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# Prion diseases: Clinical Manifestations and Diagnosis

*Enfermedades priónicas: manifestaciones clínicas y diagnóstico*

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**RESUMEN**

**Introducción:** Las enfermedades priónicas o encefalopatías espongiformes transmisibles, son un grupo de estas, pertenecientes a las neurodegenerativas que afectan al ser humano y los animales. A nivel global se registra una incidencia de uno a dos casos por millón de habitantes, son raras y tienen un desenlace fatal. La mejor comprensión de estas entidades permite, en un futuro, la identificación de potenciales dianas terapéuticas y el desarrollo de tratamientos que puedan prevenir o ralentizar su progresión.

**Objetivo:** Caracterizar las enfermedades priónicas, los avances en el diagnóstico y tratamiento.

**Métodos:** Se realizó una búsqueda en las bases de datos PubMed, SCOPUS y SciELO. Se incluyeron 28 fuentes en esta revisión, de las cuales el 100 % correspondió a los últimos cinco años.

**Desarrollo:** Las enfermedades priónicas se caracterizan por la acumulación de la proteína priónica en el cerebro, lo que causa cambios neuropatológicos que progresan hasta la muerte neuronal. Si bien se han encontrado marcadores proteicos en líquido cefalorraquídeo que tienen una sensibilidad y especificidad elevadas para su diagnóstico y se ha logrado correlacionar hallazgos imagenológicos, aún se busca un tratamiento específico para ellas.

**Conclusiones:** Resulta imprescindible detectar de manera temprana las enfermedades producidas por priones, para impactar de manera positiva en la calidad de vida de los pacientes que la padecen, solo se cuenta con el manejo y control de síntomas, hasta su muerte.

**Palabras clave:** Creutzfeldt-Jakob, enfermedades priónicas, encefalopatías espongiformes transmisibles, priones

**ABSTRACT**

**Introduction:** Prion diseases or transmissible spongiform encephalopathies are a group of neurodegenerative diseases that affect humans and animals. Globally, there is an incidence of one to two cases per million inhabitants. They are rare and have a fatal outcome. A better understanding of these entities will allow, in the future, the identification of potential therapeutic targets and the development of treatments that can prevent or slow their progression.**Objective:** To characterize prion diseases, such as advances in diagnosis and treatment.

**Methods:** A search was carried out in the PubMed, SCOPUS and SciELO databases. 28 sources were included in this review, of which 100% corresponded to the last five years.

**Development:** Prion diseases are characterized by the accumulation of prion protein in the brain, which causes neuropathological changes that progress to neuronal death. Although protein markers have been found in cerebrospinal fluid that have a high sensitivity and specificity for diagnosis and imaging findings have been correlated, a specific treatment for them is still being sought.

**Conclusions:** Early detection of prion-induced diseases is essential to positively impact the quality of life of patients who suffer from them. The only treatment available is symptom management and control, until death.

**Keywords:** Creutzfeldt-Jakob, prion diseases, transmissible spongiform encephalopathies, prions

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## INTRODUCCIÓN

Prion diseases or Transmissible Spongiform Encephalopathies (TSE) are a group of neurodegenerative diseases that occur in animals and humans, with a fatal outcome.[1] These are characterized by the conversion of the normal prion protein (PrPc) to its pathological form (PrPsc). Most of the initial processes that lead to this transformation are unknown. The deposit of the PrPsc protein in the Central Nervous System (CNS) causes spongiform degeneration in the neuropil, gliosis, vacuolization and neuronal death.[2]

The first document that records the existence of a prion disease dates back to the 18th century and is a letter to the Parliament of England, where the farmers of the Lincolnshire region report the possible contagion of scrapie after introducing infected sheep into the flocks. Likewise, in 1920, two neurologists, Hans Gerhard Creutzfeldt and Adolf Jakob, separately described a strange neurological disease that resulted in death.[3] In 1951, cases of an unknown disease began to be reported in the Fore people, east of Papua New Guinea, known as “Kuru”, a word that means “tremor” in the Fore language.[2]

Based on the neuropathological similarities between scrapie in sheep and Kuru and Creutzfeldt-Jakob disease in humans, a common mode of infection for these is postulated, leading to the term “slow viral diseases”. In 1982, Prusiner hypothesized that the etiologic agent was a small infectious protein particle, which replaced the slow virus theory with the term “prion,” derived from “protein” and “infectious”.[2]

