Prion Disease: Cruetzfeldt-Jacob Disease

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Prions are proteins that are found in the nerve cells of all mammals. Numerous prions are in each nerve cell, but no one knows for sure what the prion protein does. The brain of a human or animal infected with a prion "disease" has many abnormally-shaped prions. One hypothesis states that when a person or animal ingests an abnormally-shaped prion from contaminated food the abnormally-shaped prion gets absorbed into the bloodstream and crosses into the nervous system. The abnormal prion touches a normal prion and changes the normal prion's shape into an abnormal one, thereby destroying the normal prion's original function. Both abnormal prions then contact and change the shapes of other normal prions in the nerve cell. The nerve cell tries to get rid of the abnormal prions by clumping them together in small sacs that merge with its lysosome. However, the nerve cells cannot digest the abnormal prions, and they accumulate in the lysosomes. The lysosomes grow and engorge the nerve cell, which eventually lysis. Next, the abnormal prions are released to infect other cells. Large, sponge-like holes are left where the cells lysed. Numerous nerve cell deaths lead to loss of brain function, and the person eventually dies. (howstuffworks.com/mad-cow-disease4.htm)

Prions first came to public attention in the mid 1980s in the form of the bovine spongiform encephalopathy (BSE, or "mad cow disease") epidemic in the United Kingdom. Mad cow disease is a prion disease in cattle. There is a theory that mad cow disease came from feed contaminated with scrapie, the long established sheep prion disease. In the 1980's, producers of cattle feed (which

often included ground meat and bone meal byproducts from sheep) changed the way they processed feed. The change somehow allowed the scrapie disease agent to survive the cattle feed production process, leading to the silent spread of the mad cow disease epidemic.

The best known of the human prion diseases is Creutzfeldt-Jakob disease (CJD). This is a rapidly progressive, fatal, neurodegenerative disorder. The onset of symptoms of this disease usually occurs at about age 60. It is believed to be caused by an abnormal isoform of a cellular glycoprotein, the prion protein. CJD is classified as a transmissible spongiform encephalopathy (TSE). Spongiform refers to the characteristic appearance of infected brains, which become filled with holes until they resemble sponges under a microscope. Other human TSEs include kuru, fatal familial insomnia (FFI), and Gerstmann-Straussler-Scheinker disease (GSS). Kuru was identified in people of an isolated tribe in Papua New Guinea and has now almost disappeared. Family familial insomnia and Gerstmann-Straussler-Scheinker are extremely rare hereditary diseases, found in just a few families around the world.

There are three major categories of CJD:

1. One type is the *sporadic CJD*, this disease appears even though the person has no known risk factors for the disease. This is by far the most common type of CJD and accounts for at least 85 percent of cases.

2. Another type is *hereditary CJD*, in this case the person has a family history of the disease and/or tests positive for a genetic mutation associated with CJD. These inherited forms of CJD include the Gerstmann-Straussler-Scheinker syndrome and fatal familial insomnia that were mentioned earlier. About 5 to 10 percent of cases of CJD in the United States are hereditary.
3. Last there is *acquired CJD*, these diseases can occur from contamination through certain medical procedures of the brain or nervous tissue, and they are called *iatrogenic CJD*. Iatrogenic transmission of the CJD agent has been reported in over 250 patients worldwide. These cases have been linked to the use of contaminated human growth hormone, dura mater and corneal grafts, or neurosurgical equipment. There were six cases linked to the use of contaminated equipment. Of these, four were associated with neurosurgical instruments, and two with stereotactic EEG depth electrodes. All of these equipment-related cases occurred before the routine implementation of sterilization procedures currently used in health care facilities. No such cases have been reported since 1976, and no iatrogenic CJD cases associated with exposure to the CJD agent from surfaces such as floors, walls, or countertops have been identified.

- Another acquired CJD is called the *panencephalopathic* form. This occurs primarily in Japan and has a relatively long course, with symptoms often progressing for several years.
- Over the last few years, another type of Acquired CJD called *variant (vCJD)* has been identified in young people, which I will discuss shortly.

In the 1990's, an unusually large number of people in Great Britain developed what appeared to be CJD, and scientist began studying the evidence regarding a relationship between mad cow disease and CJD. The outbreak was alarming not only because so many people died of a presumably rare disease, but also because of their relatively young ages — the youngest victim was only 19. Even more disturbing was the way they appeared to have contracted the disease. All had eaten meat from cattle suspected of having mad cow disease. Scientists eventually concluded that the new ailment — named variant CJD (vCJD) — was a form of Creutzfeldt-Jakob disease resulting from exposure to the mad cow disease. This conclusion was based on the facts that the vCJD victims had lived in areas where outbreaks of mad cow disease had occurred years earlier. No victims were found in areas without mad cow disease outbreaks. Also, the time between the mad cow disease outbreaks and the deaths of the victims equaled the time it takes for the CJD to develop. Although there is very strong evidence that the agent responsible for the human disease is the same

agent responsible for the mad cow disease outbreaks in cattle, the specific foods that might be associated with the transmission of this agent from cattle to humans are unknown.

The "classic" CJD doesn't appear to be connected to mad cow disease, however, it's similar to the vCJD in many ways.

- They are both thought to occur when misshapen prion proteins attack brain cells.
- Both appear to have long incubation periods, even as long as 10 to 15 years, before signs and symptoms appear.
- And both cause profound mental and physical deterioration, resulting in death.

