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# Clinical/Scientific Notes

## Creutzfeldt–Jakob Disease Presenting With Alien Limb Sign

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Video 

**Abstract:** Creutzfeldt–Jakob disease is a fatal spongiform encephalopathy, which typically presents with a rapidly progressing dementia and additional neurological findings that can be quite variable and diverse. Here we report the unusual case of a patient who presented with left alien limb sign without overt cognitive impairment and was ultimately diagnosed with pathologically confirmed Creutzfeldt–Jakob disease. © 2006 Movement Disorder Society

**Key words:** Creutzfeldt–Jakob; magnetic resonance imaging; alien limb; video; corticobasal degeneration

Creutzfeldt–Jakob disease (CJD) is a member of the spongiform encephalopathies, the sporadic form of which is fatal and clinically characterized by a rapidly progressive dementia typically associated with myoclonus, pyramidal or extrapyramidal features, visual or cerebellar signs, or akinetic mutism.[1] However, symptoms can be quite variable and mistaken for other neurodegenerative disorders.[1] Here we report on an interesting patient presenting with gait disturbance, myoclonus, apraxia, and left alien limb sign, but without clear evidence of cognitive impairment, who rapidly declined and died within weeks of presentation, with a final diagnosis of pathologically confirmed sporadic CJD.

### Case Report

A 55-year-old right-handed woman with a prior history of breast cancer, treated with surgery and tamoxifen, and a remote history of aseptic meningitis presented to our emergency department with complaints of worsening gait disturbance. She had noticed minor problems beginning 10 months earlier with unexpected falls, trouble using buttons and zippers, and a change in her handwriting. Two months prior she had begun to notice burning paresthesias of the left hand and within the past month she had developed jerking movements of primarily the left upper extremity. She noted mild forgetfulness and occasional periods of inattentiveness. On initial presentation, she described a sense of discoordination with both hands. More concerning, however, was that a month earlier her left hand had "taken on a life of its own," acting independently and interfering with activities of the right hand. This hand would grasp objects without her awareness, even her own neck. She continually referred to her left hand as "it." She was not on any medications and had no known toxic exposures or any history of tobacco, excessive alcohol, or significant recreational drug use. She was adopted with an unknown family history and had received a college-level education.

On examination, mental status was intact with full orientation, normal attention/concentration, and no overt disturbance of memory. Casual conversation revealed frequent pauses with word-finding difficulty, but the patient performed well on naming tasks. Cranial nerve examination was normal. On motor testing, the patient exhibited dystonic posturing and abnormal movements of the left upper extremity. There were myoclonic jerks noted on the left side, predominantly the upper extremity but occasionally the lower extremity and trunk. Passive movement of the left arm or active movement of the right arm worsened the left arm dystonia. Both hands showed prominent apraxia. Sensation was normal and without neglect. Coordination demonstrated mild ataxia of the left leg. Reflexes were mildly increased on the left with an upgoing toe. Her gait had a spastic and rigid quality with no difficulty initiating movement or rising to walk from a seated position and she could perform several steps of tandem gait awkwardly.

Laboratory testing showed normal electrolytes, liver function tests, complete blood count, and coagulation studies. Erythrocyte sedimentation rate and C-reactive protein were normal. Thyroid studies, including thyroperoxidase and thyroglobulin autoantibody studies, were normal. Paraneoplastic studies, including Hu, Ri, Yo, MaTa, and CV2 autoantibodies, were negative. Antinuclear antibody testing was borderline positive at a 1:40 titer. CSF analysis revealed glucose 60, protein 35, one RBC, one WBC, and no malignant cells. CSF 14-3-3 protein was elevated, as was neuron-specific enolase at 43.6 ng/mL (normal $<$ 20 ng/mL). EEG showed mildly diffuse slowing. MRI of the brain with diffusion-weighted imaging showed restricted diffusion within the cortex involving the parietal, occipital, and posterior temporal lobes bilaterally but greater on the left, as well as the anterior left temporal insular cortex and the left frontal lobe (Fig. 1). There was correlation on FLAIR (Fig. 1) and no enhancement postcontrast.

Based on these findings, the patient was diagnosed with probable CJD by WHO criteria.[1] She was discharged home, where her symptoms continued to worsen with progressive cognitive dys-

