Isolated myoclonical alien hand as the sole presentation of pathologically established Creutzfeldt-Jakob disease: a report of two patients

D J L MacGowan, N Delanty, F Petito, M Edgar, J Mastrianni, S J DeArmond

Abstract
Creutzfeldt-Jakob disease may have many atypical presentations before the development of classic progressive dementia and startle myoclonus. In two patients with pathologically established disease association with a progressive alien hand syndrome was the sole initial manifestation of the disease.

Keywords: alien hand; Creutzfeldt-Jakob disease; clinical presentation
hand’s grasp. Her dementia and myoclonus rapidly progressed along with the development of bilateral 1 Hz periodic complexes with triphasic waves on the EEG. Genomic DNA was extracted from peripheral leukocytes and the prion protein (PrP) gene was amplified using the polymerase chain reaction. Denaturing gradient gel electrophoresis was used to screen the entire open reading frame of the PrP gene and did not show any mutation. The codon 129 of this gene was homozygous for methionine. A brain biopsy was not performed and she died six months later from acute bronchopneumonia and pulmonary emboli.

The formalin fixed brain weighed 1180 g and was grossly normal. Microscopical analysis with standard haematoxylin and eosin and Luxol fast blue stain showed neuronal loss with conspicuous spongiosis and reactive astrocytosis in the cerebral isocortex, neostriatum, diencephalon (particularly the mamillary bodies), the periaqueductal and medullary tegmental grey, and the red, tectal, gracile, and inferior olivary nuclei. Of note, neuritic (senile) plaques were present in the cerebral isocortex but not in Ammon’s horn. There were also no neurofibrillary tangles, granulovacuolar degeneration, or Hirano bodies. The neuropathological diagnosis was spongiform encephalopathy consistent with Creutzfeldt-Jakob disease.

Case 2
A 74 year old right handed white woman with no relevant medical or family history was referred with a seven week history of progressive weakness, jerking, and incoordination of her left arm and leg. She noticed the first symptom in her left hand which “would not do what she wanted it to do” but would jerk for no reason and interfere with the actions of her right hand during daily activities such as dressing and eating. Occasionally, her left hand performed involuntary purposeful actions such as unbuttoning her blouse and removing a hair pin. These symptoms came on over one week but soon weakness, ataxia, and myoclonus involved the left leg, such that she was no longer ambulatory after one month. By the time of presentation to our hospital, she had become unaware of the identity of her left arm and right arm had developed mild weakness and occasional jerks. She had no cognitive complaints.

On examination, her orientation, concentration, language and memory, including a mini mental assessment, were normal. Her left hand had spontaneous and stimulus sensitive myoclonus, and performed uncontrolled semipurposeful grasping movements at her blouse, face, and right hand. There was also a grasp and palmomental reflex. Similar, but much less frequent myoclonus was noted in the right hand. She had no voluntary control of her left hand and denied it as her own. She regarded the left hand with great suspicion and treated it as a hostile entity. When asked to name the owner of her left hand, she could not say but was certain that it was not her own. She had a supranuclear left facial and palatal weakness. There was a spastic tetraparesis affecting the left side more than the right. Sensory testing disclosed intact responses to pin prick bilaterally but with allodynia on the left arm. Proprioception was absent in the left arm and leg and absent to the knee and elbow on the right. Despite intact visual fields, she had a dense left visual neglect by line bisection and construction tasks. She was unable to stand unaided due to the severe weakness, myoclonus, and sensory ataxia.

Routine laboratory tests and results of examination of CSF were all normal. Brain MRI with gadolinium showed normal age related changes. Three days after admission, she deteriorated, becoming obtunded and showing pronounced bilateral startle myoclonus. An EEG disclosed a low amplitude background with diffuse delta slowing and generalised periodic 1–2 Hz complexes. Ten days later, radioimmunoassay for the presence of 14–3–3 protein in CSF using polyclonal rabbit anti 14–3–3β (courtesy of M Harrington, Caltech University) was positive. The demonstration of this normal human brain protein in the CSF of a patient with clinical dementia is 96% sensitive and specific for the diagnosis of Creutzfeldt-Jakob disease. Consequently a brain biopsy was not performed and the patient was managed with comfort care. She died in a hospice 12 weeks after the onset of the illness.

The brain weight was not recorded but generalised mild gyral atrophy was noted. At microscopy, typical widespread spongiform change with reactive astrocytosis was noted in the frontoparietal cortices and diencephalic structures, but was absent on sections of the brain stem, cerebellum, and spinal cord. The figure shows that the histoblot technique for in situ detection of protease resistant PrP, performed as previously described, was positive, but immunostaining of formalin fixed sections with α-PrP antibodies did not show PrP-amyloid plaques. Genomic DNA was extracted from brain tissue and the PrP gene amplified using the same technique as in case 1. Denaturing gradient gel electrophoresis did not show any mutation and the codon 129 status was heterozygous, methionine/valine.

