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Thorough work-up and new diagnostic criteria needed for CJD

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Abstract

The diagnosis of rapidly progressive dementias (RPDs), particularly sporadic Creutzfeldt–Jakob disease (sCJD), can prove challenging. Treatable RPDs might mimic sCJD, which is currently untreatable. A recent review of a large cohort of patients with suspected CJD highlights the extent of misdiagnosis and possible sources of error.

Sporadic Creutzfeldt–Jakob disease (sCJD), the prototypical rapidly progressive dementia (RPD), is currently untreatable. Because many other conditions mimic CJD, several of which are treatable or even curable,[1–3] it is imperative that patients with suspected sCJD be thoroughly evaluated for non-prion diagnoses.

Chitravas and colleagues investigated the pathological diagnoses, based on brain autopsies, of 1,106 patients who were referred for potential prion disease to the National Prion Disease Pathology Surveillance Center (NPDPSC) at Case Western Reserve University from 2006–2009.[4] The researchers found that approximately one-third of cases did not have prion disease, with Alzheimer disease and vascular dementia being the most common conditions among these patients. Using additional information from the clinical records of this subgroup, Chitravas *et al.* further identified that approximately one-quarter of the patients who did not have prion disease had treatable diseases that might have been amenable to life-saving or life-extending therapy. These diseases included immune-mediated disorders such as primary angiitis of the CNS, neoplastic illness such as lymphoma, and infectious and metabolic disorders. This important paper adds to the literature regarding conditions that can cause an RPD and encourages clinicians to perform a comprehensive work-up before diagnosing a condition for which no disease-modifying therapy is currently available.

The differential diagnosis of RPDs, particularly prion disease, can be difficult. The process is generally long and patients typically require extensive work-up, with multiple diagnostic tests being performed in parallel, often in an inpatient setting.[1,2] As Chitravas *et al.* note,[4] the most widely used diagnostic criteria[5] were designed by the WHO for postmortem diagnosis in epidemiological studies when pathological diagnosis is not available, and not

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Competing interests

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for early diagnosis of sCJD. The diagnostic utility of cerebrospinal fluid (CSF) biomarkers —including 14-3-3 protein, neuron-specific enolase, S100β, and total tau—is controversial. Importantly, Chitravas *et al.* found that more than 50% of patients with treatable dementias had a positive CSF 14-3-3 protein test, further illustrating the danger in relying on this test for CJD diagnosis.[4]

Currently, findings from diffusion-weighted imaging (DWI) and apparent diffusion coefficient MRI—including signal abnormalities in the cortical ribbon and deep nuclei—seem to have the greatest sensitivity and specificity for the diagnosis of sCJD.[6,7] In the recent study,[4] only three of the treatable cases (all metabolic disorders) had DWI abnormalities that overlapped with those observed in sCJD, although other MRI features not consistent with sCJD were also present. This finding provides further support for the suggestion that imaging should be incorporated in diagnostic criteria,[6,7] and that clinicians should be wary of making a diagnosis of sCJD in cases without typical imaging abnormalities.

The inclusion of MRI results in diagnostic criteria has improved our ability to diagnose prion disease premortem.[6,7] However, many CJD cases are not diagnosed initially, because the MRI findings in CJD, which occur early in the disease course, are often missed. Thus, not only are non-prion diseases mistaken for CJD, as the current study shows[4] but, in our experience, the converse is also true: some CJD cases go undiagnosed.[8] Other conditions can be mistaken for prion disease for various reasons. The time of dementia onset is often considerably earlier than initially reported by the family of the patient. A slow, subtle decline in cognitive function might occur over years—suggestive of other typical dementias such as Alzheimer disease, Parkinson disease with dementia, and dementia with Lewy bodies—before a more-rapid deterioration. In cases of true RPDs, clinicians might not have a sufficiently broad differential. For example, among referrals for suspected prion disease to RPD units, alternative diagnoses that are frequently found include other neurodegenerative diseases, autoimmune conditions and toxic–metabolic disorders.[1–3,9]

The study by Chitravas and colleagues[4] largely corroborates the findings of other studies regarding incorrect diagnoses of sCJD,[1,2,9] and adds some new diseases to consider in the differential diagnosis. The extensive pathology-confirmed sample gathered by the NPDPSC from across the USA is a great strength of the study. The exclusive reliance on pathology-proven samples, however, is also a study limitation. Unfortunately, many patients misdiagnosed with prion disease do not come to autopsy, and would not, therefore, be included in this type of study. For example, patients with neurodegenerative disease would probably survive longer than the time frame of the study, and patients with autoimmune disease might have a longer, fluctuating disease course and could even recover spontaneously. To accurately assess the frequency of misdiagnosis in suspected prion disease cases, a study would need to include all patients in whom a diagnosis of sCJD is made, rather than only those who come to autopsy.

A lack of access to complete medical records represents another limitation of the study. As the authors note,[4] clinical and imaging data were often not available. This missing information also limited the authors' knowledge of the referring physicians' thought

processes. As mentioned in the paper, some referring physicians might have availed themselves of the NPDPSC's extensive services for difficult cases of RPD when they felt that prion disease was not a likely diagnosis, but merely a possibility. This situation might be particularly true for locations where brain autopsy and/or neuropathology studies are difficult to perform. Thus, some of the non-prion diseases identified in this study—such as hereditary diffuse leukoencephalopathy with spheroids, Huntington disease and Marchiafava–Bignami disease—although referred to the NPDPSC, probably did not mimic CJD.

The fact that many of the non-prion diagnoses in the present study were potentially treatable RPDs should prompt thorough diagnostic testing in patients who are suspected of having sCJD, in order to rule out mimics. The use of CSF testing, contrast-enhanced MRI, and autoimmune antibody screening is supported by this study. New diagnostic tests for detection of prions in the CSF (and other bodily fluids) are being developed and could greatly improve premortem diagnostic accuracy, as they seem to have a high specificity—although a lower sensitivity than MRI—for CJD.[10] Future studies could aid the development of new premortem diagnostic criteria by including a more-complete clinical picture, such as a thorough examination of medical records, and detailed imaging and other biomarker studies. Improved criteria and diagnostic tests would increase the confidence of clinicians in differentiating prion disease from other RPDs, with sufficient specificity to avoid misdiagnosing patients with treatable conditions.

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