SHORT REPORT

# Sporadic Creutzfeldt–Jakob disease with cerebellar ataxia at onset in the UK

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**Objective:** To determine the frequency, in the UK, of sporadic Creutzfeldt–Jakob Disease (sCJD) with a cerebellar ataxic onset, and to describe the clinical features of the syndrome.
**Methods:** A retrospective review of autopsy-proved cases of sCJD cases in the UK, 1990–2005, identifying those presenting with cerebellar features without early cognitive decline.
**Results:** 29 of 618 (5%) patients with sCJD had an isolated cerebellar onset. Mean illness duration was 9 months. Subsequently, 21 (72%) developed myoclonus and 23 (79%) developed pyramidal features. Magnetic resonance imaging showed high signal in the basal ganglia in 11 of 14 (79%) patients. 7 of 15 (47%) patients were valine homozygotic at prion protein gene (*PRNP*)-129. Only 8 (28%) cases were referred to the surveillance unit after death.
**Conclusion:** A better definition of sCJD presenting with an isolated cerebellar syndrome might improve future case recognition and contribute to the determination of its cause.

Sporadic Creutzfeldt–Jakob disease (sCJD) is an invariably fatal neurodegenerative disease characterised typically by rapidly progressive dementia and a short duration of illness. Most patients with sCJD present with cognitive decline quickly followed by the development of a variety of neurological symptoms, usually culminating in akinetic mutism.[1] The most common differential diagnoses are Alzheimer's disease and dementia with Lewy bodies.[2] A subgroup of patients with sCJD present with a virtually isolated cerebellar syndrome,[3] and in some, cognitive decline may be delayed for weeks or even months. Although cerebellar features are common in patients with sCJD (seen in 19–47% of cases at symptom onset[4 5] and in 42–86% throughout the illness[6 7]), these largely accompany global cognitive decline and often other neurological features. The frequency of cases with a pure cerebellar onset is unclear, and the clinical description of such cases has been largely limited to case reports or as part of the phenotypic spectrum of genetic[8] or iatrogenic Creutzfeldt–Jakob disease (CJD).[9] A progressive, isolated cerebellar ataxia suggests several possible diagnoses (including inherited and metabolic disorders, paraneoplastic syndromes and demyelinating disease). Understandably, CJD is rarely the first consideration. This study aimed to determine the frequency, of pathologically proved cases of sCJD presenting with a virtually isolated cerebellar syndrome in the UK and to describe the clinical features and investigation results (including prion protein gene (*PRNP*)-129 analysis).

## METHOD

A retrospective case-note review was undertaken of all pathologically proved cases of sCJD referred to the UK National CJD Surveillance Unit (NCJDSU) between January 1990 and October 2005, to identify those with a virtually isolated cerebellar syndrome at onset (defined as individuals presenting with features of cerebellar dysfunction in the absence of any documented memory loss or confusion for at least 1 month from symptom onset). Patients were visited when alive, where possible, by an NCJDSU neurologist; a comprehensive clinical history was obtained from the patient's relatives and a full neurological examination was carried out. If not visited when alive, the patient's relatives were then visited later to confirm details of the history. Details from hospital records and general practitioner notes were requested for each case along with copies of relevant investigations (electroencephalogram (EEG), brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis). Cases were selected blinded to PRNP-129 genotype.

## RESULTS

Twenty nine of 618 (5%) patients with sCJD presented with a cerebellar syndrome in the absence of any documented cognitive impairment for at least the first month of their illness. Of these, 20 (69%) were men. The mean age at symptom onset was 63 years (median 61 years, range 48–76 years). The mean duration of illness was 9 months (median 7 months, range 2–36 months). All but one were aged $\geqslant$50 years at disease onset. PRNP gene mutation analysis was carried out in 17 of 29 (59%) cases; no disease-related mutations were identified. None of the patients without genetic analysis had a family history of dementia in a first-degree relative.

Unsteadiness or poor coordination were early features in all patients. The first documented symptoms were gait unsteadiness in 20 (69%) patients, dizziness in 6 (21%), poor coordination in 2 (7%) and dysarthria in 1 (3%). In a few patients, associated minor neurological symptoms were observed at presentation: 3 of 29 (10%) patients had sensory symptoms (burning sensations in the left upper and lower limbs in one and paraesthesia across the lumbar region in two); 2 of 29 (7%) patients had visual symptoms at onset (one with blurred vision and the other with double vision). Two others had non-specific accompanying symptoms at onset: one with headache and the other with excessive tiredness. There were no reports of excessive weight loss at onset to suggest a paraneoplastic cause.

Documented cognitive decline was delayed in all by at least 1 month (mean 3 months; range 1–9 months). Other neurological features became evident with disease progression (table 1).

