Creutzfeldt-Jakob disease

The search for definitive diagnostic tests continues

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Creutzfeldt-Jakob disease (CJD), particularly its predominant sporadic form (sCJD), is the prototype of human prion diseases—a small family of rare, fatal, and untreatable neurodegenerative disorders affecting about 1–2 persons per million per year.¹ CJD is linked to pathologic alteration of an endogenous cellular protein, the prion protein (PrP). However, in contrast to other neurodegenerative dementias involving proteinopathy, prion diseases are transmissible between individuals by an infection-like process, in which disease-associated PrP (PrP^D) can “replicate” exponentially by templating the misfolding of normal cellular PrP (PrP^C). This discovery inspired the term “prion” in order to denote the implicated proteinaceous infectious particle (Greek suffix “-on”).² Prions are notoriously difficult to remove and/or inactivate with routine disinfection methods, and evidence of accidental CJD transmission in the health care setting has been documented.^{3,4} Thus, in suspected sCJD, the importance of timely, accurate diagnosis is accentuated by the need to manage the risk of secondary exposure to prion infectivity, particularly through reuse of surgical or other instruments.⁵

Unfortunately, definite diagnosis of sCJD currently relies heavily on tissue-based neuropathologic examination, usually performed postmortem. To refine the differential for sCJD, clinicians must therefore evaluate a wide scope of information—most commonly clinical profile, EEG, MRI, and assays of certain brain proteins in CSF.⁵ However, no single method is completely diagnostic for sCJD, with sensitivities and specificities (mostly 0.80–0.90) falling short of the classic test accuracy criteria “SpPin” (specific test with positive result, rules in target disorder) and “SnNout” (sensitive test with negative result, rules out target disorder).⁶ Thus, much effort is currently being devoted to developing and refining antemortem tests for sCJD.

In this issue of *Neurology® Clinical Practice*, Forner et al.⁷ demonstrate an improved approach to diagnosing sCJD: MRI using diffusion-weighted imaging sequences (DWI-MRI). The retrospective study cohort included 57 patients with autopsy-confirmed sCJD and 41 non-CJD dementia controls whose differential had included sCJD. As a baseline, the authors first evaluated the performance of 3 CSF marker proteins (14-3-3, tau, and neuron-specific enolase), finding that they were highly specific in this cohort (0.98, 0.95, and 0.98, respectively) but lacked diagnostic sensitivity (0.50, 0.68, and 0.53, respectively). The low sensitivity may partly reflect the inherent tradeoff between sensitivity and specificity with choice of scoring cutoffs, and the authors admit that the composition of their sCJD subcohort may have been somewhat atypical in some respects (for example, disease duration was longer than average for sCJD). However, these considerations do not detract from the key finding that in

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Funding information and disclosures are provided at the end of the editorial. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp.**

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the subcohort for whom results were available (57 sCJD, 32 non-CJD), diagnostic sensitivity and specificity with DWI-MRI reached 0.98 and 0.94 respectively, higher than in some earlier studies.⁸ The impressive gain in sensitivity without a corresponding increase in false-positive rate is particularly noteworthy and suggests that in at least some clinical situations “SpPin” and “SnNout” performance for sCJD might be achievable with a single minimally invasive investigation, i.e., DWI-MRI.

What further improvements can be expected in the antemortem diagnosis of sCJD? The findings of Forner et al. certainly signal the potential value of larger prospective studies using DWI-MRI as a diagnostic readout. For CSF protein markers (still the most widely requested sCJD test), structured review can derive broad, statistically justified estimates of test accuracy that could allow for more precise and explicit evidence-based clinical practice guidelines.⁹ Another method recently employed by a Swedish research group was the use of a ratio of 2 protein marker concentrations in CSF (total tau: phosphorylated tau) to raise diagnostic specificity to >0.99 in a large retrospective dementia cohort that included 93 sCJD cases at a prevalence of about 1%.¹⁰ The approach did not improve diagnostic sensitivity, which remained relatively low at 0.79. However, this study illustrated the value of prescreening a patient population to narrow the differential as far as possible before testing—in this case by including only patients with suspected degenerative dementias.

Given the central pathologic role of PrP^D in sCJD, an optimal diagnostic test would presumably entail its detection at the extremely low concentrations found in specimens other than CNS tissue, such as CSF, blood, urine, or peripheral tissues. An exciting recent development has been the invention of a protein-based “molecular amplification” method (real-time quaking-induced conversion [RT-QuIC]), in which PrP^D in a biological specimen is presented with in vitro conditions enabling it to template conversion of synthetic PrP substrate to an abnormal form detectable with fluorescent dyes.¹¹ Using CSF specimens, several studies have now demonstrated diagnostic specificities for RT-QuIC in sCJD to be at or very close to 1.0, with sensitivities ranging from 0.77 to 0.91.^{12–14} It will be interesting to see whether further improvements in analytic sensitivity for PrP^D in CSF improve diagnostic sensitivity. It is also worth noting that one recent study demonstrated diagnostic sensitivity and specificity of 0.97 and 1.0, respectively, with the application of RT-QuIC to nasal brushing specimens, presumably reflecting a higher abundance of PrP^D in this tissue compared with CSF.¹⁴

Rapid, accurate tests for sCJD in the living patient promise to improve clinical neurology practice in a number of important ways. In addition to the inherent value of effective diagnosis for a rare, often-puzzling disease and sound decisions for hospital safety, one might consider the positive influence of evidence that the patient may have a treatable condition other than CJD, the key role played by prognosis, and, ultimately, possible early initiation of disease-modifying therapy on the basis of accurate diagnostic ascertainment.

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STUDY FUNDING

No targeted funding reported.

DISCLOSURES

M.B. Coulthart receives research support from the Government of Canada: Prion Diseases Program (1998 and ongoing). B.M. Ances serves on the editorial board of *Journal of Neurovirology* and receives research support from the Alzheimer's Association. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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