DOENÇA DE CREUTZFELDT-JAKOB: UMA REVISÃO DA FISIOPATOLOGIA, DO DIAGNÓSTICO E DAS PERSPECTIVAS TERAPÊUTICAS

CREUTZFELDT-JAKOB DISEASE: A REVIEW OF PATHOPHYSIOLOGY, DIAGNOSIS, AND THERAPEUTIC PERSPECTIVES

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RESUMO

Introdução: A doença de Creutzfeldt-Jakob (DCJ) é uma encefalopatia priônica rara, rapidamente progressiva e fatal, cuja apresentação clínica variável pode atrasar o diagnóstico. Objetivo: Revisar evidências atuais sobre as formas da doença, as manifestações clínicas, os métodos diagnósticos, o manejo e as perspectivas terapêuticas. Método: Foi realizada revisão narrativa da literatura, com busca em PubMed e acesso prioritário a textos completos gratuitos, utilizando os termos “Creutzfeldt-Jakob disease”, “prion disease”, “RT-QuIC”, “diagnosis” e “treatment”. Foram priorizados artigos de revisão, estudos de validação diagnóstica, estudos epidemiológicos e trabalhos terapêuticos publicados até agosto de 2026. Resultados: A maioria dos casos é esporádica, enquanto formas genéticas e adquiridas são menos frequentes. Demência rapidamente progressiva, mioclonias, ataxia, alterações visuais e sinais piramidais ou extrapiramidais compõem o espectro clínico. A ressonância magnética e a detecção de atividade de semeadura priônica no líquido cefalorraquidiano por RT-QuIC aumentaram a precisão diagnóstica; contudo, biomarcadores como 14-3-3 e tau devem ser interpretados no contexto clínico. Não há tratamento modificador da doença estabelecido, e os ensaios clínicos realizados não demonstraram benefício consistente em sobrevida. Conclusão: O reconhecimento precoce do fenótipo clínico, a integração de exames complementares e a comunicação cuidadosa com a família são essenciais. A pesquisa futura deve priorizar biomarcadores precoces, vigilância epidemiológica e intervenções iniciadas antes da extensa neurodegeneração.

Palavras-chave: Doença de Creutzfeldt-Jakob. Doenças priônicas. Diagnóstico. Biomarcadores. Neurodegeneração.

ABSTRACT

Introduction: Creutzfeldt-Jakob disease (CJD) is a rare, rapidly progressive, and fatal prion encephalopathy whose variable clinical presentation may delay diagnosis. Objective: To review current evidence on disease subtypes, clinical manifestations, diagnostic methods, management, and therapeutic perspectives. Method: A narrative literature review was conducted using PubMed, prioritizing freely available full-text articles, with the terms “Creutzfeldt-Jakob disease”, “prion disease”, “RT-QuIC”, “diagnosis”, and “treatment”. Review articles, diagnostic validation studies, epidemiological studies, and therapeutic studies published up to August 2026 were prioritized. Results: Most cases are sporadic, whereas genetic and acquired forms are less frequent. Rapidly progressive dementia, myoclonus, ataxia, visual changes, and pyramidal or extrapyramidal signs comprise the clinical spectrum. Magnetic resonance imaging and detection of prion-seeding activity in cerebrospinal fluid by RT-QuIC have increased diagnostic accuracy; however, biomarkers such as 14-3-3 and tau must be interpreted in the clinical context. No disease-modifying treatment has been established, and clinical trials have not demonstrated consistent survival benefit. Conclusion: Early recognition of the clinical phenotype, integration of complementary tests, and careful communication with families are essential. Future research should prioritize early biomarkers, epidemiological surveillance, and interventions initiated before extensive neurodegeneration.

Keywords: Creutzfeldt-Jakob Disease. Prion Diseases. Diagnosis. Biomarkers. Neurodegeneration.

INTRODUCTION

Creutzfeldt-Jakob disease is the most recognized human prion disease and is characterized by the abnormal conversion and accumulation of prion protein in the central nervous system. Its clinical course is usually measured in months, and the disease remains invariably fatal after symptom onset.[1] The condition is clinically important because it can resemble autoimmune encephalitis, toxic-metabolic encephalopathy, rapidly progressive dementias, and other neurodegenerative disorders, while requiring specific infection-control precautions for selected tissues and procedures.

CJD is classified as sporadic, genetic, or acquired. Sporadic disease accounts for most cases, whereas familial forms are related to pathogenic variants in the PRNP gene and acquired forms include iatrogenic disease and variant CJD.[1,3] The phenotype is heterogeneous: some patients initially present with visual symptoms or cerebellar ataxia, while others develop

cognitive, behavioral, motor, or extrapyramidal abnormalities.[1] This heterogeneity, together with the rapid progression of symptoms, contributes to diagnostic uncertainty and delayed referral to specialized services.

Advances in neuroimaging and cerebrospinal-fluid testing have changed the diagnostic pathway. Diffusion-restricted cortical or striatal abnormalities on magnetic resonance imaging and the detection of prion-seeding activity by real-time quaking-induced conversion (RT-QuIC) can support a probable diagnosis during life.[2],[4] Nevertheless, no single test replaces clinical assessment, and the definitive diagnosis remains neuropathological or biochemical. The objective of this review was to synthesize current evidence on the pathophysiology, clinical presentation, diagnosis, treatment, prognosis, and prevention of CJD.

