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Distinguishing Creutzfeldt–Jakob disease from rapidly progressive Alzheimer's disease: a two-patient case series on tau biomarkers

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INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a fatal, rapidly progressive neurodegenerative disorder caused by misfolded scrapie prion protein (PrPSc) replacing the normal host prion protein (PrPC), leading to spongiform neuronal degeneration and PrPSc deposition (Zerr et al., 2024). It belongs to the group of transmissible spongiform encephalopathies, characterised by short disease duration, long incubation period and environmental resilience of the infective agent. Three forms are recognised — sporadic (sCJD), genetic (gCJD) and acquired iatrogenic (iCJD) or variant (vCJD) — accounting for 85%, 10–15% and <1% of cases, respectively (Zerr et al., 2024). Global incidence is 1–2 cases per million per year (Uttley et al., 2020). Depending on the codon-129 (methionine/valine) genotype and PrPSc type (type 1 or 2), six major clinico-molecular subtypes of sCJD are recognised — MM1, MM2, MV1, MV2, VV1 and VV2 — differing in onset age, clinical phenotype, disease duration, imaging pattern and biomarker sensitivity (Gelpi et al., 2022). Typical features are rapidly progressive dementia, myoclonus, cerebellar ataxia, pyramidal/extrapyramidal and visual signs, psychiatric symptoms and akinetic mutism at a terminal stage, with a median survival of 5–6 months from symptom onset (Zerr et al., 2024). Diagnostic criteria combine clinical features, electroencephalography (EEG; periodic sharp-wave complexes, PSWC), magnetic resonance imaging (MRI; cortical ribboning or basal-ganglia/thalamic signal change with restricted diffusion), and diagnostic biomarkers, most recently updated in 2021 to incorporate the real-time quaking-induced conversion (RT-QuIC) assay, a highly specific seeding assay detecting disease-associated prion protein in cerebrospinal fluid or peripheral tissues (Hermann et al., 2021).

PATIENT 1

A 68-year-old man was admitted with a two-month history of rapidly progressive cognitive decline and unsteadiness, preceded by a four-month prodrome of apathy and blunted affect. His family described progressive memory loss, disorientation to time and place, impaired spatial navigation, marked psychomotor slowing and difficulty understanding speech, culminating in loss of independence in activities of daily living. On admission he was alert but disoriented, with conspicuous psychomotor slowing, dyscalculia and an inability to follow commands without repetition.

Over the following weeks he deteriorated rapidly to bradykinesia, ataxia and akinetic mutism. An extensive laboratory, infectious and autoimmune work-up was unremarkable. Cerebrospinal fluid (CSF) was non-inflammatory, with elevated neuron-specific enolase (NSE; 109 µg/L), S100 calcium-binding protein B (S100B; 14.4 µg/L), total tau (t-tau; >1912 ng/L) and phosphorylated tau 181 (p-tau181; 79 ng/L), giving a t-tau/p-tau ratio ≥24; the amyloid-β 42/40 ratio (Aβ42/40) was normal at 0.160. Brain MRI showed bilateral cortical restricted diffusion on diffusion-weighted imaging (DWI) (frontal and temporo-parieto-occipital, right greater than left) with medial-thalamic involvement, highly suggestive of CJD (Figure 1A), and was unchanged on repeat imaging one month later. Two EEGs showed diffuse slowing with focal fronto-temporal spike-and-wave activity but no PSWC. RT-QuIC on olfactory mucosa, obtained by nasal brushing, was positive. Management was supportive, and the patient was transferred to long-term care.

PATIENT 2

A 59-year-old patient was assessed for a one-year history of progressive cognitive decline on a background of balance disturbance for two and a half years. Examination revealed a diffuse cognitive deficit, sparse speech, ataxia and generalized hyperkinesias.

Brain MRI demonstrated extensive cortical restricted diffusion in the fronto-temporo-parietal regions and the anterior striatum bilaterally (Figure 1B); a contrast-enhanced study two months later showed slightly more pronounced restriction without post-contrast enhancement, and fluorodeoxyglucose positron emission tomography (FDG-PET) revealed global parenchymal hypometabolism, most marked in the left frontal lobe, with preserved occipital metabolism. CSF showed no inflammation, with elevated NSE (73.4 µg/L; reference <12), S100B (4.34 µg/L; <1.0), t-tau (1526 ng/L; <290) and p-tau181 (68 ng/L; <61), giving a t-tau/p-tau ratio of 22, with a normal Aβ42/40 ratio (0.098). RT-QuIC on olfactory mucosa was negative. Serial EEG showed a progressively worsening diffuse encephalopathic pattern with bilateral independent, temporally-predominant foci, high-amplitude spike-and-wave complexes and triphasic waves, without PSWC — a non-specific, evolving encephalopathy with epileptiform features rather than a CJD-typical periodic pattern.

