Progressive ataxia and cognitive decline in a 67-year-old male: a diagnostic challenge

Dina Osman[1], Alice Weidner[2], Mayuri Madhra[3]

Abstract

We report the case of a 67-year-old male who presented with a six-week history of progressive unsteadiness, cognitive impairment and weight loss, in the context of a recent bereavement. Magnetic resonance imaging (MRI) performed several weeks earlier excluded acute stroke.

Examination revealed gross bilateral ataxia, bradyphrenia and physical manifestations of depression. Collateral history suggested rapidly progressing symptoms over three months. Repeat MRI head showed features suggestive of Creutzfeldt-Jakob disease (CJD) including T2 hyperintensities in the basal ganglia. Cerebrospinal fluid (CSF) samples were positive for 14-3-3 protein, S100b and real-time quaking-induced conversion (RT-QuIC) proteins confirming the diagnosis of sporadic CJD (sCJD).

Correspondence to:
Dina Osman
General Internal Medicine, Cumberland Infirmary of Carlisle
Newtown Road, Carlisle
CA2 7HY, UK

Email:
Dina.osman3@nhs.net

Keywords: progressive, ataxia, Creutzfeldt-Jakob disease, sporadic Creutzfeldt-Jacob disease

Financial and Competing Interests: No conflict of interests declared

Informed consent: Verbal informed consent for the paper to be published (including images, case history and data) was obtained from the patient for publication of this paper, including accompanying images. Patient was too ataxic to sign a written consent.

Introduction

Prion diseases are a diverse group of disorders with various aetiologies, clinical manifestations and distinct natural histories.[1] In up to 90% of cases, no cause is identified, and the term 'sporadic' Creutzfeldt-Jakob Disease (sCJD) is used.[2] It is considered to be a rare disorder and has an approximate incidence of 1.2 per million per year.[3] The usual age of presentation is around the seventh decade of life, and the median time to death is five months. The mortality rate by one year is 90%.[4] From a pathophysiological point of view, prion disorders are characterised by abnormal deposition of isoform prion protein (PrP) called scrapie (PrPSc) in the grey matter of the brain which is not fully susceptible to the action of proteases.[5]

The initial clinical manifestations of sCJD are non-specific. One third of patients present with systemic complaints such as tiredness, disrupted sleep and reduced appetite.[6] The other third have behavioural or cognitive changes on presentation, whereas the final third were found to have signs such as visual loss, cerebellar ataxia, aphasia, or motor deficits.[6] This condition tends to have a rapid clinical deterioration with prominent cognitive decline and myoclonus, with startle-sensitive myoclonus in particular.[6] In conclusion, the initial neurological features generally coincide with a focal disease process; however, in the majority of cases, the disease deteriorates abruptly to involve the brain in a relatively global pattern.[7]

Establishing a diagnosis of sCJD may be difficult, especially at the early stages, and heavily relies on the combination of clinical features, neuroimaging, cerebrospinal fluid (CSF) and electroencephalogram (EEG) findings. The distinctive brain magnetic resonance imaging (MRI) findings are high signal abnormalities in the striatum, cerebral cortex (with a tendency to involve multiple lobes) and/or thalamus on fluid attenuated inversion recovery (FLAIR) or diffusion weighted (DWI) images.[2,8] EEG shows periodic or pseudoperiodic sharp wave complexes, whereas CSF diagnosis relies on the detection of 14-3-3 protein, S100b and real-time quaking induced conversion (RT–QuIC).[8] However, despite all the available diagnostic tools, the cornerstone to establishing a definitive diagnosis of CJD is the identification of the classical neuropathological triad of neuronal loss, gliosis and spongiform degeneration in addition to the detection of the deposited prion protein in the brain.[9]

Case presentation

A previously fit and well 67-year-old right-handed male was referred by his GP for medical review, with regards to a six-week history of bilateral progressive cerebellar ataxia, in the context of a sudden bereavement with the loss of his partner

[1]Core Medical Trainee, Cumberland Infirmary of Carlisle, UK; [2]Specialist Trainee in Gastroenterology and General Internal Medicine, Cumberland Infirmary of Carlisle, UK; [3]Specialist Trainee in Geriatrics and General Internal Medicine, Cumberland Infirmary of Carlisle, UK

