



An Overview of TSE Diseases

Houhua Hu

The Pennsylvania State University

*Corresponding author. Email: hqh5298@psu.edu

Abstract. Prion disease is a sparse, life threatening, and unusually dramatic neurodegenerative disease. Although there is no radical cure for prion diseases, the diseases follow an apparent pathogenic mechanism. A single gene produces a single corresponding prion protein (pRP) that could potentially transform into the only disease-causing factor, a misfolded prion. The cellular prion protein PrP C is a small glycoprotein on the cellular surface whose roles is currently unknown. Besides that, it is a critical molecule associated with a school of neurodegenerative diseases known as infectious spongiform encephalopathies (also known as prion diseases). Currently, the definitive diagnosis of TSE is determined post-mortem and is difficult to detect in asymptomatic carriers of the disease. There is a great need for improved methods to detect TSE to improve the safety of food, drugs, and blood products.

Keywords: TSE disease, Misfolded, Prion protein, Detect, Therapeutics.

1 Introduction

Transmissible spongiform encephalopathy (TSE) is a slowly degenerating disease within the central nervous system in humans and animals. TSE is caused by prions, which trigger the irregular folding of prion proteins [3] in the patient's brain. Research on TSE treatment is divided into rapid diagnosis and symptom relief. Prion agents are highly infectious through body fluids and other media [4]. Tests are being developed to buy time for treatment and to stop transmission. Effective treatment for TSE is still under development. Accurate diagnosis has become essential for disease surveillance and public health protection while treatments are being actively developed. With the accumulation of prion research over the past three decades and routine testing of bovine brains for BSE. Recent advances in PrPSc have set the course for developing assays with maximum sensitivity and specificity. Studies on experimentally infected animals suggest that the detection of prions in the blood is reaching a long-awaited milestone [11].

2 The information of TSE diseases

The TSE is distinguishable from other diseases for its deep incubation periods of up to 44 months or longer, characteristic spongiform lesions associated with loss of neural functions, and the incapability for the brain to initiate an inflammatory response. The cause of TSE are “prions,” which are “Transmissible agents” that cause abnormal foldings in prion proteins abundant in the brain. Thus, it is also called the Prion Disease. “Agent” excreted during “stress”

TSE is a highly infectious disease. Prion agents are likely to spread between animals through direct contact with body fluids like feces and urine, or indirectly contact through environmental contamination of soil, food or water that animals shared.

TSE has a range of variants for different families of animals. Some specific TSE Diseases are Scrapie that occur to sheep and goats, Bovine Spongiform Encephalopathy (mad cow disease) in cattle, Transmissible mink encephalopathy in minks and many other zoo species, Feline spongiform encephalopathy in felids, and Chronic wasting disease in cervids, as well as Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob disease (vCJD) in human, and Kuru Disease in Human [4].

2.1 The background of TSE

In 1985, cattle in the UK suddenly dead in batches. In 1986, the veterinarians named it the mad cow disease. The mad cow disease outbreak around the UK [4], reached a peak in 1992. In the following ten years, mad cow disease was reported in more than a dozen countries in Europe. In 2001, it appeared for the first time in Japan. In 2003, sick cows with mad cow disease also appeared in Canada and the United States. According to the statistics of the Animal Health Organization, as of 2015, a total of 187469 sick cows were diagnosed with mad cow disease in the world, of which 181667 were in the UK, accounting for 96.91% of the global total [5]. During this period, more than 1 million cattle were potentially infected with the mad cow disease pathogen, and almost all of these cattle entered the human food chain [6].

2.2 The definition and background of C-BSE

Classical BSE (C-BSE) was first diagnosed in Britain in 1984 as a new prion disease spreading between cattle [6], but its origin remains unclear. However, this is not the first time TSE disease has been seen in the UK, as scrapie has been prevalent in food sheep in the UK for centuries, and unlike BSE, scrapie has not been shown to have any zoonotic risk. This led to the belief for a long time that the disease had a high transmission barrier and no profound public health implications.

