Prions: A Primer and PSA

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Background

Prions are a type of non-living pathogen. They are malformed, disease-causing proteins that affect the central nervous system (CNS). These protein-based diseases are found in many organisms, from humans to sheep to yeast. These diseases are often referred to as Transmissible Spongiform Encephalopathies (TSEs). The National Institute of Neurological Disorders and Stroke (NINDS) defines TSEs as “a group of rare degenerative brain disorders characterized by tiny holes that give the brain a ‘spongy’ appearance (National Institute of Neurological Disorders and Stroke, 2023).” A hallmark of these diseases is their universal fatality. While many of these diseases have quite long incubation/dormancy periods, so some with these conditions can have only slightly reduced life expectancies, those who acquire these diseases will die from them. There are also no known treatments or cures for these diseases at the moment.

Historical Outbreaks

The initial Mad Cow Disease (BSE) outbreak happened in 1986. This was a major outbreak infecting 180,000 cows. Along with these deaths came 4.4 million cattle in an effort to eliminate the disease or at least stop its spread (The legacy of BSE. (2011). New scientist (1971), 209(2797), 3.). This disease then spread to humans in the form of Variant Creutzfeldt-Jakob Disease (vCJD). This outbreak led to over 200 cases of vCJD worldwide (Ritchie, D. L., Peden, A. H., & Barria, M. A. (2021). Variant CJD: Reflections a Quarter of a Century on. Pathogens (Basel, Switzerland), 10(11), 1413.).

Kuru was the first prion disease identified in humans. The first case was reported to have manifested around 1900 in the Fore people of eastern Papua New Guinea. Over the next few decades, kuru would spread to other neighboring groups. Before their contact with European scientists, kuru was thought to be caused by a kind of sorcery performed by one's enemies. However, scientists concluded that the disease was spread by the cannibalistic practices of those peoples. The cause of this disease, however, was still unknown until an American veterinary pathologist, William Hadlow, noticed similarities between the lesions caused by kuru and the cause by scrapie, a prion disease found in sheep and goats (Liberski, P. P., Gajos, A., Sikorska, B., & Lindenbaum, S. (2019). Kuru, the First Human Prion Disease. Viruses, 11(3), 232.).

PSA

People should know where their meat is coming from. Ensure your meat comes from a reputable source, and avoid the brain or other nervous tissues. Most cases of prion disease in humans are sporadic, meaning that their cause is either unknown or random, so unfortunately, there is not much that can be done to prevent them but watch for symptoms. Genetic testing may be warranted for genetic prion diseases to determine the presence of certain genetic markers associated with prion diseases. Cannibalism should also be avoided. Despite these warnings, it should be noted that these diseases are extremely rare, so acquiring them should not be a major worry.Hunters should generally be wary of any animal that looks or acts strangely, i.e., walking strangely, looking malnourished, acting unusually friendly or aggressive, etc. These could be signs that the animal is sick, whether that be a prion disease or not. When dressing a deer, one should wear gloves and avoid handling the brain or nervous tissue of the animal, as well as using a dedicated set of knives set aside for this specific purpose and this purpose only. It is also recommended that meat is tested before consumption. For more information, consult the CDC or USDA.

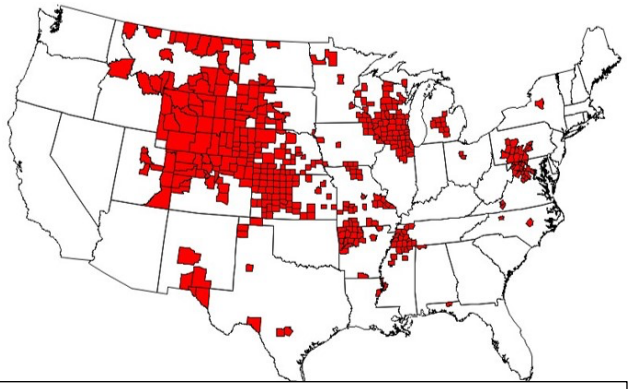

Figure 1: Chronic Wasting Disease Among Free-Ranging Cervids by County From (Centers for Disease Control and Prevention, 2023)

Farmers should be vigilant in inspecting their herds/flocks to ensure that none of their animals show signs of disease. Farmers should also avoid the use of feeds containing ruminant tissues and protein as this can spread prion disease very easily. These feeds are banned for these exact reasons. It is sometimes necessary to cull certain individuals or groups of individuals for the good of the herd/flock in order to stop the spread of disease. More information can be found by consulting the CDC, FDA, or USDA.

