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FUNDAMENTALS OF CREUTZFELDT-JAKOB DISEASE AND ADVANCES IN RESEARCH OF TREATMENT FOR CJD

Neuroscience

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ABSTRACT

Clinical studies are underway at various research centers in different countries to investigate possible treatments as there is no proven cure for Creutzfeldt-Jakob Disease. At present, supportive treatment is being provided to keep the person as comfortable as possible and reducing symptoms with medicines. For example, psychological symptoms, such as anxiety and depression, can be treated with sedatives and antidepressants. Muscle jerks or tremors can be treated with Clonazepam and Sodium Valproate and any pain experienced can be relieved using powerful opiate-based painkillers. As there is still adilemma that how to cure this neurodegenerative disorder, there can be possible ways to develop the treatment. So,in this article I have tried to highlight possible areas of work.

KEYWORDS

CJD, amyloids, sedatives, prions, neurodegenerative.

INTRODUCTION :

Creutzfeldt-Jakob Disease (CJD - also called as subacute spongiform encephalopathy) is a neurodegenerative disorder. It causes due to misfolding of prion proteins. Prions are misfolded proteins which can transmit their misfolded shape onto normal variants of the same protein. They also characterize several fatal and transmissible neurodegenerative diseases in humans and animals. The reason behind misfolding of normal protein is unclear, but the abnormal three-dimensional structure is suspected of conferring infectious properties, collapsing nearby protein molecules into the same shape. The word prion derives from 'proteinaceous infectious particle'. The role of a protein as an infectious agent stands in contrast to all other known infectious agents such as viruses, bacterias, fungi and parasites, all of which contain nucleic acids (DNA, RNA or both).

Prions form abnormal aggregates of proteins (amyloids), which accumulate in infected tissue and cause tissue damage and cell death. These amyloids are also responsible for other neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Prion aggregates are stable, and this structural stability means that prions are resistant to denaturation by chemical and physical agents. This makes disposal and containment of these particles difficult.

Early Symptoms Of Cjd:

At the onset of Creutzfeldt-Jakob disease, patients experiences memory problems, behavioural changes, poor coordination, and visual disturbances.

Later Symptoms:

As time passes, the condition of the patients worsens. The later symptoms include dementia, involuntary movements, blindness, weakness, and coma.

Onset: Around 60.

Duration:

The duration of the disease varies greatly. But sporadic or non-inherited CJD can be fatal within months or even weeks. 70% die within a year of diagnosis. Most victims die six months after initial symptoms appear, often of pneumonia due to impaired coughing reflexes. About 15% of people with CJD survive for two or more years.

Prognosis: Universally fatal.

Frequency: 1 per million per year.

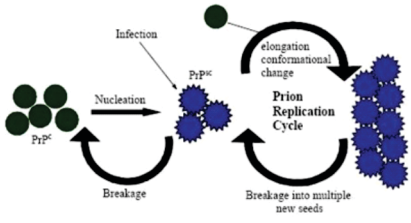
Prpc And Prpsc:

Cellular prion protein (PrPc) is a membrane associated protein occurs in a wide range of eukaryotic cells. The PrPc after a conformational change, gets converted into PrPSc ('Sc' for 'Scrapie') and is considered to be the probable cause of transmissible spongiform encephalopathies (TSEs). TSEs are fatal neurodegenerative diseases including Creutzfeldt-Jakob Disease (CJD) in humans, Scrapie in sheeps and goats, as well as Bovine Spongiform Encephalopathy (BSE) in cattle. It is cited that the irreversible conversion of psychological membrane associated cellular prion protein (PrPc) into its disease-related proteinase K (PK) resistant counterpart PrPSc, initiates an 'autocatalytic' reaction. In this reaction, the conformational transition occurs from the α-helix-rich cellular form into the mainly β-sheet containing counterpart. Cross β-sheets in a fibril (also called amyloids) are the stable structures and are unable to denaturate. Hence, they get accumulated in the Central Nervous System (CNS).

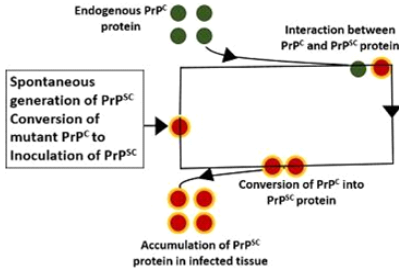
Prion Replication:

How do prions replicate is still an unanswered question. But, after some researches, the researchers came up with two models of prion replication.

