Movement disorders reveal Creutzfeldt-Jakob disease

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Abstract

Human prion diseases are sometimes difficult to diagnose because few clinical features distinguish them reliably from other neurological disorders. A new study suggests that analysis of movement disorders might contribute to the clinical differentiation of sporadic Creutzfeldt-Jakob disease from Alzheimer disease and dementia with Lewy bodies.
Movement disorders in Creutzfeldt-Jakob disease

Michael Weller and Adriano Aguzzi

Human prion diseases are characterized by progressive cognitive dysfunction and a spectrum of associated neurological disturbances, e.g., of the motor system, none of which are specific. Edler and colleagues reviewed the motor system abnormalities in a large collective of patients suspected of having Creutzfeldt-Jakob disease. Ataxia and absence of hypokinesia were identified as distinguishing features from Alzheimer’s or diffuse Lewy body disease. Hence the analysis of movement disorders may contribute to the reliable clinical differentiation between these diseases.

Main text

Prions are “proteinaceous infectious particles” that cause a group of neurological diseases affecting humans and various animals, and that can transduce disease to others iatrogenically or to experimental animals by various routes of inoculation. All human prion diseases, including Creutzfeldt-Jakob disease (CJD), are defined by progressive cognitive dysfunction resulting in dementia. In addition, most patients suffer from a spectrum of neurological disturbances including symptoms and signs of the motor system - such as myoclonic jerks and ataxia.

Compared to the most important differential diagnoses - such as Alzheimer’s disease and diffuse Lewy body disease - prion diseases are rare. Their incidence is in the range of 1-2 per 1,000,000/year. Nevertheless, the awareness of prion disease in the community has dramatically increased since bovine spongiform encephalopathy (BSE) was found to cause variant CJD which in turn can propagate iatrogenically between humans.

Despite significant progress in understanding prion pathogenesis, it has remained difficult to unequivocally establish the diagnosis of CJD at life-time (Box 1). The classical clinical triad of dementia, ataxia, and myoclonus is highly characteristic but of limited specificity. Diagnosis can be supported by typical EEG pattern referred to as triphasic complexes, by the leakage of neuronal proteins, such as neuron-specific enolase and 14-3-3 protein, from injured neurons into the CSF. Another intriguing surrogate marker is α1-antichymotrypsin (serpin 3N), whose elevation can be detected both in brain tissue and in the urine of prion-infected organisms. Because of the limited specificity intrinsic to all surrogate markers, the diagnosis is frequently only confirmed at autopsy. Familial prion diseases are a notable exception, since they are invariably associated with PRNP mutations and can be easily diagnosed by sequencing, yet most prion diseases occur sporadically and familial forms make for <10% of all cases. All prion diseases involve highly ordered protein aggregates containing the pathological PrPSc protein, and there is some hope that PrPSc detection in body fluids may facilitate early diagnosis.

To determine the differential diagnostic value of motor disturbances in the clinical diagnosis of human prion disease, Edler and colleagues analyzed the clinical presentation of 143 patients referred to the German Surveillance Unit for Spongiform Encephalopathies in Göttingen for the assessment of possible prion disease. Given the rarity of prion affections, this is indeed a very large collective. Among these patients, 100 were confirmed to have Creutzfeldt-Jakob disease, 29 had Alzheimer’s disease (AD), 7 had diffuse Lewy body (DLB)
disease, and 7 received other diagnoses. The most common motor disturbances in CJD patients were gait disorders (80%), myoclonus (80%) and cerebellar ataxia (77%). Ataxia and dysmetria along with the absence of hypokinesia suggested Creutzfeldt-Jakob disease rather than AD or DLB disease. Instead, pyramidal tract signs were associated with AD or DLB disease.

A very common polymorphic site at codon 129 of the PRNP gene encodes either methionine or valine, and the allelic state of CJD patients modulates their clinical phenotype. Among the 100 patients with Creutzfeldt-Jakob disease, ataxia and cogwheel rigidity were found to be associated with valine homozygosity whereas akinesia, was associated with methionine homozygosity.

The authors are to be commended for an extensive analysis of clinical features of sporadic Creutzfeldt-Jakob disease. Importantly, the patient groups with Alzheimer’s or diffuse Lewy body disease were by no means representative of the phenotypes typical for these diseases – instead, they represented subsets of patients suspected of suffering from Creutzfeldt-Jakob disease by the referring physicians. Therefore, the most informative results of Edler’s study are those that characterize the clinical phenotype of Creutzfeldt-Jakob disease and pit it against atypical forms of AD and DLB dementia. We are not surprised to read that the motor phenotypes were modulated by the polymorphism at codon 129 of the PRNP gene, since this important switch controls many other aspects of prion diseases including susceptibility to infection and, in familial cases, even specifies CJD versus fatal familial insomnia. This observation provides an interesting paradigm to study the impact of a distinct molecular feature on the complex manifestations of a disease phenotype. It may be of interest, in a future study, to correlate the clinical phenotypes not only to the genetic PRNP status but also to the biophysical characteristics of PrPSc aggregates – which can be ascertained, for example, by polythiophene fluorescence spectroscopy.

As to the diagnosis of human prion disease, a better characterization of the clinical phenotype is certainly welcome. The underlying unmet medical need, however, is the necessity to develop reliable and sensitive diagnostic procedures to confirm the diagnosis of human prion diseases intra vitam at the earliest possible stages of the disease. Because of their accessibility, this goal should be best attained by analyzing body fluids for PrPSc aggregates or for prion seeds. The urgency of this quest stems not only from the enormous psychological implications of a tentative diagnosis of prion disease, but also because of the incipient development of therapeutics that specifically target prions versus other types of dementing illnesses.

Box 1

Clinical and laboratory features of Creutzfeldt-Jakob disease

- Progressive dementia
- Myoclonus
- Ataxia and other motor disorders
- Triphasic complexes (EEG)
- Elevated 14-3-3 protein in the CSF
- PrPSc in tonsil biopsies (only for variant CJD)
- PRNP sequence (only for familial CJD)
Important differential diagnoses of Creutzfeldt-Jakob disease

- Alzheimer's disease
- Diffuse Lewy body disease
- Rapid-onset dementing disorders

References


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Authors biographies

Michael Weller, Chairman, Department of Neurology at the University Hospital Zurich, Switzerland, received his MD degree at the University of Cologne, Germany (1989) and his Medical Education at the Universities of Tübingen and Würzburg in Germany (1990-1991), the National Institute of Mental Health, Bethesda, MD (1992) and the University Hospital Zurich (1993-1994). From 1995-2007, he was at the Department of Neurology, University of Tübingen (Chairman since 2005). His research interests focus on the development and
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Adriano Aguzzi, MD, PhD, graduated from Freiburg University, Germany, and received further training in Switzerland, Austria and the United States. He is Professor of Neuropathology and Chairman at the Department of Pathology at University Hospital Zürich, Switzerland. His main interest is neurodegeneration. During the past 18 years, he has obsessively occupied himself with prion diseases. The Aguzzi laboratory specializes in studying the interface between the nervous and immune systems, and its relevance to the pathogenesis of prion diseases.