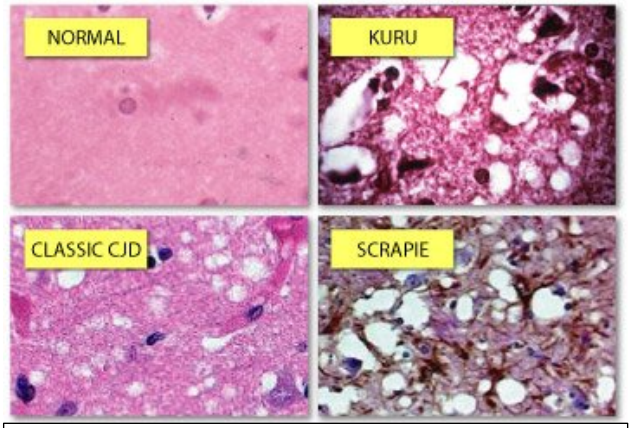

Figure 2: Microscope images of the brains of humans and a sheep affected by three prion diseases. From Genetic Science Learning Center. (2016, March 1) Prions. Retrieved March 09, 2024, from https://learn.genetics.utah.edu/content/basics/prions

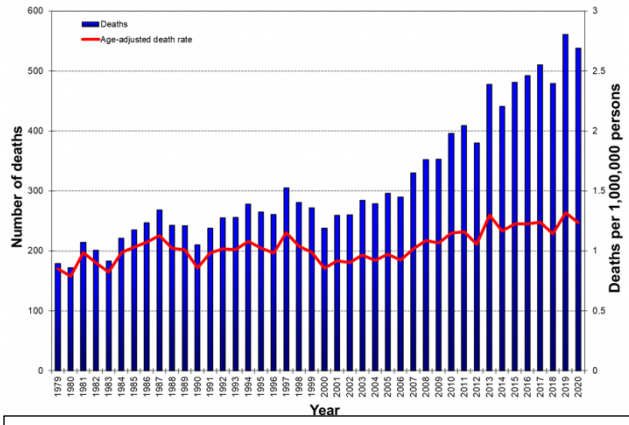

Figure 3: Creutzfeldt-Jakob disease deaths and age-adjusted death rate, United States, 1979–2020 From (Centers for Disease Control and Prevention, 2022)*

Disease Profiles

Creutzfeldt-Jakob Disease (CJD) is a human prion disease. It causes several neurological symptoms, including, but not limited to, severe mental deterioration and dementia, involuntary muscle jerks (myoclonus) or muscle movement, cognitive impairment, loss of coordination, vision changes, and insomnia. As the disease progresses, patients may experience limb weakness, blindness, paralysis, and the loss of the ability to speak (aphasia). Some may eventually fall into a coma. CJD often presents relatively late in life, around age 60. After symptoms present, the disease progresses quickly, with many patients dying within a year. There are several ways one can acquire CJD; most cases, ~85%, are sporadic, meaning one develops the mutation randomly. Another 10% to 15% of cases are hereditary, so the gene that codes for these malformed proteins is passed on through a family line.

The last and rarest method is iatrogenic transmission, meaning that one acquires the disease by coming into contact with infected brain or nervous system tissue, typically due to surgical procedures such as dura mater or corneal transplants or improperly sterilized surgical equipment. As with all prion diseases, at the moment, there are no treatments or cures for CJD, and it is universally fatal (National Institute of Neurological Disorders and Stroke, 2023).

Fatal Familial Insomnia (FFI) is, as the name suggests, an exceedingly rare genetic form of insomnia that is universally fatal. FFI is extremely rare with the mutation that causes it only being present in 50 families worldwide. Its titular symptom is progressive insomnia with sudden onset and quick progression. FFI also causes several other kinds of symptoms, such as autonomic dysfunction, meaning the autonomic nervous system, the system that controls involuntary functions such as blood pressure, heart rate, breathing, etc., is not functioning correctly, leading to high heart rate, high blood pressure, and high fevers to name a few. This disease can also lead to ataxia, loss of coordination, delirium, weight loss, depression, and double vision. FFI is commonly divided into four stages. Stage 1 starts with the presentation of progressive insomnia that worsens over the course of a few months. There will also be psychiatric symptoms such as paranoia and panic attacks. Stage 2 is characterized by the worsening of the insomnia and psychiatric symptoms and the onset of autonomic dysfunction over a 5-month period. Stage 3 is an approximately three-month period of total insomnia. The final stage, Stage 4, lasting for 6 or more months, is when patients experience acute loss of cognitive function and dementia. Patients will also lose the ability to move or speak voluntarily. The disease ultimately ends in coma and then death (Khan Z, Bollu PC. Fatal Familial Insomnia. [Updated 2023 Feb 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482208/).