DISCUSSION

Distinguishing prion disease from other rapidly progressive dementias (RPD), particularly rapidly progressive Alzheimer's disease (rpAD), is a recurring challenge (Skillbäck et al., 2014). The 2021 consensus criteria define three categories: probable sCJD requires rapidly progressive cognitive impairment plus at least two of four cardinal signs (myoclonus, visual/cerebellar, pyramidal/extrapyramidal, akinetic mutism) together with a typical EEG, typical MRI, or positive CSF 14-3-3 — or, alternatively, a positive RT-QuIC alone; possible sCJD rests on the clinical syndrome (<2 years) without supportive biomarkers, demanding rigorous exclusion of treatable mimics such as autoimmune and paraneoplastic encephalitis and neoplastic, vascular, infectious and toxic-metabolic encephalopathies; a definite diagnosis requires neuropathology (Hermann et al., 2021). The diagnostic landscape has been transformed by RT-QuIC, which amplifies and detects misfolded prion seeds in CSF, olfactory mucosa and other tissues with sensitivity 92–95% and specificity approaching 100%, outperforming classical biomarkers (14-3-3: sensitivity ≈87%, specificity ≈67–84%; t-tau: sensitivity ≈91%, specificity ≈79%) (Abu-Rumeileh et al., 2019; Senesi et al., 2023). On olfactory mucosa it reached ≈97% sensitivity versus ≈77% for CSF in head-to-head cohorts, detecting cases the CSF assay missed (Bongianni et al., 2017; Orrú et al., 2014). The remaining markers — 14-3-3, t-tau, p-tau and S100B — are non-specific

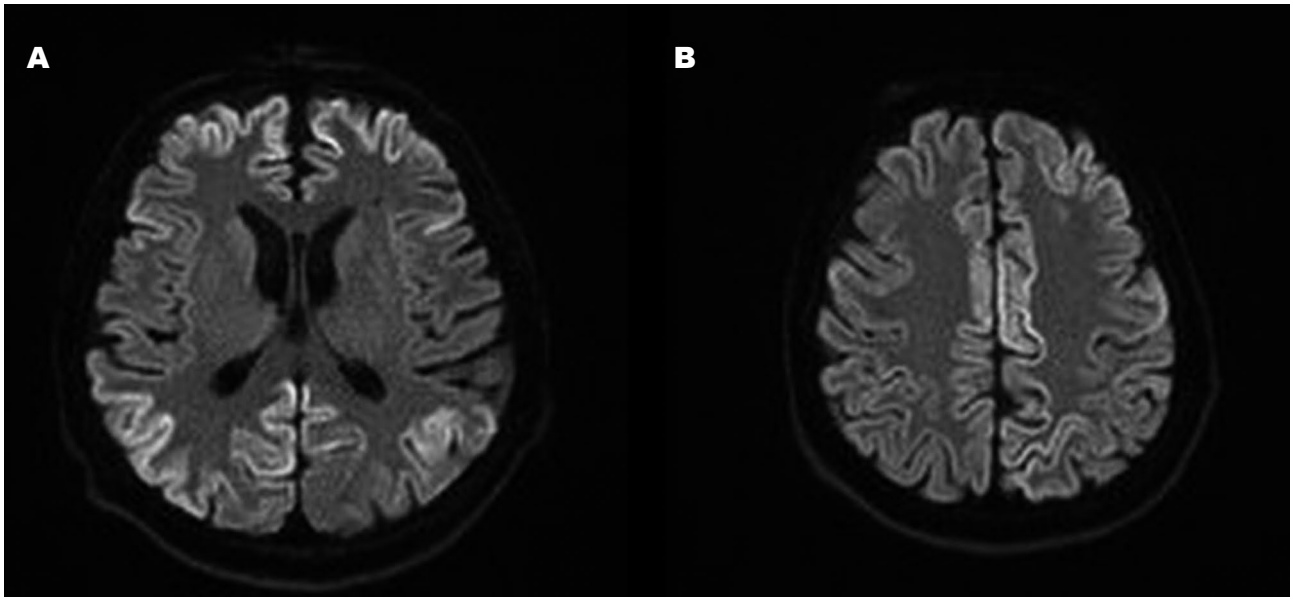


Figure 1. Axial diffusion-weighted magnetic resonance imaging. (A) Patient 1 and (B) Patient 2, each showing cortical restricted diffusion ("cortical ribboning"); DWI, diffusion-weighted imaging.

surrogates of neuronal injury; the guidelines keep 14-3-3 within the criteria, treat t-tau as supportive, and recommend the t-tau/p-tau ratio as an adjunct in ambiguous cases or uncertain differential diagnosis (Hermann et al., 2021; Šarac et al., 2008). The underlying mechanism is well understood, as the rapid neuronal destruction in CJD drives total tau sharply upward while phosphorylated tau remains relatively low, producing a high t-tau/p-tau ratio, whereas in Alzheimer's disease the characteristic tau hyperphosphorylation raises both markers in parallel and the ratio stays low. Accordingly, published cohorts indicate that a profile of t-tau >1400 ng/L combined with a t-tau/p-tau ratio >25 achieves 99% specificity for CJD, and that the ratio distinguishes sCJD from rapidly progressive Alzheimer's disease more accurately than total tau alone (Hermann et al., 2022; Skillbäck et al., 2014). Both our patients showed this signature: markedly high t-tau, low p-tau, a high t-tau/p-tau ratio and a normal Aβ42/40 ratio, favouring CJD over rpAD. Patient 1 met probable sCJD via a positive olfactory-mucosa RT-QuIC, while Patient 2 met probable sCJD through the clinical syndrome (rapidly progressive cognitive decline with cerebellar and extrapyramidal signs) combined with a typical MRI.

CONCLUSION

CJD remains the most urgent diagnosis to exclude in RPD. RT-QuIC has become the decisive prion-specific test, but the readily available t-tau/p-tau ratio retains a useful supportive role, especially for distinguishing CJD from rpAD and where RT-QuIC access is limited, as long as it is interpreted as a non-specific, supportive marker rather than a stand-alone diagnostic criterion. Our two cases illustrate how a consistent biomarker profile can support the diagnosis even when RT-QuIC results differ, highlighting the value of combining prion-specific and surrogate markers.

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