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Case report

Phenotypic similarities causing clinical misdiagnosis of pathologically-confirmed sporadic Creutzfeldt-Jakob disease as dementia with Lewy bodies

D.G. du Plessis [a], A.J. Larner [b,*]

[a] *Greater Manchester Neurosciences Centre, Humphrey Booth Building, Hope Hospital, Salford M6 8HD, UK*

[b] *Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Lower Lane, Fazakerley, Liverpool L9 7LJ, UK*

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Abstract

A patient fulfilling central, core and supportive clinical diagnostic criteria for dementia with Lewy bodies deteriorated rapidly in the absence of neuroleptic drug treatment, prompting suspicion of a diagnosis of sporadic Creutzfeldt-Jakob disease. At postmortem examination, the brain showed features typical of Creutzfeldt-Jakob disease of the MV1 subtype. We review the phenotypic overlap between dementia with Lewy bodies and Creutzfeldt-Jakob disease which may cause clinical misdiagnosis.

Keywords: Creutzfeldt-Jakob disease; Dementia with Lewy bodies; Diagnosis

1. Introduction

The differential diagnosis of dementia with Lewy bodies (DLB) and sporadic Creutzfeldt-Jakob disease (sCJD) may be challenging. "Possible" cases of sCJD referred to national prion disease surveillance units occasionally prove to have a pathological diagnosis of DLB [1–5]. This may result from the overlap of clinical features, or from investigation findings such as EEG periodic sharp wave complexes (PSWC) which, though highly sensitive and specific for the diagnosis of pathologically-confirmed sCJD [6], are not pathognomonic, occurring on occasion in pathologically confirmed DLB [2,3,7–9]. Conversely, cases have been reported in which the presentation fulfilled clinical diagnostic criteria for DLB but in which subsequent clinical course, radiological and CSF findings necessitated diagnostic revision to sCJD, though without neuropathological confirmation [10]. We report a patient presenting with a phenotype suggestive of DLB but who at postmortem proved to have sCJD of the MV1 subtype.

2. Case report

A 74 year-old right-handed man was referred to the neurology clinic by an ophthalmologist with a complaint of seeing colours for which no ophthalmological explanation could be found (normal corrected visual acuities, peripheral visual fields). If he closed his eyes, he reported "seeing" a colour, often red, which would fade over about 30 s when he opened his eyes. This simple visual hallucination interfered with watching television and shopping. He also complained of feeling unsteady on his legs but without any falls. He commented that sometimes he had the feeling that someone was standing beside him and he would say hello although no one was there. On clinical examination he had a mild bradykinesia, slightly stooped posture, hesitant gait, and hypophonic speech, but there was no tremor or rigidity and eye movements were intact. The signs were consistent with mild motor features of parkinsonism. There was no family history of neurodegenerative disease. Although there was no initial complaint of cognitive decline, the patient was requiring increased assistance with some instrumental activities of daily living and within six weeks of outpatient assessment he was admitted to hospital with increasing episodic confusion. MR brain imaging showed generalized atrophy

* Corresponding author. Fax: +44 151 529 8552.
E-mail address: a.larner@thewaltoncentre.nhs.uk (A.J. Larner).

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with periventricular ischaemic changes, particularly in the occipital regions.

Around 18 months earlier the patient had developed lightheadedness on standing from sitting or lying. Investigations showed a 20–40 mmHg systolic blood pressure postural drop which had been diagnosed as orthostatic hypotension and treated with fludrocortisone 0.1–0.2 mg/day with some clinical benefit. Formal autonomic studies had not been undertaken (tilt table, noradrenaline levels) but biochemical studies had excluded Addison's disease.

A working diagnosis of dementia with Lewy bodies was made based on widely-accepted clinical diagnostic criteria [11]: central (progressive cognitive decline interfering with activities of daily living), core (visual hallucinations; spontaneous motor features of parkinsonism), and supportive features (orthostatic hypotension) were deemed to be present.

Over the next two months the patient deteriorated progressively and rapidly to an encephalopathic state. At no time were neuroleptic medications administered. Because of the rapid and unanticipated decline the diagnosis of sporadic CJD was considered, but clinically no myoclonus was observed. CSF was normal aside from slightly elevated protein (0.67 g/l; normal range 0.15–0.45 g/l; sample was insufficient for 14-3-3 estimation). The patient was too unwell for hospital transfer for EEG. Palliative care was instituted and he died of a bronchopneumonia six weeks after admission, just over three months after the initial neurological consultation, and one year from the onset of his visual symptoms.

