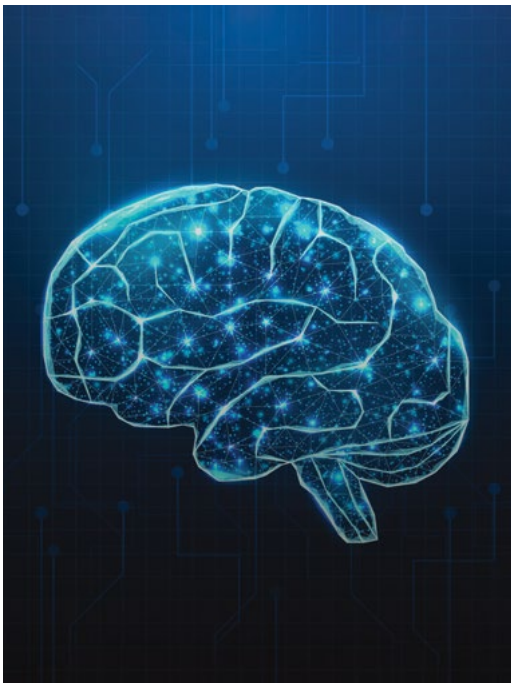

Creutzfeldt–Jakob disease: From presentation to palliative care

Debra Scott, Suzanne Solvyns, David Ralston, Mariese A Hely

CASE

A female sign writer, aged 56 years, presented with a 10-day history of subjective slurred speech, hearing loss and anxiety. Her past medical history was significant for poliomyelitis, with mild left arm residual weakness. She took no regular medications and had no significant family history or drug and alcohol history. She had not travelled to countries with variant Creutzfeldt–Jakob disease (CJD). Physical examination revealed mild left arm motor weakness globally (from poliomyelitis). Initial blood tests were normal.

Within 10 days, she developed progressive objective speech difficulties and a panic attack. Urgent neurology review and magnetic resonance imaging (MRI) of the brain was arranged.

In the subsequent seven days she developed a written and verbal expressive aphasia and was an inpatient for investigations.

Within four weeks of presentation, she exhibited signs of a rapidly progressive dementia. Extensive investigations with blood tests, imaging, lumbar puncture and electroencephalography excluded treatable causes. Repeat MRI brain demonstrated a subtle cortical ribboning sign. Cerebrospinal fluid (CSF) returned a positive result for 14-3-3 protein.

In conjunction with her rapidly progressive symptoms and the exclusion of other causes, she was diagnosed with suspected CJD. Her neurologist referred her family to the CJD Support Group Network (CJDSGN) for support and information, and she returned to her general practitioner (GP) for supportive care.

Within six weeks of presentation, she had an unsteady gait, myoclonus, receptive and expressive aphasia with worsening dementia. Her goal was to remain at home for end-of-life care. Allied health and community palliative care team involvement assisted in achieving this. Cognitive and physical deterioration were noted daily.

Within nine weeks of initial presentation, she was bedbound, akinetic, mute, with probable blindness, and she died at 10 weeks from presentation. Final histopathology confirmed the diagnosis of definite CJD.

QUESTION 1

What is CJD?

QUESTION 2

What is included in the differential diagnosis of a rapidly progressive dementia?

QUESTION 3

What investigations help diagnose suspected CJD?

QUESTION 4

Are there any treatments for CJD or research into potential future treatments?

QUESTION 5

After diagnosis of suspected CJD, as the primary care physician coordinating care, what can support you as a clinician and assist patients?

QUESTION 6

What is involved in management of symptoms and end-of-life care in suspected CJD?

ANSWER 1

CJD, or prion disease, is rare (approximately one to two per million per year and the risk of developing and dying from disease during one's lifetime accounts for a lifetime risk of approximately one in 5000).[1,2]

Although rare, its prevalence continues at this rate.[1] CJD is an always-fatal neurodegenerative disease,[3,4] typified by rapidly progressive dementia, myoclonus, ataxia, visual disturbances, pyramidal and extrapyramidal signs with progression to akinetic mutism, then death, sometimes within weeks, usually within 12 months for sporadic forms.[5,6]

CJD is caused by the misfolding of the membrane-anchored cellular prion protein (PrP^c) into abnormal forms that accumulate and cause neuronal damage and spongiform change.[3,4,6] Types of CJD are outlined in Table 1.

ANSWER 2

The differential diagnosis of a rapidly progressive dementia is broad and includes several potentially treatable causes.[5,7] Specialised investigation via neurologist referral is recommended. Table 2 shows a non-exhaustive list of potential causes.[5,7]

ANSWER 3

Most patients with eventual diagnosis of CJD are initially seen by a GP.[7] Early referral to neurology facilitates investigation for treatable causes and consideration of the diagnosis.[3,7,8] Table 3 outlines investigations that can help diagnose CJD.

ANSWER 4

Currently there are no treatments for CJD.[9] Symptomatic and supportive care with palliative care involvement helps manage symptoms and support patients and families.[10]

A recent study from the UK using prion protein monoclonal antibody (PRN100) in humans showed that it appeared to be safe and reached encouraging CSF and brain tissue concentrations.[9] Identifying suspected CJD diagnoses and specialist involvement may facilitate referral for consideration of early enrolment in future treatment or research trials if desired.[7]

ANSWER 5

Table 4 outlines the specialists, allied health and support network that can be involved in patient care. A multidisciplinary approach will assist the GP, patient and family through diagnosis, symptom management and end-of-life care.

