TRANSMISSIBLE SPONGIFORM ENCEPHALITIS(TSE) OR PRION DISEASES; A NEED TO BE AWARE!

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ABSTRACT

Prion diseases are an interesting but puzzling group of diseases affecting both animals and human, that transmits their infectivity by a misfolded protein to the host. It then recruits other normal proteins to form a β pleated amyloid sheet which affects the neurons in an as yet undefined manner causing the various symptoms. The principal site of pathology is in the brain. Many diseases have been found to be caused by prions over the last century or so and new ones are being discovered. The infectious agent is unique as it does not have any DNA or RNA and it has a long incubation period. However they evoke no immune response leading to anoninflammatory pathologic process limited to the CNS. This article provides a short review of the several diseases caused by prions, and the agent causing infection. The precautions that need to be taken by healthcare workers are also discussed.

Key words: prion diseases; transmissible spongiform encephalopathy (TSE); prion protein; kuru; CJD, scrapie.

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Introduction

Transmissible spongiform encephalitis (TSE) or prion diseases are an enigmatic group of disease that has gathered tremendous interest since the last century. The prion diseases are a closely related group of rare incurable neuro degenerative diseases affecting both humans and animals. However, they elicit no immune response, resulting in a non inflammatory pathologic process confined to the central nervous system, usually have an incubation period stretching many years, and are invariably fatal within 1 year after diagnosis[1-2].

The classical triad of spongiform vacuolation, astrocytic proliferation and neuronal loss, and accompanied by the deposition of amyloid plaques usually, was proposed by Beck and Daniel in 1987 and is a common finding in both animal and human prion diseases[3]. The agent that produced the infection was at first thought to be a slow virus; but a virus was not isolated in this disease which led to further investigations that revealed the agent to be an indigenous protein particle which was later named as prions by Prusiner[4]. It can be infectious, inherited or develop sporadically. Several types of diseases are now out in the scientific domain starting with the discovery of scrapie that was initially mentioned in the scientific literature about 1732.

Animal prion diseases

I) Scrapie

ii) Bovine spongiform encephalopathy

iii) Transmissible mink encephalopathy

iv) Chronic wasting disease

v) Feline spongiform encephalopathy

Human prion diseases

I) Kuru

ii) Creutzfeld -Jakob disease

iii) Gerstmann-Straussler-Scheinker disease

iv) Fatal familial insomnia

v) Variably protease-sensitive prionopathy (VPSPr)

Scrapie

Scrapie has been demonstrated since 18th century, initially in the reports by shepherds. Fearing economic ruin they would keep it a secret from the veterinarians resulting it being unknown to the general public[5].

The afflicted sheep showed clinical signs lasting from early as two weeks to six months or more showing peculiar social behaviour and hyper excitability to human exposure. The condition of sheep gradually deteriorates, and there might be a change in colour of the fleece which may be the first change noticed by the shepherd. The sheep shows a tendency to rub against fences apparently due to pruritis and usually bites the affected area leading to denudation. Ataxia is usually common. In the final stages of the disease, although the appetite may appear normal, the animals lose the ability to feed themselves and the condition degenerates. The reproductive ability of the sheep is not affected even though affected by scrapie, but later muscle atrophy can interfere with the ability to move. Lambs can, therefore, be born successfully to mothers in the clinical phase of the disease and rams remain fertile and active even when affected by ataxic signs[6].

Scrapie was earlier thought to be a hereditary, infectious, or sexually transmissible disease. After the demonstration of scrapie to be a transmissible disease in 1936, it took many more years until the infectious agent - the prion - could be identified.[7-8]

Bovine spongiform encephalopathy

BSE is a prion disease affecting cattle first observed in the United Kingdom in 1986, starting as an epidemic that has since come down since 1993. It was surmised that consumption of cattle feed contaminated with meat and bone meal (MBM) initiated the disease. Why the United Kingdom was affected most was suggested to be because of several factors, including a high ratio of sheep to cattle; a relatively high rate of endemic scrapie; the heavy feeding of MBM to dairy cattle; and changes in the meat processing operation used to prepare MBM[9].

Production of clinically and pathologically similar

CJD in macaques by intracerebral injection of brain material from affected cows[10] and observing the biochemical similarities between human and BSE cases[11] suggest that BSE is transmissible to man. Infection from cattle to people was theorised as to the development of a variant of Creutzfeldt-Jakob disease (vCJD) [12].

Animals like deer, elk and cat apart from sheep and cow are also susceptible to prion diseases; symptoms usually are similar to that seen in cattle and sheep.

Kuru

A strange disease among the Fore tribe in Papua New Guinea was investigated by Gajdusek and Zigas in 1957, where a section of the tribe had tremors and loss of coordination. Ritual cannibalism was found to be the cause due to the thorough research by these scientists and others. The first case, as reported by their oral history dated back to 1920s. The disease primarily affected women and children. This was later found to be due to the fact that women and children used to consume dead relatives, the act which was thought to free up the spirits of the dead[13].