Diseases caused by prions are known to be degenerative, progressive, lethal brain disorders with no known treatment, including: Creutzfeldt-Jakob disease (CJD), prionopathy with variable sensitivity to protease; the hereditary disease Gerstmann-Sträussler-Scheinker, fatal familial insomnia, and Kuru.[4]

Globally, an incidence of one to two cases per million inhabitants is recorded.[5] In Latin America, only one annual incidence is reported in Uruguay with 0.7 cases per million, Argentina with 0.85 cases per million until 2008; Chile, which recorded 3.5 cases per million for 2005, which is higher than the global average.[1]
The most common prion disease in humans is Creutzfeldt-Jakob disease (CJD). In Cuba, between 1981 and 2019, 12 cases of CJD of non-hereditary etiology have been diagnosed, despite the fact that the incidence in the country is almost zero.[5,6]

The treatment and diagnosis of these diseases is complicated. The use of sensitive tools clarifies the latter: magnetic resonance imaging and RT-QuIC, which is a sensitive and specific test to determine CJD, are very useful in this regard. However, only neuropathological examination of brain tissue ensures a definitive diagnosis; there is no treatment to improve the course of prion diseases.[7]

The international scientific community continues searching for alternatives to offer a cure for these neurodegenerative diseases, that are rare and represent a significant challenge for public health, because despite the advances in diagnosis, that include the identification of protein markers in cerebrospinal fluid with high sensitivity and specificity, as well as the correlation of imaging findings, specific treatment is an unmet need. The objective of this literature review is to characterize prion diseases, the advances in diagnosis and their treatment.

## MÉTODOS

For the development of this bibliographic review, a research was carried out in the period from August to December 2024. The information search was carried out in the databases: SciELO, SCOPUS and PubMed, the terms used were: "Prion diseases", "Spongiform encephalopathies"; "Creutzfeldt Jacob disease", "Gerstmann Sträussler Scheinker disease"; "Fatal Familial Imsomnia" and "Kuru", as well as their translations into English.

Filters were used for the selection of articles in English and Spanish that were framed in the last five years, the selection criteria were: works based on theories or methods of scientific research, relevance and timeliness of the publications.

This report was prepared using the theoretical method of analysis-synthesis. Those that did not constitute relevant contributions to the research were excluded, so of the total of 56 bibliographies consulted, 28 were selected and included in the review, with 100% corresponding to the last five years.

## DESARROLLO

The study of prion diseases was revolutionized when the American doctor Stanley B. Prusiner, in 1982, discovered that the infectious agent causing

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these diseases was a protein. At first, the scientific community of his time did not believe him and more doubts arose when it was discovered that the gene that encodes it also existed in healthy people. These contradictions were resolved when it was discovered that although we all have the harmless prion protein, only when it is folded and accumulated as PrPsc, is it capable of inducing abnormal folding in harmless prion proteins. [8]

The gene that produces this protein is located on the short arm of chromosome 20 (site 20p12.17, 14), in the locus called PRNP. This gene codes for a protein that is configured into an octapeptide that carries out the genetic variations corresponding to changes from proline to valine.[9]

The anomalous conversion of PrPc that occurs post-translation leads to a structural reduction of the alpha helices and an increase in the beta sheets, which generates the prion protein. Thus, PrPsc is the only component of the "infectious" prion particle that is established as the causal agent of TSEs. There are three known forms of prion diseases: sporadic (of unknown etiology), genetic or hereditary (associated with mutations in the PRNP gene) and unlike the rest of the neurodegenerative diseases to date, these have an acquired or infectious form (due to exposure to prions by any route).[1]

The two sporadic human prion diseases are sporadic Creutzfeldt-Jakob disease and variable protease-sensitive prionopathy (VPSPr). Genetic human prion diseases include familial Creutzfeldt-Jakob disease (fCJD), fatal familial insomnia, PrP amyloidosis (PrP-A), Gerstmann-Sträussler-Scheinker disease, and Huntington's disease type 1 (HDL1). Acquired prion diseases include variant CJD, iatrogenic CJD, and Kuru disease.[2]

**Creutzfeldt-Jakob disease**

Creutzfeldt-Jakob disease should be considered in a patient with progressive dementia associated with myoclonus and other nonspecific neurological signs such as visual or cerebellar disturbances, pyramidal or extrapyramidal features, and akinetic mutism.[10] Atypical findings include sleep disturbances, chorea, psychiatric symptoms, and peripheral neuropathies.[11]