Macroscopically, the brain showed generalized mild atrophy with relative sparing of the occipital lobes. Mild atrophy of the cerebellar vermis was also apparent. Normal pigmentation of the substantia nigra and locus coeruleus was observed on sectioning the brainstem. The spinal cord was not available for examination.

Histological examination of the brain showed striking, focally confluent, spongiform change with background gliosis and neuronal loss in the occipital lobe neocortex (Fig. 1a). Less advanced, more microvacuolar, spongiform change was apparent in the neocortex elsewhere, in the molecular layer of the cerebellar cortex, in the basal ganglia and the thalamus, with preferential involvement of the medial nucleus of the latter. Limited spongiform change was found in the midbrain tectum/periaqueductal grey matter and entorhinal cortex with relative sparing of the hippocampus. The substantia nigra showed somewhat equivocal spongiform change without significant neuronal loss or Lewy bodies.

A predominantly synaptic pattern of staining for PrP was seen with KG9 and 3F4 immunostaining, with additionally perivacuolar and focal perineuronal staining in the occipital cortex (Fig. 1b). PrP plaques were not evident. The substantia nigra was spared of PrP staining apart from very rare neurones showing fine punctuate perineuronal staining. Immunostaining for tau and α-synuclein showed no evidence for tauopathy or synucleinopathy. Biochemical analysis of frozen brain tissue by Western blot showed protease-resistant PrP with Type 1 isoform. The patient was a methionine-valine heterozygote at codon 129 (M129V). Hence the diagnosis, according to the molecular and phenotypic classification of CJD devised by Parchi et al. [12], was sporadic CJD consistent with the MV1 subtype.

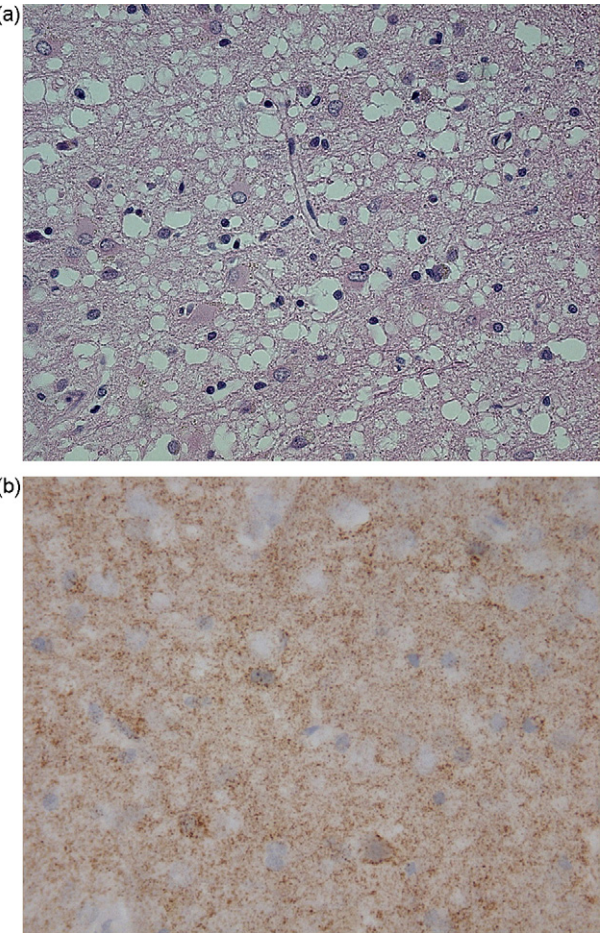

Fig. 1. (a) Occipital cortex showing marked spongiform change with confluent vacuolation in the deeper layers associated with astrocytic gliosis and neuronal loss (H&E, original magnification ×400). (b) Excessive, mainly synaptic, pattern of PrP immunostaining in the medial occipital cortex with focal perineuronal staining (KG9 antibody, original magnification ×630).

3. Discussion

The initial working diagnosis in this patient was DLB because of the clinical presentation with progressive cognitive decline (central diagnostic criterion), visual hallucinations and motor features of parkinsonism (core criteria), with a prior history of symptomatic orthostatic hypotension (supportive criterion) [11]. With respect to the latter criterion, cases of pure autonomic failure evolving to DLB have been reported [13,14]. Although patients with DLB may decline rapidly following administration of neuroleptic medications [15], this disease course is unusual in drug-naïve patients [16]. The very rapid clinical progression in this case in the absence of neuroleptic use prompted consideration of sCJD as the diagnosis [17]: abrupt decline into stupor or coma after