LETTERS

Genetic Creutzfeldt–Jakob disease mimicking variant Creutzfeldt–Jakob disease

The “pulvinar sign” on MRI brain scan is defined as hyperintensity of the posterior thalamus relative to the signal intensity of the anterior putamen.1 In the appropriate clinical context, the pulvinar sign and hyperintensity in the dorsomedial thalamic nuclei (the hockey stick sign) are sensitive and specific features of variant Creutzfeldt–Jakob disease (vCJD).1 Variant CJD is an acquired form of prion diseases or transmissible spongiform encephalopathies. Since vCJD represents bovine spongiform encephalopathy infection in humans and is a potential public health hazard, it is important that this condition is distinguished from other progressive neuropsychiatric diseases, including sporadic and genetic forms of CJD (gCJD). Here we report a middle-aged woman with clinical symptoms and MRI features highly suggestive of vCJD, with a final diagnosis of gCJD.

CASE REPORT

A 54-year-old Hungarian woman showed considerable changes in her personality and behaviour, including withdrawal, anxiety attacks, impatience and aggression. She lost 10 kg in weight. Six months later she experienced clumsiness and involuntary jerks in her right arm and, within weeks, stiffness in the fingers of her right hand, a gait disorder with stiffness of the right leg and slurring of speech. Seven weeks before death, neurological examination revealed horizontal nystagmus, gait ataxia, dystonic posturing of the right arm, distally more pronounced paucis in the right arm (3/5) and hyperreflexia on the right side, but no Babinski sign. Sensory symptoms were not described. Paranoid ideation was noted. The Mini-Mental State Examination score was 29/30. Later in the disease course, there was myoclonus in all of extremities and the face, with a startle response, dystonic movement in the right arm and progressive dysarthria, gait ataxia and mental decline. The patient developed akinetic mutism and died due to bronchopneumonia. The disease duration was 10 months.

Past medical history was negative for blood transfusion, neurosurgical procedures, human growth or gonadotrophin hormone treatment, dura mater transplant or corneal graft. Her mother was still alive and her father had died aged over 70 years. Before his death the family had noticed gait disorder and psychiatric problems. The patient had four siblings: one died at the age of 35 years from lymphoma, two were healthy and one brother is currently under psychiatric treatment for depression. In the latter case, further examinations are under study to exclude the possibility of a mutation carrier state. The proband did not have children.

Routine blood and CSF parameters were in the normal range. Protein 14-3-3 was not examined. EEG (recorded at admission and five times up to 2 weeks prior to death) showed asymmetric slowing and sharp waves (fig 1A). Periodic activity with triphasic sharp wave complexes was observed for the first time 13 days before death (fig 1B). Cranial MRI, performed at admission and 10 days before death, showed bilateral hyperintensity in the pulvinar and dorsomedial regions of the thalamus and mild hyperintensity in the left putamen. In both recordings hyperintensity was prominent on T2, diffusion weighted and FLAIR sequences (fig 1C, D, E).

DNA was prepared from peripheral blood, and analysis of the open reading frame of the prion protein gene (PRNP) was performed. The patient and family gave consent for genetic studies.

Analysis of the PRNP revealed methionine homozygosity at codon 129 and substitution of lysine (K) for glutamate (E) at codon 200 (E200K mutation).

For neuropathological examination, tissue samples from several regions of the brain were available. Immunohistochemistry was performed with the monoclonal anti-PrP antibody 12F10 (1.100; Cayman Chemicals, Ann Arbor, Michigan, USA) and anti-glial fibrillary acidic protein (GFAP, 1.300; Dako, Glostrup, Denmark). PrP biochemistry could not be carried out because no frozen tissue was available. Spongiform change along with gliosis and synaptic PrP deposition was severe in the putamen, moderate in the caudate nucleus, while the anterior nucleus, ventral striatum and thalamus showed mild alterations. Focal perivascular PrP immunopositivity was noted in the parietal cortex. Brainstem and hippocampal formation were relatively spared. In the cerebellar hemisphere, stripe-like appearance of PrP immunoreactivity in the molecular layer was observed (fig IF). In the thalamus spongiform change, neuronal loss and synaptic PrP immunoactivity was particularly evident in the pulvinar and mediodorsal nucleus, while the anterior nucleus, ventral and ventrolateral nuclei showed mild changes. In contrast with other regions, the pulvinar showed larger vacuoles and perivascular PrP deposits (fig 1G, H).

DISCUSSION

At the time of first admission, our patient had a history of early psychiatric symptoms, ataxia, dystonia and myoclonus together with the pulvinar sign on MRI brain scan. The early EEGs did not show the generalised triphasic periodic complexes, thus the MRI findings and clinical features were compatible with vCJD.2 The diagnostic criteria for vCJD include a number of preconditions. In this case these were largely fulfilled with the duration of illness exceeding 6 months, no history of potential iatrogenic exposure and routine laboratory investigations not suggesting an alternative diagnosis. Although the father of the patient showed neuropsychiatric alterations, suggestive of a familial form, identification of the E200K PRNP mutation was the only feature that disallowed classification as a case of “probable vCJD”3 as the final preconditions state that there must be no evidence of a genetic form of human prion disease.

Neuropathological examination confirmed the diagnosis of a genetic form of CJD. In our patient vacuolation and PrP immunoreactivity correlated with the high signal intensity on the MRI. A recent study on MRI in E200K gCJD reported 40% of cases with signal changes in the thalamus but overall the MRI changes, including basal ganglia high signal, were similar to the sCJD pattern.4 Clinical features of E200K gCJD may also resemble that of sCJD but cases with insomnia and thalamic involvement have also been described.5 Our case may be a representative of a thalamic form of E200K gCJD, but in our patient insomnia was not documented and in the latter study MRI examination was not performed.5

To our knowledge the present case is the first reported gCJD case with an E200K mutation to show the typical pulvinar sign on MRI that, together with clinical features, mimicked vCJD.

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Figure 1  Electroencephalogram recordings 37 (A) and 13 (B) days before death. Periodic sharp wave complexes with triphasic morphology appear only in the terminal phase. Increased signal intensity is seen in the medial thalamus and in the pulvinar in T2 (C), diffusion weighted (D) and coronal FLAIR (E) images, giving the appearance of a hockey stick. Stripe-like appearance of prion protein (PrP) immunopositivity perpendicular to the surface in the molecular layer (F) in the cerebellar cortex. Representative histopathological changes, comprising spongiform change, reactive astrogliosis and deposition of disease associated PrP, as demonstrated by haematoxylin and eosin (H&E) staining and immunoreactivity for glial fibrillar acidic protein (GFAP), and PrP in the less affected lateral thalamus (G), and severely affected pulvinar (H).
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