BSE has been spread to at least 28 countries by exporting contaminated meat and bone meal and live livestock. The infected carcasses of diseased cattle entered the food chain when farmers recycled the meat and bone powder of dead cows into cattle feed, thus triggering more extraordinary transmission. BSE has received much more attention because of its association with feline spongiform encephalopathy, its ability to spread to non-human primates, and its relationship between the recently emerging form of

severe prion disease vCJD[7]. The result suggests that all three diseases are caused by the same prion pathogen, demonstrating a link between BSE and vCJD. Despite a steady decline in vCJD cases after 2001-2002, which allowed the inefficiency of transmission of the C-BSE pathogen to humans to be confirmed [8], vCJD still has a potentially high transmission rate. Because positive samples have codon 129 methionine-methionine, methionine-valine, and valine PRNP genotypes, this suggests that BSE pathogens may infect individuals of all codons 129 genotypes individuals with this genotype may represent a 1:2000 ratio worldwide [3].

2.3 TSE disease Diagnostic test

Diagnostic tests to detect TSE rely primarily on the presence of proteinase K (PK) resistant PrP^{Sc} (PrP-res) in postmortem tissue as a sign of TSE disease. The highest levels of TSE infectivity are discovered in the central nervous system (CNS) tissues of infected animals based on tests [2]. However, the infectious agent was also present in peripheral tissues, for example the lymphoreticular system and spleen. In TSE disease, the main infectivity depends on the carrier species, the PrP genotype, and the TSE agent strain. However, the relationship between these three species and the source of infection is still undetectable by current standards of analysis, suggesting the presence of numerous atypical TSE diseases.

Standard tools include brain biopsy, PRNP analysis, and tonsil biopsy. Brain biopsies were obtained by proteinase K treatment and subsequent Western blot analysis of the prion protein PrP^{Sc} to obtain brain tissue for direct diagnosis. However, this requires proper management of the associated risk of infection and is therefore rarely done. (Mutations and variants in the PRNP gene can affect an individual's susceptibility to prion disease [7]. PRNP assays can be used to diagnose sporadic PRNP assays by analyzing 129 codon signatures that are referenced when diagnosing sCJD. A positive result performs tonsil biopsy is likely to be a diagnosis of vCJD by detecting the sediment PrP^{Sc} in Pasteurella.

Among non-laboratory tests, the results are primarily a combination of brain MRI, EEG, and CSF analysis. Magnetic resonance imaging (MRI) shows the presence of caudate and cortical nuclei [12]. Another test that identifies more than two cortical regions in the brain's temporal, parietal, and occipital on diffusion-weighted imaging (DWI) or fluid-attenuated inversion recovery (FLAIR) sequences with a super strong signal [12]. In vCJD, hyperintensity on FLAIR sequences is the norm for the bilateral posterior thalamus (Knight, 2020). An EEG is the only supportive diagnostic test.

3 New diagnostic tools

CSF RT-QuIC has been used in recent years as a practical option for routine clinical diagnosis related to sCJD, and the "second generation RT-QuIC" is on account of the use of truncated Syrian hamster proteins (rec Sha (90-231)). (The second-generation assay was optimized by modifying the reagents and incubation conditions). A direct comparison between the first and second-generation RT-QuIC showed a 21% boost in

sample detection sensitivity and a 2-day reduction in assay time [9]. RT-QuIC is now being used clinically to combine CSF laboratory results with MRI findings, making it the first best method for premortem diagnosis of TSE disease that does not require a brain biopsy.