Although there are slight variations in the way the signs and symptoms manifest themselves between the "classic" CJD and the vCJD, the two forms of the disease are far more alike than they are different. Everyone affected with these diseases must eventually contend with grave mental and physical problems. A few of the differences are:

- It often takes years or even decades after infection before someone with classic CJD develops signs and symptoms of the disease. Although it's too early to know for certain, scientists suspect that the same is true of vCJD. That's why some experts predict that an epidemic of vCJD is still to come.

- Both classic and variant CJD begin with personality changes such as anxiety, depression, memory loss and impaired thinking. As the diseases progress, mental symptoms become more severe. Ultimately, people with both forms of CJD develop dementia — a mental disorder that robs them of the ability to speak, think, reason, remember and move. With classic CJD, the progression from initial personality changes to complete dementia occurs quickly — usually within six months or less of the onset of symptoms. In the variant CJD, psychiatric symptoms are most prominent early on in the disease, but dementia develops later in the course of the disease.
- Both types of CJD affect balance and coordination, leading to stumbling, falls and difficulty walking, but these problems occur sooner in vCJD than they do in classic CJD.
- Most people lapse into coma before succumbing to these invariably fatal diseases. People with classic CJD generally live an average of only seven months after signs and symptoms appear, although some people may live as long as one or two years after the onset of symptoms. Death is usually not a result of the disease itself, but rather of complications such as heart failure, respiratory failure and pneumonia. People with vCJD tend to live slightly longer — about 12 to 14 months after signs and symptoms appear.
- Other signs and symptoms of classic CJD include blurred vision and eventual blindness, involuntary muscle contractions, difficulty speaking,

which may lead to mumbling or speech that's difficult to understand, and difficulty swallowing.

- Additional signs and symptoms of vCJD include a sense that the skin feels sticky, sensations of cold or pain, muscle paralysis, and tremors.

The main indicators that lead to a diagnosis of CJD are: rapid dementia, unsteady gait, and sudden jerky movements. There is currently no single diagnostic test for CJD. The first concern is to rule out treatable forms of dementia such as encephalitis or chronic meningitis. In most CJD patients, the presence of 14-3-3 protein in the cerebrospinal fluid or a typical electroencephalogram (EEG) pattern has been reported. However, the only way to confirm a diagnosis requires a brain biopsy or autopsy. Both brain biopsy and autopsy pose a small, but definite, risk that the surgeon or others who handle the brain tissue may become accidentally infected by self-inoculation. Because a correct diagnosis of CJD does not help the patient, a brain biopsy is discouraged unless it is needed to rule out a treatable disorder. Worldwide, doctors typically only diagnose one case per million people each year, most commonly in older adults.

There is no treatment that can cure either type of CJD, and there is nothing that will slow the progression of the disease. Current treatment is aimed at alleviating symptoms and making the patient as comfortable as possible. Opiate drugs can help relive pain, and the drugs clonazepam and sodium valproate may help relieve involuntary muscle jerks. During later stages of the disease,

changing the person's position frequently can keep him or her comfortable and helps prevent bedsores. A catheter can be used to drain urine if the patient cannot control bladder function, and intravenous fluids and artificial feeding also may be used. (Centers for Disease Control and Prevention (CDCP))

From 1995 through June 2002, a total of 124 human cases of vCJD were reported in the United Kingdom, 6 cases in France, and 1 case each in Ireland, Italy, and the United States. The case-patients from Ireland and the United States had each lived in the United Kingdom for more than 5 years during the UK "mad cow disease" epidemic. The best estimate of the annual increase in the number of vCJD cases in the United Kingdom since the outbreak began is 18% per year, which is equivalent to a doubling every 4.2 years.

A growing number of cases of vCJD are being linked to contaminated beef in Great Britain and in other countries, including Spain, Portugal, France and Germany. Scientist have identified the presence of the mad cow disease agent in the brain, spinal cord, retina, dorsal root ganglia, distal ileum, and the bone marrow of cattle experimentally infected with this agent by the oral route. In addition to cattle, sheep are susceptible to experimental infection with the mad cow disease agent by the oral route. There is a theoretical risk that in countries where flocks of sheep and goats may have been exposed to this agent through contaminated feed these animals might have developed infections caused by the mad cow disease agent and that these infections are being maintained in the flocks, even in the absence of continued exposure to contaminated feed (for

example, through maternal transmission). Regardless, as of July 2002, cattle remain the only known food animal species with disease caused by the mad cow disease agent.

In the United Kingdom, the current risk of acquiring vCJD from eating beef and beef products appears to be extremely small, perhaps about one case per 10 billion servings. In other countries of the world, this current risk, if it exists at all, would not likely be any higher than that in the United Kingdom. This is particularly true if mad cow disease-related public health control measures are being well implemented. Such as enhanced mad cow disease surveillance, the culling of sick animals, and bans of specified risk materials. The most stringent of these control measures that have been applied in the United Kingdom is an "Over Thirty Months Scheme" that excludes all animals older than 30 months from the human food and animal feed chains. This policy appears to be highly effective.

One way to reduce the already very low risk of CJD transmission from one person to another is that people should never donate blood, tissues, or organs if they have suspected or confirmed CJD, or if they are at increased risk because of a family history of the disease, a dura mater graft, or other factor. Remember that normal sterilization procedures such as cooking, washing, and boiling do not destroy prions. Caregivers, health care workers, and undertakers should take extra precautions when they are working with a person with CJD. Also, when traveling to Europe or other areas with cases of mad cow disease one

may wish to consider both avoiding beef and beef products altogether. Selecting solid pieces of muscle meat rather than beef products, such as burgers and sausages, is also a good idea. These choices might have a reduced opportunity for contamination with tissues that may harbor the mad cow disease agent. There is no evidence that CJD is contagious through casual contact with a CJD patient.

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