Although this disease is classified as sporadic, acquired, and genetic, the former corresponds to the majority of cases and these have no infectious source or evidence of familial disease. The average age of onset of this variant is 62 years. [10,11]

Acquired CJD includes the variant known as "mad cow disease" and iatrogenic CJD, the latter associated with dura mater grafting and the use of human growth hormone. The genetic or familial form, on the other hand, arises when there is a history of definite or probable CJD in a first-degree relative or a mutation in the gene encoding the prion protein. For decades, the diagnosis of this disease was only possible post mortem, by showing the spongiform modifications induced in the brain; but in recent years, more sophisticated laboratory evaluations and brain imaging studies can help diagnose the disease earlier. [10]

As it is a disease of very low incidence, with a heterogeneous clinical presentation, the differential diagnosis is exhaustive and everything possible should be done to identify conditions that mimic CJD and are susceptible to treatment. Therefore, an initial workup should include laboratory testing for dementia, such as a serum chemistry panel, liver enzymes, ammonia levels, complete blood count, erythrocyte sedimentation rate (with blood cultures if infection is suspected), assessment of thyroid function, testing for neurosyphilis, and measurement of B12 and folate levels, as well as serum levels of antiroperoxidase antibodies, to rule out Hashimoto's encephalopathy. [10,12]

Protein markers have been identified in cerebrospinal fluid (CSF) that have high sensitivity and specificity, making them a valuable aid in the diagnosis of Creutzfeldt-Jakob disease. Because assessment of these biomarkers requires a lumbar puncture, the value of plasma biomarkers has been studied; but they have lower diagnostic accuracy. [12]

The increase in the 14-3-3 protein family in the CSF shows a sensitivity of 87% and a specificity of 66% when assessed by Western Blot. The microtubule-associated protein tau is a marker of neuroaxonal degeneration used for the pre-mortem diagnosis of CJD, although it should be noted that it increases in Alzheimer's disease (AD). The cut-off points for the differential diagnosis between both entities are not yet established, although phosphorylated tau shows a greater increase in AD, so the t-tau/p-tau ratio < 0.075 increases the sensitivity, around 96% and the specificity from 98 to 100% for CJD. [12]

Other biological markers are alpha-synuclein, which also shows significant increases, with a sensitivity of around 90%. Likewise, increased

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Neurofilament light (Nfl) is related to CJD, but its sensitivity is around 85%. YKL-40, a marker of neuroinflammation, also shows an increase in the CSF of CJD patients, with a sensitivity of around 76%.[12]

A breakthrough in the early diagnosis of CJD is the development of the real-time tremor-induced conversion assay RT-QuIC, which indirectly detects PrPSc in cerebrospinal fluid, nasal fluids or the brain, even at very low concentrations. Although this technique has a high sensitivity and specificity, it is expensive and less standardized compared to other biomarkers such as the 14-3-3 protein.[10]

Magnetic resonance imaging is a useful research tool in the study of the sporadic form of CJD, it is sensitive and specific, and it is available. The classic findings of the disease are hyper intensity in T2 sequences of the basal ganglia (most frequently in the caudate and putamen) and in the cortical area, especially in the occipital and temporal areas. With the use of sequences such as DWI (diffusion-weight imaging) and FLAIR (fast fluid attenuated inversion recovery), alterations in the basal ganglia and cortex are more easily identified. [8,10]

In the early stages of the disease, diffusion restriction will be seen in the cortex and basal ganglia (striatum). The insula and cingulate cortex, superior frontal gyrus and cortical areas close to the midline are usually affected. The perirolandic cortex is spared and isolated involvement of the limbic system is rare. Signal hyper intensity or restriction on DWI with cortical and basal ganglia involvement tends to progress over time, which correlates with the duration of the disease and the degree of spongiform degeneration. [13]

However, alterations in signal intensity on DWI may decrease or disappear after disease progression, due to neuronal death and increased brain atrophy, characteristic of advanced stages of CJD. Likewise, imaging studies allow differentiating false positives due to other causes of abnormalities in the cerebral cortex, basal ganglia and cerebellum such as: severe hypoxic-ischemic encephalopathy, hypoglycemic encephalopathy, hepatic encephalopathy, SMART Syndrome, immune-mediated or infectious encephalitis and mitochondrial diseases. [13]

Electroencephalography also supports the diagnosis, although it has only 66% sensitivity. The typical finding corresponds to bilateral synchronous epileptiform discharges, such as periodic short-wave complexes (PSWC). This pattern is usually late, after three months, occurs in MM1/MV1 forms of CJD and is rare in other genotypes. [10,14]