First hypothesis explains the heterodimer model of prion propagation. This model assumed that a single PrPSc molecule binds to a single PrPc molecule and catalyzes its conversion into PrPSc. These two PrPSc molecules then come apart and can go on to convert more PrPc. However, a model of prion replication must explain both how prions propagate and why their spontaneous appearance is so rare. Manfred Eigen showed that the heterodimer model requires PrPSc to be an extraordinarily effective catalyst, increasing the rate of conversion reaction by a factor of around 10^15. The problem does not arise if PrPSc exists only in aggregated forms such as amyloid, where cooperativity may act as a barrier to the spontaneous conversion. What is more, despite considerable effort, infectious monomeric PrPSc has never been isolated.



An alternative hypothesis assumes that PrPSc exists only as fibrils, and that ends bind PrPC and convert it into PrPSc. If this happens, then the quantity of prions would increase linearly, forming ever longer fibrils. But, the exponential growth of both PrPSc and the quantity of infectious particles is observed during prion disease. This can be explained by taking into account fibril breakage. Mathematically, the exponential growth rate depends mainly on the square root of PrPC concentration. The incubation period is determined by exponential growth rate and in vivo data on prion diseases in transgenic mice match this prediction.



Types Of Cjd : Depending On The Causes Of Infection, There Are 4 Main Types Of Cjd.

1. **Sporadic Cjd:** This is most common type of CJD. The precise cause of sporadic CJD is not known, but it's been assumed that a normal brain protein misfolds and turns into a prion. Adults aged between 45 and 75 are more prone to this type and on average, the symptoms develop between the age of 60 and 65. As like its name, sporadic CJD is very rare (affecting 1 or 2 people in every million each year).
2. **Variant Cjd:** Variant CJD (vCJD) causes due to consumption of meat of cow that has Bovine Spongiform Encephalopathy ('BSE' or 'mad cow' disease), a prion disease similar to CJD. Its incubation period is still unclear. The incubation period can be very long (more than 10 years). So, those exposed to infected meat before the food controls were introduced can still develop variant CJD. The prion that causes variant CJD can also be transmitted by blood transfusion.
3. **Familial Or Inherited Cjd:** Familial CJD is a rare genetic condition. It causes due to mutation in the gene (the prion protein gene) a person inherits from their parents. It causes the formation of prions in their brain during adulthood, triggering the symptoms of CJD. The symptoms of familial CJD usually first develop in people when they're in their early 50s.
4. **Iatrogenic Cjd:** In this type of CJD, the infection spread accidentally from someone with CJD through medical or surgical treatment. Iatrogenic CJD can also occur if instruments used during brain surgery on a person with CJD aren't properly cleaned between each surgical procedure and are reused on another person. But increased awareness of these risks has made the iatrogenic CJD very rare.

DIAGNOSIS:

A diagnosis of Creutzfeldt-Jakob Disease (CJD) is based on medical history, symptoms, and a series of tests. A neurologist carry out the tests to rule out the conditions with similar symptoms, such as Alzheimer's disease, Parkinson's disease, or brain6 tumor. The diagnosis of CJD is confirmed by examining the brain tissue by carrying out a brain biopsy. Following tests are used to check the common signs of CJD :

1. An MRI Brain Scan : In this process, a detailed image of the brain is produced using a strong magnetic field and radio waves to detect the abnormalities particular to CJD.
2. An EEG (Electroencephalography) : It records brain activity and may pick up abnormal electrical patterns seen in sporadic CJD.
3. A Lumbar Puncture : A cerebrospinal fluid is drawn out from the lower part of spine. Later it is tested for a certain protein to detect CJD.
4. A Prototype Blood Test : It is carried out for the variant CJD.
5. Tonsil Biopsy : In biopsy study, a small piece of tissue is taken from the tonsils and checked for the abnormal prions found in variant CJD (they're not present in other types of CJD).
6. Genetic Test : A simple blood test is carried out to find a mutation in the gene that produces normal protein. A positive result may indicate familial (inherited) CJD.
7. Brain Biopsy: In this procedure, a small piece of brain tissue is removed by using a thin needle by drilling a tiny hole into the skull. It's only performed in a few cases where there's a concern that someone doesn't have CJD but some other treatable condition.