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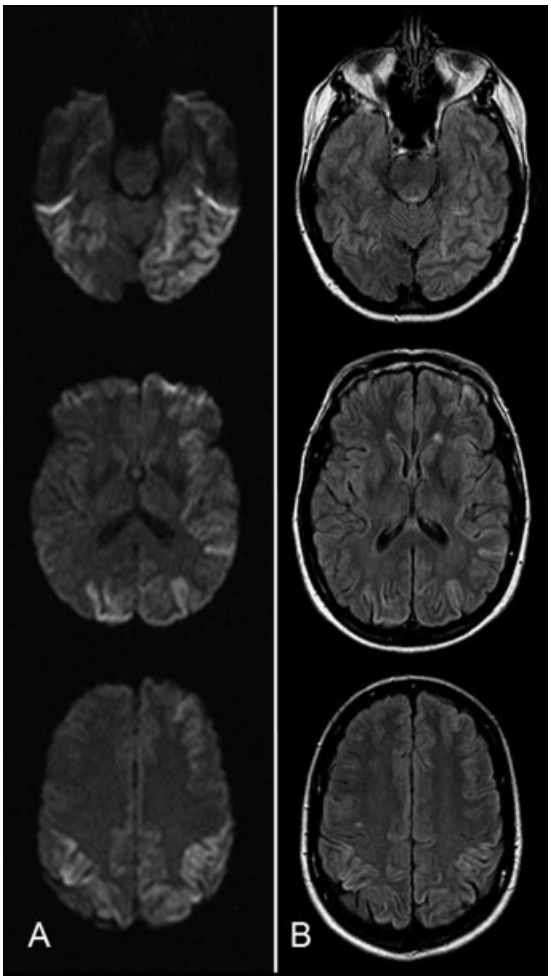


**FIG. 1.** Representative diffusion-weighted (**A**) and FLAIR imaging (**B**) of the brain demonstrating diffuse restricted diffusion and corresponding FLAIR signal hyperintensity in a cortical ribbon pattern greater on the left than the right.

function, increasing abnormal movements, and dysphagia (see Video). She developed left-sided sensory neglect and extinction to double simultaneous stimulation. She was treated symptomatically for her left upper extremity dystonia with botulinum toxin with only minimal improvement. Less than 1 month after her initial diagnosis, the patient died at home. The immediate cause of death was not determined, but aspiration was suspected, given her progressive dysphagia. Per family wishes, a limited autopsy was performed and pathology confirmed the diagnosis of sporadic CJD by immunohistochemistry (Fig. 2) and prion protein (PrP) gene sequencing (data not shown).

## Discussion

This case illustrates the importance of considering CJD in the differential diagnosis of unusual cases with alien limb sign. MacGowan and colleagues[2] identified two elderly patients with left alien limb as an initial manifestation lacking overt dementia but with CJD confirmed on pathology. Both patients had normal neuroimaging (although diffusion-weighted studies were not done), characteristic EEG findings with periodic sharp wave complexes, and one had elevated CSF 14-3-3 protein.[2] Similar presentations have been described by Cannard and colleagues[3] and Inzelberg and colleagues,[4] but these patients showed initial cognitive impairment, also did not have diffusion-weighted imaging, and only one case was confirmed by pathology.[3] Alien limb has also been seen in nonsporadic cases, as Oberndorfer and colleagues[5] identified a patient with familial CJD confirmed by pathology with left alien limb, no dementia, elevated CSF 14-3-3 protein, characteristic EEG findings, and an unremarkable MRI, although diffusion-weighted imaging was not performed. Neuroimaging, particularly diffusion-weighted imaging, may be extremely useful in these cases as Anschel and colleagues[6] described a pathologically confirmed CJD patient with left alien limb sign and cognitive disturbances, normal CSF 14-3-3 protein, and an EEG with only diffuse slowing, but with restricted diffusion abnormalities in primarily the right cortex and basal ganglia. Similarly, Moreaud and colleagues[7] described a patient with cognitive impairment and left alien limb sign with normal CSF and an EEG with pseudoperiodic waves but cortical ribbon abnormalities on FLAIR (DWI not performed) and CJD on pathology. Kleiner-Fisman and colleagues[8] have also reported a patient with disorientation and gait disturbance who rapidly developed left alien limb sign while initially lacking characteristic EEG findings but with restricted diffusion throughout the cortex on DWI and CJD by pathology. In summary, there are eight other reported cases of alien limb sign in association with either definite or probable CJD. Not all cases demonstrated clear evidence of dementia with onset