In recent years, some treatment possibilities have been investigated for the sporadic form of CJD. However, none improve symptoms or survival. Flupirtine shows cytoprotective activity in vitro in neurons inoculated with prion protein, although in clinical trials it does not have the same effects. Pentosan polysulfate (PPS) is a high molecular weight polymer similar to heparin that seems to interfere with the conversion of PrPc to PrPsc when administered by intraventricular injection, since it diffuses poorly through the blood-brain barrier. Although increased survival has been demonstrated with its use, it is an aggressive procedure with severe complications such as subdural hemorrhages, so it is not a viable treatment option. [10,12]

Quinacrine can prevent the conversion of PrP into disease-associated protein forms, but no difference in mortality rates has been demonstrated despite a transient improvement in symptoms at the start of treatment. Doxycycline has good diffusion across the blood-brain barrier and has been shown to inhibit PrP protein aggregation and reverse PrPSc protease resistance. It is regrettable that despite promising results in in vitro and animal models of prion disease, in the clinical setting it fails to prolong survival except when administered in the early stages. [10,12]

**Gerstmann-Sträussler-Scheinker Disease**

Gerstmann-Sträussler-Scheinker disease (GSS) was first described in an Austrian family in 1936 and in 1991, Kretzschmarv detected the P102L mutation in the PRNP gene. Initially, it was known that this disease exhibited an autosomal inheritance pattern; but now it is known that one third of patients with GSS are de novo.[15]

GSS is also well known for its clinical heterogeneity, depending on the genetic mutation present and even within families showing the same genetic mutations.[15] However, the exact incidence of the disease is unknown, familial clusters are not frequently reported. It is characterized by prominent cerebellar ataxia between the ages of 40 and 70, accompanied by progressive cognitive decline.[16]

It may also manifest as an isolated cognitive decline similar to Alzheimer's disease and frontotemporal dementia. On the other hand, a minority presents symptoms similar to parkinsonism and progressive

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supranuclear palsy. This clinical diversity is linked to specific mutations of the loci, as exemplified by the D202N mutation that is often associated with atypical parkinsonism. However, the distinctive genetic, clinical and pathological characteristics that distinguish the various classes of GSS are not yet defined.[17]

Neuropathological findings in GSS are also variable, with the most frequent being the presence of multicentric amyloid plaques derived from abnormal PrP products, distributed in the cerebral cortex, basal ganglia, and cerebellum.[16]

Among the auxiliary diagnostic studies for GSS, imaging tests show the highest positivity; but they are not sensitive or specific. Brain MRI of patients with GSS is usually normal early in the course of the disease, followed by cortical and cerebellar atrophy in correspondence with progression.[15,17]

RT-QuIC, t-tau protein and 14-3-3 protein analysis in CSF, as well as high signal intensity on DWI, show the lowest positivity rates compared to other types of prion diseases, which increases the difficulty in diagnosing GSS. [17,18] Despite being the most specific ancillary test for the diagnosis of GSS, RT-QuIC still requires further validation at different mutation sites and clinical presentations. [17] Since GSS cases are familial and all patients with definite GSS have been found to have mutations in PRNP, the demonstration of mutations in this gene is the primary diagnostic test. The most common mutation is P102L.[18]

**Fatal Familial Insomnia**

Fatal Familial Insomnia (FFI) is a genetic prion disease related to the substitution of aspartic acid for asparagine at codon 178 of the PRNP gene, in association with methionine at polymorphic site 129 (D178N/M129). These mutations have almost complete penetrance, leading to the onset of the disease around 50 years of age. Median survival is 18 months; but more than 50% die within a year of the first symptom.[19,20]

The most striking clinical feature is progressive insomnia, accompanied by hallucinations and staged dreams, cognitive decline, motor system disturbances (myoclonus, tremor, dysarthria and pyramidal impairment), autonomic dysfunction due to tachycardia and hypertension, 19 as well as endocrine disorders: increased cortisol, decreased ACTH, loss of diurnal variations in growth hormone, melatonin and prolactin.[18]

Neuropathology includes spongiosis, marked neuronal loss and astrogliosis, especially in the medio-dorsal and antero-ventral nuclei of the thalamus. Microgliosis is also present and may be an early neuropathological change.[19]