**Abbreviations:** CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging; NCJDSU, National CJD Surveillance Unit; PRNP, Prion protein gene; sCJD, sporadic Creutzfeldt–Jakob disease

**Table 1** Clinical features in cases of cerebellar onset seen throughout the illness

| Clinical features | Total n = 29 | % |
|---|---|---|
| Cerebellar signs | 29 | 100 |
| Pyramidal signs | 23 | 79 |
| Myoclonus | 21 | 72 |
| Psychiatric features | 17 | 59 |
| Visual disturbance | 17 | 59 |
| Dizziness or vertigo | 15 | 52 |
| Extrapyramidal signs | 12 | 41 |
| Involuntary movements | 9 | 31 |
| Sensory symptoms | 9 | 31 |
| Seizures | 1 | 3 |

### Investigations

CSF 14-3-3 protein was analysed in 15 of 29 cases, and was positive in 12 (80%) and negative in 3 (20%). Brain MRI was available in 14 of 29 cases. In all, 11 (79%) scans showed high signal in the head of the caudate nucleus and putamen, and three were normal. None of the scans displayed high signal in the cerebellum. MRI scans were carried out at a mean age of 7.7 months (range 1–34 months) after symptom onset. The first recorded positive scan was carried out 3 months after symptom onset and scans were recorded as negative as late as 12 months from onset. All patients had at least one EEG, but characteristic features of sCJD were found in only 3 of 29 (10%) patients. PRNP-129 analysis was carried out in 17 patients, 3 (18%) of whom were methionine homozygotic (MM), 6 (35%) were methionine–valine heterozygotic (MV) and 8 (47%) were valine homozygotic (VV). Prion protein glycotype analysis carried out in 13 (45%) patients showed that one patient was MM1, one was MV1, three were MV2A, one was VV1 and seven were VV2A.

A total of 21 (72%) patients were referred to the NCJDSU when alive. In five others, referral was made after death but before the results of autopsy were known. In the remaining three the diagnosis was made only at autopsy. When alive, two of these patients were thought to have paraneoplastic disease, and in the third no diagnosis was made.

## DISCUSSION

sCJD may present with an isolated, or virtually isolated, cerebellar ataxia, which is usually referred to as the Brownell–Oppenheimer variant.[3] Cerebellar features are common in sCJD[7] and often occur early.[4] In this study, we specifically selected those cases that present with an isolated or virtually isolated cerebellar syndrome and, in particular, those without cognitive impairment at presentation. The frequency of this type of presentation has previously been uncertain. We have shown that over a 15-year period of CJD surveillance in the UK, 29 patients have presented in this way, representing 5% of all cases of sCJD. Approximately one third of all patients with sCJD present with memory loss, with the next most common presentation being that of ataxia (although frequently in combination with cognitive decline).[2] In the early stages, the differential diagnosis is wide and sCJD is often not considered until dementia supervenes. A paraneoplastic cerebellar syndrome is a relatively frequent differential diagnosis. Paraneoplastic disease may manifest as a sensory peripheral neuropathy,[10] and sensory symptoms were present, at some stage, in one third of our cases. Genetic prion disease may present with a cerebellar syndrome. Twelve of our patients did not undergo genetic testing and none had a family history of CJD. No iatrogenic exposure to prion disease was detected in any of the patients.

The duration of illness in this group was longer than that typical for sCJD (overall mean illness duration 4 months).[11] Our patients often exhibited a striking delay in cognitive decline; patients may have insight into the diagnosis if it is made early enough. Ultimately, however, all patients exhibited a rapidly progressive dementia, often with myoclonus.

More men than women (M:F approximately 2:1) were observed as presenting with virtually isolated cerebellar features, but our sample size is too small to establish a true male predominance.

Investigations including CSF 14-3-3 and MRI were useful in this context, each displaying a diagnostic sensitivity of about 80%, but it must be noted that a positive 14-3-3 result may be found in other conditions, including paraneoplastic disease.[12] The EEG was characteristic for sCJD in only 3 of 29 (10%) tested cases. This may relate in part to EEG timing as one third of patients were still walking, albeit unsteadily, at the time of the last EEG recording, whereas the three patients with typical EEG findings were bed-bound with myoclonus at the time of the recording. Characteristic EEG changes are more likely in the later stages of sCJD.[13] To the best of our knowledge, high signal in the basal ganglia structures on MRI has not been reported in paraneoplastic disease.

sCJD has a considerable degree of clinicopathological heterogeneity, particularly (although not only) in relation to presenting features.[14] Reported determinants or associations of disease phenotype include age at onset, PRNP-129 genotype and PrP protein type. Early and dominant cerebellar features, in the absence of familial disease, have been associated with valine homozygosity at PRNP-129.[15] In the UK, 11% of all patients with sCJD are PRNP-129 valine homozygotic,[16] whereas 47% of our patients were of this genotype. Patients with a pure cerebellar onset are not particularly young (a median age of 61 years compared with 67 years for sCJD as a whole in the UK).[16]

The reason for the variation in the clinical presentation of sCJD is uncertain. The cause of sCJD is unknown. The dominant theory is that it results from a stochastic PrP protein change or a somatic PRNP mutation,[17] and, if so, different onsets may simply reflect random initial sites of disease.

Among the cerebellar onset group, a relatively high number of patients (28%) were not referred to the NCDJSU when alive. For complete surveillance, the need to encourage referral of unusual cases should be emphasised.

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