Discussion
Alien hand has not been previously reported as a presenting feature of Creutzfeldt-Jakob disease. Both patients presented with a non-dominant myoclonic alien hand with cortical sensory loss and a progressive spastic hemiparesis in the absence of clinically demonstrable dementia or generalised myoclonus. This clinical syndrome is identical to that of corticobasal ganglionic degeneration as described by Rinne et al, Riley et al, and Gibb et al, apart from the duration of the illness in corticobasal ganglionic degeneration which ranges from four to eight years. In the largest series, by Rinne et al, alien hand complaints were present in 14 of the 36 patients and took on average a year to develop after symptoms first started. This contrasts with our two patients who first complained of an alien hand and then developed a rapidly progressive
The alien feeling can range from denial to per-sonification of the limb and the movements usually have a purposeful appearance which terrifies the patient when they first occur. Intermanual conflict with diagonistic terrifies the patient when they first occur. The presence of a grasp reflex, other and were both experienced early by our patients. The grasp reflex, other frontal release signs, and a curious compulsive manipulation of tools, have all been related to combined callosal and dominant mesial frontal injury in the supplementary motor area. Callosal alien hand is characterised by inter-manual conflict alone and requires anterior callosal injury as in surgical callosotomy. However, isolated infarction of the middle and posterior body of the callosal causing a transient non-dominant alien hand with a domi-nant ideomotor apraxia has been recently described. The authors suggest that, as in primates, interhemispheric transcallosal fibres connecting the premotor, motor, and sup-plementary motor areas extend posteriorly in the callosal and can be injured by infarction of its middle portion. Callosal alien hand is always non-dominant, presumably because non-dominant hand movements depend on bilateral motor and supplementary motor areas through transcallosal information transfer. This may also explain the absence of an alien hand in an ambidextrous man with an otherwise complete callosal disconnection syn-drome due to haemorrhage in the body of the corpus callosum. The other two right handed patients with callosal haemorrhage in this report had a prominent non-dominant alien hand. Selective injury to the mesial frontal area, genu, and body of the corpus callosum does not explain the reported cases of alien hand due to posterior lesions and the frequent cortical sensory loss seen in both of our cases and those due to Alzheimer's disease and cortico-basal ganglionic degeneration. Poste-rior or sensory lesions include a left parietal surgical encephalomalacia, right parietal cor-tical infarction, right precommunal poste-rior cerebral artery infarction involving the thalamus, splenium of the corpus callosum, and occipital lobe, and thalamocapsular haemorrhage. Clearly, the alien hand cannot be explained by callosal disconnexion theories alone.

Decety et al have attempted to replicate the movements of an alien hand using PET imaging of normal right handed subjects observing a “virtual” right hand grasping a series of three dimensional objects. Subjects were instructed to watch the hand “as if it were their own”. This paradigm was compared with imagining grasping the objects with their own right hand. A control rest period was also recorded. Observing the “virtual” hand movements differed by activation of the extrastriate visual association areas and cerebellar hemispheres bilaterally, implying the importance of these centres for motor learning. The active motor imagery of the patient’s own right hand stimulated, as expected, areas known to be related to motor preparation and programming including the motor cortices (area 6) bilaterally and left premotor areas. It may be that the clinical alien hand represents a release phenomenon resulting from processes interfering with the coor-dinated function of motor execution and motor learning.

It seems clear that the alien hand is a poorly localising, often non-specific “sign” and is more accurately regarded as a syndrome. This syndrome may arise from injury to centres governing praxis and motor planning as well as those concerning proprioceptive sensation and spatial localisation of the involved hand. This injury may be due to a discrete structural lesion but the absence of this suggests a degenerative disorder. This is most commonly corticobasal ganglionic degeneration or Alzheimer’s disease. This report adds Creutzfeldt-Jakob disease to the list of disorders for consideration. A rapid evolution of symptoms with progressive myoclonus suggests a prion disorder. Mental deterioration was not an initial presenting fea-ture in our patients as in 15% of Brown’s series of 234 sporadic cases with Creutzfeldt-Jakob disease established by experimental transmis-sion to primates. This report adds to the wide range of presenting features of Creutzfeldt-
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Jakob disease. Stroke-like episodes and transient ischaemic-like attacks often referable to the posterior fossa are other unusual presentations, and as mentioned before may occur in the absence of clinical dementia. The rapid, progressive course with ensuing myoclonus should alert one to the diagnosis. Thus knowledge of the different presentations of Creutzfeldt-Jakob disease, often without the full classic triad of ataxia, dementia, and startle myoclonus, may be important with increased public awareness of the condition.

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