Numerous commonly used biomarkers and neuroradiological tests are not useful for the diagnosis of FFI. In CSF, 14-3-3 is not detectable, EEG does not show PSWC, and brain MRI is usually normal. Fluorodeoxyglucose positron emission tomography (FDG-PET) and sleep studies may have some clinical relevance. FDG-PET shows decreased glucose uptake in the thalamus, and sleep studies show decreased total sleep time. The main diagnostic technique is genetic testing, since all cases are associated with the D178N-129M PRNP gene mutation.[18]

The sporadic version of fatal insomnia is difficult to diagnose due to the absence of a genetic mutation. Recognition of the clinical syndrome with abnormal polysomnography and thalamic hypometabolism on brain FDG-PET with methionine homozygosity at codon 129 of PRNP may be useful for making the antemortem diagnosis of this rare prion disease.[18]

As stated above, potential antiprion drugs are tetracycline-type antibiotics, in particular the second-generation derivative, doxycycline, which improves tolerability even for prolonged treatments. However, the available scientific evidence suggests that treatment should be started as early as possible to achieve beneficial effects, in the presymptomatic phase. For this reason, in healthy individuals at risk of FFI, it is being studied whether the administration of doxycycline before irreversible neurodegeneration prevents or delays the disease.[19]

**Kuru**

Kuru is another prion disease, with a neuropathological basis in amyloid plaque deposits in the cerebellum, thalamus and cerebral cortex, followed by severe astrocyte gliosis, neuronal lesions and spongiform changes in the brain. Research by anthropologists on the Fore people suggests that Kuru began in the region between 1900 and 1920; but it was not until the 1950s and 1970s that it became an epidemic due to endocannibalistic funeral rituals practiced by the native Fore population. Today, this disease is considered eradicated by the elimination of cannibalism in the tribes. [20]

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The incubation and survival period is variable. Associations have been revealed between particular variations of the PRNP gene and vulnerability to Kuru, which illuminates the underlying genetic causes. Individuals with homozygosity for the methionine allele at codon 129 of the PRNP gene are susceptible to a short incubation period and early death. In contrast, those with heterozygosity at this position are resistant to the disease, with longer incubation periods and late death. On the other hand, heterozygotes at codon 127 exhibit strong and possibly complete resistance to Kuru. [21,22]

Clinically, Kuru disease is characterized by three stages: a first ambulatory phase that presents with features of cerebellar ataxia, a subtle gait instability that progresses to ataxia and incoordination of the muscles of the trunk and lower limbs, and chills that are exacerbated by lower temperatures. Individuals are emotionally labile and may exhibit uncontrollable laughter. This picture is followed by a sedentary phase in which the patient is unable to stand without support and ends when he or she cannot sit without support. Ataxia, dysarthria, and tremor worsen during this phase. Other symptoms include jerky eye movements, opsoclonia, and dystonia. [21]

In the terminal phase, the patient is bedridden and may develop dysphagia and incontinence. Victims are unresponsive to their surroundings, although they are conscious. A fixed dystonic posture with athetosis and chorea is seen. Dementia symptoms are also present; but they are not prominent compared to other prion diseases. Convalescents usually die from pneumonia or infection of ulcerated wounds, within nine to 24 months of the onset of the disease. [21]

**Variable protease-sensitive prionopathy**

Variable protease-sensitive prionopathy (VPSPr), the last identified human prion disease, was first reported in 2008 and since then, more than 40 cases have been reported. It owes this name to the variable resistance of PrPsc to digestion by Proteinase K (PK), which is lower than in sporadic CJD. [18,22]

Its clinical features are more similar to atypical dementia than sporadic CJD. 18 The PRNP codon 129 has a notable influence on the pathological and biochemical characteristics and, to a lesser extent, on the clinical presentation. PrPsc shows the highest sensitivity to PK digestion in individuals with the 129 Valine-Valine (VV) genotype, the lowest in 129 Methionine-Methionine (MM) carriers, and intermediate values in those with 129 Methionine-Valine (MV). The high PK resistance of the 19 kDa band in the 129 MM brain makes this case the most "CJD-like" of the three. On the other hand, the 129VV-associated disease has the most atypical profile. [22]

This variability makes diagnosis difficult. In this regard, several commonly used tests are often unremarkable in VPSPr, including normal findings or diffuse slowing on EEG, lack of diffusion restriction on MRI, and normal CSF 14-3-3 protein. RT-QuIC has a sensitivity of 66% in VPSPr. [18]