Kuru is a cerebellar syndrome with a characteristic and relentless progression through defined clinical stages, and is invariably fatal. The illness might last for one year or less. The patient becomes aware of the disease after noticing altered gait preceded by headaches and limb pains. Truncal instability, ataxia and tremor of the head and extremities aggravated by cold soon follow. Slurred speech, dysphagia, convergent strabismus, involuntary movements, emotional lability and mild dementia appear in most cases. Morphologic changes are seen in only the central nervous system[14].

William Hadlow noticed the similarity of the pathology in kuru and scrapie, which led scientists to the discovery of more similar diseases[15]. The cause of the diseases however still eluded scientists. Genetic, endocrine, hormonal, and toxic causes were explored and an infectious cause also proposed due to spread from man to man by way of cannibalism.

Creutzfeld-Jakob disease

It was first described in the early 1920s by two German neurologists[16-17]. The many different types included sporadic, familial and iatrogenic forms of the disease. Creutzfeldt-Jakob disease (CJD) is a rare, neuro degenerative, invariably fatal brain disorder. It affects about one person in every one million people per year worldwide; in India the cases are usually underreported[18]. CJD usually appears in middle age and runs a rapid course. Typically, symptoms start to be seen about age 60, and about 90 percent of individuals die within 1 year of contracting the disease. In the early stages of disease, people may have failing memory, behavioural changes, lack of coordination and visual disturbances. As the illness progresses, mental faculty deteriorates, involuntary movements, blindness, weakness of extremities and coma may occur.

There are three major types of CJD:

- In sporadic CJD, the disease appears even though the person has no known risk factors for the disease. It is thought that the normal form of the prion protein is changed into the infectious type of the protein and consequently changes all the normal proteins in a cascading pattern. This is by far the most common type of CJD and accounts for at least 85 percent of cases.

- In hereditary CJD, the person has a family history of the disease and/or tests positive for a genetic mutation associated with CJD. About 5 to 10 percent of cases of CJD in the United States are hereditary.

- In acquired CJD, the disease is transmitted by exposure to brain or nervous system tissue, usually through certain medical procedures. There is no evidence that CJD is contagious through casual contact with a CJD patient. Since CJD was first described in 1920, fewer than 1 percent of cases have been acquired CJD[19].

Variant CJD (vCJD) is another type, in which the disease is thought to be transmitted by the consumption of cattle afflicted by the agent of Bovine spongiform

encephalopathy also known as classical BSE, first reported in United Kingdom in 1986. As opposed to the other CJDs, the affected patient is often younger.

Gerstmann-Straussler-Scheinker disease

The main feature of GSS is a progressive degeneration of the cerebellum, as well as different degrees of dementia. The usual signs and symptoms develop by age 35-50 and can include weakness in the legs, poor reflexes, abnormal sensations, progressive ataxia, cognitive dysfunction, slurred speech and spasticity. After diagnosis the patients die after approximately 60 month (2-10 years), on an average[20-21].

Fatal familial insomnia

This is an inherited prion disease affecting mainly the thalamus. It is thought that loss of neurons in the thalamus, as well as other mechanisms not understood, cause the symptoms of FFI. The first symptoms of FFI usually start in middle age and may include progressive insomnia, weight loss, lack of appetite, and rapidly progressive dementia. Almost all cases of FFI are caused by certain mutations in the PRNP gene and are inherited in an autosomal dominant manner.[22] There are a very small number of reported sporadic cases of FFI.[23] There is currently no effective treatment for FFI, but research for a treatment and cure is ongoing.[24] Death usually occurs within 12-18 months of the first symptoms.[25]

Variable Protease-sensitive prionopathy

VPSPr resembles Gerstmann-Sträussler-Scheinker disease (GSS) in terms of the characteristics of the abnormal prion protein (PrPSc). However, unlike in GSS, no mutations in the prion protein gene have been identified.

Clinical manifestations differ from those of Creutzfeldt-Jakob disease, and the PrPSc is less resistant to digestion by proteases; some variants are more sensitive to proteases than others, hence the name: variably protease-sensitive.

Patients present with psychiatric symptoms, speech deficiencies, and cognitive impairment. Ataxia and Parkinsonism can develop. Average age at onset is 70 yrs., and duration of survival is 24 months. About 40% of patients have a family history of dementia.[26]

The Agent

Researchers believed for quite a long time that a "slow virus" or similar organism causes all the above mentioned diseases. However, they were never able to isolate a virus or other organism in people with the disease. The agent had some peculiarities that were unusual for known organisms such as viruses and bacteria. It was difficult to eliminate the agent and surprisingly it did not appear to contain any genetic information in the form of nucleic acids (DNA or RNA), and had an unusually long incubation period before symptoms appeared. In some cases, the incubation period may be as long as 50 years. The molecular nature of the infectious agent lay largely untested for some time until Stanley Prusiner and co-workers achieved the biochemical enrichment of infectious activity and showed its association with a specific protein. At the present time it is believed that the agent causing TSE is caused by a type of protein named asprion; short for proteinaceous infectious particle. Stanley Prusinerwas awarded the Nobel Prize in Physiology/Medicine in 1997 for prion research[27-28].

