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Characterising the uncommon corticobasal syndrome presentation of sporadic Creutzfeldt-Jakob disease

Will Lee [a,e], Marion Simpson [a,b], Helen Ling [c], Catriona Mclean [d], Steven Collins [b,**], David R. Williams [a,e,*]

[a] Department of Neuroscience, The Alfred Hospital, Commercial Road, Melbourne, Victoria 3004, Australia
[b] The Australian National Creutzfeldt-Jakob Disease Registry, Department of Pathology, The University of Melbourne, Australia
[c] Queen Square Brain Bank for Neurological Disorders and Institute of Neurology, University College London, London WC1N 1PJ, UK
[d] Department of Pathology, The Alfred Hospital, Commercial Road, Melbourne, Victoria 3004, Australia
[e] Van Cleef Roet Centre for Nervous Diseases, Monash University, Melbourne, Victoria 3004, Australia

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ABSTRACT

Background: Corticobasal syndrome (CBS), which encompasses cortical sensory loss, alien limb, bradykinesia, rigidity, limb apraxia and dystonia, is the classic presentation of corticobasal degeneration (CBD). It may occur in other neurodegenerative disorders including sporadic Creutzfeldt-Jakob disease (sCJD). Current CBD diagnostic criteria outline features of CBS but fail to distinguish CBD from other causative pathologies.

Objectives: To characterise the CBS presentation of sCJD (sCJD-CBS) in the context of existing CBD diagnostic criteria.

Method: Data of two new cases of sCJD-CBS and seven patients identified from the Australian National Creutzfeldt-Jakob Disease Registry database was reviewed. Additional data from 11 published cases was incorporated to illustrate the natural history of sCJD-CBS. Comparison was made with pathologically diagnosed CBD cases with ante-mortem CBS presentation (CBD-CBS).

Results: sCJD-CBS accounts for 1.8% of all Australian sCJD cases. Compared to CBD-CBS, disease progression is more rapid in sCJD-CBS (median time to diagnosis 48 vs.1.5 months, $p < 0.001$; and disease duration until death 68 vs. 5 months, $p < 0.001$). Although no clinical features separate the two, alien limb and myoclonus tend to occur early in sCJD-CBS following initial 'sensory' disturbance in the affected limb. Consistent with sCJD, distinctive diffusion weighted imaging (DWI) abnormalities on magnetic resonance imaging may also occur in sCJD-CBS.

Conclusion: sCJD should be suspected in patients presenting with CBS when clinical progression is rapid and accompanied by DWI abnormalities, even without cerebrospinal fluid 14-3-3 protein detection and electroencephalographic periodic sharp wave complexes. We propose the addition of rapid (<12months) progression to akinetic-mutism or death and DWI abnormalities as exclusions in future CBD diagnostic criteria.

1. Introduction

The corticobasal syndrome (CBS) is considered the classic presentation of corticobasal degeneration (CBD), a primary neurodegenerative disease characterised by widespread neurofibrillary tau-pathology affecting the cerebral cortex and basal ganglia. A CBS presentation comprises variable combinations of limb apraxia, cortical sensory loss, limb dystonia, focal myoclonus, alien limb and rigidity and bradykinesia that do not respond to dopaminergic medications. Since the original description of CBD, it has become clear that a number of neurodegenerative diseases can present with CBS such as Alzheimer's disease (AD), Parkinson's disease (PD), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB) and non-CBD frontotemporal dementia (FTD) pathologies including Pick's disease [1,2]. Indeed the diagnosis of CBD made on the basis of presentation with CBS will be correct in less than 25% of patients [1].

* Corresponding author. Department of Neuroscience, Alfred Hospital, Commercial Road, Melbourne, Victoria 3004, Australia. Tel.: +61 3 9076 2059; fax: +61 3 9076 5075.
** Corresponding author. The Australian National CJD Registry, Level 5, The Medical Building, Department of Pathology, Faculty of Medicine, The University of Melbourne, Grattan Street, Victoria 3010, Australia. Tel.: +61 3 8344 1949; fax: +61 3 9349 5105.
E-mail addresses: stevenjc@unimelb.edu.au (S. Collins), david.williams@monash.edu (D.R. Williams).