The steps of the second generation RT-QuIC assay are briefly described as follows: 20 μL of CSF is added to 80 μL of the reaction mixture in each well of a clear black 96-well plate (Nunc). The final solution contains 10 mM phosphate buffer pH 7.4, 1 mM ethylenediaminetetraacetic acid tetrasodium salt (EDTA) pH 8.0, 300 mM NaCl, 10 μM thioflavin-T (ThT), 0.002 % sodium dodecyl sulfate (SDS) and 0.1 mg/mL recombinant Syrian hamster truncated prion protein (HarPrP 90-231). Samples were tested in quadruplicate, 3 to 4 times independently, with 12 or 16 port wells per sample. Plates were sealed and incubated in a FLUOstar OMEGA reader (BMG Labtech, Germany) at 55°C with intermittent shaking cycles (60 s, dual-track, 700 rpm) and rest (60 s). Fluorescence of ThT was collected every 45 min at 450 ± 10 nm (excitation) and 480 ± 10 nm (emission). The threshold was defined as the average fluorescence of all samples plus 10 standard deviations (SD) over the 10 hours prior to incubation. Samples were considered positive when two or more of the four replicate wells exceeded this threshold. (12). The RT-QuIC test provides a rapid and quantitative tool for the early diagnosis of human prion diseases with high sensitivity (82-97%) and almost complete specificity (99-100%). Its use has increased over the past few years because of its high predictive value, relatively economical cost, and that it is an alternative to invasive technique which poses no risk to patients or health care professionals. RT-QuIC is more environmentally and technically demanding than a brain biopsy. A prerequisite for the universal availability of RT-QuIC technology is the availability of high-quality recombinant PrP. After successfully applying RT-QuIC technology to CSF samples, researchers have attempted to improve the sensitivity and utility of diagnostic tests by applying RT-QuIC technology to olfactory epithelial cell samples [13].

4 TSE disease treatment

Since the emergence of variant Creutzfeldt-Jakob disease (vCJD), many strategies and medians have been put forth for treatments of prion diseases, among which inhibition of PrP Sc accumulation is the most studied target. Various compounds are known to effectively interrupt PrP Sc accumulation, including DRC and analogs, certain cyclic tetrapyrroles like porphyrins and phthalocyanines, and sulfated polyanions dextran 500 sulfate, polyepentoses sulfate, and polyene antibiotics such as AmB. Many other compounds have been identified to affect pathological PrP Sc formation in vitro and in live subjects, but only flupirtine, an analgesic, may be effective in humans ((Vana et al., 2006)). The primary means of active immunization is through the use of truncated prion peptides as immunogens; however, although staged prion peptides trigger antibodies in animals, merely a few will slow down disease progression. In addition, active immunization requires consideration of the possibility of neurotoxic effects.

Passive immunization is more feasible than active measures. Passive immunization against PrP Sc can be accomplished by transgenic expression of a μ -heavy chain

variable fragment of PrP C-specific monoclonal antibody 6H4 in PrP +/- mice, which ultimately prevents prion infection following intraperitoneal administration of PrP Sc. The combination of pAb W3 and LRP/LR eliminates the proliferation of PrP Sc in cell culture experiments (Roettger et al., 2012). Due to the destructive nature of TSE disease, the typical six-month time frame from diagnosis to patient death, and the rare cases, it is challenging to develop effective treatment strategies. Currently, no effective treatment is in practice for clinically affected TSE patients, and as a result, patients with TSE disease usually end up dead. Still, the positive effects of active and passive immunization can be studied to prevent TSE disease.

4.1 Emerging therapeutic directions

Researchers have long believed that Genetics could offer a solid therapeutic hypothesis for prion disease: reduction of natural pRP. Genetic proof-of-concept studies suggest that reducing pRP expression has a dose-dependent protective effect. Although late truncated variants of PRNP are known to encode sequences that produce secreted proteins in humans, early truncated variants appear to convey an actual loss of pRP function and thus may have a chance of cure. This variant is often observed in a heterozygous state in healthy middle-aged and elderly subjects without syndromes or neurological health problems. Thus, reduced doses of the PRNP gene appear to be well tolerated in humans [6].

5 Conclusion

Diagnosing prion disease can be clinically challenging, and laboratories can play an essential role in helping to make that diagnosis. The development of these clinical trials and the detection of abnormal PrP in tissues as a pathological marker allows for identifying less typical cases. The most definitive test in clinical use is the CSF RT-QuIC test for sCJD. With newer technologies, RT-QuIC may become the earliest and most accurate test for TSE disease that can be used in public health and non-laboratory conditions.

To date, there have been no successful clinical trials for curing prion diseases. The low prevalence of prion diseases inherently limits the ability of researchers to conduct double-blind, randomized, placebo-controlled, multicenter trials in large patient populations. Due to the lack of prion disease-specific disease scales, initial clinical studies were conducted using cognitive test sets that were not specifically designed to address the prion disease phenotype. Because there is no effective treatment for prion disease, all medical care has been largely supportive and palliative.