The prion proteins exist in a normal form as a harmless protein in the body's cells, and also as an infectious form, which causes disease. Both the harmless and infectious forms of the prion protein have the same sequence of amino acids but the infectious form of the protein takes on a different β pleated shape than the normal protein. The transmissible agent, or prion, seems to consist principally of an abnormal isoform of the prion protein (PrP); designated PrPSc. PrPSc is known to be derived from the cellular isoform, PrPC, by a post-translational mechanism. While PrPC is fully sensitive to proteolysis, PrPSc, which accumulates in the brain during disease, is partially protease resistant. Sporadic CJD may develop because some of a person's normal prions spontaneously change into the infectious form of the protein and then alter the prions in other cells in a chain reaction[29].

Once they appear, abnormal prion proteins can aggregate, or clump together as amyloid plaques.

Investigators think these protein aggregates may lead to the neuron loss and other brain damage seen in CJD. However, the exact mechanism is still debatable.

Medical precautions

The principal target of prion pathology is the brain, yet most TSEs also display prion replication at extra-cerebral locations, including secondary lymphoid organs and sites of chronic inflammation. It has been found that the brain (including dura mater), spinal cord, posterior eye and pituitary tissue have the highest rate of infectivity. Other tissues have a low to no risk of infectivity. The proper handling of such tissues by the health care personnel, cannot be overemphasized .

The following clinical practices are recommended when handling suspected cases of prion disease[30-32]:

1. Use disposable instruments whenever possible;
2. Destruction of all used instruments, protective clothing, tissues, and body fluids by incineration;
3. Surface protection with disposable, waterproof drapes;
4. Limitation of people and items in the operating room;
5. Use of barrier protective apparel (double gloves, etc.);
6. Use of manual saws to reduce aerosol formation;
7. Washing surfaces with 1 N NaOH and leaving as a wet film for 1 hour at room temperature.

For instruments and equipment which cannot be destroyed, the following are recommended:

1. Wipe thoroughly before contaminated surface dries;
2. Gravity displacement autoclaving at 132°C for 1 hour, 1 M sodium hydroxide for 1 hour;
3. Porous load autoclaving at 134–138°C for 18 minutes, sodium hypochlorite (20,000 mg/L chlorine for 1 hour)

Dental precautions

As dental instruments have the potential to come into contact with a range of oral tissues that may carry prion infectivity, particularly the peripheral nerves and lymphoid tissue, it would be prudent on a precautionary basis to use the most effective instrument cleaning and sterilisation approaches to control this risk, especially as relatively high levels of infectivity may be present in tissues early in the disease incubation period, before clinical symptoms are observed[33].

But many case-control studies have still not found any evidence that dental procedures increase the risk of iatrogenic transmission of TSEs among humans. In these studies, CJD transmission was not associated with dental procedures (e.g. Root canals or extractions), and there was no convincing evidence of any prion detection in human blood, saliva, or oral tissues, nor have there been reports of any dental health personnel becoming occupationally infected with CJD. In 2000, prions were not found in the dental pulps of eight patients who were confirmed CJD patients, by using electrophoresis and a Western blot technique[34].

Prions exhibit unusual resistance to conventional chemical and physical decontamination procedures. Though scientific data is lacking regarding the risk of transmission of prion diseases, special precautions in addition to standard precautions in case of dental treatment might be indicated when treating known prion disease patients; the following list of precautions is recommended by CDC[35].

1. Use single-use disposable items and equipment whenever possible.
2. Items difficult to clean (e.g., endodontic files, broaches, and carbide and diamond burs) may be considered as single-use disposables and discard after one use.
3. Minimize drying of tissues and body fluids on a device; keep the instrument moist until cleaned and decontaminated.
4. Clean instruments thoroughly and steam-

autoclave at 134ºC for 18 minutes[36].

5. Do not use flash sterilization for processing instruments or devices.

Though the transmission of prion disease to the dentist is slim, nevertheless standard prevention protocols apply.

Conclusion

TSE as a group of diseases still remain a riddle among the investigators as to the nature and pathophysiology of the infections. Newer technologies and ideas have contributed to demystifying the disease to some extent. However prevention of the diseases is critical to stop the spread of the disease in the general population as the diseases have no known cure at present. Proper sterilisation techniques should be followed in hospitals and health care settings. Looking at the history thus far; the possibility of discovering newer prion diseases is a distinct possibility. The next prion disease must be still out there; waiting to be discovered and health care personnel should be aware and take necessary optimum steps to minimise its damage among the general population.

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