The incidence of prion diseases continues to be underdiagnosed. Still, the number of cases reported each year and the reported mortality from them, whether worldwide or in each country or territory, increase almost twofold from 1993 to 2020. One of the most important reasons for these increases is the implementation of strict surveillance worldwide, which improves awareness of these entities both in the professional field and in the public community. Therefore, the integration and expansion of monitoring networks is necessary and should be improved, including the development of simplified and easy detection technologies, as well as digitalized systems for collecting and analyzing information. [23]

The current literature reflects that there is no treatment available for prion diseases. Immunotherapy is considered a plausible therapeutic option for these diseases, and promising results have even been achieved with passive and active immunization strategies against them. Specific PrPsc antibodies should be sought, as well as new methods to administer these therapeutic antibodies to the CNS to make treatment more feasible. If found, it is a safe and disease-targeted therapeutic agent. [24]

Given the rapid progression of prion disease after clinical onset and the accumulation of PrPsc in the brain, these administration methods are crucial for effective therapy in the clinical stage. However, the widespread expression of PrP under physiological conditions and some toxicological concerns raised by these vaccines make the general applicability of such strategies questionable. [12,24]

The first treatment of prion diseases, with an intravenous humanized monoclonal antibody against the cellular prion protein (PRN100) in six convalescents with CJD and historical control

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in untreated patients, suggests that PRN100 is effective against PrPsc, based on two autopsied cases. However, the number of patients treated is too small to determine whether PRN100 alters the course of the disease, so a much larger study is intended, justified by these results. This treatment strategy is expected to be promising as secondary prophylaxis, in asymptomatic individuals known to be infected with prions or harbor a pathogenic mutation in PRNP. [25]

Gene therapy is an option for PRNP gene mutation carriers, symptoms appear in late adulthood and early clinical intervention can slow disease progression. Antisense Oligonucleotides (ASOs) are synthetic single-stranded nucleotides that bind to a target mRNA and prevent transcription of the target protein through RNase H degradation of the RNA-ASO complex. [12]

ASOs directed against the PRNP gene, administered intraventricularly in mouse models, have been shown to reduce PrPsc deposition. Lentiviral-mediated RNA interference (RNAi) reduces pathogenic protein expression and prolongs survival in mice as do ASOs. [12]

Stem cells, as a treatment, are promising due to their ability to regenerate damaged cells in the brains of prion-induced mice. While certain results have proven encouraging in terms of improving the life span of mice, the timing of disease onset and transplantation is critical to achieving successful outcomes. [26]

The SARS-CoV-2 spike protein contains extended amino acid sequences that have previously been established to have prion-like characteristics, so the production of spike protein induced by vaccination is also prion-like. In light of these findings, it is reasonable to assume that many more cases of neurodegenerative diseases will occur in the near future, therefore, the risk-benefit ratio of mRNA vaccines needs to be re-evaluated due to the amyloidogenic potential of the spike protein. [28]

In the case of prion diseases, even the most extreme biosecurity measures do not prevent their transmission, so special care must be taken when making a presumptive diagnosis, especially by health personnel in direct contact with prion-infected tissues. Incineration of the material used in the treatment and diagnosis of patients is the best biosecurity measure. However, there are cases in which the used material, due to its high cost and technology, cannot be disposed of; the second best method of disinfection is the use of formic acid. [28]

## CONCLUSIONS

**Despite the efforts of the international scientific community to find an effective treatment for prion diseases, they remain incurable. The high infectivity of prions poses important challenges in terms of biosecurity, as well as ethical issues related to the treatment, palliative care and management of these patients with a limited hope of survival. Early diagnosis is complicated by the lack of specific tests and the similarity of its symptoms with other neurological conditions, which highlights the need for further research into these issues.**

## SCIENTIFIC CONTRIBUTION

Prion diseases, although of infrequent incidence, constitute a priority area of research for the international scientific community; but despite diagnostic advances, current scientific literature confirms the absence of effective treatments. Therefore, their study is crucial to understand in depth the neurodegenerative mechanisms underlying these conditions. This greater understanding may in the future lead to the development of viable therapeutic options for these diseases that represent a significant challenge to public health.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## AUTHORSHIP CONTRIBUTION

**SNL:** Conceptualization, research, methodology, project administration, supervision, validation, writing of the original draft, writing, review and editing.
**YER:** Conceptualization, research, methodology, project administration, supervision, validation, writing of the original draft, writing, review and editing.
**RMGV:** Research, methodology, review and editing.

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