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Creutzfeldt-Jakob disease (CJD) is characterised by cerebral deposition of the abnormal protease-resistant prion protein. Sporadic CJD (sCJD) accounts for the majority of CJD cases and is another condition where patients may present predominantly with CBS (sCJD-CBS). This rare clinical subtype adds to the wide clinical spectrum of sCJD that includes ataxic (Oppenheimer-Brownell), visual (Heidenhain), thalamic (sporadic fatal insomnia), dyskinetic, panencephalopathic, posterior cerebral atrophy and even PSP-like variants [3–6]. Prompted by two recent cases, we sought to better characterise sCJD-CBS and consider clues that may clinically separate it from CBD.

2. Methods

We report two new cases of sCJD-CBS and include data collected from the Australian National Creutzfeldt-Jakob Disease Registry (ANCJDR) and other published cases. For this study, CBS was defined by the presence of progressive asymmetric onset of cortical dysfunction (alien limb, apraxia, cortical sensory loss) and at least one of the following three movement disorders: akinetic-rigid syndrome, limb dystonia or myoclonus. The ANCJDR includes all pathologically diagnosed cases of CJD in Australia, prospectively collected from 1993 and retrospectively identified to 1970. The ANCJDR database was screened using the terms "corticobasal", "alien hand", "alien limb" and "extrapyramidal" and seven patients were identified and case notes were reviewed. A literature search using PubMed and keywords "Creutzfeldt-Jakob disease", "alien hand", "alien limb" and "corticobasal" in combinations identified ten English language articles describing cases of pathologically-proven sCJD-CBS [2,7–15]. From these articles, sufficient clinical data from 11 cases was available (either published or supplied by the corresponding authors). In total, we identified twenty patients with sCJD-CBS (two from our clinic, seven from the ANCJDR database and 11 from published literature).

In addition, we identified pathologically diagnosed cases of CBD presenting with CBS (CBD-CBS) from the Queen Square Brain Bank for Neurological Disorders in order to facilitate comparison with cases of sCJD-CBS. Of the 1440 cases collected over a 20-year period, 19 cases with the pathological diagnosis of CBD were found. Case notes of these 19 patients were reviewed and five were found to have initially presented with CBS. The lack of access to raw data for analysis prohibited the use of additional CBD-CBS cases from published literature.

To identify the characteristics that would be most useful in separating sCJD-CBS from CBD-CBS, we only considered the clinical features that developed in the first half of the disease course. This timeframe was chosen as the clinical characteristics of sCJD-CBS converge with those of classic sCJD as the disease progresses and it is in this early phase of disease that established sCJD diagnostic criteria are likely to be least useful. Clinical signs that were not documented were considered absent. Statistical methods including chi-square, student *t*-test, Wilcoxon Rank-sum test were applied as appropriate, to compare clinical features between these groups.

3. Results

3.1. sCJD-CBS: illustrative case

A 71-year old woman presented with two months of right hand paraesthesia and was referred for neurological consultation. On examination, she was alert and oriented and was noted to have dystonia, myoclonus, ideomotor apraxia and involuntary movements consistent with alien limb affecting her right arm. In addition, there were word-finding difficulties (Video 1). Initial magnetic resonance imaging (MRI), including diffusion weighted imaging (DWI), was normal. The patient went on to develop progressive visual blurring, dysarthria and walking difficulties over weeks, leading to hospital admission. On admission, the patient was unsteady on her feet, found it difficult to stand, was virtually anarthric and had widespread spontaneous and action myoclonus. Electroencephalogram (EEG) showed diffuse delta slowing with frequent non-periodical sharp waves. Repeat brain MRI showed DWI hyperintensities without fluid attenuation inversion recovery (FLAIR) changes, involving the right frontal parasagittal, right calcarine and bilateral insular cortices, as well as the right caudate, which appeared hypointense on the apparent diffusion coefficient (ADC) map. (Fig. 1A–C) Single-photon emission computed tomography (SPECT) demonstrated extensive asymmetrical cerebral cortical and right thalamic hypoperfusion. (Fig. 1D) Cerebrospinal fluid (CSF) 14-3-3 protein was positive. The patient died shortly afterwards, five months from disease onset.