References

1. Tyler, J. W., & Middleton, J. R. (2004). Transmissible spongiform encephalopathies in ruminants. *Veterinary Clinics of North America: Food Animal Practice*, 20(2), 303–326. <https://doi.org/10.1016/j.cvfa.2004.02.002>

2. Dobie, K., & Barron, R. (2013). Dissociation between transmissible spongiform encephalopathy (TSE) infectivity and proteinase K-resistant prpsc levels in peripheral tissue from a murine transgenic model of TSE disease. *Journal of Virology*, 87(10), 5895–5903. <https://doi.org/10.1128/jvi.03469-12>
3. Houston, F., & Andréoletti, O. (2019). Animal prion diseases: The risks to human health. *Brain Pathology*, 29(2), 248–262. <https://doi.org/10.1111/bpa.12696>
4. Vana, K., Zuber, C., Nikles, D., & Weiss, S. (2006). Novel aspects of prions, their receptor molecules, and innovative approaches for Tse therapy. *Cellular and Molecular Neurobiology*, 27(1), 107–128. <https://doi.org/10.1007/s10571-006-9121-1>
5. Roettger, Y., Du, Y., Bacher, M., Zerr, I., Dodel, R., & Bach, J.-P. (2012). Immunotherapy in prion disease. *Nature Reviews Neurology*, 9(2), 98–105. <https://doi.org/10.1038/nrneurol.2012.258>
6. Vallabh, S. M., Minikel, E. V., Schreiber, S. L., & Lander, E. S. (2020). Towards a treatment for genetic prion disease: Trials and biomarkers. *The Lancet Neurology*, 19(4), 361–368. [https://doi.org/10.1016/s1474-4422\(19\)30403-x](https://doi.org/10.1016/s1474-4422(19)30403-x)
7. Connor, A., Wang, H., Appleby, B. S., & Rhoads, D. D. (2019). Clinical laboratory tests used to aid in diagnosis of human prion disease. *Journal of Clinical Microbiology*, 57(10). <https://doi.org/10.1128/jcm.00769-19>
8. Knight, R. (2020). Clinical diagnosis of human prion disease. *Progress in Molecular Biology and Translational Science*, 1–18. <https://doi.org/10.1016/bs.pmbts.2020.07.006>
8. Groveman, B. R., Orrú, C. D., Hughson, A. G., Bongiovanni, M., Fiorini, M., Imperiale, D., Ladogana, A., Pocchiari, M., Zanusso, G., & Caughey, B. (2016). Extended and direct evaluation of RT-QuIC assays for Creutzfeldt-Jakob disease diagnosis. *Annals of Clinical and Translational Neurology*, 4(2), 139–144. <https://doi.org/10.1002/acn3.378>
9. Priola, S. A., & Vorberg, I. (2006). Molecular aspects of disease pathogenesis in the transmissible spongiform encephalopathies. *Public Health Microbiology*, 517–540. <https://doi.org/10.1385/1-59259-766-1:517>
10. Lukan, A., Vranac, T., & Čurin Šerbec, V. (2013). Tse diagnostics: Recent advances in immunoassaying prions. *Clinical and Developmental Immunology*, 2013, 1–8. <https://doi.org/10.1155/2013/360604>
11. Barbosa, B. J. A. P., Castrillo, B. B., Alvim, R. P., de Brito, M. H., Gomes, H. R., Brucki, S. M. D., Smid, J., Nitrini, R., Landemberger, M. C., Martins, V. R., Silva, J. L., & Vieira, T. C. R. G. (1AD, January 1). Second-generation RT-quic assay for the diagnosis of Creutzfeldt-Jakob disease patients in Brazil. *Frontiers*. Retrieved June 22, 2022, from <https://www.frontiersin.org/articles/10.3389/fbioe.2020.00929/full#h2>
12. Chatzikonstantinou, S., Kazis, D., Karantali, E., Knights, M., McKenna, J., Petridis, F., & Mavroudis, I. (2021). A meta-analysis on RT-QuIC for the diagnosis of sporadic CJD. *Acta Neurologica Belgica*, 121(2), 341–349. <https://doi.org/10.1007/s13760-021-01596-3>

Open Access This chapter is licensed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.