Treatment:

Currently, there is no specific treatment for prion diseases. Hence, supportive treatment is being provided to the patient. Examples of this type of care includes :

1. Medications:

Some medications can be prescribed to treat symptoms. Examples include -

- reducing psychological symptoms with antidepressants or sedatives.
- providing pain relief using opiate medication.
- Reducing muscle spasms with drugs like Sodium Valproate and Clonazepam.

2. Assistance:

As the symptoms get severe, many people need help taking care of themselves and performing daily activities.

3. Providing Hydration And Nutrients:

As the disease advances, IV fluids or a feeding tube may be required.

Prevention:

Several preventive steps have been taken to avoid the transmission of acquired prion diseases. These are as follows :

- Tight regulations had been set on importing cattle from countries where BSE occurs.
- The parts of cows, such as the brain and spinal cord are prohibited from being used as food for humans and animals.
- Those with the history of or risk for exposure to prion disease are prevented from donating blood and other tissues.
- Robust sterilization measures are being used for medical instruments that has come into contact with the nervous tissue of someone with suspected prion disease.
- Destruction of disposable medical instruments.

There's currently no way to prevent inherited and sporadic forms of prion disease.

Areas Of Work For Treatment Of Cjd:

The pharmacological targets for the development of treatment of Creutzfeldt-Jakob Disease can be defined as follows :

1. Silencing of a gene by small interfering RNA targets PRP expression as the substrate of prion conversion and the mediator of neurotoxicity.
2. Another way and probably the most powerful strategy is protecting or shielding PrPC from conversion by antibodies. It has been proved in cell and animal models of prion disease. But how to engineer antibodies or fragments thereof such that they cross the blood-brain barrier is an obstacle.
3. As the intactness of cholesterol-rich detergent-resistant membranes (DRMs) is mandatory for PrP conversion, its destabilization can prevent PrPSc replication. This can cause by the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, the statins (as they are proven effective in cell models of prion disease). However, interference with DRMs that execute essential cellular functions may cause adverse effects.
4. Inactivation of the component (i.e., PrPSc) causing the PrP conversion would be a valuable pharmacological strategy.
5. Inactivating or shielding PrPSc such that its rendered conversion incompetent is the most obvious antiprion strategy. Polyanions like Congo red, dextran, heparin sulfate, and pentosan polysulfate, have been described as possessing antiprion activity in cell and animal models. By a direct interaction of these polyanions with PrPSc can show better results.

CONCLUSION:

Nowadays, there are improvements in the diagnostic methods of CJD. But, the treatment is still limited to supportive care. According to the researches, several preventive measures have been set to avoid its spread. However, the actual mechanism for misfolding of prion protein is not known; the treatment needs further researches. As this is a neurodegenerative disorder, the treatment will be associated with blood-brain barrier. It is the most challenging task to find the drug entity that can cross the blood-brain barrier. Hence, the given areas of work can be helpful for development of drug for CJD.

REFERENCES:

1. National Institute of Neurological Disorders and Stroke. (2018, May). Creutzfeldt-Jakob Disease Fact Sheet. Retrieved from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Creutzfeldt-Jakob-Disease-Fact-Sheet
2. Creutzfeldt–Jakob disease. (2020, October 14). In Wikipedia. Retrieved from https://en.m.wikipedia.org/wiki/Creutzfeldt%E2%80%93Jakob_disease
3. Kupfer L, Hinrichs W, and Groschup M. H (2009). Prion Protein Misfolding. Current Molecular Medicine, 9(7), 826–835. DOI: 10.2174/156652409789105543 Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3330701
4. Prion. (2020, October 13). In Wikipedia. Retrieved from https://en.m.wikipedia.org/wiki/Prion
5. (United Kingdom National Health Service, 2018) Retrieved from https://www.nhs.uk/conditions/creutzfeldt-jakob-disease-cjd/
6. Jill Seladi Schulman, (2019, December 13). What Is Prion Disease?. Retrieved from https://www.healthline.com/health/prion-disease
7. Korth and Peters (2006). Emerging Pharmacotherapies for Creutzfeldt-Jakob Disease. JAMA Neurology, 63(4):497-501. DOI: 10.1001/archneur.63.4.497 Retrieved from https://jamanetwork.com/journals/jamaneurology/fullarticle/791062