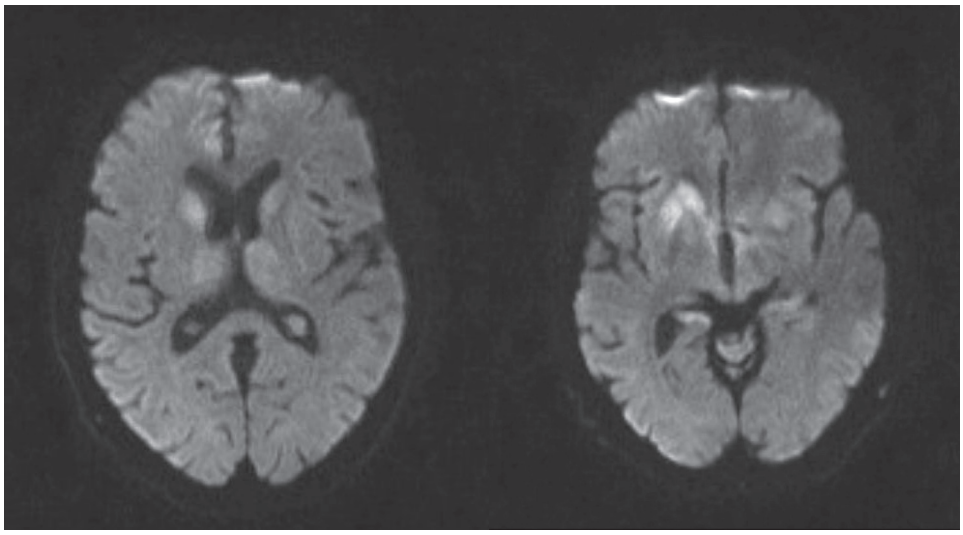

Figure 1 Bilateral caudate head and right putamen hyperintensity on FLAIR MRI sequences

in the preceding weeks. He had had three previous surgical procedures in his youth with no particular relevance to the case and there was no history of organ/tissue transplantation, growth hormone usage or blood product transfusion. He had no notable occupational history or relevant past exposure to animals, and no known family history of early onset dementia or neurodegenerative conditions. There were no neurological symptoms indicative of motor, sensory or cranial nerve involvement or features suggestive of raised intracranial pressure. Systemic review was unremarkable. He drank alcohol in moderation and was not on regular medications.

The gentleman had initially been assessed in the stroke clinic, where his presentation was deemed atypical for stroke, in view of progressive symptoms. An MRI of the brain performed at that point showed no detectable abnormalities. However, the images were of suboptimal quality because of movement artefact. Unfortunately, collateral history from the patient's brother was not readily obtained at the time of admission because he lived six hours away and hadn't seen the patient in weeks. However, it revealed that he was out of character, low in mood and had short term memory impairment for the last three months.

On examination, his speech was hypophonic, with objective evidence of blunted affect, yet his higher brain functions were intact. Neurological examination showed signs consistent with severe bilateral limb and truncal ataxia with otherwise normal motor, sensory and cranial nerve function. There was no spontaneous or startle-induced myoclonus.

The patient was reviewed again as an inpatient by the stroke team, who advised further investigations for a possible atypical stroke presentation versus an infective aetiology, with the added potential differential diagnosis of a conversion disorder in the context of an acute grief response.

All routine investigations were normal including thyroid function test. B12 and his HIV test came back negative.

In view of a large degree of movement artefact at the time of his initial MRI head, via the stroke clinic, a repeat MRI head was performed. FLAIR MRI images revealed bilateral caudate head and right putamen hyperintensity as well as insular, frontal and interhemispheric cortical ribboning on the right side (Figure 1). These findings were reported as being highly suspicious for CJD, although hepatic encephalopathy was quoted as another possible differential. A lumbar puncture was performed, which showed a white cell count of <5 with no growth. Samples for 14-3-3 protein, S100b and RT–QuIC were sent to the National CJD Research and Surveillance Unit in Edinburgh, UK and they were positive. No mutations were detected on the prion protein gene analysis. Unfortunately, our hospital did not have a neurophysiology department to arrange an EEG and finding an appointment in a neighbouring hospital would take weeks. So far, the obtained results were consistent with a probable diagnosis of sCJD based on the Euro CJD criteria.[10] The patient's mobility and speech deteriorated rapidly during his hospital stay, and given his increasing needs for care and assistance, a fast-track discharge was arranged to a nursing home where he passed away few weeks later.

Discussion

Establishing a diagnosis of sCJD can be challenging due to the combination of its rarity, variable clinical manifestations and subtle early MRI changes. Despite the fact that cerebellar ataxia is one of the chief symptoms of sCJD, the diagnosis was not initially suspected because it was an isolated finding on examination and the deterioration of cognitive state could not be established early during admission because of the lack of collateral history from the family. The differential diagnosis of CJD is broad, can range from other common neurodegenerative disorders to cerebral vasculitis, immune mediated encephalitis, metabolic, endocrine, vascular, infective, neoplastic and psychosomatic aetiologies.[2]

In this case, the diagnosis was not considered until the repeat MRI showed findings suggestive of sCJD as reported by our local radiologists. In 2012 Carswell and colleagues who worked at the regional prion centre in London, compared the centre's MRI reports to the initial reports of referring clinicians of patients suspected to have CJD. They detected

CJD-associated MRI changes in 83 out of 91 cases (91% sensitivity) as opposed to 43 cases (47% sensitivity) identified by local non-neuroradiologists from referring hospitals.[11]