ANSWER 6

There are no consensus guidelines for the palliative management of this rare disease.[11] A holistic focus with a multidisciplinary team is essential.[11] Patients can progress daily,

Table 2. Non-exhaustive differential diagnosis of rapidly progressive dementia[5,7]

Group	Examples
Neurodegenerative	Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, corticobasal degeneration, prion disease
Autoimmune	Paraneoplastic, vasculitis, Hashimoto's encephalitis, neurosarcoidosis, NMDA receptor antibody encephalitis
Neoplastic	Primary CNS lymphoma, diffuse neoplastic disease
Infectious	Viral encephalitis, Whipple disease, herpes simplex encephalitis, neurosyphilis, subacute sclerosing panencephalitis
Toxic/metabolic	Vitamin B12 deficiency, hypothyroidism, Wernicke–Korsakoff syndrome, drug adverse effects
Psychiatric	Severe depression
Vascular	Multiple strokes

CNS, central nervous system; NMDA, *N*-methyl-D-aspartate.

Table 1. Types of CJD[3,4,5]

Type	Causes	Incidence (%)[A]	Mean age of onset (years)
Sporadic CJD	Spontaneous protein misfolding	85	60–70
Genetic prion diseases Includes: • Familial CJD • Fatal familial insomnia • GSS syndrome[1]	Genetic autosomal dominant inheritance of *PRNP* gene mutation[3] Note: The first case in a family can be a genetic *de novo* mutation	10–15	Variable[3]
Acquired iCJD	• Derived from cadaveric human pituitary hormones (ie hGH and hPG) • Human dura mater grafts • Contaminated neurosurgical instruments	<5	Variable[3]
Acquired vCJD[1]	• Variant: Transmission to humans via BSE-contaminated beef • Blood transfusion (UK) recipients with blood from a donor who later developed vCJD		Variable, although vCJD predominantly presents in third decade of life[3]

[A]Percentage of cases of diagnosed prion disease.

BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt–Jakob disease; GSS, Gerstmann–Straussler–Scheinker; hGH, human growth hormone; hPG, human pituitary gonadotropin; iCJD, iatrogenic CJD; *PRNP*, prion protein; vCJD, variant CJD.

Table 3. Investigations to help diagnose CJD

Modality	Findings
Suspected CJD	
MRI brain	• MRI request form should include 'Are there any features suggestive of CJD' (generally completed by the neurologist) to facilitate optimal imaging sequences and guide reporting for specific changes • Classical abnormality is high signal on DWI/FLAIR in the striatum, cerebral cortex (cortical ribboning) +/– thalamus[3–7]
EEG	• Periodic sharp wave complexes develop in half the patients with sporadic CJD, usually in later stages[3–5]
CSF studies	• 14-3-3 protein and tau protein positivity reflect rapid tissue damage and is not specific to CJD[3–5] • RT-QuIC assay is much more specific[4,5] (Note: the RT-QuIC assay was not available at the time of this case)
Confirmation of CJD	
Neuropathology	• Neuropathology is required for confirmation of CJD and is usually done by postmortem brain-only neuropathology; brain biopsies are rare[4,5] • This does not determine whether the patient had sporadic CJD or a genetic form of prion disease, and further testing of the patient's DNA is required[1]

CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EEG, electroencephalography; FLAIR, fast fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; RT-QuIC, real-time quaking-induced conversion.

with management strategies requiring daily review in many cases.[10,11]

Assessing for reversible causes of agitation, such as urinary retention, is vital. If no reversible causes can be found, management strategies comprise non-pharmacological approaches, including providing a familiar, calm environment and behavioural management strategies, followed by pharmacological measures.[11]

Antipsychotic medications such as olanzapine, benzodiazepines like clonazepam or a combination may be required.[11] Planning for a transition to subcutaneous medications when swallowing is impaired is vital.[11] Palliative care support throughout is helpful, particularly with the transition to medications for symptoms at the end of life. Bereavement support is recommended.[11]

Research shows that families advocate for a multidisciplinary team and support by healthcare providers familiar with CJD.[10] In that study, support from an organisation familiar with the disease (eg CJDSGN) helped alleviate some of the distress of caring for someone with this rare and rapidly progressing illness.[10]

Table 4. Multidisciplinary care

Referral	Type	Examples of support available
Specialist colleagues	Neurology	• Provide the family with the option of brain-only autopsy to provide a definite diagnosis and assist with research and/or offer enrolment in treatment or research trials if and when available[3,7,8]
	Psychiatry/psychogeriatrician	• May be helpful in some cases
	Palliative medicine	• Symptom management, end-of-life care planning, palliative care unit link, spiritual care
Allied health	Speech pathology	• Swallow assessment and review, diet modification advice
	Occupational therapy	• Equipment, home assessments
	Social work	• Assessment, support, services, consideration ACAT or NDIS, bereavement
Community nursing	Home-visiting nurses	• Nursing care • Access to bladder scanner
Support groups (Note: Research shows assistance from a CJD organisation can be particularly helpful for both families and clinicians[10])	CJD Support Group Network Australia	• An Australian support network providing information, support and awareness promotion • Can provide healthcare practitioner support and information • Can also assist with information regarding *PRNP* sample storage and genetic testing and explanation of neuropathology process (Note: This is usually arranged by neurology)

ACAT, aged care assessment team; CJD, Creutzfeldt–Jakob disease; NDIS, National Disability Insurance Scheme; *PRNP*, prion protein gene.

Key points

- Sporadic CJD, and genetic prion diseases, continue at a prevalence of one to two cases per million per year in Australia, whereas the acquired from of variant CJD has never been identified in Australia.
- GPs are often the first to see the patient, so ongoing awareness of the disease is essential.
- End-of-life care is often facilitated by the GP and a multidisciplinary team is imperative.

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