MÉTODO

This study was designed as a narrative literature review. PubMed was searched in August 2026 using combinations of the descriptors “Creutzfeldt-Jakob disease”, “sporadic CJD”, “prion disease”, “RT-QuIC”, “cerebrospinal fluid biomarkers”, “diagnosis”, “treatment”, “surveillance”, and “epidemiology”, combined with the Boolean operators AND and OR. Eligible publications were peer-reviewed articles indexed in PubMed, available in English, and addressing at least one of the following domains: disease classification and pathogenesis, clinical presentation, diagnosis, epidemiology and surveillance, treatment, prognosis, or prevention. Priority was given to freely available full-text reviews and original studies published from 2017 onward, while older landmark therapeutic and diagnostic studies were retained when necessary for historical or methodological context. Case reports were used only to illustrate diagnostic challenges and were not used to establish general treatment efficacy. Publications with insufficient bibliographic information, duplicated records, or no direct relation to human CJD were excluded. The selected evidence was synthesized thematically, without quantitative meta-analysis, because of clinical and methodological heterogeneity among the studies.

RESULTADOS

Pathophysiology and clinical spectrum. Prion diseases arise from conformational conversion of the normal cellular prion protein into an abnormal, aggregation-prone form. In CJD, this process is associated with synaptic dysfunction, neuronal loss, gliosis, and spongiform change. The sporadic form is the most frequent, but genetic susceptibility and acquired exposure explain other categories.[1] The clinical syndrome commonly includes rapidly

progressive cognitive impairment, myoclonus, ataxia, visual or cerebellar dysfunction, pyramidal or extrapyramidal signs, and, in advanced stages, akinetic mutism.[1] Prodromal behavioral, affective, sleep, or appetite changes may precede the characteristic neurological syndrome and can be overlooked.

The rate of progression is a defining feature. A recent systematic review describes symptomatic survival as approximately six months on average, although the course varies according to molecular subtype and phenotype.[1] The clinical burden is also reflected in healthcare use: in a United States real-world study of 215 adults, the mean interval from symptoms to the initial CJD diagnosis was five months, and patients had frequent alternative diagnoses before CJD was recognized.[5] These findings underscore the importance of considering CJD when cognitive, psychiatric, cerebellar, and motor manifestations evolve over a short period.

Diagnosis. The diagnosis combines a rapidly progressive syndrome with supportive findings and exclusion of treatable mimics. Electroencephalography may show periodic sharp-wave complexes, although sensitivity is variable and the finding is not pathognomonic. MRI is particularly useful when diffusion-weighted and apparent-diffusion-coefficient sequences show cortical ribboning or basal-ganglia involvement.[2,6] Cerebrospinal-fluid 14-3-3 and total tau reflect neuronal injury and can be useful in the appropriate setting, but they lack absolute disease specificity.[1,4]

RT-QuIC detects the ability of pathological prion protein in a sample to seed conversion of recombinant substrate. It has become a major diagnostic advance because studies generally report high specificity and sensitivity commonly ranging from approximately 80% to 97%, depending on assay generation, disease subtype, specimen quality, and study design.[2,4] Sensitivity may be lower in rare molecular subtypes such as MV2, VV1, and MM2. Therefore, a negative result does not by itself exclude CJD, particularly when the clinical and imaging findings remain strongly suggestive. Definitive confirmation still depends on neuropathological and biochemical examination of brain tissue.

Treatment, prognosis, and prevention. At present, there is no established disease-modifying treatment for CJD. Trials and clinical studies of quinacrine, doxycycline, pentosan polysulfate, and other agents have not demonstrated a reproducible survival benefit; late intervention is a major limitation because neuronal injury is already extensive when symptoms become evident.[7] Management is therefore supportive and individualized, including treatment

of myoclonus, seizures, pain, agitation, sleep disturbance, dysphagia, and other complications, together with early palliative-care involvement and support for caregivers.

Infection prevention is based on recognizing the unusual resistance of prions to routine decontamination and on applying protocols appropriate to high-risk tissues and procedures. Surveillance systems are important because ascertainment may be incomplete in older adults, in whom rapidly progressive cognitive decline can be attributed to more common disorders.[3] A United Kingdom study of brain-tissue donations evaluated a highly sensitive screening strategy and found that a reduced protocol using three biochemical tests in two brain regions could provide sufficient sensitivity and specificity for selected surveillance applications.[3] These data support continued neuropathological surveillance and standardized reporting, without implying that population screening of asymptomatic individuals is currently indicated.

CONCLUSÃO

CJD is a rare but critical differential diagnosis in rapidly progressive neurological syndromes. The evidence reviewed indicates that accurate evaluation depends on integrating the clinical phenotype, MRI, EEG, cerebrospinal-fluid biomarkers, and, when available, RT-QuIC. RT-QuIC is highly specific but has subtype-dependent sensitivity and should not be interpreted in isolation. Despite advances in diagnosis and surveillance, no disease-modifying therapy has been established; care remains supportive, multidisciplinary, and centered on patient comfort and family communication.

The main contribution of current research is the possibility of identifying prion-seeding activity earlier and with greater diagnostic confidence. Future studies should validate accessible biomarkers, improve recognition of atypical and early phenotypes, harmonize surveillance protocols, and test interventions at preclinical or very early clinical stages. Until such advances occur, timely referral and careful differential diagnosis remain the most practical means of reducing avoidable delays and inappropriate interventions.

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