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PRION DISEASES: PATHOPHYSIOLOGY AND INTERDISCIPLINARY TREATMENT

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ABSTARCT

Prion diseases are rare, progressive, and invariably fatal neurodegenerative conditions that are classified into three main categories: sporadic, genetic, and acquired. This article presents a systematic review of the literature, based on data obtained from renowned platforms such as PubMed, Nature, and Scielo. Based on the established criteria, it was possible to develop a comprehensive analysis that discusses prion diseases from initial transmission to therapeutic perspectives and clinical outcomes. The pathophysiology involves the conversion of the normal cellular prion protein (PrPC) into its pathological form (PrPSc), resulting in protein accumulation and neurotoxicity. The diagnosis is based on a detailed clinical evaluation, complemented by tests such as electroencephalogram and magnetic resonance imaging. Recent advances in potential therapies, such as the use of heterologous prion proteins and compounds such as AP1, have shown promising results. Despite these advances, it is imperative that translational studies continue to explore existing gaps to develop effective therapies. Prion diseases remain a challenging field that requires research investigation for future scientific and clinical breakthroughs.

Keywords: Prion Diseases. Pathophysiology. Diagnosis. Treatment. Revision.

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INTRODUCTION

According to Pineheiro *et al*. (2024), neurodegenerative diseases are conditions characterized by the gradual loss of neurons in the central nervous system, which generates dementia, cognitive, and somatic symptoms. A neurodegenerative disease, of unknown etiology, was described in 1920 by neurologists Hans Gerhard Creutzfeldt and Alfons Maria Jakob, but it was only in 1982, when Stanley B. Prusiner identified a protein in the brain of hamsters infected with scrapie, which was resistant to proteases and heat, that it was possible to evaluate a significant advance in the understanding of prion diseases (Mark and Reid, 2015).

Prion diseases are rare, progressive, and fatal neurodegenerative pathologies, defined by the abnormal transformation of the cellular prion protein, and can be classified as sporadic, genetic, and acquired (Baiardi *et al*., 2023; Sigurdson, Bartz, Glatzel, 2019).

METHODS

This is a systematic review of the literature, which is suitable for seeking consensus on prion diseases. The research used electronic databases such as PubMed, Nature, Scielo, university journals, national and international newspapers, using the criteria of updated content or that are proven to have current content, excluding content that escaped these limitations. From this process, the project allows for deepening knowledge about the investigated theme and pointing out gaps that need to be filled. The articles were pre-selected based on their relevance, timeliness, and addition on the subject.

THEORETICAL FRAMEWORK

This disease is affected by a mutation in the cellular prion protein PrPC into PrPSc, either by its spontaneous conversion or by a mutation in its only PRNP encoding gene, located on chromosome 20 (Berti, 2020; Sigurdson, Bartz, Glatzel, 2022; Hirsch, Martin-Lannerée, Mouillet-Richard, 2017). PrPC is most abundantly found in the brain, among its functions its protection against toxic concentrations of metal ions, suggested by its bonds with copper, zinc and manganese ions, it is worth mentioning a possible maintenance of the oxidation-reduction state of the cell (Hirsch, Martin-Lanneréé, Mouillet-Richard, 2017; Stoner *et al*., 2023).

A study done with mice deprived them of PrPC protein, the mice showed learning and memory impairment, in addition to a loss of synaptic connection in these animals

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(Storner *et al*., 2023). As mentioned, PrPC appears to have an important neurological performance, aiding in synaptic formation, neuroprotection, cell adhesion, circadian cycle regulation, and ionic regulation (Sigurdson, Bartz, Glatzel, 2019). PrPC, the physiological form of the prion protein, is composed of glycosylphosphatidylinositol and, in its mature form, of 210 amino acids, arranged in an N-terminal domain and a globular C-terminal domain composed of three α-helices and a small β sheet, its alteration to the pathological form is associated with a resistance to protease digestion and insolubility in detergents (Baiardi *et al.*, 2023; Sigurdson, Bartz, Glatzel, 2019).

PrPSc is predominant formed by β leaves, with this it detaches from the cell membrane and is absorbed by the vesicles, accumulating in the lysosomes, consequently their rupture occurs, releasing harmful proteolytic enzymes and PrPSc into the cell, PrPSc itself appears to cause neurotoxicity through its accumulation, leading to apoptosis (Araújo, 2013). There is a preliminary understanding of some factors that can lead to the pathological conformation of the prion protein, among them it is notorious to mention mutations in the PRNP gene and oxidative stress and the so-called sporadic forms (Baiardi *et al.*, 2023; Geschwind, 2015).

Normally, prion infection does not provoke an adaptive immune response, however, there is an unbridled activation and proliferation of microglia in infected brains, as well as astrocytes, as microglia are not enough to phagocytize PrPSc, a change to a pro-inflammatory phenotype can occur, causing a harmful effect on the nervous system, the same can be said about astrocytes (Li, Chen, Zhu, 2021).

DIAGNOSIS

Factors such as rapidly progressive dementia should be clinically evaluated, with cognitive symptoms being the first most common, as well as cerebellar symptoms and behavioral abnormalities, gait ataxia, extrapyramidal features, myoclonus, asthenia/fatigue, headache, vertigo/dizziness, change in sleep pattern, and headache (Geschwind, 2015). According to Herman and Zerr (2025), the diagnosis can be supported by electroencephalogram, but the classic periodic complexes of acute and slow waves are a late feature of the disease, unlike magnetic resonance imaging, which can detect signal hyperintensity early in the disease. Chitavas *et al*. (2011) revealed the need to rule out differential diagnoses such as Alzheimer's disease and vascular dementia, after evaluating 233 erroneous diagnoses of Creutzfeldt-Jakob disease, a sporadic form of prion disease.

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TREATMENT

The scope of studies makes it possible to discuss the best treatment options for prion diseases, among which it is notorious to associate the use of heterologous PrP proteins with a reduction in the worsening of the disease, such as a delay in the loss of motor function and the onset of symptoms and an increase in the survival of infected mice (Skinner *et al*., 2015). The effects of the anti-prion were studied by Díaz-Espinoza *et al.* (2017), it was reported that AP1 can completely prevent the onset of symptoms in animals infected with the disease by significantly reducing the accumulation of PrPSc in the brains of these animals.

RESULTS

In view of the established criteria, it was possible to construct an analysis with updated data regarding the pathophysiology, diagnosis, and possible treatments for prion diseases, there is a significant number of studies available on the limitations of the disease. This article explores prion diseases from the moment the patient contracts it, seeking answers for possible therapies and outcomes.

CONCLUSION

Prion diseases pose a significant challenge to modern medicine. This study reinforces the importance of deepening the understanding of the pathophysiology of the prion protein, highlighting the mechanisms of PrPC conversion into PrPSc and its neurodegenerative consequences, such as dysregulated microglial activation and associated neurotoxicity.

From a diagnostic point of view, advances such as the use of magnetic resonance imaging for early detection and the development of specific biomarkers have shown promise for a more accurate and earlier identification of prion diseases, contributing to better clinical management. However, the complexity of differential diagnoses, such as common neurodegenerative diseases, reinforces the need for further comparative studies.

As for treatment, although interventions with heterologous proteins and anti-prion compounds have shown promising results in animal models, there is still no definitive therapy for application in humans. The continuation of translational studies is essential to identify therapeutic approaches that can delay or even reverse the effects of these pathologies. Knowledge about the existing gaps, such as the triggering factors of sporadic

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forms and the mechanisms of resistance to PrPSc, is necessary to enable the development of more effective preventive and therapeutic strategies in the future.

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