Prions: brain wasting killer proteins

By Christopher Massey

Prion research in the last century has been a puzzling challenge for infectious disease researchers. It has complicated how we define an agent of disease.

The recent endemics of prion-based diseases such as Bovine Spongiform Encephalopathy (BSE) and Transmissible Spongiform Encephalopathy (TSE) have caused much anxiety for regulatory agencies that govern agriculture and food services. The idea of a prion, an amalgam of “Proteinaceous Infectious Particle,” is a frightening concept.

Prions are mis-folded proteins found in biological systems. These mis-folded proteins then induce the mis-folding of other prion proteins. Infectious prions are highly stable in their mis-folded form and are thusly resistant to many denaturing agents and heat treatments.

The primary mode of infection is through ingestion of prion-contaminated matter. Some are infected through a genetic mutation of the prion protein (PrPc normal, and PrPsc mis-folded). Normally PrPc is water soluble and harmless. When mis-folded, PrPsc is water-insoluble and can aggregate. Prions tend to build up as amyloid plaques in brain tissue as more and more protein is mis-folded, causing damage and the characteristic sponge-like texture of infected tissue.

This causes the infected individual to lose motor function and experience convulsions and dementia.

The incubation period for a prion disease can be as long

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as 5 to 50 years, and there are no known treatments.

The first records of prion infection go back to the 1700s in Great Britain. This “Scrapie” disease caused sheep to experience great itchiness. The sheep would then “scrape” against trees and fences to try to relieve the itching, thus giving the disease its name. Eventually, the sheep would lose the ability to walk and would experience seizures before dying.

Little was learned about the disease until 1936 when J. Cullie and P. Chelle discovered that Scrapie is transmissible through intracocular injection of cerebral spinal fluid from infected animals. Further studies showed that whatever the etiological agent was, unlike bacteria, it was resistant to heat and formaldehyde treatments.

In the 1920s, scientists by the name of Hans Creutzfeldt and Alfons Jakob independently first described a prion disease in humans (Creutzfeldt - Jakob disease, CJD). CJD was characterized as a neurodegenerative disease in which the patient has brain tissue which develops telltale “holes” and a “sponge-like texture.” Of course, they had no idea what the causative agent was, but this was the first recorded description of prion infection in humans.

Perhaps the most classic epidemiological studies of prion-based disease in humans were done investigating the Kuru disease of a native Papua, New Guinea tribe called the Fore during the 1950s. “Kuru” roughly translates to “shivering from fear or cold” (in the native language which describes the early symptoms of the disease). The southern Fore people were very isolated from the rest of the world until the 1930s and it was believed that they practiced a type of ritualistic cannibalism on deceased family members. This practice was linked to the spread of Kuru by David Gadusek who studied the epidemic.

A puzzling finding was that Kuru was 8-9 times more prevalent in women and children than in men. This was later attributed to the fact that when a tribe member dies, the Fore men were allowed the choice parts of the body (meat) while the woman, children and elderly were left the scraps, including the brain, which contained the infectious prions.

However, there is doubt amongst some anthropologists and biologists that cannibalism was ever practiced by the Fore people.

Alternative hypotheses posit that the infectious prions were transmitted through open scratches and wounds of the women and children who prepared the deceased victims of Kuru for burial. In either case, the introduction of modern standards for health and sanitation have all but eliminated Kuru in the region (with the exception of a last known case in 2005; it is believed that Kuru can have an incubation period that lasts in excess of 50 years).

Figure 1: Hans Creutzfeldt (left) and Alfons Jakob (right) who independently first described CJD as a distinct neurological disorder.

Figure 2: It is estimated that 2,500 members of the cannibalistic Fore tribe of New Guinea died of Kuru during that last 100 years.
Gadusek later won a Nobel Prize for his research showing that Kuru could be spread across animal species. He took pureed brain matter from deceased Fore tribe members and poured them into the cranial cavity of chimpanzees. The chimpanzees developed symptoms similar to that of humans after an 18-30 month incubation period. With environmental toxins and bacterial infections ruled out as causative agents in earlier studies, Gadusek hypothesized that Kuru was the result of a “slow virus.”

It was not until 1967 that viruses were ruled out as the cause of prion disease. It was recently known that viruses, like bacteria and eukaryotic cells, used nucleic acids to transfer information and replicate. Therefore, it is possible to inactivate infectious agents containing nucleic acids using certain wavelengths of radiation. Tikvah Alper discovered that the causative agent of Scrapie was not inactivated after long term exposure to UV radiation. These studies showed that the infectious agent was not indeed a “slow virus” and seemed to contradict the newly-formed central dogma of molecular biology which dictates that the replication of biological agents must be mediated through the genetic coding of nucleic acids.

He was later awarded a Nobel prize for his research which greatly supported the revolutionary hypothesis that an infectious disease can replicate independently from nucleic acids. In 1992, the protein-only prion hypothesis was given further credibility when mice that had been genetically altered to knock out the PrP protein lost their ability to be infected with the Scrapie infectious agent. In 2005, scientists at the University of Texas were able to artificially synthesize PrPsc protein in-vitro and infect hamsters that developed spongeform encephalitis.

Raised awareness of TSE’s (Transmissible Spongiform Encephalitis) and the prions responsible for them have created many public health challenges. The stability of these mis-folded PrP proteins makes it extremely difficult to neutralize them through the use of mild disinfectants or heat treatments. This means that prions can possibly be transmitted from patient to patient on surgical equipment unless careful treatment is applied to clean the instruments. There are many methods recommended for sterilizing instruments used to operate on suspected CJD patients, most involve a strong chemical or enzymatic digestion followed by a long duration and/or high temperature sterilization.

Furthermore, public knowledge of TSE’s has been advanced by the media’s
coverage of so-called “Mad Cow” outbreaks. The practice of rendering dead and diseased animals into animal feeds, much like the cannibalism hypothesis used to describe the Kuru epidemic, has every now and then spread these prions into healthy farm animals. Since prions can have a long incubation period, many of these animals could become food products before they develop sickness. Accidental contact of meat with neural tissue would cause prions to contaminate the meat, leading to outbreaks of BSE. Over 160 people in the U.K., Canada, Ireland, and the U.S. have shown symptoms of vCJD (a variant of CJD caused by eating meat infected with prions). Since it can take decades for vCJD to incubate in humans, many governments have imposed regulations on the care and use of cattle for food. However, it will take years to see if they’re successful in preventing further infections. Recent developments in genetically modified organisms have led to breeds of sheep and cattle that are incapable of contracting prion disease. Through the modification of their PrP protein, infectious prions are incapable of causing the conformational change necessary to propagate the disease. This may prove a viable alternative to extensive sampling and testing of cattle for TSE’s on a routine basis and would prevent penetration of prions into the food supply.

Recent research suggests that Alzheimer’s disease may have many similarities with CJD prion disease. With Alzheimer’s, the patient’s brain shrinks and degenerates due to the loss of neuron cells. At the University of Texas, researchers noticed that mice who were infected with Alzheimer patient’s brain tissue would develop protein “plaques” that are associated with Alzheimer’s disease. Even though this research is still preliminary, it raises the question, could Alzheimer’s disease be associated with prions?

~ Christopher Massey

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