Supplementary video related to this article can be found at doi:10.1016/j.parkreldis.2012.07.010.

Post-mortem examination confirmed CJD. No macroscopic pathology was identified. Sections of the cerebral cortex, basal ganglia, cerebellar cortex and brain stem showed similar features of neuronal loss, gliosis and a "synaptic" pattern of prion protein immunoperoxidase reactivity. (Fig. 1E–F) No cortical post-ischaemic swollen eosinophilic neurons were seen and there was no tau immunoreactivity.

3.2. All sCJD-CBS case data

We reviewed case notes of twenty patients with sCJD who presented with CBS (12 women and 8 men, Table 1A) with a mean age at disease onset of 66 years (range 50–78) and median time to present to medical attention of 1.5 months (range 0.25–10). The median time from disease onset to death was five months (range 1–48). Disease duration was less than 12 months in 80% of cases.

In sCJD-CBS, symptoms began on the non-dominant side in 55% of patients and the most common signs of cortical dysfunction were limb apraxia (14/20, 70%) and alien limb phenomena (17/20, 85%). Other features that occurred in the first half of disease included dysphasia (8/20, 40%), cortical sensory loss (8/20, 40%) and neglect (3/20, 15%). The most common movement disorders were myoclonus (16/20, 80%) and dystonia (9/20, 45%). Twelve (60%) patients had rigidity but only five (25%) were documented to have both rigidity and bradykinesia. Other common features included gait ataxia (unsteadiness while walking without other specific features) in 15 patients (75%), pyramidal disturbance (presence of hemiparesis, hyper-reflexia or positive Babinski sign) in 13 (65%) and other cognitive impairment (impairment of memory or specific cognitive domains) affecting 10 patients (50%). Early visual disturbance (25%) and cerebellar signs (20%) were uncommon. (Table 1B).

The most common symptoms reported by patients to their primary care physicians were sensory disturbances in the affected limb (10/20, 50%) and limb clumsiness (7/20, 35%). Seventeen patients (85%) developed alien limb at some stage during the course of their disease and in these patients the most common features were purposeless grasping (6/17, 35%), intermanual conflict (6/17, 35%) and limb levitation (4/17, 24%). (Table 1C and D).

EEG was documented in nineteen patients while CSF 14-3-3 protein assay result was known in seventeen. In 53% of patients (10/19), typical EEG periodic sharp wave complexes (PSWC) were seen while CSF 14-3-3 testing (generally available since 1997) was positive in 59% (10/17). MRI was performed in 17 patients and nine were documented to be normal. DWI sequence was performed (or reported) in seven patients, all showing restricted diffusion in the cerebral cortices and/or basal ganglia. SPECT or positron emission tomography (PET) was performed in six patients with the universal finding of widespread asymmetrical cortical hypoperfusion. Molecular information was unavailable for the majority of identified cases.

Of the 1440 cases in the Queen Square Brain Bank, 35 patients (2.4%) either had a final clinical diagnosis of CBS (21/1440, 1.5%) or pathological diagnosis of CBD (19/1440, 1.3%). Only five patients had CBD-CBS, therefore constituting 0.3% of all archived cases. Disease characteristics including gender, age of onset, time to diagnosis and disease duration in these five cases of CBD-CBS were compared with sCJD-CBS. (Table 2) The time from disease onset to final clinical diagnosis was significantly longer in CBD-CBS (median 48 months, range 12–66) than in sCJD-CBS (median 1.5 months, range 0.25–10, Wilcoxon Rank-sum test, $p < 0.001$). The duration from disease onset until death was significantly longer in CBD-CBS