Testing CSF for 14-3-3 protein in suspected sCJD cases has been debated. It has a reasonable sensitivity and specificity when used in the appropriate clinical setting, particularly in cases of rapid progressive cognitive decline.[12] However, this test's sensitivity has been questioned as it was found that it can vary based on the duration of the illness, CJD subtype and laboratory techniques.[13,14] Subsequently, the American Association of Neurology published an evidence-based guideline in 2012 estimating that the sensitivity and specificity of CSF 14-3-3 protein assays are approximately 92% and 80% respectively. Therefore, it can be considered moderately accurate in diagnosing CJD. A negative 14-3-3 protein assay may be helpful in reducing the suspicion of sCJD.[15] The introduction of RT-QuIC assays has made a considerable positive impact on sCJD diagnosis as it has a sensitivity of 92% and a specificity of up to 100% making it an excellent diagnostic tool.[8]

In addition to supporting the diagnosis of sCJD, EEG can also point towards an alternative diagnosis as it can reveal typical patterns suggestive of toxic–metabolic or structural abnormalities, autoimmune encephalitis and subacute sclerosing panencephalitis.[2]

The European criteria for the diagnosis of probable sCJD was updated in January 2017 and is based on the clinical assessment, CSF, MRI and EEG findings. To establish a diagnosis of probable sCJD, rapidly progressive cognitive decline should be present in addition to two of the following: myoclonus, visual or cerebellar problems, pyramidal or extra pyramidal features or akinetic mutism, along with either typical EEG, typical MRI results and a positive 14-3-3 protein CSF assay. Alternatively, progressive neurological syndrome and a positive RT–QuIC can be adequate to establish a probable sCJD diagnosis.[10]

Conclusion

This case highlights the fact that neurological symptoms can be multifactorial in origin, with the added nuance of biopsychosocial influences in combination with organic disease. Common things are common, and the insidious nature of symptoms in early sCJD can be attributed to an array of organic as well as non-organic diagnoses, which are encountered more frequently in acute medical takes, and so dominate in terms of suggested differential diagnoses. This does however encourage the non-neurologist to think outside the box, and to be conscious of a potential underlying diagnosis of sCJD in the patient who presents with ataxia, in the absence of lateralising neurology.

References

1 Collinge J. Prion diseases of humans and animals: their causes and molecular basis. Prion Diseases of Humans and Animals: Their Causes and Molecular Basis. *Annu Rev Neurosci* 2001 24: 519–50.
2 Mead S, Rudge P. CJD mimics and chameleons. *Pract Neurol* 2017; 17: 113–21.
3 Collie D. Creutzfeldt-Jakob Disease. *Pract Neurol* 2002; 2: 168–72.
4 Johnson RT, Gibbs CJ Jr. Creutzfeldt-Jakob disease and related transmissible spongiform encephalopathies. *N Engl JMed 1998;* 339: 1994–2004.
5 Herrán GET, Heredia ADO, Burbano BM et al. Case series of Creutzfeldt-Jakob disease in a third-level hospital in Quito. *BMC Neurol* 2018; 18: 55.
6 Richard T, Johnson. Prion diseases. *Lancet Neurol* 2005; 4: 635–42.
7 The University of Edinburgh. National CJD Research and Surveillance Unit. Clinical features of human prion disease. https://www.cjd.ed.ac.uk/sites/default/files/clinfeat.pdf (accessed 1/12/19).
8 Green AJE. RT–QuIC: a new test for sporadic CJD. *Pract Neurol* 2019; 19: 49–55.
9 Litzroth A, Cras P, De Vil B et al. Overview and evaluation of 15 years of Creutzfeldt-Jakob disease surveillance in Belgium, 1998–2012. *BMC Neurol* 2015; 15: 250.
10 The University of Edinburgh. National CJD Research and Surveillance Unit. Protocol for surveillance of CJD in the UK. 2017, http://www.cjd.ed.ac.uk/sites/default/files/NCJDRSU%20surveillance%20protocol-january%202017.pdf (accessed 1/12/19).
11 Carswell C, Thompson A, Lukic A et al. MRI findings are often missed in the diagnosis of Creutzfeldt-Jakob Disease *BMC Neurol* 2012; 12: 153.
12 Sanchez-Juan P, Green A, Ladogana A et al. CSF tests in the differential diagnosis of Creutzfeldt-Jakob disease. *Neurology* 2006; 67: 637–43.
13 Kenney K, Brechtel C, Takahashi H et al. An enzyme-linked immunosorbent assay to quantify 14-3-3 proteins in the cerebrospinal fluid of suspected Creutzfeldt-Jakob disease patients. *Ann Neurol* 2000; 48: 395–8.
14 Zerr I, Bodemer M, Gefeller O et al. Detection of 14-3-3 protein in the cerebrospinal fluid supports the diagnosis of Creutzfeldt-Jakob disease. *Ann Neurol* 1998; 43: 32–40.
15 Taim Muayqil, Gary Gronseth, Richard Camicioli. Evidence-based guideline: Diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob disease. *Neurology* 2012; 79: 1499–1506.