Bovine Spongiform Encephalitis (BSE), also known as Mad Cow Disease, is a prion disease that affects cattle. It is an extremely rare disease with there having been only 6 cases identified in the US. In the late 80s, there was a massive outbreak of BSE in the UK, as mentioned above, but that number has dropped drastically in recent years. Because of this disease's threat to human life and our food supply, governments have put in place stringent bans on the importation of

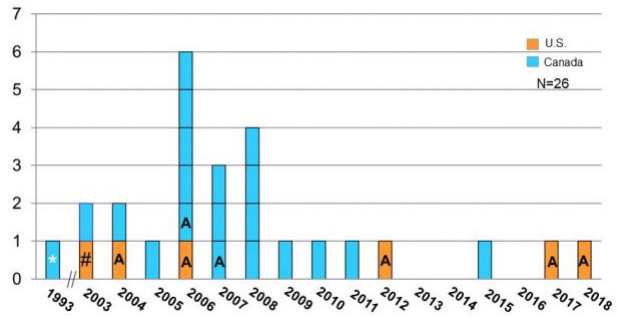

Figure 4 BSE Cases in North America, by Year and Country of Death, 1993 – August 2018 From (Centers for Disease Control and Prevention, 2021)

ruminants and ruminant products from places where BSE has been found and the use of ruminant tissue in feed, as well as many proteins and other possibly infectious agents from the supply of animal feeds, pet food, and fertilizer. BSE causes cattle to experience changes in their temperament, loss of coordination, decreased milk production, and difficulty standing, among other symptoms (Animal and Plant Health Inspection Service, U.S. DEPARTMENT OF AGRICULTURE , 2023). What makes this disease more than just a risk to the food supply is that it can be transmitted to humans as Variant Creutzfeldt-Jakob Disease (vCJD). While they do have similar names, vCJD is quite different from CJD. Firstly, vCJD affects much younger people, with the median age of death being 28 as opposed to 68 with classic CJD. Another significant difference is that patients with vCJD show major psychiatric symptoms at symptom onset, with neurological signs showing up later. vCJD also lasts much longer, with approximately 13 to 14 months between the onset of symptoms and death, compared to the 4 to 5 months seen with classic CJD (Centers for Disease Control and Prevention, 2021). vCJD also seems to be more infectious than classic CJD, with it being able to be transmitted via blood transfusion (Ritchie, D. L., Peden, A. H., & Barria, M. A. (2021). Variant CJD: Reflections a Quarter of a Century on. *Pathogens (Basel, Switzerland)*, *10*(11), 1413. https://doi.org/10.3390/pathogens10111413).

Chronic Wasting Disease (CWD) is a prion disease found in deer, elk, and moose. It is named as such because of the drastic weight loss experienced by these animals, which causes them to look like they are wasting away. CWD also causes loss of coordination, drooling, excessive thirst or urination, and lack of fear of people, among other neurological symptoms. CWD, unlike most other prion diseases, can spread through many different pathways. It can be transmitted through contact with infected bodily fluids and waste products like blood, urine, feces, or saliva. It can also be contracted through environmental means via contaminated water, soil, or food. While

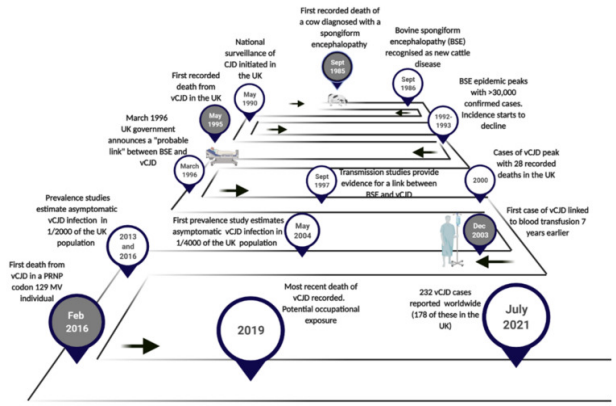

Figure 1 Timeline of the last 35 years highlighting significant dates in the origin, emergence and progression of vCJD from (Ritchie, D. L., Peden, A. H., & Barria, M. A. (2021). Variant CJD: Reflections a Quarter of a Century on. Pathogens (Basel, Switzerland), 10(11), 1413. https://doi.org/10.3390/pathogens10111413)

there is currently no conclusive evidence showing that CWD prions can infect humans, studies are ongoing to determine if those at higher risk of coming into contact with infected deer or elk meat show a higher prevalence of prion diseases (Centers for Disease Control and Prevention, 2021).

Scrapie is a prion disease found in sheep and goats. It is one of the oldest reported prion diseases we know of. It was first reported over 250 years ago. This disease causes several physical and neurological symptoms including tremors loss of wool, skin inflammation, ataxia, and altered mental status, to name a few. As with most prion diseases scrapie is most of diagnosed late in life, between 2 and 5 years old, and symptoms often don't show up until the disease has progressed (Greenwood P. (2002). Federal disease control--scrapie. The Canadian veterinary journal = La revue veterinaire canadienne, 43(8), 625–629.).

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