, herpes simplex virus 2, cytomegalovirus, and varicella-zoster virus) and serum (including Lyme antibodies, human T-cell lymphotropic virus, fungal serologies, hepatitis, and syphilis). CT chest was negative for evidence of sarcoidosis.

*These authors contributed equally to this work.

From the Department of Neurology (O.H., A.A.E.), University of New Mexico Hospitals, Albuquerque; Department of Neurology (Z.J.), The Ohio State University Wexner Medical Center, Columbus; and Department of Neurology (A.S.), University of Michigan, Ann Arbor.

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(A) Sagittal T2 sequence demonstrates hyperintense signal in the central cord spanning levels C6–T1 (arrow). (B) An axial T2 view of the lesion at the C7–T1 level. (C, D) Axial diffusion-weighted imaging sequences demonstrate diffusion restriction in the bilateral caudate and putamen (asterisks) and patchy cortical diffusion restriction (arrowheads).

One week after the patient’s presentation, while the above data were being gathered, the patient became increasingly unresponsive and was subsequently transferred to the intensive care unit, where he was intubated. With a negative infectious evaluation, he was given high-dose steroids daily for 5 days starting on the 10th day of hospitalization as empiric treatment for his myelopathy. Treatment with plasmapheresis for 5 sessions was started 5 weeks after the initial presentation. There was no clinical improvement after either of these treatments. He then developed myoclonic jerking in all extremities shortly after starting plasmapheresis. The myoclonic jerks were worsened by startle without electroencephalographic correlate. They developed in isolation of any additional neurologic symptom, other than decreased alertness, and persisted through the rest of the hospitalization. EEG showed mild to moderate diffuse slowing. Repeat MRI brain demonstrated diffusion restriction in the frontal cortex (ribbon-like), the caudate, and bilateral putamen (figure, C and D). Repeat lumbar puncture was pursued, and this time, a prion disease panel was obtained. The patient’s condition continued to deteriorate and he was transferred to hospice 7 weeks after presentation, where he subsequently died. Autopsy was declined by his family. Protein 14.3.3 and real-time quaking-induced conversion assay returned positive. A genetic panel could not be obtained.

Based on the current consensus criteria for the diagnosis of sporadic CJD,¹ a diagnosis of probable CJD was established based on the history of subacute symptom onset, including cognitive impairment and rapid development of focal

symptoms, typical MRI brain findings, the presence of startle myoclonus, and CSF laboratory findings.

Discussion

We present a case of rapidly progressive probable CJD with associated LETM that likely represents spinal cord prion disease. The patient’s major presenting symptoms (progressive clumsiness and gait instability together with bowel/bladder incontinence) initially suggested a myelopathic process that was corroborated by imaging. The differential diagnosis was expanded with the onset of worsening cognitive symptoms and narrowed with the onset of myoclonus.

Whether CJD prion spread starts rostrally in the brain and moves caudally into the spinal cord (as is typical with sporadic, familial, or hematogenously spread variant CJD) or, rather, starts caudally and moves rostrally, spinal cord involvement may portend more rapid disease progression. Animal models of CJD with spinal cord involvement have more rapid disease progression as compared to those that do not.² Of note, our patient survived 3.5 months from symptom onset, whereas average disease duration in sporadic and variant CJD ranges from 6 to 14 months.³

CJD is a prion-mediated, neurodegenerative disorder clinically characterized in part by rapidly progressive dementia. Three types exist: (1) sporadic (also called spontaneous) is most common, represents 85% of cases, and is caused by

spontaneous misfolding of a prion protein in the body; (2) genetic (also called hereditary) represents 15% of cases and is caused by an inherited mutation in the prion protein gene; (3) acquired (including both iatrogenic and variant CJD) is rarest, with iatrogenic transmitted hematogenously and variant transmitted through consumption of contaminated food. After transmission, defective proteins invade the nervous system and induce other prion proteins to misfold in a self-sustaining loop. The number of misfolded proteins exponentially increases, leading to a large quantity of insoluble protein in affected cells that results in dysfunction and death.⁴ While cerebral imaging and EEG findings have been well-characterized, spinal cord MRI findings have not been well-described in the literature, despite reports of spinal cord involvement in some series.^{2,5}

CJD subtype and mode of transmission affect disease presentation. In variant CJD, for example, prion protein is postulated to gain access to the cortical and deep gray structures of the brain through direct neural tissue propagation through peripheral nerve and spinal cord^{6,7} or via propagation through the bloodstream.⁸ Hematogenous propagation is associated with a cerebral-predominant phenotype at disease onset, whereas neural tissue propagation often presents with a spinal cord-predominant presentation earlier in the disease course. The presence of spinal cord findings that predated both MRI brain findings and clinical deterioration could be suggestive of antegrade spread, which would be more consistent with variant CJD. Of note, there was no reported history of any abnormal dietary changes or contaminated food exposure in our patient. This being said, the patient's clinical presentation and rapid disease progression are more consistent with sporadic CJD. Irrespective of CJD subtype, spinal cord involvement appears to be associated with more rapid disease progression.²

A limitation of this case is the lack of autopsy or biopsy data to definitively determine the composition of the spinal cord signal. However, in line with the 2002 TM consortium recommendations,⁹ no other plausible etiology for the patient's LETM could be found. Lack of clinical response to steroid or plasmapheresis treatment, the absence of cord enhancement, negative cytology, and a non-inflammatory acellular CSF profile would be most supportive of prion disease as the etiology.

CJD should be considered in the differential diagnosis of LETM when there is associated acute cognitive decline. In addition, LETM should be considered in the spectrum of CJD

disease phenotype. The presence of spinal cord involvement appears to suggest more rapid CJD disease progression.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Omar Hussein, MD	University of New Mexico, Albuquerque	Designed, conceptualized, and executed the study; interpreted the data; drafted and revised the manuscript for intellectual content
Zachary Jordan, MD	The Ohio State University Wexner Medical Center, Columbus	Reviewed the literature, major role in the acquisition of data, interpreted the data, revised the manuscript for intellectual content
Ahmed Abd Elazim, MD	University of New Mexico, Albuquerque	Interpreted the data, data acquisition, revised the manuscript for intellectual content
Amro Stino, MD	University of Michigan, Ann Arbor	Conceptualized the study, interpreted the data, critically revised the manuscript for intellectual content

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