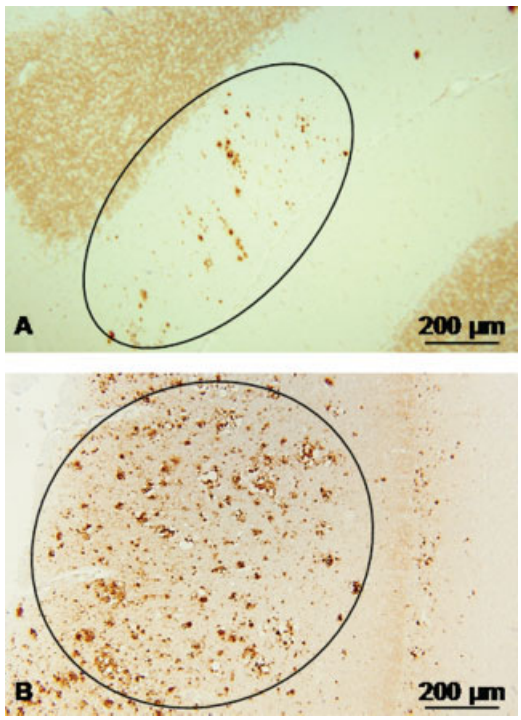


**FIG. 2.** Immunohistochemical staining of postmortem tissue sections from the cerebellum (**A**) and occipital cortex (**B**) using monoclonal antibody 3F4 demonstrating the presence of the Creutzfeldt–Jakob disease prion protein. Scale is indicated. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of the alien limb. There was also significant variability in the associated findings of CJD, including EEG and MRI abnormalities and elevated CSF 14-3-3 protein. Diffusion-weighted imaging, which has been reported in one series to be 92% sensitive and 93% specific for CJD,[9] has only been performed in 2 previous cases and has shown restricted diffusion in both, although those patients exhibited cognitive disturbances on presentation. At least two patients also had extremely rapid declines, dying within a month of diagnosis, although most lived for 3 to 6 months afterward.[2–8]

Aside from the alien limb, this patient also demonstrates another atypical finding. Her left-sided burning paresthesias are uncommon for sporadic CJD, as sensory changes are reported by only 10% or less of patients at disease onset,[1,10] with subsequent development in less than 20%.[10] In contrast, such symptoms appear relatively common in variant CJD, occurring in 31% at disease onset and up to two thirds of total cases in one study, with burning sensations in 22% and lateralization in 31%.[10] The causative lesion in variant CJD remains unknown but thalamic involvement has been implicated.[10] Our patient, however, did not have significant changes in the thalamus on either diffusion-weighted imaging or pathology (data not shown). Interestingly, sensory complaints may be more common in sporadic CJD associated with an alien limb as at least three of the previously reported eight cases also featured sensory disturbances including sensory loss or paresthesias.[2,7] This could suggest additional clinical differences between typical sporadic CJD and that associated with alien limb.

Alien limb is defined as autonomous motor activity, which can be either non–goal-directed, compulsive and goal-directed, or even self-destructive.[11] This may be accompanied by additional motor signs including apraxia, hemiparesis, hemiataxia, cortical reflex myoclonus, action dystonia, athetosis, or hemiballismus.[11] Surgical and other lesions have implicated pathways in the corpus callosum, the supplementary motor area, and the thalamus in alien limb development.[11] According to the most common method of categorization, there are two alien limb subtypes, callosal and frontal.[12] In the callosal subtype, damage to the anterior portion of the corpus callosum produces alien limb features in the nondominant (left) hand, with intermanual conflict being a prominent finding.[12] Lesions to the frontal cortex, namely, the premotor and supplementary motor areas and the cingulate gyrus, often with associated callosal damage, produce grasping, groping, and compulsive tool manipulation by the dominant (right) hand.[12] It is important to note that these distinctions were developed primarily from studies of right-handed individuals and do not provide precise anatomical and behavioral correlations in all cases, which can show significant overlap.[11,12] Alien limb sign is a frequent finding in corticobasal degeneration, seen in approximately 50% of patients, but rarely seen initially.[11] Other etiologies include stroke or CNS tumor but there is no specific anatomical lesion or clinical disorder that can be predicted accurately by the presence of an alien limb.[11] In this patient, the left alien limb, while not her first symptom, was the precipitant to her presentation and ultimate diagnosis with CJD and occurred in the absence of overt dementia. Anatomically, we suspect her alien limb was secondary to subtle corpus callosal damage, resulting in disconnection of her nondominant left hand from her left hemisphere, which is dominant for complex and fine motor activities in right-handed individuals.[12,13] However, disease involvement was not found in the corpus callosum on diffusion-weighted imaging or on pathology (data not shown), instead being most prominent in the posterior portions of the brain (Figs. 1 and 2). Intriguingly, there are several reports implicating various lesions of the parietal, occipital, and temporal lobes as well as the thalamus in alien limb development.[12] This suggests the potential for an additional posterior subtype, which is not yet clearly defined and may result from an atypical disconnection syndrome or impairment of appendicular sensory feedback.[12] Future studies will be necessary, however, to better define these lesions and their behavioral correlates.

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## Legends to the Video

**Segment 1.** Dystonic posturing of the left arm is seen at rest (0:00 to 0:30). Frequent myoclonic jerks are noted during the interview.

**Segment 2.** Prominent word-finding difficulty and cognitive impairment are noted as the patient describes her symptoms (0:31 to 1:05).

**Segment 3.** Patient exhibits left-sided autotopagnosia with complete dissociation from her left side (1:06 to 2:04).

**Segment 4.** Left alien limb phenomenon is exacerbated by the patient attempting a task with the right hand (2:05 to 2:35).

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